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CHILDHOOD CNS TUMOURS: HEALTH AND FUNCTIONAL OUTCOMES IN ADULT SURVIVORS, AND FOLLOW-UP NEEDS OF PATIENTS AND PARENTS

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“Jag har väntat så länge på just den här dan
Och det är skönt att den äntligen kommer”
Kenta

ABSTRACT

Childhood central nervous system (CNS) tumour patients represent a high-risk population regarding tumour- and treatment-related late effects. The overall purpose of the present thesis was to gain increased knowledge about the long-term consequences for survivors and their parents after a CNS tumour diagnosis in childhood. The thesis comprises four studies specifically addressing: health and functional status of adult survivors, health care needs of adult survivors, the influence of illness characteristics on parental distress, and the impact of illness on families of adult survivors.

Study I covered 321 parents (182 mothers, 139 fathers) of children diagnosed with CNS tumours, bone tumours, acute lymphoblastic leukaemia (ALL), or acute myeloid leukaemia (AML), and who were treated at one of two Swedish sites. The Studies II-IV are population-based, and involve an entire nation-wide cohort of all Swedish survivors meeting the inclusion criteria. These studies were based on data from 531 ≥18 years old childhood CNS tumour survivors, for whom >5 years had passed since time of diagnosis, 556 of their parents, and 996 general population controls, stratified by sex and age. The studies used a cross-sectional design and are based on quantitative self-report data. Parental distress was assessed by the Parental Psychological Distress in Cancer, health and functional outcomes by the Health Utilities Index™ Mark2/3, and family impact by the Impact on Family Scale. Health care needs were assessed by a multidimensional questionnaire.

When followed-up at a median time of 16 years after diagnosis, comparisons with control subjects confirm persistent disability in multiple functional domains in adult survivors of childhood CNS tumours. Specifically, survivors showed disability in domains of sensation, mobility, and cognition, whereas indices of emotion and pain were unaffected compared to control subjects. In comparison with male survivors, females showed poorer overall health and functional status. Furthermore, two fifths of survivors were found to have *unmet* health care needs in adult life, particularly regarding psychosocial services and illness education. Survivors with health-related disability had greater health care needs in adult life, and more *unmet* such needs. Findings on parental distress suggest that distress reactions are influenced by diagnosis-related factors such as great uncertainty about late effects, as parents of children treated for CNS and bone tumours showed heightened vulnerability to distress. The illness-related impact on families of adult CNS tumour survivors was subsequently addressed. At the group level, the conditions of families of adult survivors appeared to be mildly to moderately influenced by the child's past illness, although a subgroup of parents reported adverse family consequences even at this late stage of follow-up.

In conclusion, outcomes show that the consequences of cancer extend into adult life by compromising survivors' functional ability – a finding that underscores the importance of extended long-term follow-up continuing into adulthood. Addressing identified unmet health care needs in extended follow-up increases the quality of comprehensive care for this patient population. Furthermore, parents of CNS tumour patients indicate exceptional needs for supportive measures and enhanced information, an issue that needs attention in order to reduce avoidable illness-related distress and long-term adverse family consequences.

Keywords: Childhood CNS tumours; adult survivors; health-related late effects; functional disability; long-term follow up; parental distress, persistent family impact.

LIST OF PUBLICATIONS

The thesis is based on the following papers, which will be referred to by their Roman numerals I-IV:

I. Hovén E., Anclair M., Samuelsson U., Kogner P., & Boman K.K. (2008). The influence of pediatric cancer diagnosis and illness complication factors on parental distress. *J Pediatr Hematol Oncol* 30(11), 807-814.

II. Boman K.K., Hovén E., Anclair M., Lannering B., & Gustafsson G. (2009) Health and persistent functional late effects in adult survivors of childhood CNS tumours: A population-based cohort study. *European J Cancer* 45, 2552-2561.

III. Hovén E., & Boman K.K. Persistent impact of childhood CNS cancer on families of adult survivors: A population-based cohort study. (*manuscript*)

IV. Hovén E., Lannering B., Gustafsson G., & Boman K.K. Health care needs of adult survivors of childhood CNS tumors: A double informant population-based study. (*manuscript*)

RELATED PUBLICATIONS

I. Anclair M., Hovén E., Lannering B., & Boman K.K. (2009). Parental fears following their child's brain tumor diagnosis and treatment. *J Pediatr Oncol Nurs* 26(2), 68-74.

CONTENTS

LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
ANOVA	Analysis of variance
CCSS	Childhood Cancer Survivor Study
CNS	Central nervous system
CRT	Cranial radiation therapy
EORTC	The European Organisation for Research and Treatment of Cancer
GAS	General adaptation syndrome
HRQoL	Health-related quality of life
HUI	Health Utilities Index
ICC	Intra-class correlation coefficient
ICCC	International Classification for Childhood Cancer
IFS	Impact on Family Scale
IQ	Intelligence quotient
PNET	Primitive neuroectodermal tumour
PTSS	Posttraumatic stress symptoms
QoL	Quality of life
SCCR	Swedish Childhood Cancer Registry
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization

INTRODUCTION

Improved diagnostic procedures and the introduction of multimodal and refined treatment strategies have resulted in improved survival rates for childhood cancer during the last decades. However, childhood cancer is still a life-threatening disease that imposes a psychological and existential challenge for the children and their families (Dahlquist, Czyzewski, & Jones, 1996; Eiser, Eiser, & Stride, 2005; Sloper, 2000). By itself, survival following diagnosis and treatment does not ensure quality of life for the surviving children. Along with the impressive gains in survival rates, negative long-term consequences related to the illness experience, to the disease and/or its treatment, i.e. adverse late effects, have been acknowledged. The focus of psychological research has accordingly shifted. Previously, studies focused on the emotional reactions of children and their parents in relation to an almost certain death, while many studies today direct attention to aspects of survivorship, that is, how children and their families cope with survival issues. Consequently, a considerable body of literature devoted to the psychosocial adjustment in childhood cancer patients, their parents, or both are now available, and increasing numbers of studies are related to the situation of long-term survivors (Boman & Bodegård, 2004; De Clercq, De Fruyt, Koot, & Benoit, 2004; Jörngården, Mattsson, & von Essen, 2007; Norberg, Lindblad, & Boman, 2006; Robinson, Gerhardt, Vannatta, & Noll, 2009).

Prior studies focused primarily on adolescent survivors and on the psychosocial adjustment during the first years following successful treatment. Interest in the *very* long-term consequences for the survivor and the family, i.e. when the survivor has reached adulthood, is increasingly apparent in recent studies (Blaauwbroek, Stant et al., 2007; Hardy et al., 2008; Reulen et al., 2007). Nonetheless, studies that focus on the situation of parents of adult survivors are still scarce. Also, in the psychological research field, studies regularly address childhood cancer survivors and their parents as a uniform group, without distinguishing psychosocial reactions and adjustment for different diagnoses. This is particularly noticeable in research on parents' psychological reactions (Pai et al., 2007). Although the "non-categorical" approach is appropriate for some research questions, there is a need for increased knowledge about the influence of unique disease characteristics and specific conditions on psychosocial adjustment in survivors and their parents, as some stress reactions and illness consequences may be directly related to the child's type of cancer.

Compared to the general population and other childhood cancer patients, childhood central nervous system (CNS) tumour patients constitute a high-risk population regarding tumour and treatment-related medical late effects (Geenen et al., 2007; Hjern, Lindblad, & Boman, 2007; Hudson et al., 2003; Oeffinger et al., 2006). Also, survivors of childhood CNS tumours frequently experience adverse long-term psychological and social consequences. The overall purpose of the present thesis is to increase knowledge about the consequences for patients and their families following CNS tumour treatment by comprehensively addressing multiple outcomes as they appear when survivors reach adulthood. Together, findings will contribute to a more complete picture of this subtype of childhood cancer, enabling identification of subgroups at risk for negative outcomes and pointing out areas for improvement in follow-up care of patients and parents.

THEORETICAL BACKGROUND

To facilitate understanding of the empirical investigations and related research discussed in the present thesis, some theoretical models and key concepts will be introduced and defined in this section.

HEALTH

It is often argued that health is one of the major goals of medicine. Despite being a core concept in medicine and a common outcome measure in research, few studies include a definition or conceptualisation of health.

At least two principal distinct theories can be presented for determining the meaning of health. In the philosophical approach of naturalism, also referred to as the biostatical theory of health, the concept of disease is central for the understanding of health, and thus important to define to begin with (Ereshefsky, 2009; Nordenfelt, 2007). A definition of disease is as follows: "*A disease is a type of internal state which is either an impairment of normal functional ability, i.e. a reduction of one or more functional abilities below typical efficiency, or a limitation on functional ability caused by environmental agents*" (Boorse 1997 in Nordenfelt, 2007). According to the biostatical theory of health, the absence of a disease is identical with health. Functional ability is a core concept in this theory of health. A holistic theory of health, on the other hand, pertains to the whole person and the concept of health includes an individual's vital goals in life. On the basis of the holistic theory, health has been defined as: "*A is completely healthy if, and only if, A has the ability, given standard circumstances, to reach all his or her vital goals*" (Nordenfelt, 2007, p.7). Health is accordingly a function of an individual's abilities to perform intentional actions and achieve goals. The holistic perspective thus proposes that health is compatible with the presence of disease.

A third distinct definition of health, which is of importance in paediatric oncology research, is the definition made by the World Health Organization (WHO) Health Declaration, that describes health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" (WHO, 1948). This definition emphasises the broad nature of the concept, and has been referred to as a traditional approach for defining health (Brülde, 2000).

In research, a comparative definition is often suitable when studying health outcomes (Brülde, 2000). Such a definition enables comparisons of health states and the identification of health problems. Hence, health outcome measures that adopt comparative definitions argue that improvements in functional ability result in improved health. The Health Utilities Index (HUI) that measure an individual's health status in relation to several domains is an example of such a measure that places emphasis on functional ability (Horsman, Furlong, Feeny, & Torrance, 2003). The concept of health status can be defined as "*a child's level of wellness versus illness, including the presence of biological/physiologic dysfunction symptoms and/or the level of illness control*" (Drotar 2004 in Davis et al., 2006). The HUI instrument is based on

a multi-attribute approach, where health status is defined as being comprised of a number of distinct attributes, e.g. vision, hearing and cognition (Feeny, Furlong, & Barr, 1998; Furlong, Feeny, Torrance, & Barr, 2001). The developers of the HUI suggest that a multi-attribute approach provides a ‘‘holistic’’ description of an individual’s health status that facilitate the assessment of multiple sequelae, and varying levels of severity of problems.

Self-rated health has been found to be a strong predictor of subsequent outcomes, such as ill health and mortality (Kaplan et al., 2007). An individual’s self-rated health is based on both the current health status and the self-evaluation of that health status. When using measurements like the HUI, the current health status is self-assessed but the evaluation is based on community preferences. The study of self-reported health status is important as it may identify follow-up needs of survivors that may not be identified by objective measures of health, including, for example, a standard medical evaluation (Schwartz, 2003).

Health-related quality of life

Health-related quality of life (HRQoL) is a commonly used outcome measure in psychosocial research. The concept of HRQoL emerged as a way of defining the multidimensional concept of Quality of life (QoL) in the field of health (Anderson & Burckhardt, 1999). The WHO defines QoL as “*individuals’ 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*.” (WHO, 1995 p.1405). Different definitions have been suggested for HRQoL. Although there is no generally accepted definition, current consensus is that the concept of HRQoL should include physical, cognitive, social and emotional functioning (Stam, Grootenhuis, Caron, & Last, 2006). The concept refers to the broader impact of disease on everyday life as well as disease- and treatment-related symptoms. Although efforts have been made to define HRQoL separately from the more general QoL, the two concepts have been found difficult to differentiate. Hence, further conceptual work is needed to clarify the distinction (Wallander, Schmitt, & Koot, 2001). Indeed, studies examining HRQoL or QoL have been found to measure similar constructs (McDougall & Tsonis, 2009). The HUI instrument, previously mentioned, has been described as a measure of HRQoL that draw on definitions of HRQoL that emphasise *“the value assigned to duration of life as modified by impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy.”* (Furlong et al., 2001). In practice the HUI is strongly related to one’s functional status. Notably, the HUI instrument includes no subscale for social well-being.

According to Davis and co-workers (2006), three different conceptual models of the relationship between QoL/HRQoL and self-reported outcomes have been outlined: discrepancy theory, Lindstrom’s model, and utility theory. According to the discrepancy model, poorer HRQoL is the result of a discrepancy between what one wants to do (ideal self) and what one can reasonably achieve (actual self) (Eiser, Vance, & Seamark, 2000). Lindstrom’s model considers four spheres of human existence: global (ecological, societal, and political resources), interpersonal (social relationships and supports), external (social and economic resources), and personal (physical, mental,

and spiritual aspects). This model is unique since it considers both micro and macro aspects (Davis et al., 2006). The HUI derives from the utility model. On the basis of judgements made by the general population and people with specialised knowledge, the utility model assigns values to different health states (Drummond, 2001; Furlong et al., 2001). The values usually range from zero to one, where zero equals death and one equals perfect health.

STRESS

Although the concept of stress is widely used today, and of great importance in psychological research, it is difficult to find a clear-cut definition with which everyone agrees. Traditionally, three views of stress can be distinguished in stress research, defining stress either as a stimulus, a response or an interaction (Brannon & Feist, 2007; Singer & Davidson, 1991).

Studies adopting the stimulus definitions of stress are oriented toward environmental stimuli such as natural disasters, illness or workload. In the physiological tradition, most prevalent in biology and medicine, stress is understood from the perspective of the response-based theory. The reactive organism is in focus and stress is defined *only* in terms of a physiological stress response. The psychological stress concept has undergone a transition from these two formulations, emphasising the objective environment and physiological responses, to formulations that emphasise the subjective, cognitive processes that influence the perception of stress. In line with this, most contemporary views of stress are, in one way or another, related to the third model, the transactional model, which points out that the individual's stress reactions are influenced not merely by objective circumstances, but also by cognitive and emotional processes. Accordingly, psychological stress is conceptualised as the result of an interaction between the individual and the environment. Potential stressful events will consequently have different meanings and effects for different individuals (Monat & Lazarus, 1991).

Stressors and appraisal

In the transactional model of stress, a stressor is defined as any stimulus or demand that is perceived as threatening, harmful or challenging. The cognitive appraisal of the stressor and one's own resources to manage it are key components according to the transactional model of the stress process (Singer & Davidson, 1991).

Although the importance of the stressor depends on individual appraisal, prior research has established a record of events that most people, in Western countries, perceive as challenging (Holmes & Rahe, 1967). These life events have been characterised by being indicative of or requiring a significant change in the individual's ongoing life pattern. Highest degree of consensus about the significance of life events was found for events related to separation (e.g. death of spouse/family member, or divorce), and major life changes (e.g. personal illness, marriage, or dismissal from work). In line with this finding, stressors with exceptional intense psychological impact have been labelled traumatic stressors (McFarlane & de Girolamo, 1996). Traumatic stressors often refer to actual or threatened death or serious injury, or threat to physical integrity.

Continuous or recurrent stressors can have a high psychological impact without being traumatic in nature (Serido, Almeida, & Wethington, 2004). Chronic stressors have been referred to as the persistent or recurrent difficulties of life. They are often ambiguous and intangible, develop slowly and typically last for a longer time than traumatic stressors. Chronic stress can arise from ongoing conditions such as threat, excessive demands, uncertainty or restriction of choice.

Strain and stress reactions

An event perceived as a stressor results in strain (demand, pressure) (Lazarus & Folkman, 1984). Studies of stress usually place emphasis on the negative consequences following the experience of strain. It is however important to remember that stress is a natural process that has adaptive benefits. The physiological response to stress involves an endocrine activation, where the body mobilises its defences against the stressor. This activation, referred to as the fight or flight response, is characterised by increased adrenaline release that consequently elevates the heart rate and blood pressure (Aldwin, 2007). The physical reactions are adaptive as a short-term response to an emergency situation, but with prolonged stress the physiological activation is not required. Emotional stress reactions to prolonged strain generally entail feelings such as anxiety, depression, anger, and sadness (Lazarus, 1991). Cognitive stress-induced consequences include memory deficits, difficulties with concentration, intrusive thoughts or flashbacks of stressor, and avoidance of reminders. Headaches and musculoskeletal pain are frequent psychosomatic reactions to stress.

Distress

Although the definition and use of the term "distress" is somewhat vague, the term usually refers to *unpleasant* subjective stress reactions. The concept of distress derives from Hans Selye's General Adaptation Syndrome (GAS): the general physiological and psychological stress responses including three stages: acute, resistance and exhaustion (Selye, 1991). Selye (1991) distinguished between distress and eustress. Distress refers to stress responses characterised by difficulties in adapting to the stressor, i.e. internal strain, while eustress represent stimulating and energizing effects. The simple conceptualisation of distress as internal strain provoked by an external stressor was questioned by the transactional stress theory, suggesting that distress indicates that the individual's attempts to cope with the stressor are unsuccessful (Matthews, 2000).

The operational meaning of distress includes negative effects such as depression and anxiety, as well as cognitive responses such as worry and lowered self-esteem (Matthews, 2000).

FAMILY IMPACT

Family life can be disrupted by the stress that parents experience in relation to a child's illness. The concept of "family impact" is commonly used in research on childhood chronic illness, including childhood cancer, for the study of how families are affected by multiple demands simultaneously besides the "usual" family stressors (e.g. Heath, Lintuuran, Rigguto, Tikotlian, & McCarthy, 2006; Jackson, Tsantefski, Goodman,

Johnson, & Rosenfeld, 2003; Patterson, Holm, & Gurney, 2004). In a framework adapted from the work of Lazarus and Folkman (1984), family stress results from a perceived imbalance between the demands on the family and the resources available to meet such demands. In the literature on childhood illness, family impact has been conceptualised as "the effects of a child's illness on the family system" (Stein & Riessman, 1980, p.466). This conceptualisation is based on the assumption that changes occur in the family as a result of the child's illness, including both negative and positive impacts. The positive influences are related to the unifying function a child's illness can have on a family. The negative influences of illness on structure and function of the familial relationships have been conceptualised in terms of losses, such as less time for family members, or restrictions in social life.

Another concept used is 'burden of illness/injury' (Stein et al., 1987; Wade, Drotar, Taylor, & Stancin, 1995). Illness- or injury-related burden is related to injury severity and comprises stressors associated with medical management, disruption of family routines, changes in the child's behaviour, and concerns over the reactions of other family members (Schwartz et al., 2003). This concept focuses exclusively on the negative impact of the disease or the condition on the family.

The definition adopted in the current thesis describes family impact in terms of changes in the family with regard to: social life, interaction with significant others, subjective distress or strain, time for other family members (siblings), and financial status (Stein & Riessman, 1980).

SELF- AND PROXY-REPORTED DATA

Patient-reported outcome is a term referring to the subjective assessment by the patients themselves of aspects of their health, such as functional ability and HRQoL (Rothman, Beltran, Cappelleri, Lipscomb, & Teschendorf, 2007). The patient-reported data reflect how the patient interprets the experience and are distinct from proxy-reported outcomes. A proxy-rating is made by a person who evaluates the patient/survivor in terms of the concept being measured. In the context of childhood cancer research, proxy-ratings are usually made by a parent, peer, teacher or health professional (Barr et al., 1999; Fluchel et al., 2007; Meeske, Katz, Palmer, Burwinkle, & Varni, 2004; Vannatta, Gartstein, Short, & Noll, 1998). In an adult setting, the proxy-rating is mainly carried out by a relative or partner (Sandra Kooij et al., 2008).

Children and proxies sometimes differ in their assessments of the child's health status and HRQoL (e.g. Levi & Drotar, 1999; Penn et al., 2008). To some extent, the degree of agreement between patient self-reported and proxy-reported data depends on the particular areas being evaluated (Eiser & Morse, 2001; Upton, Lawford, & Eiser, 2008). In general, good agreement has been found for areas that reflect physical functioning and observable characteristics, including domains such as mobility and hearing (Glaser, Davies, Walker, & Brazier, 1997; Penn et al., 2008). Poor agreement is more often reported for subjective attributes, such as emotion, and cognition.

Regardless of the specific concept being measured, it is has been argued that in psychosocial research on children, data should be obtained from both child and parent where possible, as both perspectives can complement each other and contribute to a more comprehensive evaluation (Eiser, Penn, Katz, & Barr, 2009; Wallander et al., 2001). As for adolescents, young adults, and adults who are assumed to be capable of answering for themselves, the need for proxy-reports is perhaps not as obvious. However, due to illness-related disabilities, responders (patients or survivors) might be unable to participate or to decide independently about participation in a study. This group of individuals can still be evaluated by the use of proxy-ratings. In addition, the contribution made by a proxy-rater can still be valuable when patients/survivors are able to respond for themselves. Most studies concerning survivorship issues rely on information from patients only, despite the fact that a sole reliance on patient self-report data has been found to result in outcomes that tend to be subject to bias (Jurbergs, Long, Hudson, & Phipps, 2007; O'Leary, Diller, & Recklitis, 2007). In an adult setting, data collected from multiple sources, such as when both survivors and family care-givers act as informants, increases reliability of outcomes and adds to a more comprehensive picture (Sandra Kooij et al., 2008).

MEDICAL ASPECTS OF CHILDHOOD CANCER

In Sweden about 300 children are diagnosed with cancer each year (Gustafsson, Heyman, & Vernby, 2007). The sex and age distribution for all childhood malignancies show that cancer is more common among boys (male/female ratio=1.18), and that cancer is most common in children aged 5-6 years old (based on the child's age at the time of diagnosis). As a result of advances in diagnostics and treatment, childhood cancer has evolved from a once inevitably fatal illness to what can be defined as a chronic illness (Eiser, Hill, & Vance, 2000; Fuemmeler, Mullins, & Marx, 2001). Today, almost 80 per cent of children and adolescents diagnosed with cancer become long-term survivors, although the survival rate differs depending on the type of cancer (Steliarova-Foucher et al., 2004). The term *long-term survivors* usually refer to survivors who have completed therapy and have been disease-free for at least 5 years since end of cancer treatment (Cantrell & Conte, 2009). The concept of *very* long-term survivors has occasionally come into use to denote patients who are even further in time from their diagnosis and who have entered adulthood (Blaauwbroek, Stant et al., 2007; Stuber et al., 2010). However, despite advances in treatment, childhood cancer remains the most common cause of childhood disease-caused deaths in the Western countries (Pritchard-Jones, Kaatsch, Steliarova-Foucher, Stiller, & Coebergh, 2006).

Childhood cancer differs from adult cancer in the way it emerges, and develops. Accordingly, the types of cancers in children are different from those in adults (Kaatsch, 2010). The most common primary cancer diagnosis in children is leukaemia, followed by primary CNS tumours (Gustafsson et al., 2007). The distribution of childhood malignancies in Sweden is presented in Figure 1.

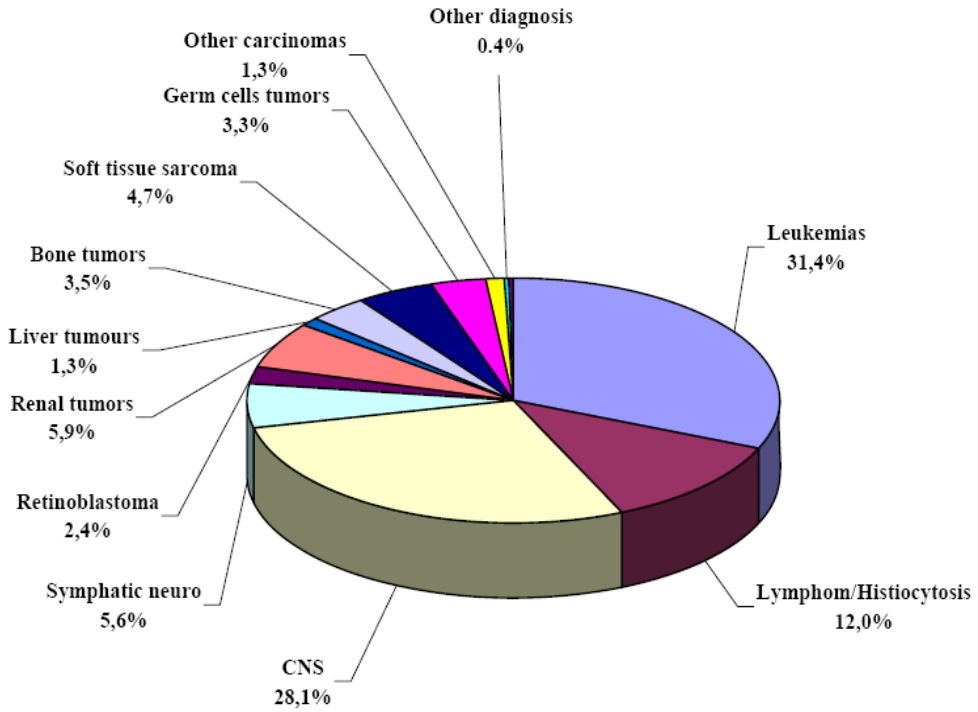

*Figure 1***.** Distribution of childhood malignancies in Sweden diagnosed 1984-2005. Reprinted with permission from Gustafsson et al. (2007) Childhood cancer incidence and survival in Sweden 1985-2005. Stockholm: The Swedish Childhood Cancer Registry.

The following section provides a more detailed presentation of childhood CNS tumours, as CNS tumour survivors and their families are of particular interest in this thesis.

CHILDHOOD CNS TUMOURS

CNS tumours are the second most common cancer diagnosis in children <15 years of age at diagnosis, and the most common solid tumours occurring in childhood, constituting 20–30% of all cases of paediatric malignancies in the Nordic countries. In Sweden, the mean annual incidence of children with CNS tumours is 4.2/100 000, with no sign of increase during the last decades. The age distribution is relatively even in regard to age at diagnoses, with a mean age at diagnosis of ~7 years (Gustafsson et al., 2007; Lannering et al., 2009).

Classification

The classification of childhood cancers is based on cell morphology and not, as in adults, on the primary site of origin (Lannering et al., 2009). The classification of childhood CNS tumours that forms the basis in the present thesis is the International Classification for Childhood Cancer (ICCC-3) (Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005).

Brain tumours are further classified according to the degree of malignant behaviour (i.e. malignancy scale) (Anderson et al., 2001; Baldwin & Preston-Martin, 2004). The grading of CNS tumours range from Grade I to Grade IV. Grade I lesions have low proliferate potential and often indicate a good prognosis, while Grade IV refers to tumours with high-proliferating cancer cells and is associated with fatal outcome. The aggressiveness of the tumour is a key factor in the choice of therapy. Surgical cure alone is usually limited to Grade I tumours, while high-grade tumours (Grade III-IV) require a more complex multimodal treatment plan.

Tumours of the CNS are often categorised anatomically as supratentorial (above the tentorium), infratentorial (below the tentorium), or hypothalamic/parasellar (Anderson et al., 2001). The tentorium is a membrane that separates the cerebellum and brain stem from the rest of the brain. The most common tumours are supratentorial low-grade tumours (Mulhern & Butler, 2004).

Treatment of childhood CNS tumours

Treatment of tumours in the CNS in children is often complex, frequently including a combination of surgery, radiotherapy and chemotherapy. The treatment depends upon diagnosis, tumour location and age of the child.

Surgical resection is regularly the initial therapy for children diagnosed with a brain tumour. Whether the tumour is surgically accessible depends, largely, on its location and histology (type and grade). Through the use of new imaging techniques, previously unresectable brain-stem tumours can be better managed today. In most cases, the goal is gross total resection of the tumour, i.e. radical surgery, as this approach is associated with improved overall survival (Partap & Fisher, 2007; Pollack, 2009). Surgery is also

used for diagnostic purposes, specifically for taking a biopsy for staging and characterising the tumour.

Radiation therapy, local or craniospinal, is a key component in the treatment of tumours in the CNS. Using high-energy rays the therapy aims at destroying the proliferating cancer cells. However, since healthy normal tissue surrounding the tumour can be damaged and irradiated tissue may fail to develop normally, children that receive radiotherapy are at risk of unwanted side effects (Anderson et al., 2001; Palmer, Reddick, & Gajjar, 2007). The severity of the side effects is age-dependent. Very young children are especially susceptible to radiation damage. For that reason, children should be over 3 years of age in order to receive radiation therapy (Lannering et al., 2009). As conventional radiation therapy is associated with severe side effects, new radiation delivery techniques are currently being evaluated, and alternatives, such as proton beam therapy and gamma knife radiosurgery, have gained increased interest (Palmer et al., 2007). The goal of alternative and refined radiation techniques is to increase the radiation exposure to the tumour while at the same time minimize radiation of surrounding normal tissue in order to reduce adverse late effects.

The role of chemotherapy in the treatment of CNS tumours is central. A large number of chemotherapeutic agents, i.e. drugs that kill cancer cells or prevent cell proliferation, have been shown to be effective. Chemotherapy has been found to be most effective when used as an adjuvant (given as a compliment to the primary treatment) to surgery and radiation to control local and metastatic disease. Children who have undergone chemotherapy in combination with radiotherapy have significantly higher survival rates compared to those who received radiation therapy alone (Mueller & Chang, 2009).

Main diagnostic subgroups

Astrocytoma

Astrocytoma tumours arise from astrocytes – the most common glial cell type (Baldwin & Preston-Martin, 2004). Glial cells are supportive cells that help brain cells (neurons) function. Astrocytoma is the largest diagnostic subgroup, accounting for 45% of all CNS tumours (Lannering et al., 2009). Astrocytomas are divided into three groups: low-grade astrocytomas, high-grade astrocytomas and optic nerve/chiasma gliomas. The majority are low-grade astrocytomas. Survival rate for the whole group of astrocytomas is currently 82% (10 year overall survival), but the three groups differ in terms of survival prognosis. The overall survival for low-grade astrocytomas and optic nerve/chiasma gliomas are 91% and 89%, respectively. High-grade astrocytomas have an inferior survival prognosis, with a current 10-year overall survival of 26% (Lannering et al., 2009).

For low-grade astrocytomas that are located outside the supratentorial midline, radical surgery has been the standard treatment. For low-grade astrocytomas in the supratentorial midline (optic nerve/chiasma), where surgery is rarely an option, chemotherapy has been given to younger children and radiation therapy to older children. High-grade astrocytomas need multimodal treatment with chemotherapy in addition to surgery and radiotherapy (Lannering et al., 2009).

Medulloblastoma/PNET

Medulloblastoma is the most common malignant brain tumour in children, constituting about 19% of all CNS tumours in children (Lannering et al., 2009). Historically, medulloblastoma was classified as a primitive neuroectodermal tumour (PNET), but it was later demonstrated that medulloblastoma was molecularly distinct from PNET (Pomeroy et al., 2002). The current 10-year overall survival for children with medulloblastoma is 53%, with girls showing a better survival rate compared to boys (girls: 58%, boys: 42%) (Lannering et al., 2009).

Medulloblastoma is highly sensitive to chemotherapy and irradiation (Partap & Fisher, 2007). Children over 3 years of age receive craniospinal radiotherapy in addition to surgery (Lannering et al., 2009). During the last decades, the doses of radiation therapy have decreased in patients with average risk, and chemotherapy has been intensified.

Ependymoma

Ependymoma is a glial tumour that arises from ependymal cells – a type of glial cell (Cohen, Broniscer, & Glod, 2001). Ependymoma is the third most common childhood CNS tumour after astrocytomas and medulloblastomas (Lannering et al., 2009; Mueller & Chang, 2009). In Sweden, the current survival rate at 10 years follow-up is 60% (Lannering et al., 2009).

The first-line treatment for ependymomas is surgery, repeated if necessary. Also, most children with ependymomas are given radiotherapy. A combination of chemotherapy and radiotherapy is used in cases of metastatic disease (Lannering et al., 2009).

Craniopharyngioma

Childhood craniopharyngiomas are histologically benign non-glial intracranial tumours arising in the sellar region, in the hypothalamic-pituitary region (Poretti, Grotzer, Ribi, Schonle, & Boltshauser, 2004). Craniopharyngioma constitute 1.2–4% of all intracranial tumours in children (Muller, 2008; Poretti et al., 2004). In Sweden, the current 10-year overall survival for children with craniopharyngioma is 92% (Lannering et al., 2009).

The method of treatment of craniopharyngiomas has been radical surgery in all cases. Over time, this strategy has changed towards a more conservative surgical approach combined with radiotherapy, especially for larger tumours (Lannering et al., 2009).

Oligodendroglioma

Oligodendroglioma arise from oligodendrocytes, a type of glial cells. The current 10-year survival rate is 77% for the oligodendroglioma group (Lannering et al., 2009).

Oligodendrogliomas are subdivided and treated according to low- or high-grade glioma protocols (Lannering et al., 2009).

Intracranial or intraspinal nerve sheath tumours

Two principal types of tumours that arise from the nerve sheath can be distinguished (Jaspan & Griffiths, 2004). The first type is neurofibromas, which typically occurs in patients with neurofibromatosis type I, and the second type is schwannomas. In Sweden, 20 children were diagnosed with an intracranial or intraspinal nerve sheath tumour in a study period from 1984 to 2005 (Lannering et al., 2009). All 20 children were alive at the time of follow-up, i.e. 2005.

Intracranial germ cell tumours

Intracranial germ cell tumours are a heterogeneous group of lesions, that most frequently arise in the pineal or suprasellar regions of the brain (Calaminus & Garré, 2004; Packer, Cohen, & Cooney, 2000). Germ cell tumours are a rare group in the paediatric age group. In Sweden in a study period from 1984 to 2005, 38 children (23 boys, 12 girls) were diagnosed with a germ cell tumour at an intracranial location (Lannering et al., 2009). Of these children, 25 were alive at follow-up.

The treatment of malignant germ cell tumours follows a multimodal treatment that may include tumour resection, radiation therapy and chemotherapy (Calaminus & Garré, 2004).

Survival

As for all childhood malignancies the overall survival for childhood CNS tumours has improved significantly during the last three-four decades: from a 45% survival rate for patients diagnosed in the 1970s to 66% in the 1990s (Steliarova-Foucher et al., 2004). The reasons for the improved rates of survival are several and include improved post-operative care, better diagnostic techniques, more aggressive surgery, improved radiation therapy and neurosurgical techniques, and refined chemotherapy dosing and timing (Packer, 2005). However, compared with most other types, improvements in survival after a tumour in the CNS have been modest (Arndt, Kaatsch, Steliarova-Foucher, Peris-Bonet, & Brenner, 2007). Also, a recent study of children diagnosed in Sweden 1984-2005 show no significant improvement in survival rates for children with CNS tumours diagnosed before or after 1995 (Lannering et al., 2009). The survival rate for all CNS tumours at 10 years follow-up is 72%. However, as described previously, the survival prognosis differs considerably between tumour types and according to diagnostic markers such as age, and extent of surgical resection. The lowest 10-year survival rate (17%) has been found for brain-stem tumours (Lannering et al., 2009).

Late effects

The potential “cost” of childhood cancer in terms of late effects following the tumour and its treatment has been well documented. Late effects have been defined as effects occurring after the successful completion of medical therapy, usually five years from the time of diagnosis (Anderson et al., 2001). Compared to the general population and other childhood cancer patients, survivors of childhood CNS tumours, as a group, are more likely to sustain a higher burden of tumour- and treatment-related late effects (Geenen et al., 2007; Oeffinger et al., 2006).

The tumour location within the CNS and the use of multi-modal therapy place these children at risk for long-term morbidity. The treatment modality associated with greatest risk for adverse sequelae is radiotherapy, due to the child having a vulnerable, and developing brain (Pollack, 1999). Nonetheless, surgery alone and chemotherapy can also cause adverse late effects.

Medical late effects

Many survivors of childhood CNS tumours live with permanent changes to physical appearance and body image. These include visible scars from surgical procedures, some degree of alopecia (hair loss) and noticeable changes to bone structure of the skull following cranial irradiation (Turner, Rey-Casserly, Liptak, & Chordas, 2009).

In addition to a variety of localised changes in physical appearance, survivors who have been treated with craniospinal irradiation and/or who have a disruption of the hypothalamic-pituitary axis can develop more global changes in physical appearance such as short stature (Turner et al., 2009). The hypothalamic-pituitary axis is the primary connection between the endocrine system and the nervous system, and disruptions to this connection can lead to a range of endocrine-related medical conditions (Shaw, 2009; Turner et al., 2009). Damage to the hypothalamic-pituitary axis is particularly common in patients with tumours that are directly located in this area, i.e. hypothalamic tumours (craniopharyngiomas) and optic pathway tumours. Endocrine adverse late effects were reported by 43% of survivors of childhood brain tumours (Gurney et al., 2003). Compared with siblings, survivors were found to be at increased risk for growth hormone deficiencies, hypothyroidism, and the need for medications to induce puberty. Other endocrine-related complications include long-term osteopenia (lower bone mineral density), and obesity (Turner et al., 2009).

A large proportion of survivors suffer long-term neurological and neurosensory sequelae, even when treatment only involved surgery (Packer et al., 2003; Sonderkaer et al., 2003). Neurological impairments include strokes, seizures, epilepsy, ataxia, coordination and motor control problems. Neurosensory dysfunctions refer to effects on vision, hearing and pain. These can be a direct result of tumour locations/involvement (e.g. optic pathway gliomas) or result of treatment toxicity (e.g. hearing deficits resulting from chemotherapy) (Turner et al., 2009).

One of the most devastating medical late effects following illness and its treatment is the development of a secondary malignancy. The most common secondary malignant neoplasms are CNS tumours, specifically meningiomas and glial tumours, followed by thyroid cancer and soft tissue sarcomas (Armstrong et al., 2009; Neglia et al., 2006). New primary CNS tumours developed from 5 to 28 years after time of original diagnosis, with a median time to occurrence for meningiomas of 17 years, and 9 years for gliomas (Neglia et al., 2006). The single most important risk factor for the occurrence of a new CNS malignancy was radiation therapy for the original tumour.

Neurocognitive late effects

Radiation therapy and newer aggressive and more effective therapies directed at the tumour, and consequently the brain, are often associated with neurocognitive impairment, that may extend into adulthood (Ellenberg et al., 2009; Mulhern, Merchant, Gajjar, Reddick, & Kun, 2004; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001; Turner et al., 2009). The adverse effects of cranial radiation therapy begin to emerge about 1 year after treatment and can deteriorate further for years following cessation of radiation therapy (Ris et al., 2001). Some cognitive late effects may not become apparent before three years after diagnosis, and additional deficits may first be prominent as late as about five years or later after diagnosis. However, it has been indicated that most of the knowledge on cognitive outcomes in brain tumour survivors is based on findings obtained during the first years following treatment (Briere, Scott, McNall-Knapp, & Adams, 2007). In general, neurocognitive late-occurring deficits are assumed to be chronic (Mulhern & Butler, 2004), but ongoing cognitive remediation training is important as it may improve the conditions (Hooft et al., 2005).

The most common methods used to determine neurocognitive late effects in children treated for CNS tumours have been intelligence quotient (IQ) tests, as a measurement of overall cognitive ability, or academic achievement (Mulhern et al., 2004; Turner et al., 2009). For example, in a study of long-term survivors of brain tumours, the mean full IQ was significantly below the normative mean, and 5% of the survivors were too mentally disabled to participate in IQ testing (Reimers et al., 2003). The current focus has shifted to the study of specific neurocognitive constructs and their relation to the more generic outcomes, such as IQ. The neurocognitive late effects range from mild learning issues to severe deficits in intellectual function. Long-term survivors of childhood CNS tumours were most likely to report neurocognitive impairments in processing speed and working memory (Ellenberg et al., 2009). For these, more than 40% of survivors of medulloblastoma/PNET had impaired function (Armstrong et al., 2009). Other neurocognitive structures affected include problems with visual-spatial organisation, learning ability, attention/concentration, emotional regulation and executive functioning.

Risk factors for cognitive deficits include female sex, younger age at treatment, longer time since treatment, type and dose of radiation therapy, and clinical features such as hydrocephalus (Mulhern et al., 2004; Turner et al., 2009). As for tumour location, supratentorial tumours are associated with greater cognitive impairment compared to infratentorial tumours (Anderson et al., 2001).

Psychological and social consequences

The illness experience and the medical late effects, in particular cognitive deficits, can result in negative psychological and social outcomes (Bellanti & Bierman, 2000; Poggi et al., 2005). A reciprocal association has been documented between psychological and cognitive problems (Poggi et al., 2005). Specifically, the psychological consequences following illness and treatment include general behavioural problems, symptoms of depression and anxiety, poor self-concept, and deficits in social skills (Poggi et al., 2005; Turner et al., 2009). Social consequences found for survivors of brain tumours

concern poorer educational attainment, greater dependence on societal well-fare aid, and employment difficulties (Boman, Lindblad, & Hjern, 2010; Gurney et al., 2009). Psychosocial consequences are presented in more detail in the "Previous research" section.

Follow-up care

With steadily growing numbers of long-term survivors of childhood cancer, it has become increasingly evident that many survivors need follow-up health care for lasting sequelae, both physical and psychological (Wallace & Green, 2004). Providing appropriate follow-up care has been recognised as a major emerging challenge in paediatric oncology (Landier & Bhatia, 2008). Accordingly, in recent years, a need of research on follow-up health care has become ever more acknowledged. The goals of long-term follow-up of survivors include monitoring of late adverse effects, and the providing of illness education and psychosocial services (Friedman, Freyer, & Levitt, 2006; Skinner, Wallace, & Levitt, 2007).

During the first five years following end of treatment, survivors are scheduled in regular follow-ups, including clinical examinations to detect disease recurrence. As adverse sequelae can emerge later in life it is important that survivors participate in long-term or even life-long medical follow-ups (Blaauwbroek, Groenier, Kamps, Meyboom-de Jong, & Postma, 2007; Edgar, Morris, Kelnar, & Wallace, 2009). The follow-up of adult survivors in Sweden has been described as a function of problem-oriented referral, being discharged by a doctor, or the survivor's initiative (Arvidson, Söderhall, Eksborg, Björk, & Kreuger, 2006). Problem-oriented referral means having a diagnosed condition or sequelae that require further follow-ups when discharged from paediatric health care. To ensure age-appropriate care, a successful transition from paediatric to adult-focused health care is critical for adolescent, young adult and adult survivors of childhood cancer (Arvidson et al., 2006; Edgar et al., 2009; Michel et al., 2009). There is currently no obvious consensus on how, by whom and where to best implement a transition model for long-term survivors (Aziz, Oeffinger, Brooks, & Turoff, 2006).

PREVIOUS RESEARCH

The increase in survival rates for childhood cancer has resulted in a growing body of literature examining the quality of life, and adjustment of children and parents following the diagnosis of cancer and its treatment. In the following section, a selective literature review on childhood cancer survivors and parents will be presented.

CHILDHOOD CANCER SURVIVORS

The actual meaning of cancer for the child depends on a variety of individual and family characteristics, including the child's cognitive and developmental level, prior life experiences, and family relationships (Hymovich, 1995). Although the onset of cancer and the "curative" treatment occur in childhood, the medical and psychological literature shows that survivors of childhood cancer may experience a range of consequences following the disease and the treatment (Patenaude & Kupst, 2005). Childhood and adolescence constitute important periods in one's life. The fulfilling of age-specific developmental tasks and achieving developmental milestones is of importance to one's adjustment in adult life. The cancer and its treatment can cause a disruption that interfere with the process of accomplishing milestones or normal developmental tasks, including the attainment of social and academic competence, identity formation, the development of friendships, and autonomy in relation to parents (Boman & Bodegård, 2004; Boman et al., 2010). The child's social life has been reported to be negatively impacted, for example by not being able to go to school or participate in normal activities (Enskär, Carlsson, Golsater, Hamrin, & Kreuger, 1997). Other specific stressors for children with cancer undergoing treatment relates to the experience of physical discomfort, i.e. being in pain, the hospitalisation, feeling different, and the fear of death. After cessation of treatment, stressors concern uncertainty about the future, and fears of cancer recurrence (Langeveld, Grootenhuis, Voute, de Haan, & van den Bos, 2004; Zebrack & Chesler, 2002).

The term *cancer survivorship* reflects a dynamic process of living after cancer, beginning at the time of diagnosis and continuing throughout one's lifespan (Doyle, 2008; Zebrack & Zeltzer, 2003). The outcomes of childhood cancer are often framed in terms of physical, existential, psychological and social effects. Research on aspects of surviving childhood cancer has applied different theoretical frameworks and outcome measures for facilitating the understanding of such effects. In terms of psychological problems, two of the most prominent outcome measures used are QoL and HRQoL (Langeveld et al., 2004; Speechley, Barrera, Shaw, Morrison, & Maunsell, 2006; Zebrack & Chesler, 2002). The three models presented in the theoretical background – the discrepancy theory, Lindstrom's model and the utility theory – can be distinguished in the literature addressing the impact of childhood cancer on the dimensions of QoL and HRQoL. Models based on the assumption that both cancer and its treatment are fundamentally traumatic events propose that aspects of survivorship fit the posttraumatic stress framework (Hobbie et al., 2000; Kazak, Alderfer, Rourke et al., 2004).

Childhood cancer has been conceptualised as a psychological crisis that may impact psychological well-being for survivors later in life. Research has found that during the first years after diagnosis, survivors experience emotional distress (Eiser et al., 2005; Jörngården et al., 2007). However, findings from studies of the *long-term* psychological impact are inconsistent and present somewhat contradictory findings, with both negative and positive consequences (McDougall & Tsonis, 2009; Sundberg, Lampic, Björk, Arvidson, & Wettergren, 2009). Results from some studies indicate that long-term childhood cancer survivors show equal or even better QoL and psychological functioning in comparison with control subjects (De Clercq et al., 2004; Elkin, Phipps, Mulhern, & Fairclough, 1997; Langeveld et al., 2004; Maunsell, Pogany, Barrera, Shaw, & Speechley, 2006; Sharp, Kinahan, Didwania, & Stolley, 2007). In contrast, findings from other studies suggest that both male and female survivors experience poorer overall HRQoL when compared to the general population (Grant et al., 2006). A recent study on psychological distress reported important findings with regard to these contrasting outcomes (Michel, Rebholz, von der Weid, Bergstraesser, & Kuehni, 2010). In this study, mean psychological distress was lower for the survivor group in comparison to population norms. A larger proportion of survivors did, however, indicate clinically significant psychological distress in comparison to the norm population, suggesting that survivors experience either high distress or very low/no psychological distress. In addition, although most studies report that survivors' psychological functioning appear within normal levels when assessed by overall outcome measures such as QoL, more specific areas may be adversely affected in long-term survivors (Patenaude & Kupst, 2005). These areas include survivors' impaired or diminished social relationships (Boman & Bodegård, 2004), symptoms of global distress (Zeltzer et al., 2009), posttraumatic stress symptoms (Kazak et al., 2001), and affected identity (Madan-Swain et al., 2000).

The adverse medical and psychological late effects of childhood cancer and/or its treatment can result in adverse long-term social consequences for the survivor (Boman et al., 2010; Gurney et al., 2009). Findings from some studies show that childhood cancer survivors have poorer educational achievement in comparison with control populations (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Boman & Bodegård, 2004). In other studies there is no consistent evidence that survivors have educational deficits, with the exception of survivors treated for CNS tumours (Boman et al., 2010; Koch, Kejs, Engholm, Johansen, & Schmiegelow, 2004). In these studies, survivors of other types of childhood cancer have educational outcomes similar to the general population. Furthermore, a range of other social late effects has been found to be impacted by childhood cancer survival. These relate to employment difficulties, school attendance, lower marriage rates, social activities, and dependence on social well-fare aid (Hjern et al., 2007; Johannesen, Langmark, Wesenberg, & Lote, 2007; Langeveld et al., 2003). The majority of studies conclude that social outcomes differ by cancer type. Survivors of CNS tumours are often distinguished as a unique group, with a stronger negative impact of illness and treatment on several studied social outcome domains.

Health status of childhood cancer survivors

The potential medical late effects following illness and treatment may predispose survivors for long-term morbidity, and increase the risk of late mortality (Armstrong, 2010). Recognition of potential late illness-related morbidity for childhood cancer survivors has been followed by recent research indicating that chronic disabilities can become apparent with time and interact unfavourably with normal ageing (Blaauwbroek, Stant et al., 2007; Hawkins, Diehl-Svrjcek, & Dunbar, 2006; Oeffinger et al., 2006). A growing body of research aims to evaluate the burden of illness by addressing adverse health outcomes and health status in long-term survivors of childhood and adolescent cancer (Geenen et al., 2007; Hudson et al., 2003; Oeffinger et al., 2006; Pogany et al., 2006; Reulen et al., 2007; Schwartz, 2003).

Despite many survivors reporting favourable health and functional outcomes, as a group survivors of childhood cancer have been found to exhibit adverse outcomes in different domains that result in poorer overall health status in comparison to control subjects (siblings or peers) (Hudson et al., 2003; Oeffinger et al., 2006; Pogany et al., 2006). Studies have reported that two-thirds of survivors experience at least one significant late health problem, with as many as 25 to 40 per cent of these experiencing severe or even life threatening chronic conditions (Hudson et al., 2003; Oeffinger et al., 2006). However, outcomes differ with regard to the domains of health status. For example, in a study of 10,189 long-term survivors in Britain no differences in mental health were found between survivors and the norm population, while physical health was affected for survivors at older ages compared to population norms (Reulen et al., 2007). Specific attributes reported to be most severely affected in survivors relate to health status domains of emotion, cognition and pain (Frange et al., 2009; Grant et al., 2006; Pogany et al., 2006).

A variety of factors help explain the great variability in health status outcomes when survivors are looked upon as a uniform group. In studies addressing survivors in their teens, adolescence or young adulthood generally poorest health outcomes have been found for those diagnosed with a CNS tumour, retinoblastoma, or a bone tumour (Alessi et al., 2007; Grant et al., 2006; Oeffinger et al., 2006). In addition to diagnosis-related differences, most studies indicate that female survivors of childhood cancer present poorer health status compared to male survivors (Alessi et al., 2007; Hudson et al., 2003; Oeffinger et al., 2006). Age at assessment, and time elapsed since diagnosis have also been related to health status outcomes, with older survivors and greater time elapsed since diagnosis being associated with more adverse outcomes in several domains (Hudson et al., 2003; Oeffinger et al., 2006; Reulen et al., 2007). Older age at diagnosis has further been distinguished as a risk factor for adverse chronic health conditions (Oeffinger et al., 2006). However, this result contrasts findings from a study where survivors diagnosed at <10 years of age were at increased risk for impaired health status compared to survivors who had been diagnosed at an older age (Alessi et al., 2007).

Follow-up care

Survivors of childhood cancer constitute a population that often requires follow-up health care due to their relatively heightened susceptibility to adverse late effects.

Research on health care utilisation of survivors have found that they report higher use of health care services in comparison to general population controls of the same age and sex with no cancer history (Shaw et al., 2006). Higher overall use was found to be attributable to the fact that survivors were more likely to consult with specialists. Survivors and control subjects did, however, not differ in primary health care use provided by general practitioners. Although lifelong follow-up is recommended by many, a study in the United Kingdom report that according to their general practitioner only 35% of survivors remain in regular long-term hospital follow-up (Taylor et al., 2004). This outcome corresponds to results from a Swedish study of adult survivors of acute leukaemia, lymphoma and Wilms' tumour, where 34% of survivors reported a medical follow-up visit during the past year (Arvidson et al., 2006). In the Swedish study, scheduled follow-up visits differed between diagnoses and sex, while survivor perceived treatment-related complications was not a significant predictor for having a scheduled follow-up visit. Studies on health care utilisation and survivor participation on follow-up visits have found that visits to oncologists and other specialists decrease with age (Oeffinger et al., 2004; Shaw et al., 2006). Such a decrease in utilisation of health care services occurs at a period in life when the incidence of some late effects of cancer therapy may increase. Two important barriers to follow-up health care identified by a panel of adult survivors concern survivors' and primary care physicians' lack of knowledge about late effects and lack of availability of follow-up programs (Zebrack, Eshelman et al., 2004).

Findings from studies that address survivors' satisfaction with follow-up care indicate that more than one third of them are, to some extent, dissatisfied with provided follow-up (Arvidson et al., 2006). In some studies, satisfaction has differed by sex, with female survivors being less satisfied with follow-up than men (Absolom et al., 2006; Arvidson et al., 2006). In contrast, others report no differences between male and female survivors in regard to satisfaction with follow-up care (Michel et al., 2009).

Survivors of CNS tumours

To date, research has identified various subgroups of paediatric cancer survivors (e.g. bone tumours and CNS tumours) that are at heightened risk for adverse psychological sequelae, with considerable issues remaining unaddressed (Calaminus, Weinspach, Teske, & Gobel, 2007; Langeveld, Stam, Grootenhuis, & Last, 2002; Patenaude & Kupst, 2005). Still, relatively few studies aim to provide insight into the specific challenges pertaining to illness-related consequences for such diagnostic subgroups (McDougall & Tsonis, 2009). In the psychosocial oncology literature, studies have in fact sometimes excluded children diagnosed with brain tumours (e.g. Madan-Swain et al., 2000), for reasons concerning for example the severe cognitive sequelae children with brain tumours may develop.

In comparison to control subjects and survivors of other childhood cancer diagnoses, survivors of CNS tumours have demonstrated poorer health status, worse HRQoL and QoL, and poorer social outcomes (Alessi et al., 2007; Boman et al., 2010; Grant et al., 2006; Hudson et al., 2003; Maurice-Stam, Oort, Last, & Grootenhuis, 2009; Pogany et al., 2006; Zebrack & Chesler, 2002). Overall, about 60% of long-term CNS tumour survivors are left with a pronounced disability (Aarsen et al., 2006; Kennedy &

Leyland, 1999; Macedoni-Luksic, Jereb, & Todorovski, 2003). As previously mentioned, studies on childhood cancer survivors have rarely found signs of poorer psychosocial functioning compared with general population samples. Although few survivors of brain tumours report long-term psychological distress, they do show adverse impact on psychological well-being by reporting significantly higher rates of global distress, symptoms of fatigue, depression, and diminished life satisfaction in comparison with siblings (Zebrack, Gurney et al., 2004; Zeltzer et al., 2009). Also, in comparison with survivors of leukaemia and lymphoma, survivors of CNS tumours scored lower on psychosexual development, implying lower maturation with respect to love and sexual relations (Maurice-Stam, Grootenhuis, Caron, & Last, 2007). Nevertheless, few studies have specifically addressed psychological outcomes, or health status of adult survivors of childhood and adolescent CNS tumours, using standardised assessments and multiple informants together with study-specific control data. Such an approach essentially adds reliability to the evaluation of the range of late-occurring health and functional consequences. Also, despite recognition that childhood CNS tumour survivors are a unique population at risk for multiple sequelae, there is limited research-based knowledge about how this may result in increased or unique health care needs in adult life. Despite a lack of consensus on how to best provide long-term follow-up care and ensure quality of life of survivors, increased firmly founded knowledge about the health-related late effects and survivor-perceived needs of health care provides guidance for enhanced and appropriate follow-up care.

PARENTS OF CHILDREN WITH CANCER

Today, even though most children with cancer survive the illness poses a significant threat. For the majority of parents the word ‘cancer’ is still associated with death (Koocher & O’Malley, 1981). Being confronted with the diagnosis imposes an existential crisis and stressful situation on the entire family. In line with this, parents of children with cancer constitute a group at risk for experiencing chronic psychological stress (Hoekstra-Weebers, Jaspers, Kamps, & Klip, 2001; Miller, Cohen, & Ritchey, 2002). The process is initiated when the child is diagnosed, or earlier when initial symptoms arise (Young, Dixon-Woods, Findlay, & Heney, 2002). From the time of diagnosis onwards, parents face a number of potential stressors which differ in predictability, durability and final impact (Grootenhuis & Last, 1997a; Kazak, Simms, & Rourke, 2002). Some of the specific stressors are associated with the threat of losing a family member, living with a seriously ill child, the burden of adhering to complicated treatment regimes, changes in daily life, disruption of social and family roles, and the threat of late effects. During the treatment phase, many of the stressors are characterised as external and situational. After cessation of treatment the stressors may rather be internal, such as worries about the development of the child, fear of a relapse, and memories of traumatic experiences during the course of the disease. The outcome of the psychological stress process initiated at diagnosis has generally been referred to as adjustment (Grootenhuis & Last, 1997a; Lindahl Norberg, 2004).

Psychological reactions

Being a parent of a child with cancer thus presents both emotional and practical stressors that may have several emotional, physical and social consequences. A large

amount of research has been devoted to the study of such consequences. Among different approaches, psychological distress appears to be one of the most common outcome measures (Boman, Lindahl, & Björk, 2003; Fuemmeler et al., 2001; Sloper, 2000). Other studies focus on more situational-specific emotional reactions, such as uncertainty, helplessness, disease-related worry and concerns about the child's future health and relapse (Anclair, Hovén, Lannering, & Boman, 2009; Grootenhuis & Last, 1997b; Maurice-Stam, Oort, Last, & Grootenhuis, 2008; van Dongen-Melman et al., 1995). Broader measures of parental well-being, psychiatric symptomatology, and neuroendocrine outcomes have also been the subject of study (Dockerty, Williams, McGee, & Skegg, 2000; Eiser et al., 2005; Hoekstra-Weebers, Jaspers, Kamps, & Klip, 1999; Miller et al., 2002). Furthermore, a growing body of research suggests that the psychological impact of childhood cancer on the parents can be defined in terms of trauma-related symptoms or posttraumatic stress symptoms (PTSS) (Kazak, Alderfer, Rourke et al., 2004; Kazak, Alderfer, Streisand et al., 2004; Manne, DuHamel, & Redd, 2000; Norberg & Boman, 2008; Phipps, Long, Hudson, & Rai, 2005). Additionally, the childhood cancer literature consists of many studies that address parental coping, i.e. how parents handle stress and adapt to the life situation, and their strategies of coping (Goldbeck, 2001; Norberg, Lindblad, & Boman, 2005a; Trask et al., 2003).

Previous studies of parental psychological reactions indicate that parents of newly diagnosed children and of children in treatment exhibit elevated levels of distress and psychological problems when compared to normative data and data from parents of healthy children (Dahlquist et al., 1993; Hoekstra-Weebers et al., 1999; Sawyer, Antoniou, Toogood, Rice, & Baghurst, 2000). Negative emotional reactions and psychological problems reported to increase included anxiety, depression, sleep disturbances, and helplessness. The high levels of psychological distress at the time of diagnosis are often followed by a decline over time (Sawyer et al., 2000; Wijnberg-Williams, Kamps, Klip, & Hoekstra-Weebers, 2006). The same pattern of parental adjustment has been found in studies including other outcome measures. For example, parents of children recently diagnosed or currently in treatment report higher rates of PTSS and psychiatric symptoms compared to parents of childhood cancer survivors (Hoekstra-Weebers et al., 1999; Norberg, Lindblad, & Boman, 2005b; Phipps et al., 2005). However, findings from studies addressing late psychosocial consequences for parents have been somewhat contradictory. Despite the decline with time of distress levels, some studies have found that parents continue to experience psychological distress (Norberg et al., 2005b; van Dongen-Melman et al., 1995; Wijnberg-Williams et al., 2006), while others have found that the elevated levels of distress decline and become, within a few years, comparable to the levels in the general population (Dahlquist et al., 1996; Sawyer et al., 2000). Uncertainty regarding late effects and lifetime expectancy appear as typical parental stressors after completion of treatment (Anclair et al., 2009; Freeman, O'Dell, & Meola, 2004; Vance, Eiser, & Horne, 2004). Specifically, studies on parental uncertainty have indicated that parents may continue to be uncertain about the well-being of their children many years after the cessation of treatment (Grootenhuis & Last, 1997b). Furthermore, in some studies, mothers of paediatric cancer patients have been found to present severer signs of psychological distress than fathers of children with cancer (Frank, Brown, Blount, & Bunke, 2001; Pai et al., 2007; Sloper, 2000), although findings at this point have to some extent been ambiguous (Norberg & Boman, 2008).

Prior studies have been somewhat inconsistent in clarifying the relationship between type of cancer/illness characteristics and parental reactions (Dahlquist et al., 1993; Eiser, Eiser, & Greco, 2004; Hutchinson, Willard, Hardy, & Bonner, 2009; McGrath, Paton, & Huff, 2004). For example, objective measures of treatment intensity have been found to be indirectly related to specific symptoms of psychological impact, i.e. posttraumatic stress (Kazak et al., 1998). Furthermore, history of relapse has sometimes been recognised as influential for parents' psychological reactions. Parents of children who had suffered a relapse have been found to report higher levels of posttraumatic stress than parents of non-relapsed children (Jurbergs, Long, Ticona, & Phipps, 2009), and higher anxiety levels than parents of surviving and deceased children (Wijnberg-Williams et al., 2006). History of relapse has further been indicated as an important predictor for parental emotional adjustment (Grootenhuis & Last, 1997b). Others have found no association between illness characteristics, including history of relapse, and parental psychological reactions (Sloper, 2000; van Dongen-Melman et al., 1995). Still, a better understanding of the impact of illness characteristics and primary diagnosis would make it possible to tailor information and support to parents at risk for adverse psychological outcomes.

Impact on the family

The stressors inherent in the diagnosis of childhood cancer present not only exceptional challenges for the parents, but for the entire family (Grootenhuis & Last, 1997b; Kazak et al., 1997). Family stress arising from a child's cancer may lead to disturbances in family communication, changes in parental roles and routines, adjustment problems for siblings, and restrictions in social life. Studies that focus on familial adjustment have used various outcome measures, including family impact and family/parental functioning (Foley, Barakat, Herman-Liu, Radcliffe, & Molloy, 2000; Hardy et al., 2008; Heath et al., 2006; Kazak et al., 1997; Streisand, Kazak, & Tercyak, 2003; Trask et al., 2003).

Families of childhood cancer patients have reported various negative effects of the diagnosis on daily life including financial strain and disrupted family and social life (Heath et al., 2006; Patterson et al., 2004). In a study based on focus group interviews with 26 families of children treated for various cancer types, a variety of family strains were identified (Patterson et al., 2004). Observed themes were related to siblings, financial strains, couple/marital conflict, and disruptions in "normal" family life. Difficulties in balancing multiple family needs, for example with regard to work, school, and hospital visits, were expressed by two fifths of families. More than half of families experienced strains with regard to the parent-child relationship, including uncertainty about child rearing and the risk of being overly protective. Not all families, however, are negatively affected (Kazak et al., 1997; Noll et al., 1995). As a result of the crisis, some families may indeed draw closer together. Findings from a meta-analytic review of family conflict and adaptation suggest that mothers of children with cancer perceive higher family conflict than mothers of physically healthy children, whereas family adaptation was not significantly affected (Pai et al., 2007).

The determinants of family consequences following childhood chronic illness are not fully known, although factors related to the child's social functioning, neurodevelopmental sequelae, distance to specialised treatment centres, and utilisation of care services have all been pointed out as potentially influential (Ireys & Silver, 1996; Peterson & Drotar, 2006; Schwartz et al., 2003; Thyen, Sperner, Morfeld, Meyer, & Ravens-Sieberer, 2003; Yantzi, Rosenberg, Burke, & Harrison, 2001). In addition, factors related to coping, social support, socioeconomic status, and other life events are potentially influential for familial adjustment. However, a study of the impact childhood hypothalamic brain tumours on family functioning found no association between illness severity, treatment intensity and family adaptation (Foley et al., 2000).

The caregiving demands and stressors associated with the time of diagnosis and cancer treatment differ from the concerns that persist or occur after cessation of treatment. Accordingly, family stress and family impact need to be evaluated in relation to time, with outcomes presented for different time points in the child's illness trajectory. As mentioned, parents may experience ongoing cancer-related stressors still years after completion of treatment. Due to the lack of large-scale studies, the long-term impact of such stressors on family functioning has yet to be established. Prior studies of the illness-related impact on the family have typically involved parents of younger patients, on and off treatment (Björk, Nordström, Wiebe, & Hallström, 2010; Bonner, Hardy, Willard, & Hutchinson, 2007; Heath et al., 2006; Hutchinson et al., 2009; Jackson et al., 2003; Ljungman et al., 2003; Sawyer, Antoniou, Toogood, & Rice, 1999). Results from these show that parents of young children (mean age at assessment 8-11 years) on or off treatment do not differ with regard to objective family burden, characterised by loss of personal time, disruption of relationships with family or friends, or changes in daily routines and social activities (Hutchinson et al., 2009). The existing literature on the persistent impact on the families of adult survivors is limited. Nonetheless, the responsibilities of parents of children suffering from irreversible morbidity or even a mild disability do not end with the child's transition into adulthood (Hardy et al., 2008; Kinahan et al., 2008).

Parental distress and family impact of childhood CNS tumours

The majority of studies of parental conditions following a child's cancer diagnosis have sought to evaluate parental distress and familial adjustment by studying parents as a single group, regardless of their child's specific cancer diagnosis and treatment (Pai et al., 2007). The impact on parents could, however, be expected to vary significantly depending on the child's specific cancer diagnosis, as some types of cancer differ regarding potentially influential illness characteristics, while others are more similar. For example, chronic conditions that affect neurological functioning can be particularly challenging for parents (Peterson & Drotar, 2006; Reiter-Purtill et al., 2008). The increased risk for sequelae associated with the diagnosis of a CNS tumour and its treatment may constitute a particular threat for parents and pose a unique set of ongoing challenges (Vance et al., 2004). In view of this, in recent years more attention has been directed towards parents of brain tumour patients (Anclair et al., 2009; Forinder & Lindahl Norberg, 2009; Freeman et al., 2004; Fuemmeler et al., 2001; Jackson et al., 2003; Norberg, 2007).

Although much of the acute stress of caring for a child with a brain tumour is reduced post-treatment, there are several ongoing aspects that may remain difficult for parents of survivors, including long-term uncertainty about late effects and threat of relapse (Anclair et al., 2009; Grootenhuis & Last, 1997b). Indeed, parents of young brain tumour survivors have been found to display posttraumatic stress, distress, heightened concern about their child's health, relapse, and the ability of the child to take care of itself (Freeman et al., 2004; Fuemmeler et al., 2001; Hutchinson et al., 2009; Jackson et al., 2009; Jackson et al., 2003; Norberg & Steneby, 2009; Vance et al., 2004). Whether these findings apply to parents of adult survivors of childhood CNS tumours has to our knowledge not been addressed in large scale studies, resulting thus far in incomplete knowledge about the persistent illness-related consequences for parents and the family.

AIMS OF THIS THESIS

To complement prior knowledge of childhood cancer survivors and their parents, the overall purpose of the present thesis was to investigate survivors and their parents after childhood CNS tumour treatment, according to the following outcomes:

- health and functional status of adult survivors
- socio-demographic outcomes (e.g. education) of adult survivors
- health care needs of adult survivors
- parental distress
- the parent perceived persistent impact of illness on the family

Childhood CNS tumour patients and parents are thus the primary focus of this thesis, which aims to provide a composite empirical account of the long-term consequences and follow-up needs of patients and parents after a child's CNS cancer and treatment. Increased knowledge about the health and functional late effects of survivors, the survivor and parent perceived needs of health care, the influence of illness-characteristics on parental distress, and the long-term impact on the families constitute the basis for the development of improved treatment and follow-up care for patients and families.

STUDY SPECIFIC AIMS

The overall purpose will be addressed by four studies with the specific research aims described below.

- **Study I**
  In Study I two specific aims were outlined. A first aim was to evaluate whether severity of self-reported psychological distress differentiates parents of children with more complicated cancers from a reference group of parents. Secondly, the influence of the child's primary cancer diagnosis and risk for diagnosis-related complications was specifically evaluated in relation to parental distress.

- **Study II**
  The main aim of Study II was to empirically determine the incidence and nature of persistent adverse health-related and functional late effects in adult survivors of childhood CNS tumours in comparison to outcomes from a general community population sample. A second aim of this study was to identify diagnostic subgroups at particular risk for impaired health and functional status.

- **Study III**
  The aim of Study III was to investigate the adverse impact on families perceived by parents of adult survivors of childhood CNS tumours. Impact on the family was evaluated in relation to potential determinants, including history of relapse, time elapsed from diagnosis to assessment, health status of survivor, parent perceived health care needs of their child, information satisfaction, and distance to a specialised treatment centre.

- **Study IV**
  The aim of Study IV was to investigate adult CNS tumour survivors' health care needs in multiple essential domains: medical care, care coordination and communication, education about illness, and psychosocial and social counselling. An additional aim was to specifically study the extent of health care needs, and identify *unmet* such needs in relation to survivors' current health and functional status and other potentially modifying factors.

METHODS

PARTICIPANTS AND PROCEDURES

The characteristics of the study groups in each study are presented in Table 1. Studies II-IV are based on the same basic cohort, but depending on the primary measure used, the number of valid cases for analysis differs somewhat between the studies.

Study I

Parents in Study I were consecutively recruited at two Swedish childhood cancer centres: Astrid Lindgren Children's Hospital and Linköping University Hospital. To meet the criteria for inclusion, parents had to have sufficient knowledge of the Swedish language, to be able to comprehend the questionnaire. Knowledge in Swedish was considered insufficient if parents used an interpreter for communication with the medical staff. Secondly, parents of children undergoing palliative treatment and parents who had lost their child were not approached, neither were parents of children with a known poor prognosis at the time, that is, parents of children for whom curative treatment had been resigned. Only cases of pontine glioma, known to be 100% incurable at the time of the study, were excluded *a priori* on the basis of diagnosis.

The data for Study I were collected as part of a larger research project investigating the psychosocial situation for parents of children with cancer. The data collection of this larger study was made between October 2000 and April 2003. Outcomes from other sub-studies included in the larger project have been presented elsewhere (Boman et al., 2003; Norberg et al., 2005a, 2005b, 2006). The study group for Study I consisted of 321 parents (182 mothers, 139 fathers) of 188 children in curative treatment for childhood cancer or who had completed successful treatment, i.e. all had an ongoing contact either with the inpatient unit or the outpatient clinic for post-treatment follow-up. Four diagnostic groups were covered in Study I: CNS tumours, bone tumours, acute lymphoblastic leukaemia (ALL), and acute myeloid leukaemia (AML). Parents of children in later stages of treatment or off-treatment follow-up were recruited by approaching all parents who visited the outpatient clinic during two randomly selected months. Parents visiting the inpatient clinic were informed about the study during their child's hospitalisation, whereas parents of children in a later treatment stage or in follow-up were informed by telephone. Eligible parents obtained written and oral information provided by a member in the research group or a research nurse. After their initial contact, parents received a letter with written information, and the questionnaire booklet. Parents filled out the questionnaire at home, and returned them by mail in a prepaid return envelope. Both parents received the booklet along with instructions to complete the questionnaires independently, without consulting the other parent. A telephone reminder was first administered to parents who had not returned questionnaires. This reminder was followed, when necessary, by up to six additional written reminder letters. The overall response rate was 77%. The study was approved by the Regional Research Ethics Committee, and all participants provided informed consent.

Table 1. Characteristics of the study groups.

		Study I	**Study II**	**Study III**	**Study IV**
Valid cases	Children/survivors	188	531	NA	526
	Parents	321	556	551	550
		n (%)	n (%)	n (%)	n (%)
Child sex	Male	96 (51.1)	275 (51.8)	293 (53.2)	272 (51.7)
	Female	92 (48.9)	256 (48.2)	258 (46.8)	254 (48.3)
Parent responder	Mother	47 (25.0)	409 (73.6)	406 (73.7)	406 (73.8)
	Father	8 (4.3)	31 (5.6)	31 (5.6)	30 (5.5)
	Both parents	133 (70.7)	112 (20.1)	111 (20.1)	112 (20.4)
	Not stated	-	4 (0.7)	3 (0.5)	2 (0.4)
Diagnosis[a]	ALL	177 (55.1)	NA	NA	NA
	AML	31(9.7)	NA	NA	NA
	Bone tumours	29 (9.0)	NA	NA	NA
	CNS tumours:	84 (26.2)	531 (100)	551 (100)	526 (100)
	- Astrocytoma	NA	249 (46.9)	252 (45.7)	246 (46.8)
	- Ependymoma	NA	45 (8.5)	52 (9.4)	44 (8.4)
	- Medulloblastoma/PNET	NA	68 (12.8)	68 (12.3)	68 (12.9)
	- Oligodendroglioma	NA	21 (4.0)	21 (3.8)	20 (3.8)
	- Germ cell tumours[b]	NA	22 (4.1)	25 (4.5)	22 (4.2)
	- Craniopharyngioma	NA	45 (8.5)	46 (8.3)	45 (8.6)
	- Nerve sheath tumours	NA	10 (1.9)	10 (1.8)	10 (1.9)
	- Mixed/unspecified gliomas	NA	13 (2.4)	14 (2.5)	13 (2.5)
	- Other specified	NA	58 (10.9)	63 (11.4)	58 (11.0)
		Study I	**Study II**	**Study III**	**Study IV**
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Child age at diagnosis (years)		7.3 (5.0)	10.6 (4.4)	10.3 (4.5)	10.6 (4.4)
Child age at assessment (years)		8.7 (5.0)	26.3 (5.0)	25.9 (5.0)	26.3 (5.0)
Time elapsed since diagnosis (years)[a]		1.6 (1.7)	15.6 (5.0)	15.8 (5.1)	15.8 (5.2)

[a] Descriptive statistics based on subjects of primary interest in the studies, i.e. parents in Studies I and III, and survivors in Studies II and IV, where parents are included as proxy responders.
[b] Intracranial/intraspinal germ cell tumours.
NA: Not applicable.

Studies II-IV

Studies II-IV are part of a nationwide research project, involving all six childhood cancer centres in Sweden. Childhood CNS tumours survivors and their parents were recruited using the Swedish Childhood Cancer Registry (SCCR). The SCCR contain information about primary cancer diagnoses classified according to the ICCC-3 (Steliarova-Foucher et al., 2005). The diagnosis had been confirmed by imaging and histology in the absolute majority of cases. Eligibility criteria included: diagnosed with

a primary CNS tumour between 1982 and 2001, before their 19th birthday, ≥18 years of age at time of assessment, and ≥5 years elapsed from diagnosis to date of assessment. Of 5,443 children diagnosed with cancer 1982–2001, 1,535 were diagnosed with a primary CNS tumour. For the Studies II-IV, parent and survivor characteristics are presented in Table 1, and a participant consort diagram is presented in Figure 2. Responding and non-responding survivors did not differ with regard to time elapsed since diagnosis to assessment, age at invitation, sex, or diagnosis. However, a difference was found regarding age at diagnosis (P=0.023). Non-responding survivors were younger at the time of diagnosis (mean: 9.52 years; SD: 4.97) compared to responding survivors (mean: 10.56 years; SD: 4.43). Responding and non-responding parents did not differ regarding diagnosis, child's sex, age at diagnosis, time elapsed since diagnosis, and age at follow-up (child and parent age). Comparison data from a stratified (age, sex) random, general-population sample of 2,500 subjects was collected for use in Study II. Sixty of these were unreachable, and questionnaires were returned by 996 of the remaining (41%). The individuals from the general population sample will hereafter occasionally be referred to as control subjects. The data collection procedure for the Studies II-IV is illustrated in Figure 3. Data collection took place between June 2006 and December 2007, using a mail-back questionnaire. The research project was approved by the Regional Research Ethics Committee.

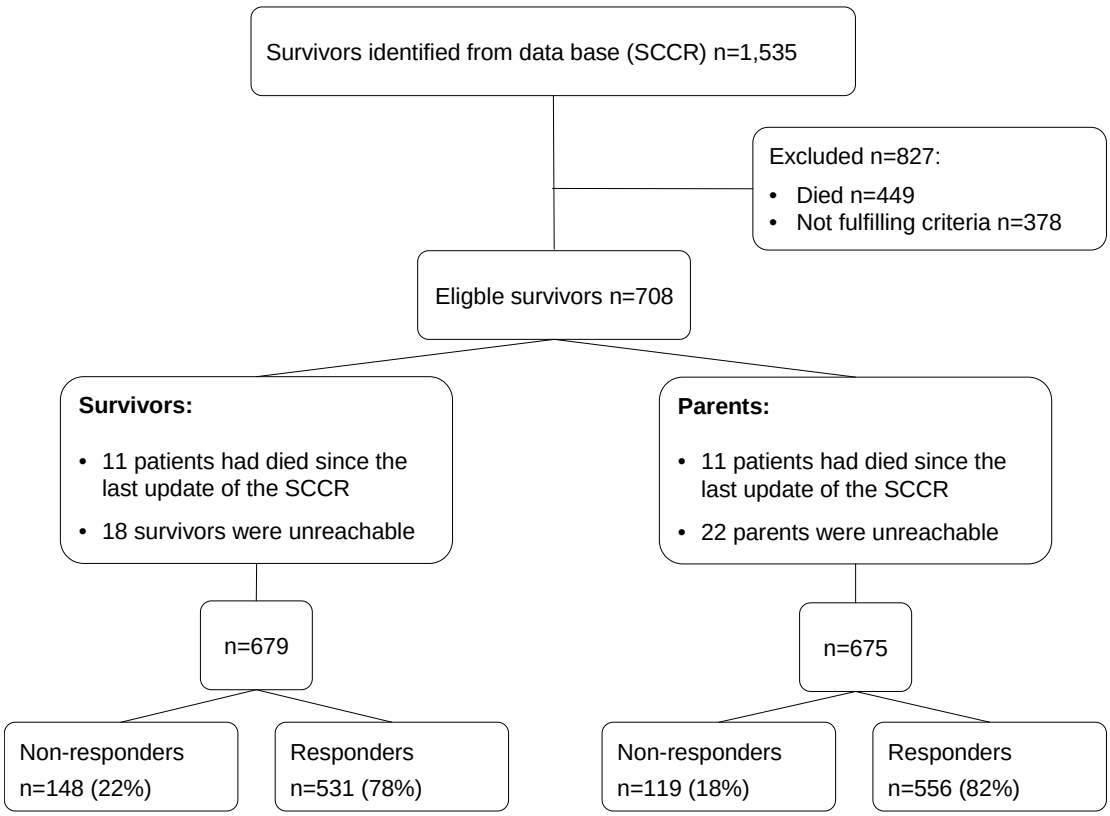

Figure 2. Survivor and parent participants for Studies II-IV.

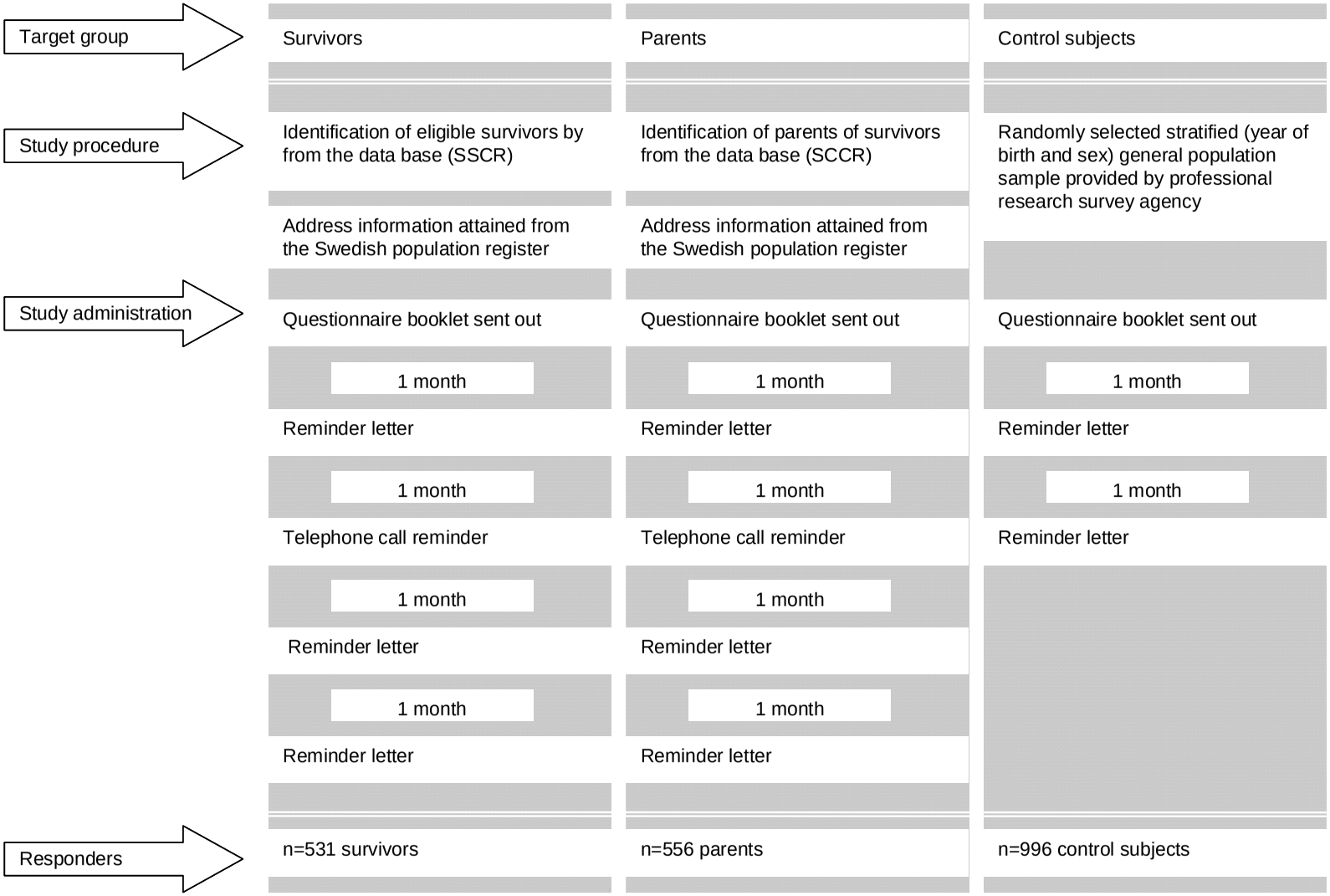

Figure 3. The data collection procedure for the Studies II-IV.

ASSESSMENTS

The four papers are based on quantitative self- or proxy-reported data collected via questionnaire booklets. Each questionnaire used is described in the following section. The outcome variables of primary interest in respective study are presented in Table 2.

Parental Psychological Distress in Cancer

Parental distress was assessed using the Swedish version of the Parental Psychosocial Distress in Cancer (PPD-C). This questionnaire was originally developed by researchers in the Netherlands. The PPD-C is a reliable, self-report, multidimensional measure that addresses particular worries and distress symptoms of the specific stressors that parents of children with cancer encounter (van Dongen-Melman, 1995; van Dongen-Melman et al., 1995).

The PPD-C comprises 125 items organised in eleven subscales addressing illness-specific (seven subscales) and general indicators of distress with no references to the child's disease (four subscales). The illness-specific subscales cover uncertainty, loss of control in relation to parents' own functioning and parenting, loss of control with respect to the ill child, loss of control in relation to sibling, disease-related fear, loneliness, and sleep disturbances. The conceptual framework of the assessment model for the illness-specific subscales is based on theoretical modelling, literature on emotional consequences of childhood cancer, and in-depth interviews with parents of childhood cancer patients. The generic subscales relate to self-esteem, state anxiety, depression, and psychological and physical distress. The three latter subscales were adapted from commonly used psychological scales, that is, the State-Trait Anxiety Inventory, the Zung Self-Rating Depression Scale, and the Rotterdam Symptom Checklist. The bound response format of the items composes 2, 3, or 4-point Likert scales (van Dongen-Melman, 1995; van Dongen-Melman et al., 1995). The Swedish version of PPD-C showed high internal reliability, with a Cronbach's Alpha of 0.97 (Study I).

Health Utilities Index

The 15-item Health Utilities Index™ Mark 2/3 (HUI2/3) was used to assess health-related and functional late effects in survivors. The respondents were asked to answer the questionnaire based on the health and functional status during the last week. The HUI is a preference-based measure, i.e. outcomes (utility) scores derive from general population preferences (Feeny et al., 2002; Torrance et al., 1996). The HUI2/3 was designated to collect sufficient information for classifying an individual's health status according to both the HUI Mark 2 (HUI2) and Mark 3 (HUI3), two complementary health classification systems (Feeny et al., 2002; Furlong et al., 2001; Horsman et al., 2003). The instrument can be used in a wide variety of clinical and general populations, including survivors of childhood CNS tumours (Frange et al., 2009; Furlong et al., 2001).

Of the possible ways of evaluating HUI2/3 outcomes, nine single functional attributes were considered; vision, hearing, speech, cognition, pain, emotion, ambulation, dexterity, and self-care. The attributes covered by the HUI2/3 were selected in large part because they were rated as being the most important dimensions of health status by the general population (Kaplan et al., 2007). In addition to the single attributes, three compound multi-attribute outcome measures were evaluated; i.e. sensation (derived through a multiplicative function using weighted outcome scores for vision, hearing, and speech), mobility (derived through a similar scoring algorithm based on ambulation and dexterity), and overall health status (calculated similarly, and based on HUI3 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain) (Furlong, Feeny, & Torrance, 2002). The different outcome measures of HUI2/3 are illustrated in Figure 4.

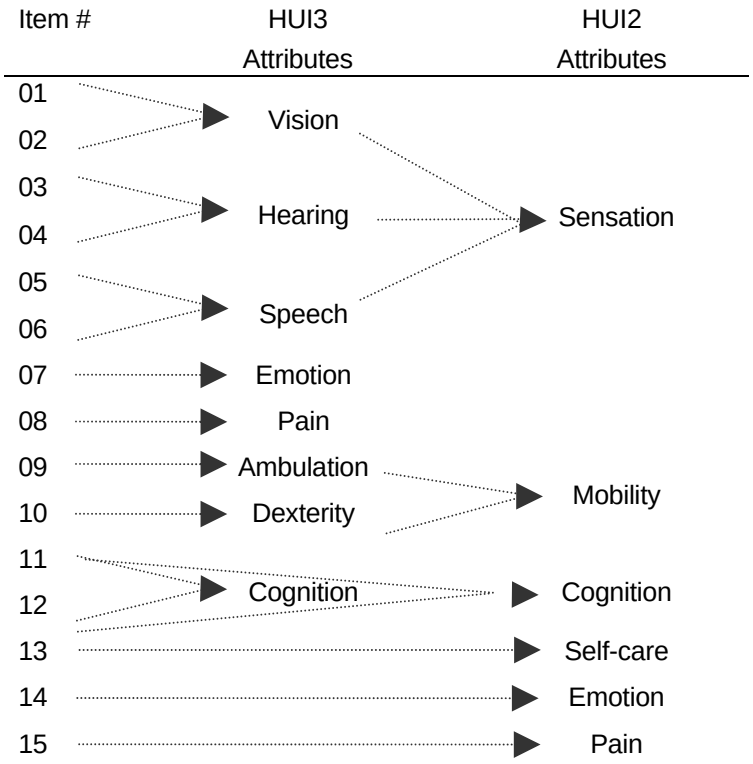

Figure 4. The 15-item HUI2/3 outcomes. Reprinted with permission from Health Utilities Inc., Canada.

The HUI2/3 provides both a descriptive categorical outcome measure, and an interval-scale measure of morbidity for each single-attribute and multi-attribute outcome (utility scores) (Furlong et al., 2002). Single-attribute utility scores range from 0.00 (most severe impairment) to 1.00 (perfect health). The utility scoring for multi-attribute overall health (HUI3 summary score) is defined on a scale ranging from -0.36 to 1.0, where dead = 0.00, and perfect health = 1.00. Scores below 0.00 for overall health signify states considered worse than death (Feeny et al., 2002; Torrance et al., 1996). The descriptive measure ranges from no disability to severe disability. HUI3 scores for mild disability states fall in the 0.89-0.99 range, moderate disability states in the range of 0.70-0.88, and severe disability states are indicated by scores below 0.70.

Impact on Family Scale

The Impact on Family Scale (IFS) was used to assess illness-related impact on the family. The IFS measure reflects the parental perception of two things: changes in family life and attributions of those changes to the child's illness (Stein & Jessop, 2003). The conceptual framework and development of the IFS is based on patient interviews, the literature, and clinically attained knowledge about patients with chronic conditions (Stein & Riessman, 1980). It has been used for the study of various diagnostic groups, including childhood cancer (Heath et al., 2006; Ireys & Silver, 1996; Sawyer et al., 1999).

Family impact was addressed by 33 items covering five domains; social and familial disruption, personal strain, financial burden, mastery/coping, and sibling impact. Responses to each statement (item) were made on a 4-point Likert scale, with alternatives ranging from strongly agree to strongly disagree. The IFS provides separate outcomes for each domain, and a total impact score. Higher scores correspond to greater adverse impact. In line with recommendations, the mastery/coping domain was disregarded due to its unsatisfactory psychometric features (Stein & Jessop, 2003), and a revised scoring algorithm with improved psychometric properties was used (Stein & Jessop, 2003; Williams, Piamjariyakul, Williams, Bruggeman, & Cabanela, 2006). The internal reliability estimated by Cronbach's Alpha ranged from .78 (sibling impact) to .92 (total impact), indicating high internal consistency for the Swedish version of IFS (Study III).

Health care needs

For information about survivors' health care needs in adult life, an eleven-item questionnaire was used. Items cover health care needs with regard to four domains: medical care, care coordination and communication, education about illness, and psychosocial and social counselling. The questionnaire was originally developed by Stein and Jessop (1984), and has thereafter been further developed for the study of satisfaction with health care services (Thyen et al., 2003). The study of survivors' health care needs also included a single question that asked whether the survivor's need of health care was judged to be greater than the average person in the community due to one's past illness and/or its treatment.

For the eleven-item questionnaire, respondents were asked to indicate on a four-point scale, whether they/their child, 1) received the health service in question; 2) received it partly; 3) did not receive it, and had no need for it; or 4) did not receive it, but had a need for it. Health care needs were categorised as no need (response category 3), met need (response category 1 and 2), and unmet need (response category 4). A health care need was considered to be present for those who responded positively regarding response alternative 1, 2 or 4. If the respondent answered, "do not receive the service but need it" to at least one question within one of the domains, an *unmet* health care need in that domain was recorded. The same approach was used when classifying possible existing health care needs within a specific domain. Regarding the psychosocial and social counselling domain comprising a larger number of items than the other domain subscales, a need verified in response to at least two questions was required for a health care need to be considered present. In the same way, for this

domain at least two unmet needs had to be verified for an unmet health care need to be recorded.

Information

Survivors' and parents' satisfaction with the extent of information provided during treatment and follow-up were assessed using a summary item from an EORTC QOL-INFO26-based questionnaire (Arraras et al., 2007), adapted for this study population. In Study IV, if survivors reported insufficiently met information needs they were asked to specify, in an open-ended question, the kind of information they felt a need for.

Background data

Data on demographic factors were collected from the survivors and the parents via the questionnaire booklet. Medical and treatment-related information was derived from the SCCR and patients' medical records. The questionnaire booklets for Studies II-IV covered socio-demographic data and selected social background on the childhood CNS tumour survivors with regard to their family status, former need of remedial school training, academic attainment, employment status, prior and present needs of medical care services, and utilisation of social insurance or governmental subsidies.

Table 2. Primary outcome variables of primary interest in Studies I-IV.

	Variables	**Study I**	**Study II**	**Study III**	**Study IV**
Parental distress	Uncertainty - general	X			
	Uncertainty - illness	X			
	Uncertainty - late effects	X			
	Control - personal functioning	X			
	Control - parenting the child	X			
	Control - parenting sibling(s)	X			
	Self-esteem (low)	X			
	Anxiety	X			
	Disease-related fear	X			
	Loneliness	X			
	Sleep disturbances	X			
	Depression	X			
	Physical/psychological distress	X			
Health status	Overall health status[a]		X	X	X
	Sensation		X		
	Mobility		X		
	Vision		X		
	Hearing		X		
	Speech		X		
	Dexterity		X		
	Ambulation		X		
	Cognition		X		
	Emotion		X		
	Pain		X		
	Self-care		X		
Impact on the family	Total family impact			X	
	Personal strain			X	
	Social/Familial disruption			X	
	Financial burden			X	
	Sibling impact			X	
Health care needs[b]	Total			X	X
	Medical care				X
	Care coordination/communication				X
	Illness education				X
	Psychosocial services				X
Information	Information satisfaction[c]			X	X
	Information needs, reported				X

[a] Survivor- and parent proxy-reported in Study II, parent-reported in Study III, and survivor-reported in Study IV.

[b] Extent of health care needs and unmet such needs.

[c] Parent-reported in Study III, and survivor-reported in Study IV.

DATA MANAGEMENT AND ANALYSES

Statistical analyses used in Studies I-IV are presented in Table 3. All effects were tested using a significance level of $P<0.05$, except for Study III. Considering the total number of statistical tests performed in that study, an alpha level of $P<0.01$ was chosen as the threshold for statistical significance. The adjustment for multiple testing was used to decrease the risk of Type I error (Veazie, 2006). Two-tailed testing for statistical significance was applied in all studies. Analyses were carried out using the SPSS statistical packages version 15.0 (Studies I-II) and version 17.0 (Studies III-IV) for Windows (SPSS Inc., Chicago, Illinois).

Data management and analyses for specific for each study are presented below.

Table 3. Statistical analyses in Studies I-IV.

Methods used	**Study I**	**Study II**	**Study III**	**Study IV**
Chi-square		X	X	X
Mann-Whitney U	X			
Kruskal Wallis	X			
Independent *t*-tests	X	X	X	X
Dependent *t*-test			X	
One-way ANOVA[a]	X	X	X	X
Multi-way ANOVA		X	X	
Repeated measures ANOVA			X	
ICC[b]		X		
Percent agreement		X		X
Kappa statistic				X
Pearson's r		X		
Cronbach's Alpha	X		X	

[a] Bonferroni post-hoc tests applied.
[b] Intra-class correlation coefficient.

Study I

For the purpose of investigating the significance of objective, diagnosis-related illness variables for parental distress, a model which included a "complicated cancer" category was used. This model was used with the intention of effectively representing malignancies that are more likely to be associated with a set of disease complication variables with a potential influence from a parental distress perspective. The created complicated cancer category included parents of children with CNS tumours, AML, and bone tumours. In our model, parental psychological distress in that category was compared to distress in parents of children diagnosed with ALL.

In line with suggestions (van Dongen-Melman, 1995), only those respondents who had completed ≥75% of items on a given subscale were included in analyses for that particular scale. The generic uncertainty subscale covers a variety of issues confronting parents after a child's diagnosis. In this study, additional analyses were conducted to

illuminate the significance of the particular sources of parental uncertainty covered by the extensive uncertainty subscale. Thus, the uncertainty subscale was split before analyses to enable us to specifically evaluate parents' illness/treatment-related uncertainty, and late effects-related uncertainty, respectively.

For a better understanding of factors that modify parental distress reactions, the following potential confounding variables were considered, first analysed in adjusted models separately, then simultaneously: age at diagnosis, child's sex, time elapsed from diagnosis to assessment, and child's treatment situation at assessment (i.e. active/maintenance treatment; completed treatment; no treatment; other).

Study II

In Study II, survivors' *self-reported* data was primarily used in analyses of health and functional outcomes. However, in the case of un-returned survivor questionnaires, the parent proxy-rating was used if available (done in 72 cases).

Survivors' sex and age at assessment were inserted as covariates in adjusted multivariate analyses comparing HUI2/3 outcomes for survivors and control subjects. The clinical importance of statistical group differences was established according to recommendations for the HUI2/3 instrument (Drummond, 2001; Furlong et al., 2002; Horsman et al., 2003; Samsa et al., 1999). Mean differences greater than or equal to 0.03 in compound HUI2/3 measures are associated with clinically important variations in level of functioning, and of 0.05 for single attributes.

Agreement regarding the HUI2/3 outcomes for survivors and parent proxies was evaluated by calculating percent agreement, and one-way, single-measure, intra-class correlations (ICC) (Schuck, 2004). The ICC can vary from -1 to 1, with 0 indicating no agreement beyond chance, and 1 perfect agreement. Specifically, agreement was designated as poor to fair (ICC, ≤ 0.40), moderate (ICC, 0.41-0.60), good (ICC, 0.61-0.80), or excellent (ICC, 0.81-1.00) (Bartko, 1966).

Study III

Parent-reported data were the focus of all analysis in Study III, i.e. only parent proxy-reported outcomes for survivors' health and functional status, and their health care needs were included in analyses.

Dependent tests were used when parent-reported data were analysed in relation to IFS scores, i.e. comparing outcomes from the same respondents (Wright, 1997).

In Study III, scores on the IFS measure ranged from 1.0-4.0. Scores of ≥ 2.5 were considered to indicate significant impact. This cut-off score for significant family impact was rationally based on how the response alternatives to the item questions of the questionnaire were expressed.

Study IV

Frequency statistics for *unmet* health care needs were based on survivors' and parents' initially indicating a need related to the specific item or domain.

Furthermore, in Study IV, as a response to an open-ended question survivors were able to specify the issues where they had additional information needs beyond that which had been provided. Based on the content, the answers were categorised into particular areas, for example information about illness and treatment, late effects, psychological services, and rehabilitation services. Survivor's answers could relate to several of these areas.

Agreement between survivor-reports and parent proxy-reports in the health care need questionnaire was assessed using Kappa statistics and by presenting percent agreement. A Kappa value of 0 equates to chance agreement, and a Kappa value of 1 equates to perfect agreement. Furthermore, Kappa values of 0.20-0.40 represent fair agreement, 0.41-0.75 moderate to good agreement, and >0.75 substantial to excellent agreement (Landis & Koch, 1977; Viera & Garrett, 2005).

SUMMARY OF RESULTS

The following section presents main findings for studies I-IV separately.

STUDY I

The outcome from initial analyses showed that parents in the complicated cancer category (parents of children who had been diagnosed with CNS tumours, AML, and bone tumours) reported more disease-related fear in comparison to the reference group of parents of children with ALL (*P*=0.009). In subsequent analyses the effects of potentially confounding variables were statistically controlled for. Outcomes from these adjusted analyses, simultaneously controlling for the child's age at assessment, treatment situation, and time elapsed since diagnosis to assessment, showed that, in addition to more disease-related fear, parents in the complicated cancer category reported more depressive symptoms (*P*=0.014), loss of control regarding personal functioning (*P*=0.005), loss of control regarding parenting the child (*P*=0.045), and poorer self-esteem (*P*=0.041).

As children's treatment situation differed for the diagnostic groups, analyses that only included parents of children for whom treatment was completed were conducted. These analyses showed that parents in the complicated cancer category reported more loss of control regarding personal functioning (*P*=0.005), loss of control with respect to parenting the child (*P*=0.021), disease-related fear (*P*=0.025), and depressive symptoms (*P*=0.030) in comparison to the reference group of parents.

When distress outcomes were evaluated for parents in the single diagnostic groups, a main effect of the child's diagnosis was found for disease-related fear (*P*=0.007), general uncertainty (*P*=0.033), illness-related uncertainty (*P*=0.017), and uncertainty about late effects (*P*=0.009). Specifically, parents of children with CNS tumours experienced more disease-related fear compared with parents of children with ALL. More general uncertainty was reported by parents of children with bone tumours or CNS tumours compared to parents of children with AML or ALL. Furthermore, in comparison to parents of children with AML, parents of children with bone tumours reported significantly more illness-related and late effects-related uncertainty. Differences in parental distress outcomes between single diagnostic groups remained significant when background variables were statistically controlled for. Additionally, analyses simultaneously controlling for the three background variables indicated that parental loss of control regarding personal functioning was higher among parents of AML patients compared with parents of ALL patients (*P*=0.037).

Cranial radiation therapy (CRT) is a known risk factor for immediate and/or late sequelae. To gain supplementary information about its impact, additional analyses were conducted for parents of children with CNS tumours, for whom radiation therapy was part of the treatment. These analyses revealed that parents of children treated with CRT (n=42) reported poorer self-esteem (*P*=0.025), more depression (*P*=0.004), and more

state anxiety (P=0.012), compared with parents of CNS tumour children who had not received CRT (n=41).

STUDY II

Survivor and control group comparisons

Adult survivors of childhood CNS tumours showed poorer health and functional outcomes than general population control subjects when comparing the overall health status scores (Survivors: mean=0.77, SD=0.27; Control subjects: mean=0.85, SD=0.17, P<0.0001 for sex and age adjusted comparison analyses). Figure 5 illustrates the proportions of survivors and control subjects showing perfect health, on the one hand or mild, moderate or severe disability, on the other.

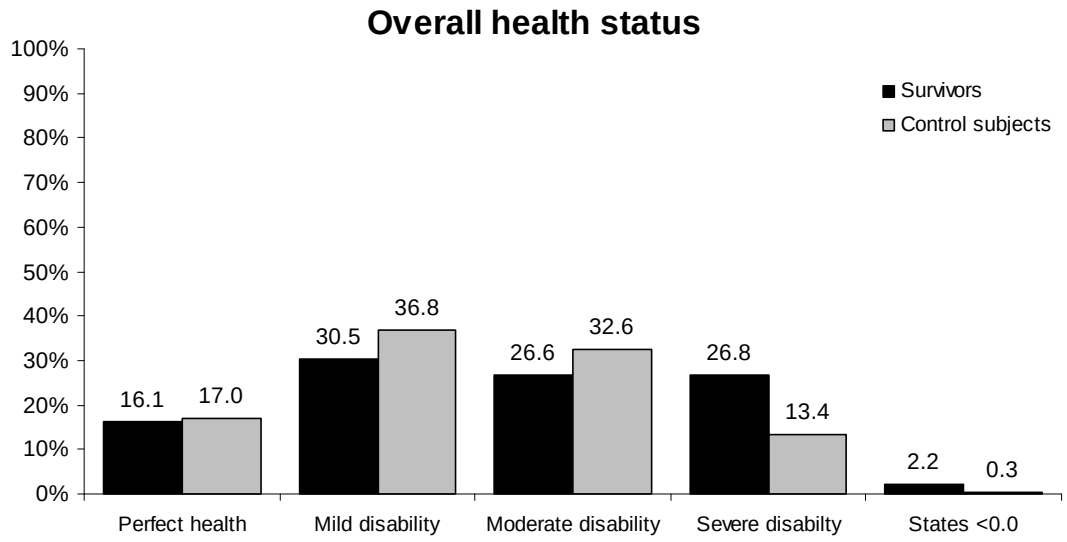

Figure 5. Overall health status by HUI2/3 disability category.
Note: Survivors and control subjects contrasted: χ^2 = 42.2, df 3, P< 0.0001.
Overall health status below 0.0 is part of the severe disability category.

Compared to general population controls, survivors indicated disability in all single-attribute functions, except for emotion and pain where no differences were found (Emotion: P=0.64, Pain: P=0.65). Most severe sub-normality in comparison to control subjects was found for cognition, sensation and overall health.

Furthermore, survivors and control subjects differed significantly in the number of affected functional attributes. Of eight addressed attributes, 16.5% of survivors presented disability in ≥four attributes compared to 6.5% of control subjects. Severity of the disability varied by the specific functional attribute addressed. Scores for survivors (self-reported), for whom proxy-reported data also were available, indicated moderate to severe disability in 18.7% of survivors for sensation and in 4.0% for mobility, compared to 5.5% and 0.2% in the control population. Specifically, in the sensation domain, 6.9% of survivors indicated moderate to severe disability for vision

(compared to 0.6% of control subjects), 4.2% for hearing (compared to 0.6% of control subjects), and 4.6% for speech (compared to 1% of control subjects) (these results not presented in the published article version). In the mobility domain, the corresponding figures of survivors indicating moderate to severe disability were 3.1% for dexterity (0.3% of control subjects) and 3.9% for ambulation (0.2% of control subjects).

In comparison to control subjects, survivors received significantly more often extraordinary assistance including remedial training in school, attained lower educational goals, lower employment status, greater use of social insurance or governmental subsidies and had less frequently become parents ($P<0.0001$ for all these survivor and control group comparisons).

Within-group comparisons

Female survivors showed greater functional disability in comparison to male survivors – demonstrated by poorer overall health status ($P=0.013$). Except for hearing, female survivors presented a general pattern of lower scores for all attributes than male survivors, although differences were statistically significant only for pain ($P=0.001$).

Age at diagnosis was unrelated to health and functional outcomes. Age at assessment was negatively related to sensation (based on vision, hearing and speech; r =-0.13, $P=0.001$), mobility (based on ambulation, and dexterity; r =-0.09, $P=0.024$), pain (r =-0.13, $P=0.002$) and overall health (r =-0.10, $P=0.012$). A similar pattern was not found for the control subjects. Time elapsed since diagnosis was negatively related to sensation (r =-0.15, $P=0.0004$), mobility (r= -0.08, $P=0.049$) and overall health (r =-0.14, $P=0.001$). Survivors diagnosed during an earlier period reported more adverse impact on sensation (r =0.15, $P= 0.0003$), dexterity (r =0.10, $P=0.011$) and overall health (r =0.14, $P=0.001$), than those diagnosed later (Note: study sample diagnosed between 1982 and 2001).

In comparison to control subjects, survivors in all subdiagnostic groups presented compromised overall health status (based on utility scores). Disability was most prominent in survivors of germ cell tumours, oligodendroglioma, “other gliomas” (non-astrocytoma) and medulloblastoma. Clinically important differences, according to HUI2/3 guidelines, indicated greater disability specifically among survivors of germ cell tumours, oligodendroglioma, “other gliomas” (non-astrocytoma) and medulloblastoma (in line with the established statistical differences). A significant main effect of diagnosis was demonstrated for six attributes (hearing, ambulation, dexterity, cognition, self-care and mobility) and for overall health. Compared to control subjects and survivors of other diagnostic groups, survivors of astrocytoma, and other specified/unspecified CNS tumours indicated the best health and functional ability.

Survivors’ current health- and functional status was related to educational and social outcomes. In comparison to survivors with less pronounced educational and social sequelae, survivors with lower educational attainment ($P<0.0001$), more remedial training in school ($P<0.0001$), lower employment status ($P=0.0004$), greater use of social insurance or governmental subsidies ($P<0.0001$), and who less frequently had become parents ($P=0.013$), also had poorer overall health.

Informant agreement

In Study II, parents were included as proxy respondents for their adult child's current health and functional status. Overall agreement between survivor- and parent proxy-ratings for participants with both sets of data (n = 482) was good, but varied by attribute. Poor agreement was found for single attributes of emotion (ICC=0.40) and pain (ICC=0.47). The best agreement was found for single attributes of self-care (ICC=0.95), ambulation (ICC=0.96) and dexterity (ICC=0.82).

STUDY III

Impact on Family Scale (IFS) scores did not significantly differ for parent constellations (if the questionnaire was answered by mothers alone, fathers alone or together). Nor did outcomes differ regarding treatment site. Therefore, data from all respondents and treatment sites were merged for the subsequent IFS outcome analyses.

Impact on family

At group level, the conditions of families of adult CNS tumour survivors appeared as mildly to moderately influenced by their child's past illness (total impact score=1.6). However, only 7% of parents reported no persistent impact on the family whatsoever. The proportion of parents reporting significant family impact (scores ≥2.5) varied with domain. Greatest impact was found for *personal strain* and *financial burden*, where 18-20% of parents reported a significant impact, followed by *sibling-related impact* (11%) and *social/familial disruption* (7%) (Table 4).

Table 4. Proportions (%) of impacted families by severity.

Level of impact	Impact scores	Personal Strain	Social/ familial disruption	Financial burden	Sibling impact
		No. (%)	No. (%)	No. (%)	No. (%)
No impact	1.00	127 (23.0)	169 (30.7)	178 (32.3)	83 (18.3)
Mild impact	1.01-1.49	77 (14.0)	207 (37.6)	67 (12.2)	91 (20.1)
	1.50-1.99	106 (19.2)	66 (12.0)	71 (12.9)	108 (23.8)
Moderate impact	2.00-2.49	133 (24.1)	71 (12.9)	136 (24.7)	122 (26.9)
	2.50-2.99	69 (12.5)	31 (5.6)	52 (9.4)	37 (8.2)
Great impact	3.00-3.49	28 (5.1)	6 (1.1)	36 (6.5)	9 (2.0)
	3.50-4.00	11 (2.0)	1 (0.2)	11 (2.0)	3 (0.7)

Modifying factors

Analyses of potentially modifying factors for IFS outcomes showed that the impact on families of survivors with compromised health was significantly greater than in those of survivors with mild, or no health-related sequelae (Total family impact: $P<0.001$). This relationship was established also when survivor self-reported data was used in analyses (results not presented in the Study III manuscript version). Families of female survivors reported greater impact on the family compared to families of male survivors (Total family impact: $P<0.001$). However, in adjusted multivariable models, survivor's sex was not significantly associated with any of the IFS outcomes at the applied $P<0.01$ level. Furthermore, the family impact was significantly greater in families of survivors where the parents perceived unmet health care needs of their child compared to cases where such needs were perceived as fully or partly met. In Study III, parents (48%) that reported no satisfaction, or only minor satisfaction with the illness-related information provided during treatment and follow-up had greater family impact compared to parents who reported moderate or great satisfaction with the information provided (Total family impact: $P<0.001$).

However, family impact was unrelated to survivor's current age, parent's age, and distance to specialised treatment centre. Parents of survivors who had suffered a relapse (n=68) presented somewhat higher mean scores in all domains of family impact, but these outcomes were not significantly different from outcomes of parents of survivors with no history of relapse (n=483). Time elapsed from diagnosis to assessment was unrelated to reported family impact in all domains, except for social and familial disruption. For this domain, a longer period since diagnosis was associated with greater social and familial disruption ($P=0.003$).

No significant interaction effects involving studied modifying factors were noticed.

STUDY IV

Thirty-nine per cent of survivors (n=192) experienced their health care needs due to their illness and treatment as exceeding the assumed general population average. For the eleven-item main outcome questionnaire, 89% of survivors (n=467) indicated some kind of present health care need in adult life, by expressing either that the health service had been received (fully/partly) when needed, or by expressing an unmet need. Greatest needs were found for the domain of illness education (n=386, 74%), followed by care coordination and communication (n=367, 70%), medical care (n=366, 70%), and psychosocial services (n=273, 52%). The most frequently reported specific health care needs concerned that of information about their illness-related condition, including possible late effects, followed by the need of having access to a medical doctor for referrals to a specialist if necessary.

In terms of unmet health care needs, 41% (n=191) of the survivors who initially indicated that they had health care needs in any of the domains covered by the questionnaire reported that they had an *unmet* such need. Most frequently, unmet needs were found in the domain of psychosocial and social counselling services (n=106; 39% of those having needs) and illness education (n=135; 35% of those having needs). The

most frequent specific unmet health care need concerned the lack of counselling on educational or behavioural problems, and insufficient information about patient survivor groups/self-help organisations.

Survivors (n=261) with additional information needs beyond that which they had been provided with, had greater *unmet* health care needs in comparison to survivors with no additional information needs (n=232) (Total: 57% to 23%, $P<0.001$). Among the 232 survivors who specified issues where they had additional needs of information beyond what was provided, 42% mentioned *late effects*, 21% mentioned their *illness*, and 13% mentioned *treatment issues*. Furthermore, insufficiently met information needs were considerably reported regarding the *causes of illness* (12%), and *the possibilities for psychological services* (10%), and *rehabilitation services* (9%).

Health care needs by functional late effects

Survivors (n=192) who reported that their need for health care due to the past CNS cancer exceeded the supposed population average suffered from more severe functional disability, as measured by HUI2/3, compared to survivors with no such pronounced health care needs (n=296, $P<0.001$).

For the eleven-item questionnaire, the proportion of survivors who reported health care needs in adult life differed according to their current status of functional late effects. Survivors with severe disability had the most prominent needs, followed by survivors with moderate, mild and no disability (Total: $P<0.001$). Also, a significant association was found between survivors' current status of functional late effects and *unmet* health care needs. In total, 58% of survivors (n=73) with severe disability had an unmet need compared to 42% of survivors (n=54) with moderate disability, 31% of survivors (n=42) with mild disability, and 23% of survivors (n=15) with no disability ($P<0.001$).

Health care needs by demographic and medical factors

Male and female survivors differed significantly in extent of health care needs regarding medical care ($P<0.05$), and care coordination and communication ($P<0.01$), where female survivors reported more needs. Female survivors also reported significantly more *unmet* needs in the domains of medical care ($P<0.05$), care coordination and communication ($P<0.01$), and psychosocial and social counselling services ($P<0.05$).

Furthermore, survivors who received social insurance or governmental subsides (n=174) had greater health care needs compared to survivors with no use of such economic aid (n=342, Total: $P=0.004$), and also greater *unmet* health care needs compared to survivors with no use of such economic aid (Total: $P<0.001$). No significant associations were found for survivors' self-reported health care needs or *unmet* needs in terms of which childhood cancer centre the survivors had belonged to. Time elapsed since diagnosis to assessment, and survivors' age at assessment were unrelated to reported health care needs. However, a younger age at diagnosis was related to having more health care needs for psychosocial services ($P=0.005$) and *unmet* needs regarding care coordination and communication ($P=0.006$).

Informant agreement

As with in Study II, parents in Study IV were included as proxy-raters of the survivors' health care needs. For survivors for whom both sets of data were available (survivors and parents paired, n=472 pairs), Kappa statistics for survivors' need of health care were satisfactory, ranging from 0.37 (illness education domain) to 0.63 (medical care domain). The Kappa statistics for self-reported and parent-reported *unmet* health care needs, varied between 0.26 (psychosocial services domain) and 0.46 (medical care domain), indicating poor to satisfactory agreement. In general, parents reported more *unmet* health care needs than did the survivors themselves. The proportion of survivors and parents who reported *unmet* health care needs differed significantly only with regard to the psychosocial services domain (37% of survivors and 47% of parents indicated an unmet need, P=0.025), while no other significant differences in reported health care needs were found.

DISCUSSION

The overall purpose of the present thesis was to gain knowledge about the long-term consequences and follow-up needs of patients and parents after a child's CNS tumour diagnosis. Findings show that adult survivors suffer from continuous consequences of their past illness and its treatment, in terms of an adverse impact on health- and functional status, and poorer social outcomes when compared to outcomes of the general population sample. The verified impact varied by diagnosis, and by survivor's sex. In addition to demonstrating greater health care needs in adult life, survivors with health and functional disability showed lower satisfaction with the provided follow-up care. Outcomes from the studies focusing on parents indicate that parents of children diagnosed with a CNS tumour are particularly vulnerable to experiencing illness-related distress. Among parents of children with CNS tumours, the illness-related stressors continue to influence a subset of families, even after the child has reached adulthood. Together, findings from the studies enable identification of subgroups at risk for negative outcomes, and point out areas of improvement in follow-up care for this population of survivors and parents.

In the following sections, some of the specific results from the four studies will be considered.

ADULT SURVIVORS OF CHILDHOOD CNS TUMOURS

The importance of addressing the consequences of childhood cancer as they appear in *very long-term survivors* has been acknowledged in recent studies (Blaauwbroek, Stant et al., 2007; Reulen et al., 2007). Despite an increased interest in the conditions of survivors who have reached adulthood, there is still limited knowledge based on large studies about the patterns of adverse health-related late effects (Armstrong et al., 2009; Frange et al., 2009), and socio-demographic outcomes for diagnostic subgroups. The present thesis addresses this concern by presenting outcomes related to health and functional disability, and to survivors' needs of follow-up and after-care. Three of the studies are population-based, and address an entire nation-wide cohort of adult survivors of childhood CNS tumours. Large cohorts of survivors enable the influence of diagnosis and demographic factors, such as sex and age, to be reliably evaluated. The largest current documentation of outcomes for long-term childhood cancer survivors is the Childhood Cancer Survivor Study (CCSS), conducted in the United States and Canada (Robison et al., 2002), and thus reporting findings that emerge from another society and cultural context. In the CCSS, survivors were diagnosed between 1970 and 1986, whereas the present studies targeted survivors diagnosed between 1982 and 2001. Society-related dissimilarities and the difference in era of diagnosis are of importance when comparing outcomes from the CCSS and the present research. Therapeutic modalities have changed considerably since patients in the CCSS were diagnosed and treated. These include the increased use of chemotherapy, a reduction in radiotherapy doses, and adoption of improved techniques for surgery and radiotherapy (Armstrong et al., 2009). Current therapeutic regimens will probably improve long-term outcomes, and possibly reduce the risk of adverse late effects. Indeed, in the present research, era of diagnosis was found to be associated with health and functional

outcomes, with survivors diagnosed during a later era found to report less disability than survivors diagnosed earlier.

Health and functional outcomes

In comparison to general population samples and survivors of other childhood cancer diagnoses, survivors of CNS tumours have been found to suffer from greater adverse consequences for overall health status (Alessi et al., 2007; Hudson et al., 2003). With a 16-year median follow-up, these findings were supported by the results from Study II, where health and functional disability were found to be more apparent in survivors of childhood CNS tumours than in comparison subjects of the general population. To our knowledge, Study II is the first large study of a population-based cohort of CNS tumour survivors using the HUI2/3 for evaluation of late effects in adult life, and where outcomes are presented with study-specific comparison data. The approach considerably adds to the reliability of findings. The adult survivors in the present work particularly distinguished themselves by demonstrating persistent deficits in relation to cognition, sensory functions (vision, hearing, and speech), and mobility (dexterity and ambulation), whereas outcomes for emotion and pain were comparable to that of the general population. It is noteworthy that, on a whole-group level, health and functional disability among survivors appeared to be in the mild to moderate range. The poorer health and functional outcomes of survivors in comparison to control subjects were attributable to the more frequent occurrence of sequelae in multiple domains, together with the greater proportion of survivors with severely compromised overall health status. The influence of the documented health and functional late effects on survivors' life could not have been adequately understood without the collected information about survivors' social and educational status. In the present work, in comparison to the general population, survivors reported greater reliance on social insurance or governmental subsidies, lower educational status, greater (passed) need of extraordinary assistance in school, including remedial training, and they had less frequently become parents. Survivors with health and functional disabilities (poor HUI outcomes) reported poorer educational and social outcomes, which is indicative of an influence of illness-related consequences on the addressed social outcomes. The self-reported educational and social outcomes correspond with findings from large-scale register-based studies of childhood cancer survivors in Sweden (Boman et al., 2010; Hjern et al., 2007). Taken together, the present findings show that the experience of cancer extends into adult life for many survivors by compromising health and functional ability, and by increasing the risk of late negative socioeconomic outcomes.

Survivors of all diagnostic subgroups demonstrated clinically important disabilities in overall health when compared to the general population sample. However, it was evident that the amount and severity of health- and functional disability varied by tumour type. Most prominent disability was found for survivors of germ cell tumours, oligodendroglioma, 'other gliomas' (non-astrocytoma) and medulloblastoma. The relatively favourable outcome found for the astrocytoma group may reflect the fact that it comprised a low number of high-grade astrocytomas. The majority of survivors in the astrocytoma group thus had low-grade tumours, which are primarily infratentorially located. In these cases, irradiation therapy is less likely to cause significant functional damage, and survival is high. When interpreting findings of diagnostic differences one

needs to consider that the diagnosis-specific differences in grade- or risk-classification influences the outcomes. Still, the outcomes for survivors of the main diagnostic subgroups within the entire CNS tumour group suggest that survivors of certain diagnostic groups suffer from unique consequences that need to be evaluated separately.

Although functional impairment was apparent in the survivor group in terms of poorer outcomes in multiple attributes of the HUI2/3 compared to the general population sample, no pain or emotional sequels were demonstrated. In contrast, a recent study from the CCSS found that adult survivors of childhood CNS tumours differed from control subjects by reporting higher rates of pain (Armstrong et al., 2009). These seemingly contrasting outcomes could be related to the differing inclusion criteria for era of diagnosis, as discussed above, but also to different methods of assessment. In the study by Armstrong and co-workers (2009), the concept of pain referred to "prolonged pain or abnormal sensations in arms, legs, or back". In the present study, questions on pain concern the *severity* of pain, and whether it hinders participation in activities (Horsman et al., 2003). Furthermore, in a recent study of adult medulloblastoma survivors diagnosed during a similar era as the present studies, authors concluded that pain was one of the most frequently affected attributes covered by the HUI2/3 (Frange et al., 2009). Pain was one of the most affected attributes in the cohort of survivors studied here as well. However, results showed that neither the medulloblastoma group, nor the group of CNS tumour survivors as a whole distinguished themselves regarding pain when compared to outcomes of the general population sample. This finding demonstrates the importance of collecting comparison data from an appropriate group when evaluating and interpreting the significance of disabilities found in survivors of childhood cancer.

Although the HUI2/3 provides a relatively basic measure of emotional outcomes, the finding in the present work of an absence of emotional consequences is still noteworthy and interesting, especially as prior studies have indicated that survivors suffering from substantial late physical effects demonstrate lower QoL (Zebrack & Chesler, 2002), and that younger survivors suffer from emotional consequences when assessed by the HUI (Glaser et al., 1999; Grant et al., 2006). In line with what has been indicated by previous studies (De Clercq et al., 2004; Lannering, Marky, Lundberg, & Olsson, 1990; Zebrack, Gurney et al., 2004), the findings from Study II demonstrate that emotional sequelae need not parallel functional disability, nor be characteristic of survivors of CNS tumours when they have reached adulthood. A common assumption, nonetheless, is that an increase in adverse late effects decreases the quality of life and emotional well-being of survivors. Accordingly, the result that functional disability does not parallel emotional sequelae is somewhat theoretically challenging. Different theoretical explanations have been supplied for these perhaps unpredicted outcomes. According to the response shift theory, the frame of reference for the subjective ratings (e.g. self-reports about personal data) can change over time for individuals living with disability. Such a change may lead to relatively favourable ratings. In other words, the result can be an underestimation of disability and treatment effects (Lipscomb, Snyder, & Gotay, 2007; Schwartz, Andresen, Nosek, & Krahn, 2007). Subjective aspects, such as emotion, have been found to be more influenced by this adaptive process than concrete aspects of health, such as self-care (Jurbergs, Russell, Long, & Phipps, 2007). Another

explanation for the absence of emotional sequelae is related to denial. Denial or minimisation of distress might be a way of coping with unpleasant and unavoidable consequences of the cancer experience. Such coping mechanisms may also develop into a personality trait that can extend to issues other than those concerning the illness. This phenomenon has been referred to as self-deception response bias (O'Leary et al., 2007). Another possible explanation for similar emotional outcomes for survivors and the general population is the possibility that a life threatening condition such as cancer can, for some, result in personal growth. The absence of emotional sequelae can thus reflect a beneficial psychological adjustment and personal growth, and may function as an adaptive way of coping with the demands dictated by the illness and its unavoidable consequences. Such a process has been referred to as post-traumatic growth (Barakat, Alderfer, & Kazak, 2006; Barskova & Oesterreich, 2009; Jim & Jacobsen, 2008).

As phenomena like response shift bias, and self-deception response bias may influence on survivors' self-reported outcomes, the complementary collection of data from multiple sources appears as unquestionably important. In this thesis, parent proxy-ratings were therefore collected in addition to survivors' self-reported data. Overall, the agreement between survivor-reported and parent proxy-reported health and functional status was good. However, in line with previous findings, the level of agreement varied according to the areas being measured (Grant et al., 2006; Penn et al., 2008; Upton et al., 2008). In Study II, poorer agreement was established regarding emotion, cognition and pain. The analyses of survivor and parent-reported outcomes for these specific attributes do not indicate that the survivors under-reported or denied problems/emotional consequences. This finding is in contrast with that from a study by O'Leary and co-workers (2007), where adult survivors of childhood cancer were found to have a biased response pattern, indicating a systematic tendency to deny negative symptoms and difficulties. Relevant to the finding of no significant pain or emotional sequelae, inspection of these two outcomes show that the Swedish general population sample in Study II showed relatively low scores compared to general population scores shown by other general population samples presented previously (Grootendorst, Feeny, & Furlong, 2000; Maddigan, Feeny, & Johnson, 2005). However, comparisons with other general population outcomes have to be made with caution, as society-related and cultural differences can play a role, studies are inconsistent regarding key HUI assessment variables used in the different studies, study groups' characteristics, mode of data collection, data analysis, and presentation of findings.

Follow-up health care needs of survivors

In the present work, adult survivors of childhood CNS tumours were found to be at risk for developing persistent functional and health-related late effects, particularly related to the domains of cognition and sensation. In addition to the factual risk of disease recurrence (Armstrong, 2010), such sequelae require follow-ups in terms of both medical and psychosocial after-care. The majority of survivors reported that they had health care needs in adult life, and a considerable portion of survivors judged their needs to exceed those of the assumed general population average because of their past CNS tumour and its treatment. These findings emphasise the fact that life-long follow-up of survivors is justified.

In a prior study on follow-up care for adult childhood cancer survivors in Sweden, the authors concluded that the problem-oriented approach used at two childhood cancer centres was unsuccessful, and that more than one third of survivors were dissatisfied with the follow-up programme (Arvidson et al., 2006). However, the study did not cover survivors of primary CNS tumours, and as a result did not provide information about these former patients' need for health services. As Study IV is the first to systematically evaluate the survivor perceived needs of health care in a large Swedish nation-wide cohort of adult survivors of childhood CNS tumours, findings provide important requisite knowledge about the follow-up needs for these patients. A main finding of the present thesis relates to the substantial proportion of survivors who report that they had health care needs that were not adequately met by the follow-up and after-care. Survivors with health problems and functional disability reported, as expected, greater need of health care in adult life. However, the association found between *unmet* needs and compromised health/functional ability was not obviously expected. This finding suggests that survivors with comparatively extensive needs for intensified follow-up health care tend to be in the unfortunate situation where needed after-care is insufficiently provided.

In the present research, most frequent unmet needs concerned psychosocial services. Survivors' need for better access to psychosocial services is in line with prior findings of adjacent study groups (Earle, Davies, Greenfield, Ross, & Eiser, 2005). In addition, findings of the present thesis showed that more than one-third of survivors had unmet needs regarding information and knowledge about their illness. Too few appear to have been provided sufficient information about, for example, their diagnosis and treatment, the long-term risks of treatment, and whom to contact about condition-related questions and concerns. The fact that the survivors' expressed a general need to learn more about issues related to their illness, treatment, and late effects is particularly worth considering. A lack of such knowledge has been found to be a barrier to the motivation for continued follow-up (Oeffinger & Wallace, 2006; Zebrack, Eshelman et al., 2004), and related to poor compliance with after-care programs. Although patients today are regularly given a written treatment summary, only one fourth of the adult survivors responded that they had received written information about their diagnosis and treatment (these results are not presented in the Study IV manuscript version). Despite the unclear value of providing survivors with a written treatment summary only (Eiser, Hill, & Blacklay, 2000; Kadan-Lottick et al., 2002), a minimum requirement should be that survivors and/or their parents are provided with a written summary including information about diagnosis and treatment, side effects of treatment, and a follow-up plan. A subset of the survivors specifically expressed a need for additional information as they grew older – when new questions and worries had arisen. This indicated that illness education should be provided over time, extending into adulthood, and that written information should continually be up-dated and provided at follow-up visits.

Sex differences in survivor outcomes

In the present studies, health and functional outcomes and outcomes related to health care needs differed, in part, according to sex. Previous studies addressing health status of adult survivors of childhood cancer, and CNS tumours in particular, have found that females have worse health-related outcomes than males (Hudson et al., 2003;

Langeveld et al., 2004; Oeffinger et al., 2006; Pogany et al., 2006). Paralleling these findings, the present studies show that female survivors are at increased risk for late health sequelae and functional disability. Specifically, in prior studies on long-term survivors of various cancer diagnoses using the HUI2/3, female survivors have been found to report poorer overall health, and greater disability for dexterity, emotion and pain (Alessi et al., 2007; Pogany et al., 2006). In our survivor cohort, the sex differences were less pronounced. Despite lower scores for the majority of the HUI2/3 outcomes, survivors' sex was significantly associated only with overall health status, and pain.

In this thesis, female survivors were furthermore found to have greater health care needs, and more *unmet* such needs in comparison with male survivors. Specifically, females reported more unmet health care needs with regard to medical care, care coordination and communication, and psychosocial services. These outcomes contrast prior findings where satisfaction with follow-up care was unrelated to sex (Michel et al., 2009), but correspond to findings from studies with smaller samples covering various childhood malignancies, and survivors of adult-onset cancer (Absolom et al., 2006; Arvidson et al., 2006; Sanson-Fisher et al., 2000).

The observed differences between male and female survivors in health and functional outcomes, and regarding satisfaction with follow-up, may reflect sex differences in health outcomes found also in the general population, or relate to differences in reporting style, or to sex-related differences regarding vulnerability to late effects. The observed sex differences can thus reflect an existing pattern in the general population, where women are more likely to report poor health (Crimmins, Kim, & Sole-Auro, 2010). In the general population sample, however, men and women were found to present similar health and functional outcomes. A recent review study has pointed out treatment-associated sex differences in outcomes, with females being at increased risk for cognitive dysfunction following cranial radiation, and radiation-associated early onset of puberty (Armstrong, Sklar, Hudson, & Robison, 2007). This can be an additional explanation to the differences observed between male and female survivors, where a greater proportion of female survivors were found to be severely disabled. The sex-related differences found for health status and satisfaction with follow-up may furthermore be associated with a difference in reporting style, where females appear to be more willing to report discomfort than males (Greenberg & Meadows 1991 in Vrijmoet-Wiersma et al., 2008). In the present work, information about the survivors' actual access to and utilisation of the studied health care services was not available. The greater proportion of females reporting unmet health care needs could thus be related to differing expectations and preferences regarding follow-up care (Michel et al., 2009; Zebrack, Mills, & Weitzman, 2007), rather than intrinsic health system barriers being higher for females than males, a suggestion which has been made regarding other areas of health care (Foss & Sundby, 2003). Regardless of what might be the most valid explanation, the observed sex differences require an awareness in clinical practice that males and females appear to have different needs and/or expectations concerning after-care.

PARENTAL DISTRESS

In the present research, parental distress after a child's cancer diagnosis was studied with specific focus on the associations between distress reactions and factors related to the child's disease and/or the treatment. Findings enable understanding how uncertainty, anxiety, and other parental stress reactions may differ depending on the child's type of cancer – an issue that has rarely been studied (Pai et al., 2007).

The statistical average survival prognosis for the child's diagnosis did not appear to be significantly influential on the level of parental distress. This finding parallels previous research regarding the influence of disease severity on parental stress (Boman et al., 2003; Kazak et al., 1998; Sloper, 2000), although different study outcomes can be found regarding this issue (McGrath et al., 2004). The present findings of heightened disease-related fear and uncertainty among parents of children with CNS and bone tumours indicate that the late effect profile of the child's diagnosis is an influential parental stressor. Indeed, survivors of bone tumours constitute another risk group for late effects, particularly related to the increased risk of impaired physical functioning (Langeveld et al., 2002; Pogany et al., 2006; Reulen et al., 2007; Zeltzer et al., 2009). Despite the lengthy treatment of ALL, which could be a significant parental stressor during treatment, children with leukaemia (both AML and ALL) are an intermediate risk group regarding medical sequelae after end of treatment (Hudson et al., 2003; McGrath & Pitcher, 2002). The findings of Study I seem to reflect the fact that, despite the success of modern therapies, the actual or potential long-term consequences of illness remain a source of stress for parents of children with CNS and bone tumours in particular. Parents appear to be aware of documented late effects predisposing them for greater illness uncertainty – experienced in situations where outcomes are unknown due to, among other things, lack of sufficient information about the illness (Koocher & O'Malley, 1981; Mullins et al., 2007).

Increased illness-related parental distress following a child's brain tumour diagnosis and treatment corresponds with prior findings, where these parents have been found to demonstrate greater worries and disease-related fears when compared with parents of children with ALL (Anclair et al., 2009; Eiser et al., 2004). However, in contrast to prior findings (van Dongen-Melman et al., 1995), within the CNS tumour group covered in Study I, parents of children who had received CRT showed poorer self-esteem, more depressive symptoms and anxiety in comparison with parents of children for whom treatment did not include CRT. The finding that treatment including CRT came across here as a parental stressor could be related to the well known association between radiation administered in childhood and adverse sequelae, for example neurocognitive impairment. Such significant impairment can make it even more difficult for parents to cope with their child's condition, and may leave them anxious and uncertain about their child's future outcomes (Peterson & Drotar, 2006; Reiter-Purtill et al., 2008). In conclusion, Study I identified parents of children with CNS tumours together with those diagnosed with a bone tumour as being at "psychological risk", and thus signalling a need of extraordinary psychosocial follow-up and early individualised information.

LONG-TERM FAMILY IMPACT

Findings from Study I show that parents of children with CNS tumours are particularly vulnerable to heightened distress. Despite a growing body of literature with particular focus on parents of CNS tumour patients, Study III appears to be among the first large-scale studies about parents of adult brain tumour survivors that evaluate the persistent impact on the family. The cessation of treatment has been found to be accompanied by further stressors that interfere with family functioning (Björk et al., 2010; Deatrick et al., 2006; Eiser, Eiser, & Greco, 2002; MacLean, Foley, Ruccione, & Sklar, 1996; Streisand et al., 2003). The degree to which the family was affected in the long term by such illness-related stressors was evaluated in the present thesis. In part, it addressed parents' perception of adverse family impact on social life, interactions with significant others, subjective strain, time for other family members (siblings), and economy. Although families differed in terms of persistent impact ranging between none and strong, results showed that, at the group level, the conditions of families of adult CNS tumour survivors were generally mildly to moderately influenced. Previous studies of families with children in treatment or young survivors have found families to be more strongly affected than found in Study III (Bonner et al., 2007; Heath et al., 2006; Sawyer et al., 1999). Considered together, these findings indicate that while the family impact is greater when caretaking involves a child who is undergoing cancer treatment, or who is younger, the stressors may be less frequent or less serious for the majority of families of *very* long-term survivors. Still, findings clearly demonstrate that in a considerable subgroup of parents persistent adverse family consequences are present at this late stage of follow-up.

In smaller studies of parents of younger clinical populations, late effects have occasionally been found to be associated with family consequences (Foley et al., 2000; Ireys & Silver, 1996; Schwartz et al., 2003). In the present thesis, the long-term negative family outcomes were clearly related to the health and functional status of the adult survivor. Study III is the first study to report this relation for *adult* survivors of CNS tumours. It is noteworthy that this relationship was also evident when analyses were based on survivor self-reported health/functional data. This indicates that survivors' late effects *per se* are influential, and show that the lasting influence is not transmitted only through how disabilities are perceived by the parents. The greater impact on families of survivors suffering from comprised health could be a result of higher care needs of survivors with sequelae.

In addition to the relationship found between adverse family impact and survivors' current health status, negative family consequences were related to unsatisfied informational needs of parents, and with parental experience of the *unmet* health care needs of their adult child. These findings show that perceived shortcomings of long-term follow-up can lead to parental difficulties, and that illness-related information is also clearly important for the families of adult survivors. These two factors require particular attention, because they appear as causes of adverse family impact that, partly at least, are avoidable.

In the present thesis, long-term family impact was not related to survivor's sex, parent's age, or distance to specialised treatment centre. Interestingly enough, time elapsed since

diagnosis and survivor's age were also unrelated to family impact. This finding indicates that the strength of illness-related impact found in some families persists unchanged over time. Another potential determinant studied in this thesis was whether or not the child had suffered from a relapse. According to a "two-hit hypothesis" (Jurbergs et al., 2009), an additional stressor (e.g. a relapse) can result in a relatively strong adverse impact because the initial diagnosis has left the parents more vulnerable. Such a suggestion was not supported by the findings in the present research as the child's history of relapse was found to be unrelated to the parent-perceived impact on the family.

METHODOLOGICAL CONSIDERATIONS

Representativity and generalizability

One of the major strengths of the four studies relates to the high response rates. In Study I, the number of parents included was large and comparable to, or larger, than usual sample sizes of similar published studies. Study I comprised parents from two childhood cancer centres. Perhaps, one cannot generalize fully the findings from Study I to the entire Swedish population of parents of children who had a cancer diagnosis. Nevertheless, the large study sample ensures that findings are satisfactory representative for the population of parents of children with a cancer diagnosis of the type covered. Sufficiently rigorous inclusion procedures for Study I also support the generalizability of findings and ensure an unbiased selection of study participants. Owing to the fact that the Studies II-IV are population-based, involving an nation-wide cohort of all Swedish survivors meeting the inclusion criteria, the study cohort size can be considered large enough for drawing general conclusions about the target population. However, for all four studies, the generalization of findings to non-Swedish parent and survivor populations must naturally be made with more caution, and with adequate consideration taken into account for possible nation/society-specific differences including medical and psychosocial care and social remedial programs.

Although all four studies in the thesis were characterised by high response rates, attrition is a constant concern that sometimes threatens representativity and validity in questionnaire studies. Importantly, attrition analyses revealed no systematic differences on key background variables between responders and non-responders. For parent populations in general, the most commonly found reason for not participating is lack of time (Landolt, Boehler, Schwager, Schallberger, & Nuessli, 1998), a factor which may be associated with strain. In line with what has been seen in surveys of the general population (Stordal et al., 2001), those with poorer mental well-being may be overrepresented among non-responders. Alternatively, refusal to participate could indicate that the invited subject is well off, and therefore considers participation irrelevant for him/herself. The use of telephone call reminders enabled a direct contact with parents and survivors from whom questionnaires had not been received. These personal contacts provided valuable information about reasons for delays in responding or refusal to participate. Some subjects reported reasons such as lack of time, while others explained that low motivation to participate was because the tumour and the cancer treatment had left no considerable sequelae. Also, a few thought that they were not suited as participants as the illness had no influence whatsoever on their well-being.

One advantage with the personal telephone contacts was that questions could be answered directly and additional information about the study's aims could be presented if necessary. Together, this opportunity for receiving personally provided study information had a positive motivating effect and resulted in an increased response-rate, particularly because survivors and parents who were managing well returned questionnaires after realising that we were interested in their responses as well. Additional factors associated with attrition, based on the impression from the telephone contacts, concern survivors' and parents' experiencing the questionnaires as being too distressing to answer (evoking painful memories), or non-relevant given the length of time passed since diagnosis and treatment.

A further issue related to representativity concerns the lower proportion of survivors in the upper end of the age range. As a consequence, mean age at assessment differed between survivors and control subjects in Study II, although individuals in both groups were within the same age range. Because of this potential cause of bias, the reported health and functional outcomes were consistently evaluated adjusted for age. In addition, as health outcomes usually worsen with age (Lindström, 2009), the age-related differences between survivors and control subjects ought not reasonably to have negatively biased the conclusions drawn. Such a bias would have had the effect that obtained group differences in Study II (survivors-general population comparisons), become under-estimated rather than over-estimated. Furthermore, the adult survivor cohort was relatively young (mean age=26 years). Given that some late effects emerge with time, the incidence of some sequelae could become more pronounced as these survivors grow older. Finally, although diagnosed at a later date than survivors in the American and Canadian CCSS project for example, the results of the adult survivors may still not be generalizable to "tomorrow's" very long-term survivors due to the ongoing change in treatment protocols and medical procedures.

Validity and reliability

All studies used a cross-sectional design. Cross-sectional studies can be thought of as providing a "snapshot" of the situation for a population at a particular point in time. Accordingly, cause and effect relationships are not certain and conclusions cannot be drawn about individual change. A longitudinal approach would provide a more reliable estimation of the progress of certain late effects, parental distress and family impact over time.

A possible limitation of the present research relates to the self-report evaluation of outcomes, which is one of the most conventional and convenient methods of studying large cohorts. A subjective measurements approach was applied since it provides a better fit with a client autonomy model where the client is viewed as the expert with respect to his/her life (Dijkers, 1999). Furthermore, studying self-reported outcomes is important because it enables identification of needs that may not be detectable through other objective methods of assessment. Still, using self-report as way of collecting information is associated with certain limitations. Different response styles such as self-deception bias, response shift bias or a tendency to over- or under-report symptoms and problems can, depending on respondent group or their characteristics, systematically influence outcomes. The use of double informants, i.e. parents as proxy-responders,

was therefore applied. This approach, to some extent, allows for the managing of a potential self-report bias, strengthening reliability in the evaluation of survivor-related outcomes. Regarding the HUI instrument and used outcomes, findings about applicability, inter-rater agreement and principles for item construction indicate that the HUI is relatively robust against response shift bias (Barr et al., 1999; Furlong et al., 2001; Kennedy & Leyland, 1999).

The psychometric properties of the assessment instruments have been evaluated in various ways. The PPD-C questionnaire is an illness-specific measure constructed for the assessment of parental distress in a childhood cancer setting. As the PPD-C is an illness-specific measure focusing on parental distress particularly in the case of a child's cancer, many of the subscales of the instrument are difficult to validate against other generic distress measures. However, correspondence between outcomes have been demonstrated when PPD-C or subscales of it have been used together with other measures of parental distress, for example, traumatic stress and general psychiatric symptoms measured by the General Health Questionnaire (Norberg & Boman, 2008), and Swedish general population norms are available for the generic parts of the questionnaire (Boman, Viksten, Kogner, & Samuelsson, 2004). In addition, the process of constructing the PPD-C and its subscales ensures content and construct validity for the illness-specific subscales (van Dongen-Melman, 1995). As described previously, the Swedish version of the PPD-C demonstrated high internal reliability.

The HUI2/3, used for the assessment of health and functional late effects of survivors, has well-documented psychometric properties, including adequate validity (face validity, content validity, discriminative validity, construct validity, predictive validity), reliability, and responsiveness (Horsman et al., 2003). The HUI is a generic measure of an individual's health status. Although multidimensional, certain informative elements of survivors' health and functional status may not have been covered. Naturally, the diversity of subtle cognitive impairments caused by, e.g. common brain tumour treatment, may only become evident through the use of thorough neuro-cognitive assessments.

The persistent illness-related impact on the family was assessed using the IFS questionnaire, which has well-documented psychometric properties when using the revised scoring (Stein & Jessop, 2003; Williams et al., 2006).

Survivors' health care needs were assessed using an eleven-item 4-dimensional questionnaire. As in the case of PPD-C, the instrument construction process ensures content validity (Stein & Jessop, 1984). Furthermore, the wording used in some of the questions were adapted for use in Sweden and to correspond with the Swedish health care system. This questionnaire was chosen because it covers central health care issues for which the medical care system is responsible.

IMPLICATIONS

The present findings show that the consequences of illness and its treatment continue to influence a substantial proportion of childhood CNS tumour patients and their families many years after the end of treatment. This implies that from day one, a lifespan perspective needs to be implemented. For a group at particular risk for sequelae, individualised comprehensive follow-up needs to be built upon an evidenced-based understanding of how the tumour, the treatment, and late effects affect the survivors and their families in the long term. The four studies provide empirically based knowledge for understanding post-treatment medical and psychosocial care needs of patients and their parents, and the extent to which follow-up and after-care should be extended into adulthood.

Findings from the present thesis show that adult survivors of childhood CNS tumours are at risk for late morbidity related to their disease and the tumour treatment. This strongly confirms the importance of an extended systematic and careful monitoring of persistent late effects in adult survivors. The studies present findings about medical, social and psychological follow-up care needs of adult survivors, and about how lasting disabilities result in increased and unique needs of after-care. Together, the results provide evidence-based guidelines for a more effective clinical long-term follow-up care that can be offered to those survivors who are in the most obvious need of additional intervention. The studies present survivor-reported information about domains where follow-up and surveillance needs are most urgent, and they identify areas where these needs are *unmet*. Based on this knowledge, health care providers are afforded tools to facilitate the use of limited resources in a way that best satisfies the needs of survivor subgroups. Overall, findings verify that adequate psychological services should always be integrated into ordinary patient follow-up. Furthermore, age-relevant information about illness and possible late effects, and ways of making contact with other survivors, are pointed out as measures adding to the value of comprehensive extended follow-up and after-care.

The identification of factors that influence and modify parental distress and long-term familial impact has obvious implications for family care. This knowledge enables health care providers to identify families at risk and better meet their psychosocial needs. The provision of tailored information for families of CNS tumour patients is important in reducing persistent negative family consequences. Finally, the findings also imply that the child's individual risk of developing a specific type of disability should constitute an important part of educational programs for parents. The studies contribute to an awareness of how the needs of families persist over time, and, by doing so, they verify the need to offer extended follow-ups for parents as well as patients.

CONCLUSIONS

- On a group level, health and functional disability among adult survivors of childhood CNS tumours was in the mild to moderate range. Still, survivors generally showed significantly poorer health and functional outcomes compared to the general population sample.
- The pattern and severity of health and functional outcomes differed significantly between survivors in diagnostic subgroups.
- A majority of survivors reported some kind of health care need in adult life, with a greater need found in those with compromised health and functional ability.
- A substantial proportion of survivors (~40%) reported unmet health care needs in adult life. Most unmet needs concerned illness education and psychosocial services.
- Male and female survivors differed regarding current health and functional status, and regarding the extent of health care needs and *unmet* such needs in adult life. Female survivors were at higher risk for health-related late effects, and less satisfied with follow-up health care.
- In comparison with parents of children with leukaemia, parents of children with CNS tumours and bone tumours showed heightened distress in terms of greater illness-related fears and uncertainty.
- The persistent illness-related impact on families of the adult CNS tumour survivors was in the mild to moderate range. However, adverse cancer-related consequences were found in a considerable portion of families of these survivors.
- Family impact was aggravated by patients' lasting sequelae, and by parent perceived shortcomings of long-term follow-up.

FUTURE PERSPECTIVES

Forthcoming studies could benefit from an approach where longitudinal follow-up is combined with multiple assessments of health and functional status in adult survivors to either verify or discard indications that some late effects become aggravated with time. Furthermore, other key determinants of late morbidity could be addressed in forthcoming studies, e.g. the influence of tumour and treatment factors. Such a project could specifically investigate the relationship between therapeutic modalities and the risk of long-term adverse health and functional outcomes in a very long perspective.

Furthermore, ways of enhancing follow-up and after-care for this relatively small (compared to survivors of adult cancers), diverse (in medical terms), geographically widespread but growing population have yet to be systematically implemented and evaluated. To date, research has predominantly focused on psychological interventions for childhood cancer patients and their parents in general, without addressing specific risk groups in need of extraordinary support measures. The findings presented in this thesis highlight the need for research that focuses on the support needs of such risk groups identified here. A subsequent step could thus concentrate on developing and evaluating feasible and adapted support interventions that address parent distress, family impact and family functioning.

Specifically addressing the long-term psychological status of parents of *adult* survivors with the use of more complex and/or multiple outcome measures appears to be an important direction for future research. Also, further in-depth studies could address the vital question of shaping, timing and delivery of illness-related information for childhood cancer patients and their parents, and how information needs may vary depending on the child -, illness -, and treatment characteristics.

Finally, the findings regarding heightened distress among parents of children diagnosed with a bone tumour are challenging (Study I). The identification of this risk group points out a direction for forthcoming studies, an especially urgent issue since psychosocial research focusing on parents of children diagnosed with bone tumours is rare.

SUMMARY IN SWEDISH

I Sverige drabbas omkring 300 barn av cancer varje år. Tumörer i centrala nervsystemet (CNS) är den näst vanligaste barncancersjukdomen och utgör ~25% av fallen. Barn som har drabbats av tumörer i CNS löper särskilt stor risk för sena effekter efter tumör och/eller cancerbehandlingen. Syftet med det föreliggande arbetet var att få ökad kunskap om kvarstående konsekvenser hos barn som haft tumörer i CNS, samt konsekvenser för barnets föräldrar/familj. Arbetet inkluderar fyra delarbeten med fokus på funktion och hälsa hos vuxna överlevare, medicinska och psykosociala uppföljningsbehov hos långtidsöverlevare, sjukdomsspecifik inverkan på föräldrars psykologiska belastning, samt kvarstående påverkan av sjukdom på familjen när barnet nått vuxen ålder.

I delarbete I ingick 321 föräldrar till barn diagnostiserade med tumörer i CNS, bentumörer, akut lymfatisk leukemi, eller akut myeloid leukemi från två barnonkologiska centra i Sverige. Delarbetena II-IV var populationsbaserade, och riktade sig till samtliga överlevare i Sverige som uppfyllde inklusionskriterierna. Dessa delarbeten kom att baseras på data från 531 överlevare av tumörer i CNS, för vilka >5 år hade passerat sedan diagnostidpunkt, och som vid datainsamling var ≥18 år gamla, 556 av deras föräldrar, samt en jämförelsegrupp stratifierad efter kön och ålder (n=996). De fyra delarbetena var tvärsnittstudier och baserades på kvantitativa data insamlade med självskattningsinstrument.

Resultaten visade att barn som behandlats för tumörer i CNS har en ökad förekomst av negativa effekter på hälsa ända upp i vuxen ålder. Detta var än mer påtagligt för kvinnliga överlevare. Kognitiva och sensoriska funktioner samt övergripande hälsostatus var särskilt påverkade i förhållande till jämförelsegruppen, medan det emotionella utfallet inte skilde mellan grupperna. Två femtedelar av de tidigare patienterna ansåg sig ha otillfredsställda uppföljningsbehov i vuxen ålder. Jämfört med dem som hade få eller inga effekter på hälsa och funktion, hade de med hälsorelaterade seneffekter ett större behov av eftervård och stöd i vuxen ålder samt fler otillfredsställda sådana behov. Resultaten beträffande föräldrars psykologiska belastning visade att barnets typ av cancer och seneffektsprofil var av betydelse för föräldrarnas reaktioner. Belastningen var jämförelsevis hög hos föräldrar till barn med CNS-tumörer och bentumörer. Den eventuellt kvarstående inverkan av barnets sjukdom på familjen undersöktes därefter specifikt för föräldrar till barn med CNS-tumörer. Det visade sig att de flesta föräldrar ansåg att familjelivet inte var allvarligt påverkat vid tiden för studien. Dock upplevde en mindre grupp negativa konsekvenser på familjelivet då barnet nått vuxen ålder och då många år förflutit sedan diagnos och behandling.

Tillsammans visar studierna att barn som behandlats för CNS-tumörer lider av konsekvenser som fortfarande påverkar dem som vuxna. Detta påvisar ett behov av långtidsuppföljning även för patienter i vuxen ålder. De identifierade otillfredsställda uppföljningsbehoven ger vägledning för hur en allsidig långtidsuppföljning för denna patientgrupp kan utformas. Vidare påvisar resultaten behovet av en mer individualiserad syn på omhändertagande och information till familjer med barn med cancer. För föräldrar till barn med tumörer i CNS, bör det psykosociala stödet och informationen särskilt inriktas på barnets seneffektsproblematik för att minska en bestående påverkan på familjen.

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