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CNS TUMOURS OF CHILDHOOD/ADOLESCENCE: OUTCOMES RELATED TO DISABILITY AND IDENTITY IN ADULT SURVIVORS

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CNS TUMOURS OF CHILDHOOD/ADOLESCENCE:
OUTCOMES RELATED TO DISABILITY AND IDENTITY
IN ADULT SURVIVORS
THESIS FOR LICENTIATE DEGREE

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ABSTRACT

Central nervous system (CNS) tumour survivors are at increased risk for adverse health and functional late effects. Results from previous studies from the Swedish LIFE project, of which this licentiate thesis is a part, indicate needs of expanded clinical surveillance, and long-term follow-up in order to reduce late effects and protect quality of survival. The focus of the licentiate thesis is on psychological consequences of illness- and treatment-related late effects in adult survivors of childhood CNS tumours. Particularly, the studies address outcomes associated with identity and self-perception. These factors are usually considered as vital components of mental health and psychological well-being. The aim combined of Study I and II of the licentiate thesis was to examine the long-term impact of childhood CNS tumours and their treatment on self-perception of adult survivors. Study I investigated the extent to which health- and functional status of survivors predicted outcomes in self-confidence related to body image and physical ability, as they appeared in adult age. In Study II survivors and general population individuals were compared as regards self-perception in six domains: body, sports/athletics, peers, work, and family, and as to a global self-esteem index. Data in Study I and Study II covered between 526 to 528 survivors from the entire national cohort of Swedish survivors diagnosed between 1982 and 2001 with a primary CNS tumour. Comparison data in Study II were collected from 995 randomly selected stratified general population individuals. The outcomes were based on quantitative self-report data, including the multidimensional Self-Esteem Questionnaire (SEQ-42) and, in Study I also Health Utilities Index™ Mark2/3 (HUI2/3), which provides patients' self-reported outcomes regarding health and functional status. Findings from Study I indicated that self-confidence related to body image and physical ability was negatively affected by health, functional status, and disability in adult survivors. Findings from Study II showed that self-perception of CNS tumour survivors were poorer in all domains (except family) and in the global self-esteem summary measure, compared with the general population. The long-term CNS tumour survivors constitute a high-risk group regarding functional and psychological late effects. The poorer self-perception outcomes of survivors can be interpreted as a likely indirect effect of the cancer diagnosis and treatment. Self-perception and self-esteem are significant elements of mental health and quality of survival. The findings show the importance of paying attention to both medical and psychological care and follow-up needs in early and post-treatment surveillance of CNS tumour survivors.

Keywords: childhood CNS tumours, adult survivors, late effects, self-perception, self-esteem, self-identity

LIST OF PUBLICATIONS

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LIST OF ABBREVIATIONS

CNS Central Nervous System

BI Body Image

SPAS Sport/Physical Activities

PSC Physical Self-Confidence

GHFS Global Health and Functional Status

HUI Health Utilities Index

SEQ-42 Self-Esteem Questionnaire

SCCR Swedish Childhood Cancer Register

SUMMARY IN SWEDISH

Överlevare efter CNS-tumör i barndomen löper hög risk att drabbas av en mångfald av hälsokomplikationer och funktionella seneffekter. Resultat från tidigare studier i det svenska LIFE-projektet, som denna licentiatavhandling är del av, visar att det finns behov av en utökad, långsiktig klinisk uppföljning för att minska seneffekter och för att värna om livskvaliteten hos överlevare. Licentiatavhandlingens fokus ligger på psykologiska konsekvenser av sjukdoms- och behandlingsrelaterade seneffekter hos vuxna överlevare efter CNS-tumör i barndomen. Studierna adresserar utfall relaterat till identitet och självkänsla/självuppfattning, viktiga komponenter inom psykisk hälsa och psykiskt välbefinnande. Syftet med Studie I och II var att undersöka de långsiktiga effekterna av CNS-tumörsjukdom och dess behandling på vuxna överlevares självkänsla/självuppfattning. Studie I undersökte i vilken utsträckning och hur överlevarnas hälsotillstånd och funktionella status förutspådde självkänsla relaterat till kroppsuppfattning och fysisk förmåga i vuxen ålder. I Studie II jämfördes överlevarnas utfall med utfallen hos allmänna befolkningsindivider avseende självkänsla/självuppfattning i sex områden; kroppsuppfattning, sport/idrott, kamrater, arbete och familj, och ett globalt självkänslindex. Studierna omfattade mellan 526 och 528 svenska patienter, diagnostiserade mellan 1982 och 2001 med en primär CNS-tumör. Jämförelsedata i Studie II inhämtades av 995 slumpvis utvalda individer från den allmänna befolkningen. Resultaten baseras på kvantitativa självrapportdata, och inkluderar det flerdimensionella självkänslformuläret (SEQ-42) och i Studie I Health Utilities Index TM Mark2/3 (HUI2/3), vilken mäter patienternas självrapporterade hälsa och funktionsförmåga. Resultaten från Studie I indikerade att självkänsla/självuppfattning relaterat till kroppsuppfattning och fysisk förmåga var negativt påverkat av hälsa, funktionsstatus och handikapp hos vuxna överlevare. Resultaten från Studie II visade att i jämförelse med den allmänna befolkningen uppvisade överlevarna av CNS-tumörer lägre självkänsla/självuppfattning på alla områden förutom familj. Vuxna överlevare av CNS barncancer utgör en högriskgrupp avseende funktionella och psykologiska seneffekter. Lägre utfall avseende självuppfattning kan tolkas som en indirekt effekt av CNS-tumördiagnos och behandling. Resultaten visar på vikten av att uppmärksamma såväl medicinska som psykologiska vård- och uppföljningsbehov, i den tidiga och långsiktiga kliniska uppföljningen efter CNS-tumör.

Nyckelord: CNS tumörer hos barn, vuxna överlevare, seneffekter, självuppfattning, självkänsla, identitet

INTRODUCTION

Surviving cancer in childhood or adolescence is usually followed by considerable psychosocial consequences for survivors and family, and is associated with the risk of persistent illness and treatment-related disability among survivors (Anclair, Hoven, Lannering, & Boman, 2009; Kinahan, Sharp, Seidel et al., 2012; Oeffinger & Hudson, 2004; Oeffinger et al., 2006; Skinner, Wallace, & Levitt, 2007; Zeltzer et al., 2009). Despite successful treatment of the tumour, many survivors experience physical, psychological and social disabilities as well as compromised health and morbidity (Essen, Enskär, Kreuger, Larsson, & Sjöden, 2000; Hudson, Mertens, Yasui, et al., 2003; Speechley, Barrera, Shaw, Morrison, & Maunsell, 2006; Zeltzer et al., 2009). The risk and extent of late sequelae is commonly associated with diagnosis, treatment characteristics, and age at diagnosis.

THEORETICAL BACKGROUND

Childhood central nervous system (CNS) tumour survivors

Developments in the medical field have resulted in a significant increase in survival rates (to over 74%) in children with brain tumours (Howlader, Noone, Krapcho, et al. 2014). In turn, we face a growing number of paediatric central nervous system (CNS) tumour survivors with tumour- and treatment related late effects.

Within the childhood cancer survivor population as a whole, those treated for a childhood CNS tumour are at highest risk for severe late effects or life-threatening conditions (Foreman et al., 1999; Hjern, Lindblad, & Boman, 2007). Studies evaluating health status in childhood cancer survivors often exclude survivors of childhood brain tumours (Zebrack, Gurney, Oeffinger, 2004). This may partly be due to the impact of these survivors' cognitive limitations on the validity of assessment, or/and that the CNS tumour survivors are not considered representative of the larger population of childhood cancer survivors. The treatment of CNS cancer often affects neurocognitive functions, involving attention, processing, speed and memory (Tonning Olsson, Perrin, Lundgren, et al. 2014). Many survivors suffer from multiple conditions, and in addition to functional, cognitive/neurocognitive, neurological dysfunction, and endocrinopathies, CNS tumour survivors frequently present poorer psychological health and socioeconomic outcomes in comparison with survivors of other paediatric malignancies or healthy controls (i.e. Boman, Hovén, Anclair, Lannering, & Gustafsson, 2009; Boman, Lindblad, & Hjern, 2010; Bull & Kennedy, 2013; de Ruiter, 2016; Doyle & Sastry, 2013; Ehrstedt, Kristiansen, Ahlsten, et al., 2016; King, 2016; Ullrich & Embry, 2012).

Studies of *younger* survivors or survivors of *other cancer malignancies*, have demonstrated that the functional limitations and physical changes resulting from the cancer affect the survivors' overall quality of life and mental health (Bradley Eilertsen et al., 2012; Li et al., 2013). Additionally, it has been demonstrated that CNS tumour survivors, particularly, present

poorer physical and mental health outcomes compared to the general population, while survivors of *other* cancer diagnoses present poorer physical health, although mental health outcomes equal those of the general population (Reulen et al., 2007). Functional limitations, neurocognitive impairments, and visible sequelae have been related to psychological distress and poorer self-esteem in the population of childhood CNS tumour survivors (Kinahan et al., 2012; Zeltzer et al., 2009). Accordingly, after-care and follow-up treatment of survivors should consider both medical and psychological outcomes.

The impact of late effects of childhood CNS tumours on quality of survival should be longitudinally studied. Not least because of the late effects that may endure or occur in adolescence or adult life, due to the illness, and traditional and constantly developing novel treatments. Previous research addressing late sequelae in CNS tumour survivors have usually included samples of children, teenagers or young adults (Butler, Fairclough, Katz et al., 2013; Hjern et al., 2007; Langeveld, Grootenhuis, Voute, de Haan, & van den Bos, 2004). Longitudinal studies of childhood cancer survivors will provide us with important knowledge about the impact and *development* of late effects in the long-term perspective. As brought up by others (Skinner et al., 2007) many of the potentially more severe late effects may develop long after completion of treatment. Thus, studying health in long-term survivors of childhood CNS tumours is particularly important. In turn, this can favour development of individualised clinical follow-up to meet health care-, rehabilitation-, and psychosocial needs.

The present licentiate thesis is part of a Swedish nation-wide longitudinal study; Late effects, Identity, Function and Extraordinary needs (LIFE) of survivors, referred to as the Swedish childhood CNS tumour LIFE study. Findings from the first data collection in this project revealed that Swedish adult survivors of childhood CNS tumours exhibit disability in sensation, mobility and general health outcomes, compared to general population controls (Boman et al., 2009). Survivors had received more remedial training in school, attained lower educational levels, were more often unemployed, and had less often become parents (Boman et al., 2009; Boman et al., 2010). Most affected areas of functioning in these subgroups of disabled survivors were vision, mobility, and self-care. At a group level, low-grade astrocytoma survivors presented the most severe overall disability.

The extent to which functional and physical disabilities may influence self-perception, self-identity and self-esteem of adult survivors of childhood CNS tumours has not yet been explored in longitudinal large-scale studies. The aim of this thesis was therefore to address psychological outcomes related to self-identity, and to identify factors associated with such outcomes in adult survivors of childhood CNS tumours.

Epidemiology

Next to leukemia, CNS tumors are the second most common of all childhood malignancies. In Sweden they constituted 27,5% of all children diagnosed with cancer <5 years of age during 1984-2010 (Figure 1). They appeared during that period with an incidence of 4,6 cases/100 000 children (Gustafsson et al., 2013). CNS tumours are classified as benign or malignant or high-grade and low-grade tumours. Malignant brain tumours are - after leukaemia - the second most common type of paediatric cancer. These tumours are also the leading cause of deaths from cancer among children (Baldwin, & Preston-Martin, 2004).

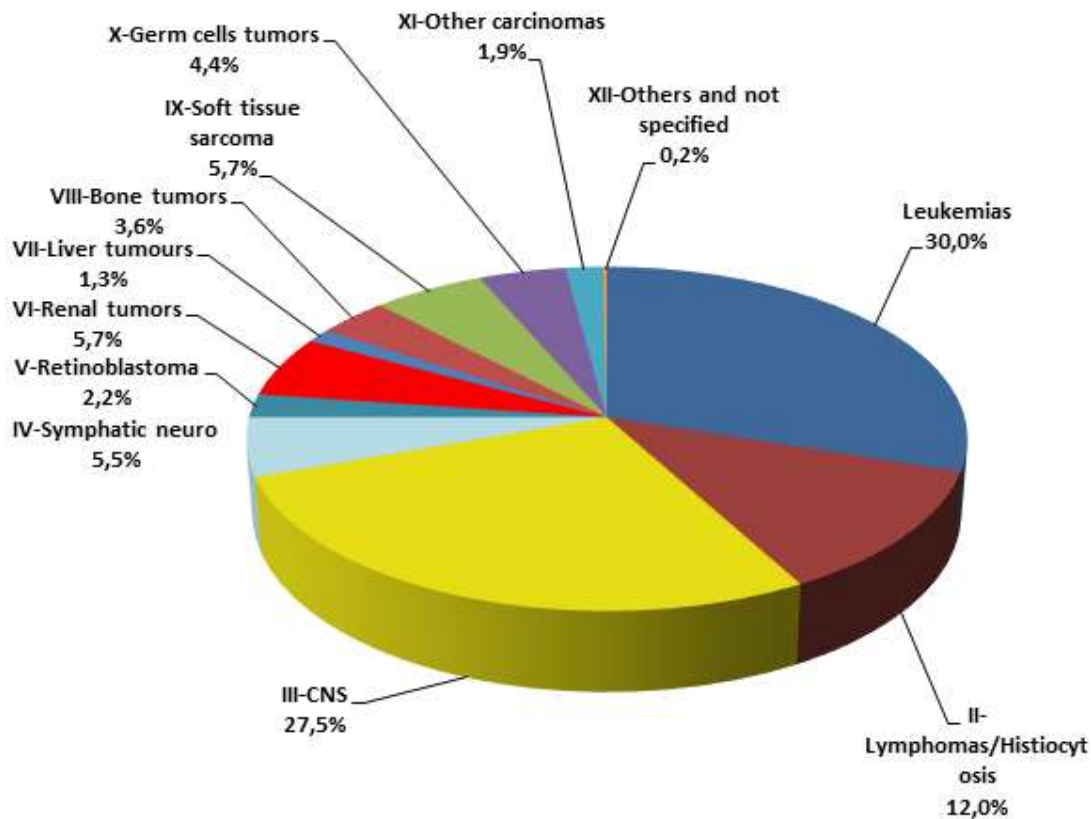


Figure 1. Distribution of childhood malignancies in Sweden diagnosed 1984-2010 < 15 years of age at diagnosis (n= 7 065). (with permission: Gustafsson et al., 2013).

Diagnostic subgroups

Astrocytoma

Astrocytoma is the largest subgroup (45%) of all CNS tumours (Lannering et al., 2009), including three different clinical subtypes; low-grade astrocytomas, high-grade astrocytomas, and optic nerve/chiasma gliomas. The low-grade astrocytomas are the most commonly

diagnosed tumours. The high-grade astrocytomas, have a survival rate of 26% (Lannering et al., 2009). The low-grade astrocytomas have a survival rate of 91%, while the optic nerve/chiasma gliomas have a survival rate of 89%. Low-grade astrocytomas are commonly treated with radical surgery, while optic nerve/chiasma gliomas are commonly treated with chemotherapy to younger children and radiation therapy to older children. High-grade astrocytomas are treated with surgery, radiotherapy and chemotherapy (Lannering et al., 2009).

Ependymoma

Ependymoma, mostly treated with surgery and radiotherapy, is the third most common childhood CNS tumour and has a survival rate of 60% (Lannering et al., 2009).

Oligodendroglioma

Oligodendroglioma are low- or high-grade gliomas that require different treatment protocols. The survival rate of oligodendroglioma is 77% (Lannering et al., 2009).

Intracranial or intraspinal nerve sheath tumours and intracranial germ cell tumours

There are two tumour types that arise from the nerve sheath; neurofibromas and schwannomas. Intracranial germ cell tumours are malignant and are commonly treated with surgery, radiation therapy and chemotherapy (Calaminus et al., 2004).

Craniopharyngioma

Craniopharyngioma is a benign non-glial intracranial tumour that constitutes 1.2-4% of all intracranial tumours in children (Müller, 2005). The survival rate is 92%. The tumour is commonly treated with radical surgery, and sometimes in combination with radiotherapy (Lannering et al., 2009).

Medulloblastoma/PNET

Medulloblastoma (19% of all CNS tumours) is the most common malignant CNS tumour in children. The survival rate of this tumour is 53%. The tumour is commonly treated with surgery, irradiation and chemotherapy (Lannering et al., 2009).

Survival

The prognosis for CNS tumours has improved significantly over time (NOPHO 2016). The survival is influenced by both diagnostic and prognostic factors. The improvement in survival rate can be explained by several factors, such as improved diagnostic techniques resulting in earlier and better detection of the tumour, a more aggressive surgery and post-operative care, improved techniques in radiation therapy, and timing and dosing of chemotherapy (Gatta et al., 2005; Green, & Wallace, 2003). Indeed, improvements and changes in treatment also imply a need to study potential new occurring late effects.

Treatment

Treatment of childhood CNS tumours depends mainly on tumour type, tumour location, and age at diagnosis (Green, & Wallace 2003). The treatment may be a combination of surgery, radiotherapy and/or chemotherapy. Adverse late effects have in particular been associated with radiation therapy. Radiation therapy may result in temporary or permanent adverse effects on CNS tissue and blood vessels. Recent experimental and clinical research demonstrates that normal, non-dividing CNS cells are damaged by the radiation therapy (Rogers, 2012). It has been emphasised that in most cases tissue or vascular injury from radiation therapy is unavoidable, and no “safe” dose has yet been identified. The risk for and extent of injury on the CNS depends on the radiation dose, the fraction size, the site and treatment volume, and administration of concomitant chemotherapy. Higher dose, higher fraction size, larger treatment volume, and younger age at diagnosis are factors associated with more adverse tissue and vascular effects. Certain regions of the brain such as the medial temporal lobes, which include the hippocampi are especially vulnerable to radiation therapy in the young.

Health status and treatment/illness-related late effects

Neurocognitive, neurological, endocrinology, cardiovascular late effects

As mentioned earlier, the extent and severity of late effects in survivors of childhood CNS tumours depend to a great extent on tumour type, age at diagnosis and treatment characteristics (Green, & Wallace, 2003). Naturally, during a period of anatomically, functionally, and psychologically development younger children are at higher risk for developing disabilities. These are often more severe in children treated at a young age. Additionally, the decline in neurocognitive functioning seem to increase with age (de Ruiter et al., 2013; Stargatt et al., 2006).

Damage to the peripheral nervous system mainly affecting motor skills, are most often caused by the tumour itself and/or surgery. CNS-associated adverse events during treatment i.e hydrocephalus, hemorrhage, infection, may contribute to neurological and neurocognitive damage. Common complaints among CNS tumour survivors include headache, seizures, lethargy, fatigue, pain, deficits related to neurocognitive functions, balance, memory, attention and processing speed (Lovely, 2004; Molassiotis, Wilson, Brunton et al., 2010; de Ruiter et al., 2013; Shepherd, Woodgate, & Sawatsky, 2010; Tønning et al, 2014). Radiation therapy has thus been directly related to significant impairments in neuropsychological functions and intellectual functioning (Butler et al., 2013). Delayed CNS symptoms especially affecting cognition may develop several years after radiation therapy. They are considered as the most feared complications of radiation therapy as they can be disabling (Rogers, 2012).

Survivors of CNS cancer are not only suffering from complications of physical and neurocognitive nature, but also psychological and emotional difficulties (i.e. Langeveld et al., 2004; Li et al., 2013; Michel et al., 2010; Shaw et al., 2006).

Psychological and social outcomes

Among the most essential undertakings for health care is to help childhood cancer survivors maintain physical, psychological and social well-being (Bradwell, 2009; Shepherd, & Woodgate, 2010). Previous research of long-term psychological impact of illness/treatment on childhood cancer survivors (mixed diagnoses) are somewhat inconsistent, indicating both positive and negative psychological health outcomes in comparison with healthy individuals (McDougall, & Tsonis 2009; Michel et al., 2010; Sundberg et al., 2009). However, there is consistent evidence that the cancer diagnosis and treatment may adversely affect psychological well-being and result in consequences such as increased depression and decreased self-esteem (Langeveld et al., 2004; Li et al., 2013; Michel et al., 2010; Recklitis et al., 2006; Servitzoglou et al., 2008; Shaw et al., 2006; Zeltzer et al., 2009). A Swedish study of adolescent and young adult survivors of cancer, found that psychosocial distress is common both during and after treatment, while problems related to physical distress are more common during the treatment period (Enskär, & von Essen 2007).

When examining studies of psychological and psychosocial aspects of childhood cancer survivors, one should take into account that findings may also be related to research design and to respondent characteristics. As demonstrated in a recent study (de Ruiter et al., 2016), survivors presented similar outcomes as their healthy siblings regarding their psychosocial adjustment problems, while parents and teachers reported worse outcomes. This may be explained by a general tendency both among healthy individuals and individuals with chronic conditions to differ in how they appraise their psychosocial well-being in comparison with respondents such as teachers or parents (Sattoe et al., 2012).

It is important to pay attention to the possible effects of the cancer and its treatment on the long-term quality of survival related to psychological well-being. As we have seen, CNS tumour survivors are distinctive as they are at heightened risk for an adverse impact of illness/treatment on physical, neurological and social outcomes in comparison with other malignancies (Boman et al., 2010; Bull et al., 2013; Ellenberg et al., 2009). That fact may have implications for psychological outcomes as well. Additionally, research has demonstrated that survivors of childhood paediatric brain cancer have not only decreased physical, and generic health-related quality of life, but also poorer psychological health, fatigue and concentration difficulties in comparison with the norm (de Ruiter et al., 2016). Treatment for CNS cancer often involves radiation which can result in neurocognitive dysfunctions and learning disabilities, which in turn may affect daily life including school performance, education and work (Boman et al., 2010; Ellenberg et al., 2009; Green, & Wallace, 2003; Wakefield et al., 2010).

In a meta-study it was found that adult survivors of CNS cancer were nearly 5 times more often unemployed than were controls (de Boer et al., 2009). Despite employment and school attendance, childhood CNS cancer survivors show difficulties related to social activities, interaction with peers and dependence on social well-fare aid (Aukema et al., 2013; Hjern et al., 2007; Johannesen et al., 2007). The illness experience and the late effects following the medical treatment, may also contribute to behavioural difficulties in terms of internalising

problems (Poggi et al., 2005). Indeed, these factors may naturally affect the survivors' general psychological well-being, self-identity, and self-esteem. In a previous study CNS tumour survivors predicted lower life satisfaction 5 years into the future, in comparison to survivors of other cancers and control subjects (Zeltzer et al., 2008).

Psychological symptoms and health-related quality of life have also been associated with visible physical sequale in childhood cancer survivors in general (Kinahan et al., 2012). CNS tumour survivors often experience treatment-related head/neck region lesions and many of these remain visible and persistent. Changes to physical appearance and body image caused by treatment factors such as surgery and cranial irradiation are common among survivors of childhood CNS cancer (Turner et al., 2009). Specifically, body image concerns have been related to social anxiety, which may not develop until several years after treatment termination (Pendley, Dahlquist, & Dreyer, 1997).

In summary, the heightened risk for affected psychosocial, emotional adjustment and psychological well-being seen in CNS tumour survivors, could naturally be associated with their heightened risk for illness- and treatment-related impairments in neurological, neurocognitive and physical domains (i.e. Bull et al., 2013; Ellenberg et al., 2009; Zeltzer et al., 2008). Finally, problems related to social outcomes, depression and anxiety have been demonstrated in this population, as well as difficulties related to the self/self-concept (Aukema et al., 2013; Boman et al., 2010; Poggi et al., 2005; Turner et al., 2009).

Self-esteem, self-identity, self-perception

The concepts of self-perception, self-esteem, and self-identity are related and refer to how an individual view, value, accept, and appreciate him or herself (Pruessner et al., 2005). The "self" develops through a cognitive-developmental maturation process (Harter, 1983) and throughout the lifespan the "self" continues to be influenced by direct and indirect experiences in one's environment (Bracken, 1996). Emotions, internal beliefs, social experiences and perceptions of them, influence on how an individual value him/herself throughout the lifespan. Adolescence is often characterized by the process of identity formation; to find out "who am I?" (Erickson, 1998). In this process the individual commonly undergo different stages (such as testing out various identities, adapting to someone else's identity) until she/he arrives at the stage of her/his own identity achievement (Erickson, 1998).

Indeed, adolescents and young adults with cancer may be faced with more challenges in the process of forming an identity. As mentioned earlier, many survivors of CNS tumours are exposed to treatment-related cognitive deficits. These cognitive deficits can result in impaired processing speed and thereby difficulties figuring out self-identity (Evan et al., 2006). The process of developing a sense of self and liking oneself may also be affected by the different life situation that is during a cancer diagnosis; factors such as lack of social activities, school activities because of treatment/hospital visits, and affected appearance as an effect of treatment etc.

Self-esteem is closely related to mental health and quality of life (Calaminus et al., 2007; Johnson, & Patching, 2013; Langeveld et al., 2004; Moffitt et al., 2007; Strauser et al., 2012). Studies have shown that low self-esteem has been associated with problems such as social risk behaviours, bullying, and suicidality (Trzesniewski et al., 2006; Wild et al., 2004). As discussed by others (Recklitis et al., 2006) feelings of depression may affect self-esteem and contribute to the higher risk of suicidal tendencies seen in childhood cancer survivors (Gunnes et al., 2017).

The relation between an internal basic self-esteem and a competence related self-esteem has been studied, and the latter deals with the individual's ambition to receive positive and negative feedback (Johnson, & Patching, 2013). It has been suggested that competence may improve a good sense of self-esteem (Johnson, & Patching, 2013). Yet, if the basic self-esteem is deprived, competence may contribute fairly. Stability of self-esteem has been distinguished from basic and level of self-esteem (Johnson, 1998; Kernis et al., 2005) It has been suggested that self-esteem stability has a predictive value beyond the predictive value of self-esteem level (Kernis et al., 2005). Stability of self-esteem deals with the feelings of self-worth, while level of self-esteem refers to the *representations* of an individual's general feelings of self-worth. It has been suggested that to receive a complete understanding of self-esteem processes one has to consider multiple components of self-esteem (Kernis et al., 2005).

In previous research examining self-perception and self-esteem in childhood cancer survivors, focus have been on different aspects and domains of self-esteem; such as self-esteem related to physical appearance, education/school/work, social activities and peers (Evan et al., 2006; de Ruiter et al., 2016). Domain-specific self-esteem may factor into a global self-esteem, in such a way that low self-esteem related to a specific domain (such as low self-esteem regarding body image) contribute to a low global self-esteem and vice versa (Evan et al., 2006). Given that the specific domain/domains is/are significant for the individual's self-perception, (for instance, that it is important to feel good about one's body) a lowered self-perception in a specific domain can result in a lower global self-esteem, i.e. an overall feeling of lowered self-esteem.

In a study by de Ruiter et al. self-esteem of survivors between the ages 8-18 years were studied in relation to scholastic competence, social acceptance, athletic competence, physical appearance, behavioral conduct, close friendship, and global self-worth (de Ruiter et al., 2016). The findings indicated that self-esteem of the survivors were similar to their siblings, although a tendency toward lower scholastic self-esteem and athletic competence was found among the survivors (de Ruiter et al., 2016). A trend towards lower self-esteem in relation to school has been found in another study (Aukema et al., 2013). Such findings can possibly be related to the neurocognitive deficits of the survivors, although the causal interrelationships should be further investigated. It should also be emphasised that persistent disabilities may interact negatively with an individual's *normal aging* and in turn have a poor impact on the individual's self-perception and self-esteem (Annunziata et al., 2012.). Thus, difficulties related to self-identity and self-esteem may not develop until many years after diagnosis and completed treatment.

Research on self-esteem and psychosocial functioning in the population of paediatric brain tumour survivors is still scarce (de Ruiter et al., 2016). As these survivors are exposed to more aggressive treatment, often resulting in multiple problems covering a variety of domains (i.e. physical, neurocognitive, behavioural) they are frequently excluded in studies of childhood cancer survivors with mixed diagnoses (Patenaude et al., 2005). Nevertheless, this fact makes it even more important to address their psychological well-being, self-perception, and self-esteem. When examining childhood cancer survivors *in general*, it has been found that self-esteem and psychosocial functioning were quite similar to the normative levels (Maunsell et al., 2006). However, survivors of CNS cancer showed poorer outcomes related to self-esteem, psychosocial and general health, findings that are consistent with earlier studies (Carpentieri et al., 2003). Affected psychological health could possibly reflect a sensibility for affected self-esteem in these patients. Investigations examining self-identity more in depth among survivors of childhood CNS tumour survivors could clarify issues like this furthermore.

AIMS OF THIS THESIS

In the population-based cohort study, of which this licentiate project is a part, we study health-related, functional, and psychological late effects in adult survivors of childhood CNS tumours. The *general* aim of the childhood CNS tumour project is to provide new knowledge regarding needs of clinical care interventions, follow-up, and supportive, preventive, and rehabilitation measures for survivors of childhood CNS tumours. The aim of the licentiate thesis was to study psychological consequences of illness- and treatment-related late effects in adult survivors of childhood CNS tumours, particularly, outcomes associated with identity and self-perception.

Study I

To investigate the extent to which health and functional ability may predict body image (BI) and self-confidence regarding sports and physical activity (SPAS) in adult survivors of childhood CNS tumours. And to identify predictive or associated factors (e.g. gender, age at diagnosis, tumour type) that may increase the risk for persistent or late-occurring late effects.

Study II

To study the long-term impact of childhood CNS tumour and its treatment on self-perception in multiple (six domains) significant domains in adult survivors by comparing outcomes with those collected from the general population. And to identify predictive or associated factors (e.g. gender, age at diagnosis, tumour type) that increase the risk for persistent or late-occurring late effects.

Methods

The comprehensive host research project

The longitudinal LIFE project, as a nation-wide large-cohort project, includes childhood CNS tumour patients and their parents treated at any of the six childhood cancer centres in Sweden. The original cohort includes ~720 patients, and ~1400 parent-proxies in addressing patient outcome data of the study. The larger LIFE project, within which this licentiate thesis and its two studies were carried out, includes both register studies and clinical studies. Studies use quantitative and qualitative self-report data and register data, and the research questions are addressed using descriptive, comparative, and register-based epidemiological methodology, and combined-approach study designs. Patient data in the clinical studies (self-report-based) are contrasted to data from the general population after questionnaires for corresponding were sent out to ~2 400 general population controls. In the clinical studies, standardised self-report questionnaires, standardised psychological assessment scales, analyses of medical and social registry data, and data from patients' medical records are used. First wave of data collection (T1) in the longitudinal clinical study took place in 2006/2007. In the second wave of data collection (2012/2013) in the clinical studies, i.e. T2, data collection addresses patients primarily, while parent-proxies will be addressed for gaining patient-related outcomes in case questionnaires sent to the patient is not returned. This use of parent proxies for getting

information about patient status is an important measure, as it increases the base and accuracy of outcomes (Glaser, Kennedy, Punt, & Walker, 1999), and allows for achieving data regarding patients who may be unable to respond due to suffering from disability.

The thesis project: respondents and procedures

Study I

Participants were identified through the Swedish Childhood Cancer Register (SCCR) that nationally covers patients diagnosed with a primary cancer diagnosis during childhood or adolescence, classified according to the International Classification for Childhood Cancer (ICCC-3) (Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005). Ninety-nine percent of SCCR registered patients are diagnostically specified, and morphologically verified at one of six university hospital paediatric cancer centres (Gustafsson, Heyman, & Vernby, 2007). Inclusion criteria were: a primary CNS tumour diagnosis between 1982 and 2001 occurring before the patient's 19th birthday, ≥ 18 years of age at follow-up, and ≥ 5 years since date of diagnosis.

After approval from the Regional Research Ethics Committee and individual written informed consent from participants, data on self-perception were collected using as part of a mail-return questionnaire package.

Study II

Study II covers the same national cohort as Study I, and in addition a comparison sample identified in national general population registries. The comparison sample consisted of 2,500 randomly selected Swedish general population individuals stratified for year of birth, sex, and residential location.

Assessments

Study I

First part of the study questionnaire booklet included background data; survivors' medical and treatment history and current status regarding self-perceived overall health (length, weight, care needs), and social and demographic variables (e.g., own family/children, education, work, beneficiary of socio-economic aid).

Dependent psychological outcomes were assessed using 1) the Body Image sub-scale for addressing body image (BI) and 2) the Sports/Athletics sub-scale for addressing sport/physical activity (SPAS), two modules of the standardised multidimensional Self-Esteem Questionnaire (SEQ-42) (DuBois, Felner, Brand, Phillips, & Lease, 1996). Together they comprise ten items appearing as statements on a four-point Likert scale with response alternatives ranging from strongly agree to strongly disagree. High scores reflect positive and low scores negative self-confidence. The outcomes are presented by the sub-scale means. A mid-scale cut-off limit

(score 2.5) allows for distinguishing between negative and positive physical self-confidence (PSC) (DuBois et al., 1996).

Health and functional status in specific domains was assessed using the 15-item Health Utilities Index TM Mark2/3 (HUI2/3), which provides patients' self-reported outcomes regarding health and functional abilities (Furlong, Feeny, Torrance, & Barr, 2001). The HUI2/3 provides utility scores derived from general population preferences (Furlong et al., 2001; Glaser et al., 1999; Kennedy & Leyland, 1999). HUI2/3 covers nine single health/function attributes that can be combined into three comprehensive outcomes: sensation (vision, hearing, speech), mobility (ambulation, dexterity), and global health (here termed Global Health and Functional Status, GHFS, based on vision, hearing, speech, ambulation, dexterity, emotion, cognition, pain). Sensation and mobility scores range from 0.00 (most severe impairment) to 1.00 (perfect health). GHFS summary scores range from 0.00 to 1.00, where 0.00 = death, and 1.00 = perfect health (Furlong et al., 2001), i.e., higher scores indicate less disability.

Study II

Information about illness and treatment background factors, including sub-diagnosis, current age, and age at diagnosis, was collected in a separate partition of the questionnaire package and from the SCC. The first part of the study questionnaire booklet included background data; survivors' medical and treatment history and current status regarding self-perceived overall health (length, weight, care needs), and social and demographic variables (e.g., own family/children, education, work, beneficiary of socio-economic aid).

The Self-Esteem Questionnaire (SEQ-42) was used to investigate self-perception in 5 domains (DuBois et al., 1996). Answers were scored on 4 graded Likert-type scales. The domains included: (i) body image, (ii) sports/physical activities, (iii) peers, (iv) work (including involvement in education), and (v) family. In addition, the SEQ-42 provides a grand scale global self-esteem index based on all items of the questionnaire. As in Study I, a mid-scale cut-off score of 2.5 was applied to identify individuals with a negative/positive self-perception within domains and negative/positive self-esteem within the self-esteem index (DuBois et al., 1996). Responses were coded so that a higher score consistently indicated a more positive self-perception.

A single question was also included to elicit information concerning visible physical sequelae: "When you think of your appearance, do you have any visible lesions, or is your appearance affected in any other ways due to your illness or its treatment?" (Yes/No). If the response was affirmative, the respondent was asked to describe the problem(s) in further detail in an open-ended format.

Statistical analyses

Study I

Correlation analysis was used for exploring associations between the primary study variables and background variables considered as potential mediating factors (confounders). Health/function outcomes (HUI2/3 predictors), and BI and SPAS (respectively as dependents) were presented with measures of central tendency and dispersion for the entire group, and for males and females separately. Proportions were compared using Fisher's exact test. The significance of potential confounders was analysed in adjusted regression models with the summary GHFS measure as predictor. The significance of sub-diagnosis for the relationship between health/functional status and PSC was analysed using ANOVA and post hoc Bonferroni correction. To specifically examine whether the impact of GHFS on BI varied with time passed since diagnosis, an analysis of interaction effect of time from diagnosis and GHFS (ANOVA; time, GHFS) on self-perception outcomes was carried out. An alpha of 0.05 was applied for statistical significance in other analyses. The SPSS statistical package 20.0 for Windows (SPSS Inc., Chicago, IL) was used for all calculations.

Study II

Survivor and general population sociodemographic characteristics were compared using the t-test, chi-square test, and One-way analysis of covariance (ANCOVA). In the main analyses, self-perception outcomes of survivors and controls were compared in linear regression models, with group (survivor/general population) as the primary independent factor, and were adjusted for the potential disease-unrelated confounders sex and current age. Cohen's d was calculated for the tentative estimation of effect size of group mean differences (Cohen, 1988). Survivors and controls were also compared by group and sex regarding the proportions of individuals showing negative self-perception. Males and females were compared using ANOVA adjusted for age. In addition, in a multivariate analysis of variance (MANOVA), males and females in the general population and survivor groups were analysed separately. One-way MANOVA and Fisher's least significant difference post hoc tests were used to study the extent to which self-perception varied with age at diagnosis and with CNS tumour subtype.

Table 1. Characteristics of the study group in Study I and Study II.

Diagnosis	n (%)	age at assess	age at diagn
Astrocytoma	247 (46.8)	26.1 (4.9)	10.1 (4.4)
Germ cell - intracranial and intraspinal	22 (4.2)	29.0 (5.2)	13.0 (3.5)
Oligodendroglioma	21 (4.0)	26.8 (5.1)	9.7 (4.9)
Other specified incl. fibrosarcoma and CNS unspecified	67 (12.7)	26.4 (5.0)	13.8 (2.7)
Craniopharyngioma	45 (8.5)	26.2 (5.5)	10.0 (4.0)
Medulloblastoma/PNET	68 (12.9)	25.9 (4.5)	9.1 (4.7)
Ependymoma	45 (8.5)	26.8 (5.1)	10.1 (4.9)
Mixed and unspecified gliomas	13 (2.5)	24.2 (3.9)	10.1 (3.6)
Visible appearance sequelae	430 (73.9)		

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

Variables	Study I	Study II
Health Status		
Global health status (Sensation, Mobility, Emotion, Pain, Cognition)	X	
Sensation (Vision, Hearing, Speech)	X	
Mobility (Ambulation, Dexterity)	X	
Self-perception dimensions		
Body image	X	X
Sport/physical activities	X	X
Peers		X
Work/education		X
Family		X
Grand scale global self-esteem index		X

SUMMARY OF RESULTS

Study I

Of 5,443 children diagnosed with cancer in Sweden 1982–2001, 1,535 had a CNS tumour. At the time of this study, 449 patients had died. Of the 708 meeting the inclusion criteria, an additional 11 had died since the last update of the register. Of the remaining 697, fully or partly completed questionnaires were returned by 528 patients. Non-responders were similar to responders regarding time passed since diagnosis, age at study invitation, sex, and sub-diagnosis. Three responders with <50% of completed items in a questionnaire were excluded

from analyses, leaving between 526 and 528 patients for calculations, the variation in number depending on the occurrence of missing responses in individual data sets. Female survivors had poorer BI and SPAS than males ($P<0.00001$), and nearly half (48%) had a borderline or negative (score B 2.5) BI, while the corresponding proportion among males was 31 % ($P<0.001$). Regarding SPAS, the proportions of borderline or negative self-confidence was females: 65%; males: 47% ($P<0.0001$). Although GHFS was lower in females ($P=0.043$), the differences in PSC outcomes between sexes remained when controlling for GHFS. Emotion and pain were most strongly associated with the BI and sports/physical activity outcomes, followed by cognition, vision and speech.

Health/function and self-confidence outcomes

Body image

At a group level, the compound sensation and GHFS outcomes significantly predicted BI outcomes (sensation: $P=0.0012$; GHFS: $P<0.0001$), whereas mobility did not. Both were positively related, i.e. more of indicated impairment predicted poorer BI. GHFS predicted BI in both sexes (males, $P<0.0001$; females, $P<0.00001$). Furthermore, sensation predicted BI in males ($P=0.005$). The most influential single attributes that contributed to the predictive significance of GHFS for BI were emotion, pain, and sensory functions (vision and speech, but not hearing), while motor functioning and ambulation were less influential.

Sports and physical activity

In the entire group, sensation ($P=0.009$), mobility ($P=0.047$), and GHFS ($P<0.0001$) significantly predicted SPAS outcomes. GHFS predicted SPAS in both males and females (males, $P<0.00001$; females, $P<0.0001$). In males, an association was found between sensation and SPAS ($P=0.003$). A non-significant tendency ($P<0.068$) indicated that mobility was also, to some extent, influential regarding SPAS in males. As with BI, emotion, pain, and sensory functions contributed most to the effect of health/function on SPAS, motor functioning and ambulation being less influential.

Adjusted regression

Correlations verified significant associations between gender and the primary study variables. Therefore, the two adjusted regression models were applied for the entire group, and for males and females separately. As initial analyses verified that time from diagnosis to assessment and age at diagnosis were both associated with BI and SPAS, and inter-correlated, only time since diagnosis was used in adjusted regressions. Being unrelated to health/function and BI/SPAS, age at assessment was excluded from adjusted analyses. Therefore, Model I was adjusted for gender, while Model II was adjusted for gender and time elapsed from diagnosis. In both models, GHFS significantly predicted both BI and SPAS in all separately analysed groups (males, females, all survivors, $P < 0.0001$ throughout).

Influence of confounders

In Model I entire group analyses, gender, along with GHFS, predicted BI ($P < 0.0001$), and SPAS ($P = 0.0001$). In Model II, gender predicted both BI ($P < 0.0001$) and PSC ($P = 0.0016$). Similarly, in Model II/entire group analyses, time elapsed from diagnosis predicted BI ($P = 0.0030$) and SPAS ($P = 0.0114$). A main effect of sub-diagnosis on BI/SPAS was found for BI ($P = 0.009$), caused by craniopharyngioma survivors' poorer BI compared to "other specified tumours" survivors. A marginally significant interaction effect was found for GHFS and time elapsed since diagnosis on SPAS alone. This was not due to a direct effect of the time factor, but merely due to a variation of the impact of GHFS on SPAS with time. A somewhat stronger impact of GHFS was indicated in patients with shorter time since diagnosis.

Study II

We identified 5443 Swedish children diagnosed with cancer between 1982 and 2001, of which 1535 were diagnosed with a primary CNS tumour. However, at the time of the study, 460 of these patients had died, and out of 697 who had fulfilled the inclusion criteria, 5 were unreachable and 164 did not return the questionnaires. Non-responders included those prevented from reading, comprehending, or completing study forms because of persistent disability due to their past illness. Apart from this, non-responders were similar to responders regarding the time since diagnosis, age at invitation, sex, and diagnosis. Calculations were carried out for 528 patients (i.e., 75.8% of 697 identified as eligible).

Of the 2500 selected general population individuals, 60 participants could not be reached, and 995 (41%) completed the questionnaires. Compared with the survivor group, individuals in the general population group were older, and the proportion of females was smaller ($P < .001$). More individuals in the survivor group had a lower level of education and were unemployed, dependent on welfare benefits, childless, and single. This was expected and had been hypothesised as being a direct consequence of the cancer history. These differences remained in complementary ANCOVAs controlling for sex and current age, (F_1)=21.85–110.96, all $P < .0001$.

Self-perception profiles

Compared with the general population, survivors had significantly ($P < .001$) poorer self-perception in all domains (except family) and in the global self-esteem summary measure. The largest difference ($P < .001$) was found in the domains of work (survivors mean [m] 2.97 compared with controls m 3.19) and peers (survivors m 2.94 compared with controls m 3.15). The smallest difference ($P < .001$) was found in the sports/physical activities domain (survivors m 2.47 compared with controls m 2.61). In the family domain, self-perception in survivors paralleled that in the general population. Although survivors generally exhibited weaker results, they displayed similar profiles to the general population as to how self-perception varied with the domains. Self-perception profiles showed that negative self-perception vis-à-vis a particular domain was notably frequent among survivors: body image (survivors, negative: 30.1%, general population, negative: 17.0%), peers (survivors: 30.1%, general population: 17.0%), and work (survivors: 22.2%, general population: 8.4%). The frequency of negative self-perception regarding sports/physical activities of survivors was 48.1%, quite similar to the frequency of 41.6% reported by the general population. Outcomes of both male and female survivors were inferior compared with corresponding outcomes in the general population. However, the differences were considerably greater for females, who were 2–4 times more likely to have a negative self-perception in terms of work, peers, and body image and a negative global self-esteem compared with females in the general population. Poor self-perception outcomes among females were also less extensive in the general population group, that is, restricted to 2 domains (body image and sports/physical activities), compared with 4 domains for survivors.

Compared with females in the general population, female survivors had poorer self-perception in all domains (except family), with the largest significant difference in work and the smallest in sports/physical activities. Male survivors had poorer self-perception than males in the general population group in all domains (except family), with the largest difference in peers, body image, and sports/physical activities, and the smallest in the global self-esteem index.

Within Survivor Group Outcomes

Visible appearance sequelae

Scars in the head-neck region were the most commonly occurring appearance-affecting sequelae. Although visible, they could sometimes be hidden by, for example, the person's own hair. Approximately 61% reported having such scars. The second most frequent symptom in this category was partial or almost complete loss of hair, reported by 19%. Being overweight was also rather common, reported by 7%. Other visible sequelae included strabismus due to tumour pressure on the optic nerve, partial facial paresis, and limping. Survivors who reported visible sequelae often had several types of such late effects. Persistent visible physical sequelae were associated with poorer self-perception in terms of body image ($P < .001$), while being in a partner relationship was associated with better body image ($P < .001$) and peers domain ($P < .001$) and higher global self-esteem ($P < .001$). In univariate analyses, sex, age at assessment, and

visual physical sequelae were all found to be associated with body image (sex, poorer in females, $P<.001$; age at assessment, poorer in younger, $P<.01$; visual physical sequelae, poorer in those with visible physical sequelae, $P<.001$). Sex and age at assessment also were associated with self-perception in sports/physical activities (sex, poorer in females, $P<.001$; age at assessment, poorer in younger, $P<.002$) and with global self-esteem (sex, poorer in females, $P<.001$; age at assessment, poorer in younger, $P<.04$). In adjusted regression analyses it was indicated that poorer self-perception and/or self-esteem was predicted by female gender (in domains of peers, work, body image, sports/physical activities, and global self-esteem), older age at assessment (in domains of peers, family, body image, sports/physical activities, and global self-esteem), and the occurrence of visible sequelae (in body image).

When subgroups of different ages (4, 6, 7, 9, 11, and 12 years) at diagnosis were contrasted one by one with each other, one or more groups of patients who were younger at diagnosis had poorer self-perception in certain domains compared with patients diagnosed at 13 or 14 years of age.

Outcomes by Tumour Type

A significant group effect of tumour type (sub-diagnosis) on self-perception was found in the domains of peers ($P=.006$), work ($P=.004$), and body image ($P=.009$). Overall, patients treated for oligodendroglioma, intracranial/spinal germ cell tumour, or medulloblastoma/primitive neuroectodermal tumour (PNET) had significantly poorer self-perception outcomes in the aforementioned domains compared with those treated for other tumours. Out of the 3 diagnostic groups of survivors with the poorest self-perception, 2 groups also had the highest proportion of patients treated with cranial radiation therapy (CRT), alone or as part of multimodal treatment; that is, medulloblastoma/PNET 90.7% or intracranial/intraspinal germ cell tumours 85.7%. This indicated a particular significance of CRT and/or CRT-associated sequelae for self-perception outcomes. In the group with the third poorest self-perception level, oligodendroglioma survivors, 38.9% had received CRT, while proportions for the remaining groups were: astrocytoma 26.2%; ependymoma 65.2%; craniopharyngioma 48.6%; glioma other, unspecified 9.1%; other, specified/unspecified 16.1%.

GENERAL DISCUSSION

The general aim of the licentiate thesis was to study psychological consequences after childhood CNS cancer related to self-identity, self-esteem and self-perception in adult survivors. In comparison with other paediatric malignancies CNS tumour survivors appear as being at higher risk for affected self-perception, likely as a result of the past CNS cancer, treatment and sequelae.

The study findings indicated a negative impact of illness and/or treatment on self-perception and self-esteem of adult survivors of childhood CNS tumours. Study I showed that late effects of diagnosis and treatment predicted body image and self-confidence regarding sports and physical activity. Our findings are supported by an earlier study (Hoffman, Mulrooney, Steinberger et al., 2013) indicating that the underlying physiologic cancer and treatment-related changes in childhood CNS cancer survivors have a significant impact on the physical functions, and thus the quality of life of survivors. Indeed, it is challenging to overcome the early physiologic changes, even if the survivors implement a healthy lifestyle. Study II which compared outcomes of survivors with the general population, showed that survivors had poorer self-perception outcomes in domains of peers, work, body image, and sports/physical activities, and poorer global self-esteem.

Certain characteristics were associated with poorer self-perception outcomes, such as female gender, tumour type (oligodendroglioma, intracranial/spinal germ cell tumour, or medulloblastoma/primitive neuroectodermal tumour), being treated with cranial radiation therapy, and having visible physical sequelae. Poorer body image was associated with having survived craniopharyngioma. This can be considered in the light of earlier research indicating that craniopharyngioma and its treatment is linked to significant medical, psychological, and emotional difficulties (Pedeira et al., 2006). Additionally, the results indicate that the adverse consequences of treatment not merely result in neurologic complications (Rogers, 2012), but also psychological complications.

Affected self-perception found in these studies was considered as a possible consequence of the *entire* CNS cancer experience. Considering patients' susceptibility for physical, neurological deficits, visible scars (Boman et al., 2009; Boman et al., 2010; Bull et al., 2013; Doyle et al., 2013; Ellenberg et al., 2009; Foreman et al., 1999; Hjern et al., 2007; Ness et al., 2010; Ullrich et al., 2012), and the following treatment-related effects on school, education/work, participation in social activities/sport activities etc., childhood CNS tumour survivors may feel doubts about their future (Zeltzer et al., 2008). These negative experiences may indeed affect the survivors' self-identity. Many patients have to adjust to living with health and functional impairments, cognitive disabilities, and subsequent undesirable psychosocial consequences. In studies of younger patients treated for solid tumours, it has been indicated that their body image and emotional functioning were associated with severity of illness and treatment related late effects (Calaminus et al., 2007). Our studies take a further step and demonstrate that these associations between cancer- and treatment-related sequelae and psychological health can persist into, or alternatively develop during, adulthood.

It has been emphasised that examining psychological health of childhood cancer survivors should be done at an early stage in order to promote their psychological well-being (Li et al., 2013). Our studies reveal the importance of following up survivors of childhood cancer late during adulthood, i.e., a longer time after diagnosis and end of treatment, to identify those with negatively affected psychological outcomes and mental well-being. Again, difficulties may develop many years after end of cancer treatment, and during the subsequent period of life when hospital visits and customary clinical follow-up has ended. However, the challenge is to identify *when and how* the psychological consequences of cancer/treatment and affected self-esteem progress, and the extent of their impact on the survivors' quality of survival. In contrast to our findings (indicating poorer self-esteem outcomes in all studied domains except for the family domain) de Ruiter et al. found that survivors and their siblings reported quite similar self-esteem (de Ruiter et al., 2016). A tendency toward lower scholastic self-esteem and athletic competence was found and is supported by earlier study findings (Aukema et al., 2013). Anyhow, both those studies involved significantly younger survivors (age 8-18 years) in comparison to our sample of <18 years of age participants. Certain domains of self-esteem may thus be of particular importance depending on the age of the respondent (Evan et al., 2006). While school and sport seem to be of particular significance for the younger survivors (Aukema et al., 2013; de Ruiter et al., 2016), the adult survivors of our study experience affected self-esteem in additional domains. Although, neurocognitive deficits associated with treatment could, indeed, be linked to the poorer self-esteem outcomes seen in school and sport domains. These treatment-related complications may add burden that spreads into other areas in adulthood.

Despite findings that adverse sequelae may progress with time in this high-risk population, there's a lack of research examining the long-term health in adult survivors of childhood CNS tumours (Boman et al., 2009; Skinner et al., 2007). Our study illuminates the most prominent self-reported complications occurring 10-20 years after the CNS cancer diagnosis. The findings imply that for many survivors complications associated with the childhood cancer illness have a significant impact on their adult lives and well-being, and that the adverse consequences of the cancer are long-lasting or even lifelong. Longitudinal studies are therefore essential to increase our knowledge about the impact and development of late effects.

Self-perception of survivors was found to vary with sex and the degree of the survivor's visible physical sequelae. The finding that female survivors reported poorer self-esteem than males can be understood in the light of previous research (Boman et al., 2009), which has shown that female adult survivors of CNS tumours have a higher risk for late effects related to the tumour and treatment. Regarding the general population there is a consensus that adolescent females report poorer self-esteem than adolescent males (Kling et al., 1999). In Study II borderline or negative PSC in terms of body image and sport/physical activities was found in near every other female survivor, and significantly more often than among males. In this respect, it could therefore be concluded that in the long-term perspective, our adult female survivors who were treated and followed up during the actual era in question, and followed up according to past

and current clinical and psychosocial surveillance routines, are still at heightened risk for psychological self-identity disturbance.

Compared to the medical and neuro-behavioral CNS tumour-related late effects that cannot be fully compensated for by remedial measures, the late effects in self-perception, and identity constitute well-suited targets for treatment interventions known from, and practiced in, other areas of psychological treatment and promotion of mental health. There was an association between physical late sequelae and psychological outcomes. Therefore, proper and specifically adapted information regarding the possibly persisting or late occurring late effects of illness and treatment on psychological well-being should be provided to all, as part of a necessary life-long surveillance program.

In this context one could also pay attention to the understanding of the various facets of the concept of self-esteem. As previously suggested, one should keep in mind the multiple aspects of the self-esteem concept, and consider the extent to which the studies presented here relate to those usually addressed aspects (Johnson, 1998; Johnson, & Patching, 2013; Kernis et al., 2005). Due to the construction and format of the SEQ-42 our outcomes seem to cover the aspects of both internal basic self-esteem and the competence related self-esteem, while the stability of self-esteem was not possible to address. Stability of self-perception outcomes, and whether certain component(s) of self-perception, and self-esteem especially, are particularly significant for, or affected by a childhood CNS cancer history remains to be explored. Longitudinal follow-up studies could shed light over these questions, and add further to our knowledge about the role of factors related to medical background, treatment and late-effects status.

Methodological considerations

Representatively and generalisability

The strength of this Swedish LIFE project is that it covers all six childhood cancer centres in Sweden. We may therefore assume that the study findings are representative for this population of adult survivors of childhood CNS cancer. Additionally, the project as a whole covers data provided not only by patients, but also by families/parents of the patients (concerns especially other parts of the comprehensive project: i.e., evaluation of care and follow-up, unmet health care needs). The use of parent proxies for getting information about patient status is an important measure. It increases the base and accuracy of outcomes (Glaser et al., 1999), and allows for achieving data regarding patients who may be unable to respond due to suffering from disability.

Assessment validity and reliability

In interpreting the findings, it should be considered that the assessments of main outcome factors were carried out using self-report measures, which are subject to the general limitations of patient-reported data. Outcomes may have been influenced by gender-related differences in response style, or by response shift bias; the latter referring to a situation where patients with

chronic illness or disability have become more accepting because of a change in standards, values, and conceptualizations of themselves and their lives (Parry & Chesler, 2005; Stam, Grootenhuis, Caron, & Last, 2006). In evaluating findings from Study II, one should also bear in mind that comparisons with the general population may have been influenced by response shift bias. If such an influence was present, it can have diminished "real" differences between survivors and general population outcomes in this study.

Conclusions

Our findings show that childhood CNS cancer is followed by the risk for a negative impact on self-perception in adult survivors. This adds to the accumulated burden from other late effects that CNS tumour survivors are exposed to. A sub-set of survivors indicate the need for remedial measures to promote healthy self-perception and to protect against unwanted psychological consequences of CNS tumour damage, treatment, and unavoidable health late effects. The differences between survivors and the general population outcomes found in Study II was statistically highly significant, and the findings need to be interpreted for their implications for patient care.

Integrated medical and psychological rehabilitation should in a coordinated approach address health- and functional impairments and avoidable adverse psychological consequences, combined with lifetime follow-up.

Future perspectives

Medical and psychosocial follow-up should be extended to cover adulthood for survivors, and effectivised for survivors now left with unmet health care needs and insufficient psychosocial observation. Forthcoming research should be expanded to investigate the extent to which unavoidable residual morbidity in survivors instigates disturbances in the normal course of other aspects of psychological development as well.

Furthermore, the negative impact of the entire illness history on self-perception, self-esteem and psychological well-being often unnecessarily adds to the burden of physical disabilities placed on survivors. For a large sub-set of survivors with considerable or substantial sequelae, the impact of tumour history on self-perception and identity constitutes a potential threat to the quality of survival, life satisfaction, and mental health. Therefore, aftercare and follow-up extended into adulthood appear as important for identifying survivors at risk and to provide protection against known potential late effects. Patients with, or at risk for, affected self-perception could be identified via screening similar to the method used in Study II, to detect needs specialised treatment or supported intervention.

Further studies should include investigation of the detailed health and functional outcomes as they appear in fully covered longitudinal data derived during the adulthood of very long-term childhood CNS cancer survivors. The patterns of how, and the extent to which such health data are related to psychological outcomes in the longitudinal perspective should be further examined. Health and psychological outcomes should be investigated as to the role of type,

intensity and timing of past CNS cancer treatment. Furthermore, survivors' subjectively experienced type and harmfulness of disabilities should be addressed in studies that include open-end questioning and qualitative analysis – a methodological expansion that could add knowledge by detecting so far unknown problems, not caught up by use of standardised instruments alone with their focus on predetermined health threats to quality of survival.

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