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ABSTRACT

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Health and quality of life after young age onset brain tumor

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The survivors of young age onset brain tumors (BT) often experience several late-effects due to their tumor and its treatment, and their quality of life (QOL) may be compromised. The aim of this study was to explore in detail these late-effects and the QOL after diagnosis of young onset BT.

We identified 740 survivors diagnosed with childhood and 315 survivors with adolescence and young adulthood (AYA) BT between 1970 and 2004 from Finnish Cancer Registry. Morbidity emerging at least five years after the BT diagnosis was analyzed based on data from the Hospital Discharge Registry and compared with a sibling control group. Data was analyzed from Social Insurance Institution of Finland concerning neurological and endocrinological drug purchases for 602 young age onset BT survivors diagnosed between 1988 and 2004. The QOL for 21 childhood ependymoma or medulloblastoma survivors was evaluated in a mixed method analysis.

Both childhood and AYA BT survivors had an increased hazard ratio for endocrinological, psychiatric, neurological, and cerebrovascular diseases as well as for disorders of vision and hearing. Survivors also experienced cognitive and developmental disorders. AYA survivors had an increased risk for developing nephrological morbidity. Medications for endocrinological and neurological morbidity were frequently used, and the need for new medication still occurred many years after the BT diagnosis. Several aspects of health-related QOL were impaired in childhood BT survivors. However, there was extensive variability in QOL, with many survivors also relating positive consequences from their cancer. Survivors themselves assessed social relationships as important for their QOL.

Young age onset BT survivors may encounter multiple health related late-effects and are at risk of experiencing social difficulties. For these reasons, it is important that they should be systematically followed up in a health care unit specialized to deal with their adult life needs.

Keywords: Brain tumor, children, young adults, late-effect, quality of life

TIIVISTELMÄ

Erika Gunn, LL

Terveys ja elämänlaatu nuorena sairastetun aivokasvaimen jälkeen

Turun Yliopisto, Lääketieteellinen tiedekunta, Lastentautioppi, Turun kliininen tohtoriohjelma (TKT); Turun yliopistollinen keskussairaala, Lasten ja nuorten klinikka

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Nuorena aivokasvaimen sairastaneilla esiintyy syöpähoitojen jälkeen useita myöhäisvaikutuksia aiempaan kasvaimeen ja sen hoitoihin liittyen. Lisäksi heillä saattaa esiintyä elämänlaadullisia ongelmia. Tutkimuksen tavoitteena oli kartoittaa yksityiskohtaisesti kyseisen potilasryhmän elämänlaatua ja sairauteen liittyviä myöhäisvaikutuksia.

Rekisteripohjaisessa tutkimuksessa keräsimme Suomen Syöpärekisteristä tiedot 740 lapsuudessa ja 315 nuoruudessa/nuorena aikuisena aivokasvaimen sairastaneesta ja sen jälkeen vähintään viisi vuotta elossa olleesta henkilöstä. Tutkimus rajoittui vuosina 1970-2004 todettuihin aivokasvain tapauksiin. Hoitoilmoitustietokannasta saadut tiedot koskien potilaiden vähintään viisi vuotta aivokasvaimen jälkeen ilmaantuvaa sairastavuutta analysoitiin ja niitä verrattiin verrokkiryhmän sairastuvuustietoihin. Lääkeostorekisteristä hankittujen tietojen perusteella analysoitiin 602 nuorena aivokasvaimen vuosina 1988-2004 sairastaneiden henkilöiden aineenvaihdunnallisiin ja neurologisiin sairauksiin liittyviä lääkeostoja. Lisäksi 21 lapsena ependymooman tai medulloblastooman sairastaneen henkilön elämänlaatua tarkasteltiin eri menetelmin.

Lapsena ja nuorena/nuorena aikuisena aivokasvaimen sairastaneilla todettiin suurentunut riski aineenvaihdunnalliseen, psykiatriseen ja neurologiseen sairastavuuteen, sekä aivoverenkiertoon, näköön ja kuuloon liittyviin häiriöihin. Aivokasvaimen sairastamisen jälkeen nähtiin myös kognitiivisia ja kehityksellisiä ongelmia. Nuoruudessa/nuorena aikuisena sairastuneilla oli myös suurentunut riski munuaissairauksiin. Lääkitys aineenvaihdunnallisiin ja neurologisiin sairauksiin oli käytössä monilla ja uusien lääkitysten aloittamisen tarve oli nähtävissä vielä vuosia aivokasvaindiagnoosin jälkeen. Lapsena aivokasvaimen sairastaneilla todettiin terveyteen liittyvä elämänlaatu alentuneeksi monella eri osa-alueella. Elämänlaatu vaihteli kyseisessä potilasryhmässä suuresti ja moni koki syövästä selviydyttyään saaneensa myös positiivisia vaikutuksia sairaudestaan. Tutkittavat itse kuvasivat sosiaaliset suhteet tärkeiksi elämänlaatunsa kannalta.

Nuorena aivokasvaimen sairastaneilla esiintyy runsaasti myöhäisvaikutuksia ja heillä on suurentunut riski sosiaalisen kanssakäymisen ongelmiin. Tämän vuoksi heille tulisi järjestää systemaattinen myöhäisseuranta asiaan perehtyneessä terveydenhuollon yksikössä usean vuoden ajan diagnoosin jälkeen.

Avainsanat: Aivokasvain, lapset, nuoret aikuiset, myöhäisvaikutus, elämänlaatu

TABLE OF CONTENTS

ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ALL	Acute lymphoblastic leukemia
AYA	Adolescent and young adult
BDI	Beck Depression Inventory
BT	Brain tumor
CCSS	Childhood Cancer Survivor Study
CI	Confidence interval
CNS	Central Nervous System
DI	Diabetes Insipidus
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
FCR	Finnish Cancer Registry
GHD	Growth hormone deficiency
GHRH	Growth hormone-releasing hormone
Gy	Gray
HDR	Hospital Discharge Registry
HP	Hypothalamic-pituitary
HR	Hazard ratio
HRQOL	Health-related quality of life
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
IQ	Intelligence quotient
ITT	Insulin tolerance test
KELA	The Social Insurance Institution of Finland
MRI	Magnetic resonance imaging
NOS	Not otherwise specified
PFS	Posterior fossa syndrome
PNET	Primitive neuroectodermal tumor
QOL	Quality of life
SEIQoL-DW	Schedule for the Evaluation of Individual Quality of Life – Direct Weighting
SF-36	Short Form Health Survey
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
SHH	Sonic Hedgehog
SMART	Stroke-like migraine attack after radiation therapy
TP53	Tumor protein 53
TSH	Thyroid stimulating hormone
WHO	The World Health Organization

LIST OF ORIGINAL PUBLICATIONS

I Gunn ME, Lähdesmäki T, Malila N, Arola M, Grönroos M, Matomäki J, Lähteenmäki PM. Late morbidity in long-term survivors of childhood brain tumors: a nationwide registry-based study in Finland. Neuro Oncol. 2015 May;17(5):747-56.

II Gunn ME, Malila N, Lähdesmäki T, Arola M, Grönroos M, Matomäki J, Lähteenmäki PM. Late new morbidity in survivors of adolescent and young-adulthood brain tumors in Finland: a registry-based study. Neuro Oncol. 2015 Oct;17(10):1412-8.

III Gunn ME, Lähdesmäki T, Malila N, Arola M, Grönroos M, Matomäki J, Lähteenmäki PM. Use of endocrinological and neurological medication among 5-year survivors of young onset brain tumors. J Neurooncol. 2016 Jul;128(3):473-9.

IV Gunn ME, Mört S, Arola M, Taskinen M, Riikonen P, Möttönen M, Lähteenmäki PM. Quality of life and late-effects among childhood brain tumor survivors: a mixed method analysis. Psychooncology. 2016 Jun;25(6):677-83.

1 INTRODUCTION

In Finland, there are around 900 000 children under 15 years of age and more than 600 000 young people aged 15 to 24 years old (Tilastokeskus, Väestörakenne). Approximately 0.08% of this population has been diagnosed with a central nervous system (CNS) tumor by the age of 15, this figure rises to 0.13% by the age of 25 years (Engholm et al. 2010). Almost 80% of childhood brain tumor (BT) patients (Madanat-Harjuoja et al. 2014) and approximately 60% of young adults become 5-year survivors (Gatta et al. 2009). As treatment results for childhood cancer have improved markedly during the past decades, more research has focused on the late-effects of childhood cancer and its treatment. However, there is surprising little data available concerning BT survivors diagnosed in young adulthood. With BTs, the improvement in the survival rates has unfortunately been less pronounced than with acute lymphoblastic leukemia (ALL) (Pizzo et al. 2001). Brain tumor survivors encounter many severe late-effects (Gurney et al. 2003a) and have a more impaired quality of life (QOL) than for example ALL survivors (Wengenroth et al. 2015). Surgery, chemotherapy and especially irradiation treatment may cause morbidity long after the end of the treatment (Gurney et al. 2003a, Armstrong et al. 2009).

In Finland, the use of comprehensive national health care registries, such as the Finnish Cancer Registry, Hospital Discharge Registry and Drug Purchase Registry provide a unique opportunity to study diseases with a low incidence such as young onset BTs. The aim of this study was to explore the late-effects of 5-year survivors of young onset BTs to guide the organizing of the late follow-up clinics in an evidence based manner. To minimize the risk of potential bias in registry based studies, we intended to evaluate the late-effects with different methods. For this reason, the actual purchases of endocrinological and neurological medications were also analyzed.

There has been divergence in the results of studies evaluating QOL in childhood BT survivors, with most of the studies reporting lowered QOL (Aukema et al. 2013, Brinkman et al. 2013), but some also showing at least comparable QOL to normative populations (Musial-Bright et al. 2011, Maddrey et al. 2005). Most of the QOL studies have used quantitative methods which enable comparison between studies, but give no possibility to hear the voices of BT survivors describing the areas most important for themselves.

The aim of Study IV which evaluated the QOL of childhood BT survivors was to explore health-related QOL by applying a quantitative approach, but also to enable the survivors to describe their QOL in their own words and to define the areas most important to themselves with qualitative interviews. Qualitative interviews were

regarded as particularly important in this population, because our hypothesis was that cognitive limitations of BT survivors could impact on the results obtained from questionnaire based surveys.

2 REVIEW OF LITERATURE

2.1 Brain tumors in childhood, adolescence and young adulthood

2.1.1 Incidence and etiology

The central nervous system tumors are the most common solid tumors occurring during childhood. They account for 28-30% of all childhood malignancies (van der Horst et al. 2006, Johannesen et al. 2004). However, in adolescence and young adulthood, the incidence of testicular and thyroid tumors increases, i.e. by adolescence, CNS tumors are only responsible for approximately 10% of all cancers (Wu et al. 2003). In young adults aged 20-24 years, the proportion declines further to 6%.

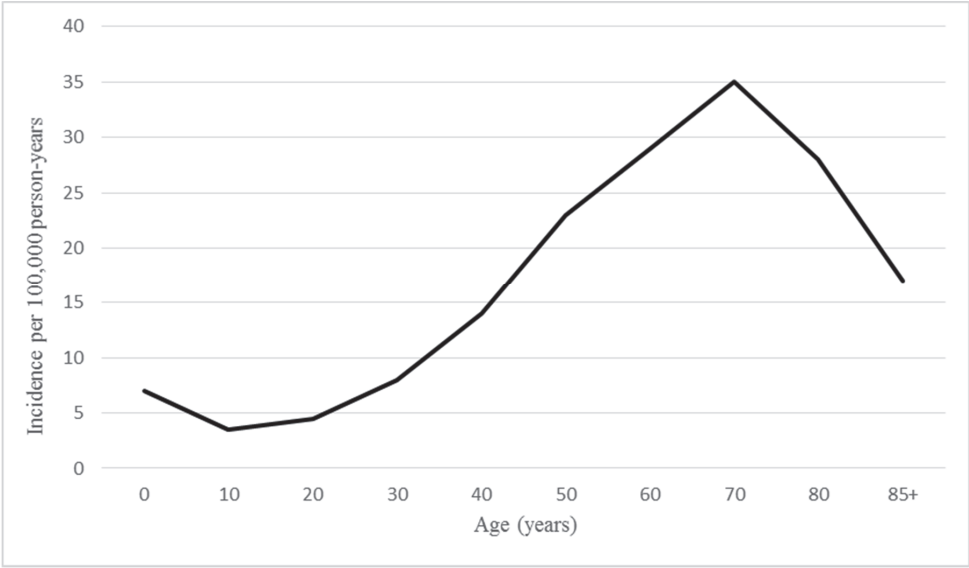

Figure 1. Incidence of CNS tumors by age group in Norway between 1990 and 1999. Modified from Johannesen et al. 2004.

The lifelong incidence of BTs is at its lowest in school-aged children, falling from its peak in the early years of life (Johannesen et al. 2004). The BT incidence begins to increase continuously in adolescence until it reaches another peak at the age of 70 years (Figure 1). The annual incidence rate for childhood BTs is 2.7-4.2/100,000 children (Patel et al. 2014, Keene et al. 1999, Lannering et al. 2009). Among adolescents (15-19 years old) and young adults (20-24 years old), the incidence rate is approximately 1.6 and 1.8 per 100,000 years at risk, respectively (Birch et al. 2002). In northern Europe, the incidence of pediatric BTs has been reported to be somewhat higher than in other parts of Europe (Kaatsch et al. 2006). Based on NORDCAN-project (Engholm et al. 2010) by Association of the Nordic

Cancer Registries, the incidence of malignancies originating from brain or nervous system for children aged 0-14 years, in 2014, was 4 and 4.9 per 100,000 person-years for females and males, respectively (Engholm et al. 2016). The comparable figures for young people aged 15 to 24 years were 5.2 and 7.0.

The incidence of BTs, similarly to the incidence of childhood cancer in general, seemed to increase in the 1980's and 1990's (Birch et al. 2002, Kaatsch et al. 2006). Based on Automated Childhood Cancer Information System (ACCIS) project that collates registry data from 15 European countries, a 2.0% annual change in the incidence occurred in childhood BTs between 1978 and 1997 (Kaatsch et al. 2006). In particular, between 1983 and 1986, the increase was clear at the same time while the use of magnetic resonance imaging (MRI) as part of diagnostics became more popular (McKean-Cowdin et al. 2013). A similar increase in incidence has been found in young adults (Arora et al. 2010). It has been speculated that at least some of the increase probably reflects the more extensive use of imaging techniques (McKean-Cowdin et al. 2013). More exact classification of BTs in case of some histologic diagnoses may also have impacted the figures (McKean-Cowdin et al. 2013). It is debatable whether there has been an actual non-biased increase after the aforementioned period (Patel et al. 2014, Kaatsch et al. 2006, McKean-Cowdin et al. 2013, Bleyer 2002, Gittleman et al. 2015). Some findings have indicated that there may be actual increase in the case of some histologic diagnoses such as pilocytic astrocytomas, anaplastic astrocytomas and glioblastomas (Arora et al. 2010). In the Nordic countries, however, no change in childhood BT incidence has been recorded between 1985 and 2006, in fact a small but significant decrease (1.26% annual change) in the incidence of astrocytomas has been detected (Schmidt et al. 2011).

There are only a few known risk factors for BTs for which there is sufficient evidence. In the majority of individual cases, no cause can be defined. There is convincing evidence that childhood BTs are associated with certain syndromes such as neurofibromatosis (Lannering et al. 1990, Varan et al. 2016), tuberous sclerosis (Kotulska et al. 2014), Li-Fraumeni syndrome (Olivier et al. 2003), nevoid basal cell carcinoma syndrome (Evans et al. 1993), Rubistein-Taybi syndrome (Lannering et al. 1990) as well as cranial irradiation (Walter et al. 1998, Tsang et al. 1993). The development of secondary BTs after cranial irradiation is dose-dependent; the latency from irradiation to a possible secondary BT has varied from median of 9 years with high-grade gliomas to 19 years with meningiomas (Walter et al. 1998). The latency period seems to correlate with the age at which irradiation have been received (Strojan et al. 2000). Males have a slightly increased risk for childhood BTs compared with females, in general, the male-female ratio varies between 1.1-1.6 (Rickert et al. 2001, Bauchet et al. 2009). This, however, is strongly dependent on the histology of a tumor. Several other risk factors for BTs have been examined, but they are still considered to lack sufficient reliable evidence (Johnson et al. 2014).

Table 1. Classification of CNS tumors. Classification of CNS tumors originating from neuroepithelial tissue based on 4th edition of World Health Organization classification published in 2007. [1]0= benign tumor, 1=borderline/uncertain, 3=malignant. Modified from Loius et al. 2007.

Group of tumors	Tumor	Behavior code [1]
Astrocytic tumors	Pilocytic astrocytoma	1
	Pilomyxoid astrocytoma	3
	Subependymal giant cell astrocytoma	1
	Pleomorphic xanthoastrocytoma	3
	Diffuse astrocytoma	3
	Fibrillary astrocytoma	3
	Gemistocytic astrocytoma	3
	Protoplasmic astrocytoma	3
	Anaplastic astrocytoma	3
	Glioblastoma	3
	Giant cell glioblastoma	3
	Gliosarcoma	3
	Gliomatosis cerebri	3
Oligodendroglial tumors	Oligodendroglioma	3
	Anaplastic oligodendroglioma	3
Oligoastrocytic tumors	Oligoastrocytoma	3
	Anaplastic oligoastrocytoma	3
Ependymal tumors	Subependymoma	1
	Myxopapillary ependymoma	1
	Ependymoma	3
	Cellular	3
	Papillary	3
	Clear cell	3
	Tanycytic	3
	Anaplastic ependymoma	3
Choroid plexus tumors	Choroid plexus papilloma	0
	Atypical choroid plexus papilloma	1
	Choroid plexus carsinoma	3
Other neuroepithelial tumors	Astroblastoma	3
	Choroid glioma of the third ventricle	1
	Angiocentric glioma	1
Neuronal and mixed neuronal-glial tumors	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	0
	Desmoplastic infantile astrocytoma/ganglioglioma	1
	Dysembryoplastic neuroepithelial tumour	0
	Gangliocytoma	0
	Ganglioglioma	1
	Anaplastic ganglioglioma	3
	Central neurocytoma	1
	Extraventricular neurocytoma	1
	Cerebellar liponeurocytoma	1
	Papillary glioneuronal tumour	1
	Rosette-forming glioneuronal tumour of the fourth ventricle	1
	Paraganglioma	1
Tumours of the pineal region	Pineocytoma	1
	Pineal parenchymal tumour of intermediate differentiation	3
	Pineoblastoma	3
	Papillary tumour of the pineal region	3
Embryonal tumours	Medulloblastoma (mbl)	3
	Desmoplastic/nodular mbl	3
	Mbl with extensive nodularity	3
	Anaplastic mbl	3
	Large cell mbl	3
	CNS primitive neuroectodermal tumour	3
	CNS neuroblastoma	3
	CNS ganglioneuroblastoma	3
	Medulloepithelioma	3
	Ependymoblastoma	3
	Atypical teratoid/rhabdoid tumour	3

2.1.2 Classification

The World Health Organization (WHO) has created a classification for CNS tumors (Louis et al. 2007). The modified version of its 4th edition's section on neuroepithelial tumors is presented in Table 1. Another classification based on International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) has been created to focus especially on childhood cancer: the International Classification of Childhood Cancer (ICCC), 3rd edition (Table 2.) (Steliarova-Foucher et al. 2005). These classifications were valid during the period of this thesis work. In 2016, the most recent WHO classification was published (Louis et al. 2016). In the new classification system, molecular biology has an essential role both in diagnostics and classification of young age onset BTs.

Table 2. Classification of childhood CNS tumors. Classification of CNS and miscellaneous intracranial and intraspinal neoplasms based on the International classification of childhood cancer, 3rd edition (ICCC-3), which follows International Classification of Diseases for Oncology (ICD-O-3). Modified from Steliarova-Foucher et al. 2005.

Diagnostic group	Subgroup
Ependymomas and choroid plexus tumor	Ependymomas Choroid plexus tumor
Astrocytomas	
Intracranial and intraspinal embryonal tumors	Medulloblastomas Primitive neuroectodermal tumor Medulloepithelioma Atypical teratoid/rhabdoid tumor
Other gliomas	Oligodendrogliomas Mixed and unspecified gliomas Neuroepithelial glial tumors of uncertain origin
Other specified intracranial and intraspinal neoplasms	Pituitary adenomas and carcinomas Tumors of sellar region (craniopharyngiomas) Pineal parenchymal tumors Neuronal and mixed neuronal-glial tumors Meningiomas
Unspecified intracranial and intraspinal neoplasms	

Brain tumors in childhood, young adulthood and older adulthood differ from each other in multiple ways. There are differences in the distribution of histological subtypes, typical location of a tumor, feasible treatment methods, and prognosis

between patients at different ages. The distribution of BT subtypes in patients diagnosed in their childhood is presented in Figure 2. During childhood, pilocytic astrocytoma and medulloblastoma/PNET are the most common individual diagnoses, accounting for approximately half of all childhood BTs (McKean-Cowdin et al. 2013). With increasing age, in adolescence and young adulthood, the numbers of embryonal tumors decrease and whereas the proportion of anaplastic astrocytomas, glioblastomas and oligodendrogliomas increases (Johannesen et al. 2004). Histological diagnosis and location have a major impact on symptoms and signs present at diagnosis, choice of the treatment protocol, patients' survival, and later cancer related morbidity. Thus, it is essential to consider that some changes have been made in classifications over the last decades (Erridge et al. 2011). It is also worth taking into account that low-grade BTs are usually included in childhood BT studies, as they can cause both direct tumor related damage as well as morbidity related to treatment especially when brain is still developing (Aarsen et al. 2006, Zuzak et al. 2008, Armstrong et al. 2011).

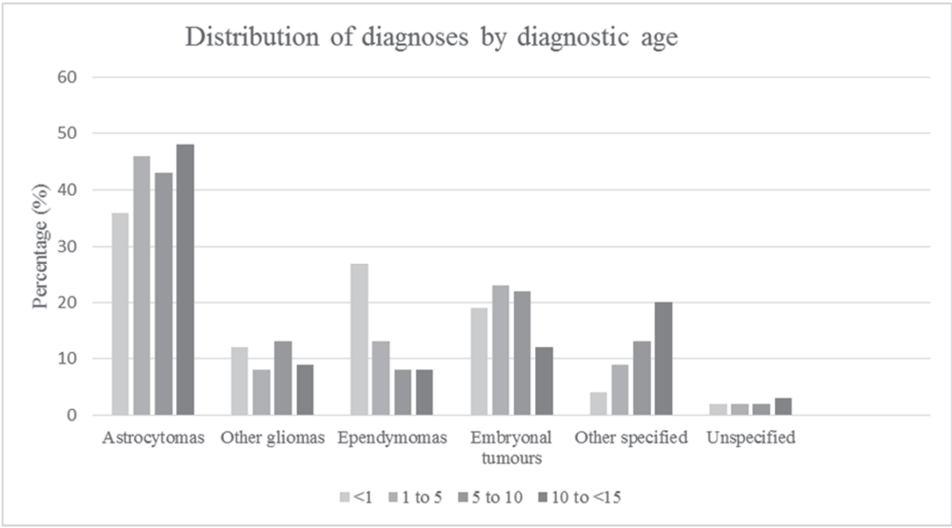

Figure 2. Distribution of histological diagnoses in childhood brain tumors at different age. In figure, choroid plexus tumours are classified under ependymomas and explain 59% of ependymomas among age group younger than 1 year old. "Other specified"- category includes pituitary, pineal and sellar tumors, neuronal and mixed neuronal-glial tumours as well as meningeomas. Adapted from Lannering et al. 2009.

Approximately 52% of all pediatric BTs are infratentorial (Keene et al. 1999, Molineus et al. 2013). With increasing age, the supratentorial tumors increase in number and in children older than 10 years of age, 67% of the tumors are supratentorial (Keene et al. 1999). In a pediatric population, 50-60% of the tumors which are located supratentorially are hemispheric tumors (Keene et al. 1999, Molineus et al. 2013). The rest of the supratentorial tumors are considered midline tumors and may be located for example in suprasellar, pineal, sellar, intraventricular or

thalamus region, in order of decreasing frequency (Keene et al. 1999). Approximately 80% of childhood infratentorial tumors are located in the cerebellum and 20% in the brain stem (Keene et al. 1999).

2.1.3 Incidence, treatment methods and prognosis by a tumor type

Treatment of BTs may include surgery, irradiation, chemotherapy, or any combination of these therapies. Surgery is performed in most of the cases with the exception of diffuse brainstem tumors, in which the risk to injure vital areas is considered too high. Irradiation can be given locally, cranially and/or to the entire craniospinal area. Irradiation techniques such as proton therapy, intensity modulated radiotherapy, stereotactic radiotherapy and altered fractionation (Laprie et al. 2015, Gregoire et al. 2015, Kirsch et al. 2004) have shown promising results as they are reputed to protect healthy tissue from irradiation without compromising survival. Sensitivity to radio- and chemotherapy depends on histological type of the tumor. Treatment protocols have changed during recent decades, which has an inevitable impact on the late-effect profile of the survivors. The current treatment methods for each histological type separately are reviewed in the following chapters.

There are several tumor type-, patient- and treatment-related factors affecting the prognosis of BTs. The histological tumor type specific survival figures will be detailed in the following sections. Brain tumor patients may suffer from late mortality which may be related to a relapse of a tumor as well as morbidity resulting from the treatment itself. However, most of the tumor-related mortality occurs within the first five years after diagnosis. Thus, the probability for long-term survival from a tumor is better for those who have already survived for some time. Porter et al. found less than 70% three year survival for patients with malignant childhood/adolescence BT (Porter et al. 2011). However, for those individuals surviving for two years, the conditional three year survival increased to 91%. Irrespective of the tumor type, any delay in diagnosis is a major factor affecting the prognosis. Studies have shown a median delay from the first symptoms to diagnosis can be as high as 2 to 3 months (Molineus et al. 2013, Dobrovoljac et al. 2002, Thulesius et al. 2000) and only every third case is diagnosed within the first four weeks after first signs or symptoms (Dobrovoljac et al. 2002).

2.1.3.1 Astrocytic tumors

Astrocytomas are the most common BTs in childhood and adolescence. They account for 32-48% of all BTs (Rickert et al. 2001, Bauchet et al. 2009). Pilocytic astrocytoma (grade I) is the most common histological type of astrocytic tumors

in all pediatric populations (Rickert et al. 2001) with a frequency of approximately 70% (Bauchet et al. 2009). Ten percent of astrocytomas are anaplastic astrocytomas or glioblastomas (Bauchet et al. 2009). Subependymal giant cell astrocytoma (SEGA) is a histological subtype associated with tuberous sclerosis complex (Kotulska et al. 2014).

For pilocytic astrocytoma, the primary treatment method is surgery, with gross total resection being associated with a better prognosis (Johnson et al. 2012). However, as this may be achieved in less than half of the cases, irradiation may be offered for progressive tumors (Johnson et al. 2012). Treatment of low grade gliomas in general will be discussed in chapter 2.1.3.2. Irradiation and chemotherapy after total resection may improve the results in glioblastoma multiforme (GBM) (Mahvash et al. 2011).

In Sweden, the overall 10-year survival for low-grade and high grade astrocytomas between 1984 and 2005 was 82% and 26%, respectively (Lannering et al. 2009). In children, the 5-year survival for pilocytic astrocytoma has been approximately 95%, declining to 90% in young adults, with the decrease continuing with increasing age (Johnson et al. 2012). Survival for glioblastoma multiforme (GBM) in children has been somewhat longer than in adults but the mean survival still remains at 20 months (Mahvash et al. 2011).

In brain stem tumors, MRI finding of diffuse infiltration correlates well with a high-grade histological pattern, whereas low-grade astrocytomas are usually focal and show exophytic growth (Kwon et al. 2006). For high-grade brain stem tumors, irradiation tends to postpone but not avert mortality, i.e. it is not curative (Lam et al. 2015). Some chemothery regimens for diffuse intrinsic pontine gliomas have been investigated. Angiocomp protocol contains topotecan as radiosensitizer and anti-angiogenic treatment with etoposide, celecoxib and thalidomide (Porkholm et al. 2014). Although statistically significanct difference for improvement of overall survival with anti-angiogenic therapy was not reached, the treatment might support the quality of life (Porkholm et al. 2014). For low-grade focal, exophytic and cystic tumors of brain stem, surgical treatment is recommended, with midbrain focal tumors representing an exception, since in these cases close follow-up and shunting may be adequate (Rubin et al. 1998). High-grade brain stem tumors have a poor prognosis with a two year survival of 34% and 9% for anaplastic astrocytoma and glioblastoma multiforme, respectively (Lam et al. 2015).

2.1.3.2 Other gliomas

Treatment for low-grade gliomas is usually restricted to surgical resection (Peters et al. 2004). When operative treatment is out of the question due to the location of a tumor, or when tumor progress is seen, irradiation may be used in older children

whereas chemotherapy is preferred in younger children (Nageswara Rao et al. 2014). Several chemotherapy regimens have been studied (Nageswara Rao et al. 2014). For example, carboplatin alone or in combination with vincristine or cisplatin combined with etoposide has been shown to be efficacious (Nageswara Rao et al. 2014).

Treatment of BTs associated with cancer predisposition syndromes such as tuberous sclerosis complex (e.g. associated with SEGA), neurofibromatosis 1 (e.g. associated with optic pathway and brain stem gliomas) and 2 (e.g. associated with vestibular schwannomas), needs particular consideration because of a few specific issues. BTs associated with these syndromes may behave differently than tumors not related to cancer predisposition syndromes (Rosser et al. 2002, Huttner et al. 2010). Thus, for example, in patients having neurofibromatosis 1, asymptomatic brain lesions not growing may be followed without any treatment (Rosser et al. 2002). When there are signs of lesion progression or the patient becomes symptomatic, surgery has been considered the first choice of treatment. Recently, mammalian target of rapamycin (mTOR) inhibitors, especially everolimus, have shown promising results in the treatment of SEGA (Franz et al. 2013). Treatment with irradiation is avoided whenever possible, because patients with cancer predisposition syndromes may carry an increased risk for secondary malignancies (Broniscer et al. 2004). There may also be cognitive limitations associated with the predisposing syndrome itself prior to a BT (Rosser et al. 2003, Overwater et al. 2017); these may worsen with irradiation. Patients with neurofibromatosis also have an increased risk for moyamoya syndrome potentially induced by irradiation (Ullrich et al. 2007).

The overall 10-year survival for oligodendrogliomas has been 77% (Lannering et al. 2009) with histological grade and location of a tumor being the most significant prognostic factors (Peters et al. 2004, Rizk et al. 1996). Mixed/unspecified gliomas and neuroepithelial glial tumors of uncertain origin have a significantly worse prognosis, with overall 10-year survivals of 40 and 12%, respectively (Lannering et al. 2009). This can be explained by the localization of the majority of these tumors in the brainstem.

2.1.3.3 Embryonal tumors

Embryonal tumors cover approximately 20% of childhood BTs (Johannesen et al. 2004, Lannering et al. 2009, McKean-Cowdin et al. 2013, Bauchet et al. 2009). Their incidence declines steeply after a peak in the first early years of life (McKean-Cowdin et al. 2013). At the age of 15-39 years, they are responsible for less than 5% of BTs (Johannesen et al. 2004). Earlier, medulloblastomas, primitive neuroectodermal tumors (PNET) and atypical teratoid/rhabdoid tumors were considered as the same entity with a divergence solely in location between MBs and

PNETs, but nowadays, there are known to be histological differences between these entities.

Medulloblastomas comprise the majority of embryonal tumors with a 15% frequency of all childhood BTs (Lannering et al. 2009, Bauchet et al. 2009). In the latest WHO classification, medulloblastomas are divided into four different groups based on their histological (classic, desmoplastic/nodular, with extensive nodularity, large cell/anaplastic) and molecular genetic characteristics (WNT-activated, SHH-activated/TP53-mutant, SHH-activated/TP53-wildtype, non-WNT/non-SHH) (Louis et al. 2016). The majority of medulloblastomas show histologically classical or desmoplastic subtype (Park et al. 1983). Medulloblastomas originate from the cerebellum or the fourth ventricle. Contrary to other childhood BTs, embryonal tumors have a distinct male predominance (Lannering et al. 2009, McKean-Cowdin et al. 2013, Smoll et al. 2012), however, this predominance is not carried into adulthood (Smoll et al. 2012).

The treatment of embryonal tumors has traditionally been multimodal and consisted of a resection of a tumor, craniospinal irradiation with a high dose boost to the tumor bed area and chemotherapy. The selection of an appropriate treatment protocol has been based on tumor histology, stage and age of the patient (Mynarek et al. 2015). Irradiation has a major impact on survival. At present, small children (aged <3-5 years), however, are not administered irradiation (Mynarek et al. 2015) to prevent significant treatment-related late effects in the developing brain. To minimize irradiation-related late-effects the dose of craniospinal irradiation among older children has been reduced from 35 Gy to 23.4 Gy with good results (Packer et al. 2006). Different irradiation techniques such as three-dimensional conformal radiotherapy, intensity-modulated radiotherapy and most recently proton therapy have been examined in attemps to minimize the harmful effects of irradiation to normal tissue with some encouraging results (Miralbell et al. 1997, Breen et al. 2004). Chemotherapy can also improve outcome to some extent (Taylor et al. 2003), although not all studies have been able to confirm its beneficial effect (Rieken et al. 2011).

HIT-MED guidance, based on results gathered from the HIT-2000 trial (von Bueren et al. 2011), recommends a following protocol for medulloblastoma treatment (Mynarek et al. 2015). Small children (aged <3-5 years) are treated with chemotherapy protocol including cyclophosphamide, vincristine, high dose methotrexate, carboplatin and etoposide with or without intraventricular methotrexate, with an intensified protocol being used for those with other than desmoplastic or extensive nodularity histology type and in cases where there is a metastasis. Children older than 5 years of age with desmoplastic or classic meduloblastoma are treated with conventional radiotherapy with 23.4 Gy craniospinal irradiation with

a tumor boost and maintenance chemotherapy (including cisplatin/lomustine/vincristine). In other histological types with M0-1 disease or desmoplastic/classic medulloblastoma with a residual >1,5cm2 craniospinal irradiation is elevated to 35.2 Gy. For a disease with metastasis outside the cerebrospinal fluid, the chemotherapy protocol is further intensified and craniospinal irradiation is given hyperfractionated up to 40 Gy.

In Finland, the SIOP-PNET5-SR protocol has been started for the therapy of low and standard risk medulloblastomas for children older than 3 years of age (ClinicalTrials.gov Identifier: NCT02066220). In this protocol, 18 Gy of irradiation is delivered to the craniospinal axis and 54 Gy to the primary tumor. The previous Packer-type (vincristine, lomustine and cisplatin) chemotherapy has been modified such that Packer courses alternate with cyclophosphamide and vincristine containing courses. For smaller children, the Head Start protocol has been used (Dhall et al. 2008). This protocol avoids cranial irradiation and exploits intensive chemotherapy and autologous stem cell rescue.

The five year survivals for average (patients aged ≥3 years, residual < 1,5cm2 and no metastasis) and high risk medulloblastoma have been 83-90 and 50-63%, respectively (Frange et al. 2009, Ramanan et al. 2012, Oyharcabal-Bourden et al. 2005). Children younger than 3 years of age at diagnosis have an unfavourable prognosis compared with older children (Zeltzer et al. 1999). With a protocol in which irradiation has been delayed until 3 years of age or if there is a relapse, these children have a 59-67% 10 year overall survival (Rutkowski et al. 2009). Factors known to influence prognosis are tumor stage at diagnosis, completeness of a tumor resection, a recurrence and time from surgery to the beginning of irradiation therapy (Rieken et al. 2011, Zeltzer et al. 1999).

PNETs of CNS are a heterogenous group, which may be either poorly differentiated or have differentiation to neuronal, astrocytic and ependymal lines (Louis et al. 2007). They account for 2-3% of childhood BTs (Lannering et al. 2009, Bauchet et al. 2009). For children younger than 4 years of age, HIT-MED-guidance recommends only chemotherapy after tumor resection. Older children receive 36-40 Gy hyperfractionated irradiation with a local tumor boost in addition to chemotherapy (Mynarek et al. 2015). 5-year survival for supratentorial PNETs in Sweden has been 47% (Lannering et al. 2009).

Atypical teratoid/rhabdoid tumors (AT/RTs) have been identified as an individual entity since the beginning of 1990's. They occur primarily in young children, with close to 80% being diagnosed in children younger than 3 years of age (Lau et al. 2015, Lafay-Cousin et al. 2012). Half of AT/RTs are located infratentorially (Lafay-Cousin et al. 2012) and 38%-70% show metastasis at the time of diagnosis (Lafay-Cousin et al. 2012, Schrey et al. 2016). Due to the rarity of AT/RT and thus

the small number of randomized trials, treatment protocols are variable. Surgical resection is usually performed, however, gross total resection can be accomplished in less than half of the cases (Lau et al. 2015, Lafay-Cousin et al. 2012, Schrey et al. 2016), and irradiation (focal, craniospinal or both) and chemotherapy may be included in the treatment. In 2015, a new European Rhabdoid Registry (EU-RHAB) created a recommendation for the therapy of AT/RT, which includes conventional/high-dose chemotherapy and irradiation for children older than 18 months of age (Frühwald et al. 2010). AT/RTs are highly aggressive tumors with poor outcome (Burger et al. 1998). Median survival of 11-14 months have been reported (Lau et al. 2015, Lafay-Cousin et al. 2012, Schrey et al. 2016) and 3 year overall survival has been 20% (Schrey et al. 2016). Progression or relapse is commonly seen within 12 months from diagnosis (Lafay-Cousin et al. 2012). It seems that gross total resection, high dose chemotherapy with autologous stem cell rescue and irradiation can significantly extend the time of survival (Lau et al. 2015, Lafay-Cousin et al. 2012, Schrey et al. 2016).

2.1.3.4 Ependymal tumors

Ependymomas are responsible for approximately 10% (Johannesen et al. 2004, Lannering et al. 2009, McKean-Cowdin et al. 2013, Bauchet et al. 2009) of childhood and 5% (Johannesen et al. 2004) of adolescent and young adulthood BTs. Most childhood ependymomas arise from posterior fossa, and approximately 30% are located supratentorially (Vinchon et al. 2005). The proportion of supratentorial location increases with advanced age (Aizer et al. 2013). The majority (80%) of supratentorial tumors are located in hemispheres (Landau et al. 2013). Anaplastic subtype compared with lower grade tumors is an independent risk factor for prognosis (Merchant et al. 2009). Proportion of anaplastic tumors in different studies has varied between 34 and 76% (Landau et al. 2013, Korshunov et al. 2004, Grundy et al. 2007). Childhood and supratentorial tumors have exhibited a trend for a higher proportion of high grade tumors compared with tumors diagnosed in adulthood or located infratentorially.

Surgical removal is the most important, and in some low grade tumors, the only treatment method. The extent of surgery has an impact on prognosis, which has been confirmed in several studies (Vinchon et al. 2005, Aizer et al. 2013, Korshunov et al. 2004). Total resection can be achieved in approximately half of the cases (Vinchon et al. 2005), higher age and supratentorial location increasing the success (Vinchon et al. 2005). Irradiation, when given, is usually prescribed with high ≥54 Gy doses locally (Landau et al. 2013). However, the results concerning the beneficial effect of irradiation have not been concordant, especially with low grade tumors (Aizer et al. 2013, Merchant et al. 2009, Korshunov et al. 2004). Many protocols have recommended the avoidance of irradiation in children

under 3 and possibly even under 5 years of age, to avoid detrimental effects of irradiation to developing brain (Grundy et al. 2007, Grill et al. 2001), but conformal irradiation has also been suggested for infants to achieve more optimal survival (Merchant et al. 2009). Currently, HIT-MED guidance recommends local irradiation with or without chemotherapy depending on age and the extent of a tumor resection (Mynarek et al. 2015).

The 5-year overall survival for ependymomas has varied between 63-82% (Lannering et al. 2009, Ramanan et al. 2012, Vinchon et al. 2005), but it declines to 38% after re-operation for recurrence (Vinchon et al. 2005). A higher diagnostic age has been associated with a better prognosis (Korshunov et al. 2004).

2.2 Late-effects of brain tumors and tumor therapies

2.2.1 Endocrinological late-effects

The risk of an endocrinopathy is high after a BT compared with other childhood malignancies (de Fine Licht et al. 2014). However, some of the endocrinological late-effects do not emerge until years after a BT diagnosis and its treatment (Armstrong et al. 2009). Endocrinological disturbances may be related to a tumor directly (for example, a functioning pituitary adenoma or the compressing effect of a tumor on the hypothalamic-pituitary (HP) axis), or treatment with a surgery, irradiation and/or chemotherapy. Pituitary function may well be normalized after a surgical resection of a pituitary tumor (Jahangiri et al. 2014). Improvement in these cases can usually be seen within six weeks after the operation (Jahangiri et al. 2014).

The location of a tumor has a significant impact on the incidence of endocrinological sequlae with disturbances being most common if the tumor is located in the diencephalon or optic chiasm (Aarsen et al. 2006). The prevalence of an endocrinopathy with supratentorial midline tumors may be as high as 95% and is frequently seen already post-operatively (Muirhead et al. 2002). With non-midline tumors endocrinopathies after surgical treatment alone are rare (Muirhead et al. 2002).

Endocrinological disturbances caused by irradiation are most frequently seen in patients who have received more than 40Gy of irradiation to HP axis (Greenberger et al. 2014), although smaller doses can also be detrimental. A large study of 1713 adult survivors of childhood cancer found that 56% of all cancer survivors with irradiation dose of ≥ 18Gy to HP axis had at least one endocrinopathy (Hudson et al. 2013). The association between endocrinopathies and chemotherapy has been less clear (Gurney et al. 2003a, Muirhead et al. 2002).

The rate of endocrinopathies after BTs at young age with all histological types combined (or excluding pituitary tumors) have varied between 43-50% (Gurney et al. 2003a, Vinchon et al. 2011, Shalitin et al. 2011). Low grade astrocytomas have been reported to carry an 18% risk of endocrinopathy (Aarsen et al. 2006), whereas with craniophangyngiomas, the prevalence of an endocrinopathy may reach 100%. Childhood pituitary adenomas are usually hormonally active (85%) with the majority of them being prolactinomas (Steele et al. 2010).

Frequencies to specific hormonal disturbancies are presented below. Differences between studies may be caused by true differencies in which patient sample being studied (for example, caused by differences of distribution in histological subtypes, location, treatment regimens) as well as by differences in follow-up protocols (how systematic has the follow-up been) and also due to variations in the methods used for analysis.

2.2.1.1 Growth hormone deficiency, height and weight

Growth hormone deficiency (GHD) is found in 29-48% of survivors after both childhood and adulthood non-pituitary BTs (Armstrong et al. 2011, Shalitin et al. 2011, Saha et al. 2014, Agha et al. 2005, Ribi et al. 2005), and it may increase to 60% in the case of hypothalamic tumors (Armstrong et al. 2011).

Factors which have been associated with an increased risk of GHD in BT survivors are young age at diagnosis (Shalitin et al. 2011), tumor location in diencephalon (Armstrong et al. 2011), irradiation therapy (Armstrong et al. 2011, Shalitin et al. 2011, Saha et al. 2014), higher dose of irradiation (Agha et al. 2005), and less than a total extent of a surgery (Armstrong et al. 2011). A large registry based study from Childhood Cancer Survivor Study (CCSS) Group noted that the highest risk was observed in those patients treated with multimodal therapy comprising surgery, irradiation and chemotherapy compared with surgery alone or surgery in addition to irradiation (Gurney et al. 2003a)). Other studies, on the contrary, have not been able to show an independent effect of chemotherapy (Armstrong et al. 2011, Agha et al. 2005). Most GHD cases will be diagnosed within ten years from BT diagnosis (Armstrong et al. 2011). In the study of Shalitin et al., the mean time to GHD diagnosis after BT diagnosis was 4.4 years (Shalitin et al. 2011).

Growth hormone deficiency can be tested by measuring the growth hormone response to a stimulus. The insulin tolerance test (ITT) and GHRH-arginine tests are considered as the most reliable testing methods (Molitch et al. 2011). In BT patients particularly, these studies have certain problems. ITT is not considered safe in patients with seizures and the GHRH-arginine test may not be sensitive enough with hypothalamic GHD, for example caused by cranial irradiation (Molitch et al.

2011). Studies analyzing GHD of BT survivors have used also several other methods such as the glucagon stimulation test and arginine stimulation test. These methodological differences may to some extent exert an impact on the discrepancies between different studies.

Many childhood BT survivors do not reach their expected height. This may be associated with GHD, precocious puberty or damage to vertebral body caused by irradiation. It has been noted that almost 40% of survivors in their adulthood stay below the 10th percentile in height, and more than 10% score below 2SD (Gurney et al. 2003b). Adulthood height in males and females remain approximately 10 and 7cm shorter than expected, respectively (Gurney et al. 2003b). Young age at diagnosis (Gurney et al. 2003b, Beckers et al. 2010, Gleeson et al. 2003), histology of PNET (Gurney et al. 2003b), cranial and craniospinal irradiation (Gurney et al. 2003b) and chemotherapy (Gleeson et al. 2003) have been associated with compromised final height. The effect of irradiation to hypothalamic-pituitary axis has been dose-dependent (Gurney et al. 2003b). Unfortunately, the results achieved with a growth hormone therapy have not been optimal with respect to the final height, especially in children treated with craniospinal irradiation (Beckers et al. 2010). However, an improvement in the results during past decades has been reported (Gleeson et al. 2003). This might be due to improved GH schedules, an earlier start of GH medication and the use of gonadotrophin-releasing hormone analogs to delay puberty in case of a precocious puberty (Gleeson et al. 2003). Unfortunately, there is currently no method available to overcome the effect of irradiation on growth plates.

In 2006, the Subcommittee of the Endocrine Society issued guidelines of the use of growth hormone replacement treatment in adults with growth hormone deficiency (Molitch et al. 2011). They recommended GH replacement therapy for adults with severe GHD to improve body composition, exercise capacity, bone mineral density and quality of life. They noted that the decision to start replacement therapy should, however, always be based on an individual evaluation (Molitch et al. 2011). In Finland, the Social insurance (KELA) guideline for reimbursement of GH therapy demands that there needs to be another central hormone deficiency (except in cases of hypoprolactinemia) diagnosed as well. In childhood BT survivors no increased risk of recurrence of a primary tumor related to GH therapy has been found (Swerdlow et al. 2000, Packer et al. 2001). However, there has been some evidence that GH replacement might increase the risk of a secondary tumor to some extent (Ergun-Longmire et al. 2006). Data on this specific concern are still considered insufficient.

It has been estimated that approximately 17-53% of BT survivors suffer from overweight (Armstrong et al. 2011, Pietila et al. 2009, Schulte et al. 2010). There are several potential causes for obesity within this patient group, but damage to the

hypothalamus probably has the most important influence (Armstrong et al. 2011). As many as 75% of the survivors of hypothalamic tumors may become overweight (Armstrong et al. 2011). Not all the survivors, however, are affected and some studies have found the childhood BT survivors can have a body mass index similar to or even lower than expected (Gurney et al. 2003b, Schulte et al. 2010). An increased risk for underweight has been reported as well (Schulte et al. 2010). Factors that are shown to increase the risk for obesity are location of a tumor in diencephalon (Armstrong et al. 2011, Lustig et al. 2003), high dose of irradiation to hypothalamus (Gurney et al. 2003b, Lustig et al. 2003), presence of endocrinopathy or any hormone replacement therapy (Pietila et al. 2009, Lustig et al. 2003) and impaired mobility (Pietila et al. 2009). Results concerning the effects of gender and diagnostic age have not been consistent (Gurney et al. 2003b, Pietila et al. 2009, Lustig et al. 2003).

2.2.1.2 Hypothalamic-pituitary-thyroid axis

Hypothyroidism with BT survivors may result from damage to the HP axis inducing central hypothyroidism or scattered irradiation to thyroid gland from craniospinal irradiation. Higher TSH levels have been found in those patients receiving craniospinal radiotherapy than in those treated with cranial therapy alone (Schmiegelow et al. 2003). The prevalence of hypothyroidism (both primary and central) with childhood BT survivors has varied between 19 and 44% (Armstrong et al. 2011, Vinchon et al. 2011, Shalitin et al. 2011, Saha et al. 2014, Ribi et al. 2005, Schmiegelow et al. 2003, Madanat et al. 2008). A few studies have analyzed the prevalence of central hypothyroidism separately, with a similar frequency between 6 and 15% being found from patients who were diagnosed with a BT in childhood and adulthood (Shalitin et al. 2011, Agha et al. 2005, Schmiegelow et al. 2003). In the study of Shalitin et al., only 5% of childhood BT survivors had primary hypothyroidism and half of the cases were developed after thyroidectomy because of thyroid nodules or hyperplasia (Shalitin et al. 2011). The same study also found that 26% of the survivors who had received spinal irradiation for their BT had later developed goiter or thyroid nodules (Shalitin et al. 2011). A long time may elapse before developing hypothyroidism after the BT; the mean time has been estimated at 13.5 years (Shalitin et al. 2011). It has been estimated that 37% of diagnoses are made after more than 5 years from the BT diagnosis (Armstrong et al. 2011).

Increased risk for hypothyroidism has been strongly associated with irradiation therapy (Armstrong et al. 2011, Shalitin et al. 2011, Saha et al. 2014) and tumor location in diencephalon (Armstrong et al. 2011), but not with gender (Armstrong et al. 2011), or the extent of a surgery (Armstrong et al. 2011). With respect to chemotherapy, several studies have found no association with thyroid disturbances

(Armstrong et al. 2011, Schmiegelow et al. 2003, van Santen et al. 2003). Nonetheless, one registry based study detected the greatest risk for hypothyroidism among a group who received multimodal therapy including chemotherapy (Gurney et al. 2003a). There is some evidence suggesting that suppression of TSH secretion with thyroxine medication during craniospinal irradiation may protect the thyroid to some extent from damage caused by irradiation (Massimino et al. 2007).

2.2.1.3 Hypothalamic-pituitary-gonadal axis

About every fourth adult non-pituitary BT survivor (27%) has been reported to experience a gonadotrophin deficiency (Agha et al. 2005). Two studies reported similar frequencies of gonadal insufficiency among childhood BT survivors, but the level of the dysfunction (central or peripheral) was not determined (Vinchon et al. 2011, Ribi et al. 2005). A study with BT survivors diagnosed before the age of 24 years reported that 11% of survivors required medication for hypogonadotropic hypogonadism (Shalitin et al. 2011). Both irradiation therapy and chemotherapy, especially with alkylating agents, have been associated with hypogonadism (Romerius et al. 2009, Schmiegelow et al. 2001). However, hypogonadism has been detected also in BT patients treated with surgical methods only (Romerius et al. 2009). Two studies, one studying survivors of childhood supratentorial ependymomas and another evaluating childhood and young adulthood BTs in general found 17-18% frequency of a precocious puberty (Landau et al. 2013, Shalitin et al. 2011). The need for a medication to induce puberty, on the other hand, is also increased in survivors with multimodal therapy when they are compared with survivors treated with surgery alone (Gurney et al. 2003a). A registry based study of childhood and adolescence BT survivors reported that 28% of female survivors required hormonal therapy to have menstrual periods compared with 15% of female siblings (Gurney et al. 2003a). In childhood BT survivors, a dysfunction of gonadal axis may develop or be first recognizable still after several years from BT diagnosis. The mean delay from any childhood BT diagnosis to detect gonadal dysfunction has been 15 years (Shalitin et al. 2011).

2.2.1.4 Hypothalamic-pituitary-adrenal axis

Hypocortisolism due to an adrenocorticotrophic hormone (ACTH) deficiency is important to recognize and to treat because if untreated, it may lead to even a life-threatening situation in times of stress (Burman et al. 2013). There are several methods used for testing the function of hypothalamic-pituitary-adrenal axis. Diagnostic methods have varied between studies probably influencing the results. For example, the following methods have been used: low dose ACTH test (Rose et al. 2005), standard dose ACTH test alone (Shalitin et al. 2011) or in addition to

glucagon stimulation test (Agha et al. 2005), metyrapone test (Rose et al. 2005) and insulin tolerance test (Agha et al. 2005).

ACTH deficiency in the BT patients has been strongly associated with cranial irradiation and a tumor location in diencephalon (Armstrong et al. 2011, Rose et al. 2005).

A study analyzing childhood low grade gliomas found 26% of survivors in general had an adrenocorticotrophic deficiency, whereas only between 2 and 10% of survivors with their tumors located in posterior fossa and cerebral hemispheres, respectively, were ACTH deficient (Armstrong et al. 2011). In concordance, a study on non-pituitary BT survivors diagnosed in adulthood detected a 21% frequency for ACTH deficiency (Agha et al. 2005). Another study with young onset BT survivors reported 8% as having hypocortisolism (Shalitin et al. 2011), whereas a study on childhood medulloblastomas found no case of ACTH deficiency (Ribi et al. 2005).

2.2.1.5 Diabetes mellitus

There are some findings indicating that the risk of diabetes might be slightly increased among BT patients, but data on probable causative mechanisms are still unconvincing. Childhood cancer survivors who have received irradiation to the HP axis have displayed a 7.8% prevalence for diabetes compared with 4.5% among those who had had no irradiation (Hudson et al. 2013). Extensive registry based data from Nordic countries showed the childhood BT survivors seem to have a slighty increased risk of hospitalization because of a type 2, but not type 1 diabetes (Holmqvist et al. 2014). The authors speculated that the increased risk could be associated with irradiation to the pancreas from craniospinal radiotherapy (Holmqvist et al. 2014). Another study, focusing on childhood low-grade glioma survivors found a 24% cumulative incidence for hyperinsulinism/insulin resistance at 15 years after a BT diagnosis (Armstrong et al. 2011). This study found no significant association between hyperinsulinism and irradiation therapy, the extent of surgery or tumor location. However, the frequencies of hyperinsulinism among hypothalamic/chiasmatic, brainstem and posterior fossa/hemispheric tumors were 57%, 28% and <10%, respectively (Armstrong et al. 2011). The increase in the cumulative incidence curve of hyperinsulinism followed in parallel with the curve of obesity, although the cumulative incidence of obesity started to rise several years earlier. An increased risk for hyperinsulinism was found with survivors diagnosed after the late 1990's (Armstrong et al. 2011).

2.2.1.6 Diabetes insipidus

Young age onset BT survivors in general have been reported to have a frequency of 11-13% for developing diabetes insipidus (DI) (Vinchon et al. 2011, Shalitin et al. 2011). The study of Ribi et al. examining 18 childhood medullobastoma survivors, instead, detected no single case of DI (Ribi et al. 2005). With craniopharyngioma patients, DI is present at a high frequency because of the tumor's location close to the HP axis (Pratheesh et al. 2013). In a study with 102 cranopharyngioma patients DI was recognized in 15% of the patients already preoperatively (Pratheesh et al. 2013). Post-operatively, DI was seen in the majority of the patients and a triphasic response with alteration between DI and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was present in 23% of pediatric patients (Pratheesh et al. 2013). Permanent DI in craniopharyngioma patients has been found in 56% and 33% of pediatric and adult survivors, respectively (Pratheesh et al. 2013).

2.2.2 Neurological late-effects

The treatment of a BT has a wide-spread effect on the CNS. As many as 85% of the BT patients exhibit at least one neurological symptom already prior to any treatment (Houdemont et al. 2011). Some of the symptoms may resolve with tumor resection and the treatment of hydrocephalus (Houdemont et al. 2011). Some symptoms, however, may be sustained, or develop later during the treatment or follow-up.

Treatment with irradiation as well as chemotherapy may cause oxidative stress and inflammation damaging cell membranes, and triggering cell death and demyelination in the central nervous system (Baron et al. 2013). It has been hypothesized that mutations in mitochondrial DNA caused by irradiation and chemotherapy and mitochondrial dysfunction may result in early aging which can be seen as neurodegeneration (Ness et al. 2015). Irradiation has detrimental effects on the blood brain barrier by affecting endothelial cells (Baron et al. 2013). Irradiation damages neurogenesis in hippocampus both quantitatively and qualitatively (Monje et al. 2002). Imaging studies have revealed that BT survivors have a decreased white matter volume and an increased volume of cerebrospinal fluid, but no change in the gray matter volume (Reddick et al. 2014). A similar decrease of white matter volume has been detected in acute lymphoblastic leukemia patients, in whom however, the reduction has been less significant (Reddick et al. 2014). Furthermore, a reduced white matter volume has been associated with a poorer neurocognitive performance (Reddick et al. 2014). Younger age at diagnosis also seems to asso-

ciate with an increased risk of loss of white matter (Reddick et al. 2014). Functional magnetic resonance imaging has indicated that after a brain injury, certain functions may be repaired by neural reorganization in certain areas, whereas some functions remain impaired as reinnervation of new areas is not achieved (Thompson et al. 2009).

2.2.2.1 Cognitive late-effects

Most of the childhood BT studies have detected a decline in cognitive function among the survivors (Briere et al. 2008, Pietila et al. 2012, Macedoni-Luksic et al. 2003, Reimers et al. 2007). However, the survivors with tumors treatable with surgery and with or without local irradiation may achieve their full scale intelligence quotient (IQ) (Greenberger et al. 2014), especially when a tissue saving irradiation technique such as conformal irradiation has been applied (Landau et al. 2013, Netson et al. 2012). The mean full scale IQ reported in childhood BT studies has varied from the normal range among tumor survivors treated with a surgery alone (Steinlin et al. 2003) to a mean of 75 in long-term medulloblastoma survivors (Maddrey et al. 2005). Some of the survivors suffer from major cognitive decline, and full scale IQ less than 70 has been found in 15-29% of the childhood BT survivors (Pietila et al. 2012, Macedoni-Luksic et al. 2003). The majority of cognitive difficulties is considered to be related to the general decline in full scale IQ (Reimers et al. 2007). However, despite normal full scale IQ, some deficiencies in attention, memory and processing speed may be evident also in children treated with surgery only (Steinlin et al. 2003). For this reason, it has been suggested that a general ability index derived from verbal comprehension and perceptual reasoning would be better than the full scale IQ to describe the general reasoning in BT patients (Kahalley et al. 2016). In a study that included long-term survivors of pediatric medulloblastoma treated with multimodal therapy, the majority of the survivors displayed difficulties in attention and processing speed (79%), learning and memory (88%), and executive function (64%), although intelligence deficits were reported only in 39% (Ribi et al. 2005).

Family factors such as educational and marital status of parents are known to have an effect on children's baseline skills in working memory and attention (Palmer et al. 2013) but their impact cannot be taken into account during the follow-up of BT survivors (Palmer et al. 2013). Several factors have been reported to be associated with impaired cognitive skills in the follow-up. Probably the most significant risk factor, found in many studies, has been a young age at diagnosis (Maddrey et al. 2005, Greenberger et al. 2014, Macedoni-Luksic et al. 2003, Palmer et al. 2013, Aarsen et al. 2009). Other risk factors which have been shown in some, but not all studies have been a longer time since diagnosis/older age at assessment (Maddrey et al. 2005, Aarsen et al. 2009), high risk disease (Palmer et al. 2013), malignancy

of a tumor (Callu et al. 2009), size of a residual tumor (Aarsen et al. 2009), re-operation (Pietila et al. 2012), recurrence (Macedoni-Luksic et al. 2003), hydrocephalus (Reimers et al. 2007, Aarsen et al. 2009), posterior fossa syndrome (Knight et al. 2014), a location encompassing the dental nuclei (Callu et al. 2009) or hemispheres (Landau et al. 2013, Reimers et al. 2007), epilepsy (Landau et al. 2013, Macedoni-Luksic et al. 2003), chemotherapy (Landau et al. 2013, Pietila et al. 2012), and irradiation (Armstrong et al. 2011, Aarsen et al. 2009), especially to the left temporal lobe or hippocampus (Greenberger et al. 2014). It has been claimed that the effect of the longer follow-up time could be due to two factors i.e. prolonged biological effect of irradiation on neuronal development and cumulative damage emerging when new abilities normally gained during child's development cannot be reached causing limited cognitive potential (Aarsen et al. 2009). In particular, hippocampal injury is believed to affect the ability to learn new skills (Forsyth 2010). On the other hand, it has been suggested that frontal lobe may be less active in childhood and its possible damage may not show up until more active functioning of frontal cortex is required in young adulthood (Forsyth 2010).

There are cognitive limitations also in survivors diagnosed with a BT as adults (Calvio et al. 2009), although adult populations have been far less studied. A study focusing on adults with a malignant BT showed more limitations in memory, executive function and attention in the survivors compared with a normal population, at a mean of four years after the BT diagnosis (Calvio et al. 2009). In adults, the cognitive limitations may be associated with depression (Calvio et al. 2009).

There are few studies suggesting that cognitive problems and inattention found in childhood cancer survivors may be alleviated by treatment with methylphenidate. Mulhern et al. conducted a double-blind placebo-controlled trial and detected benefits of methylphenidate therapy to reduce inattention and cognitive problems among ALL and BT survivors (Mulhern et al. 2004). The effect also seemed to be sustained in the long-term use (Conklin et al. 2010).

2.2.2.2 Other neurological late-effects

Surgical treatment of a tumor located in the posterior fossa may cause a posterior fossa syndrome (PFS). PFS refers to mutism after posterior fossa surgery not explained by other forms of morbidity; it is often accompanied with emotional lability (Kupeli et al. 2011). This syndrome affects 9-25% of patients after posterior fossa surgery and it develops usually during the first postoperative week (Houdemont et al. 2011, Kupeli et al. 2011). Mutism usually lasts from days to two weeks, rarely to several months, and a 100% recovery has been reported (Kupeli et al. 2011). There is a new ongoing international study on this topic organized by NOPHO. A histopathological diagnosis of medulloblastoma and the location of

a tumor at a midline seem to be associated with an increased risk of PFS (Kupeli et al. 2011). Dysfunction of speech, however, is not restricted to patients with PFS. Based on a Finnish study, 13% of all childhood BT survivors had dysarthric speech (Pietila et al. 2012). The majority (77%) of survivors with a posterior fossa tumor, although not suffering from PFS, suffer permanently from some dysarthria, and some of them may need speech therapy (Morgan et al. 2011). Deficits may appear in all areas of speech: pitch, loudness, voice quality, resonance, respiration during speech, prosody and articulation (Morgan et al. 2011). Dysarthria seems to appear with a higher frequency if there is a right cerebellar tumor compared with left side lesions (Morgan et al. 2011). Associations between age at BT diagnosis, follow-up time or hydrocephalus and severity of dysarthia have not been found (Morgan et al. 2011).

A significant proportion i.e. 49-77%, of childhood BT survivors suffer from some motor impairment (Maddrey et al. 2005, Pietila et al. 2012, Macedoni-Luksic et al. 2003, Aarsen et al. 2009, Packer et al. 2003). For example, typical motor impairments for BT survivors are disturbances with balance or coordination, hemiparesis, ataxia and cranial nerve palsies. Motor impairments have been more common with malignant tumors and tumors located in dental nuclei (Callu et al. 2009), or infratentorially (Aarsen et al. 2009). Motor impairments have also been associated with shunt revisions (Pietila et al. 2012). A study by CCSS found an elevated risk for motor dysfunction with a high dose irradiation to the frontal cortex (Packer et al. 2003). No association with chemotherapy has been shown (Packer et al. 2003). A Finnish study of 52 patients stated that 21% of childhood BT survivors developed hemiparesis and 12% had a facial paresis (Pietila et al. 2012). A study on 5-year low-grade glioma survivors found 24% cumulative incidence for cranial nerve deficits altogether (Armstrong et al. 2011). In brainstem tumors separately, the frequency of cranial nerve deficits increased to 53% (Armstrong et al. 2011).

Epilepsy and seizures are primarily encountered in patients with supratentorial tumors (Armstrong et al. 2011, Macedoni-Luksic et al. 2003, Aarsen et al. 2009), and they have been associated with cortical irradiation treatment (Packer et al. 2003). However, no associations with irradiation therapy in general or with the extent of surgery or chemotherapy have been found (Armstrong et al. 2011). In general, epilepsy/seizures are present in 5-25% of childhood BT survivors during follow-up (Pietila et al. 2012, Aarsen et al. 2009, Packer et al. 2003). For childhood low grade gliomas, the 15 year cumulative incidences for a seizure have been 6%, 27% and 76%, for posterior fossa, brainstem and cerebral hemisphere tumors, respectively (Armstrong et al. 2011). Packer et al. stated that 6.5% of childhood BT survivors with no history of epilepsy did develop seizures as long ass 5 years after a BT diagnosis (Packer et al. 2003). In adults, the frequency of epilepsy associated

with a BT seems to be somewhat higher, since it has been reported to occur in 38% of new BT patients (Lynam et al. 2007).

2.2.3 Sensory late-effects

Several visual disturbances have been associated with brain tumors. In the CCSS with 1877 childhood CNS tumor patients, survivors self-reported a 20-year cumulative incidence of 5.7% for double vision, 5.3% for dry eyes, 2.1% for cataracts, 1.8% for legal blindness, 0.8% for glaucoma and 0.7% for retinal condition (Whelan et al. 2010).

The location of a tumor in proximity to the optic pathway multiplies the risk for ocular disturbances. For example, a study with 146 operated adulthood craniopharyngioma patients showed that preoperatively 82% of patients had abnormal visual acuity and 62% had some visual field defect (Kim et al. 2012). Visual acuity improved in 42% of cases during the follow-up, and worsened in 25% compared with the original assessment (Kim et al. 2012). Visual field status, on the other hand, remained unchanged in 60%, and half of the rest improved (Kim et al. 2012). Qu et al. showed an increased risk for glaucoma-like optic neuropathy among meningioma, pituitary adenoma and craniopharyngioma patients (Qu et al. 2011). The prevalences for neuropathy were 11%, 9% and 1% for parasellar, suprasellar and intrasellar tumors, respectively (Qu et al. 2011). However, another study showed that if one examined BT survivors without any apparent risk for ocular late-effects due to the location of the tumor, as many as 15% may be suffering an undiagnosed visual field defect of which the family is unaware (Harbert et al. 2012). This study included, for instance, two posterior fossa tumors, in which infection and infarct were considered as etiological factors (Harbert et al. 2012).

In addition to the location of the tumor, an increasing dose of irradiation to the eye has been especially associated with a risk of blindness and cataract (Whelan et al. 2010). The study conducted by Stava et al. found no increase in risk among BT survivors for cataract before the age of 45 years; the risk among survivors with another cancer type was increased with bone marrow transplantation, and thus probably also with total body irradiation (Stava et al. 2005). Results considering the possible risk for ocular late-effects related to treatment with corticosteroids have been somewhat discordant (Whelan et al. 2010, Stava et al. 2005).

Childhood CNS tumor survivors treated in the 1970's and 80's have reported a 20 year cumulative incidence of 11% for difficulties in hearing sounds and between 5% to 10 % cumulative incidence for tinnitus, hearing loss and deafness (Whelan

et al. 2011). Although typical sensorineural hearing loss caused by cisplatin treatment may begin early during treatment, an increased risk for auditory complications can be observed more than 5 years from the diagnosis (Whelan et al. 2011), while ototoxicity may manifest itself months after treatment (Bertolini et al. 2004).

Three major risk factors for auditory late-effects are treatment with cisplatin, cranial irradiation and young age at diagnosis. Children treated in their early years have a significant risk of experiencing hearing loss compared with older patients (Li et al. 2004, Schell et al. 1989). In a study which investigated young children diagnosed with a malignant BT at the median age of two years and who were treated with an irradiation –sparing approach, as many as 62% had an abnormal result on either an audiogram or brainstem auditory-evoked response and 38% needed a hearing aid (Orgel et al. 2012). The cumulative cisplatin doses of cisplatin and carboplatin for children in the aforementioned study were 281 mg/m2 and 1205 mg/m2, respectively (Orgel et al. 2012). Exposure to platinum compounds increases the risk for hearing loss and tinnitus (Whelan et al. 2011). An increased risk is encountered particularly with cisplatin (Einar-Jon et al. 2011) while conventional doses of carboplatin do not seem to increase the risk independently (Bertolini et al. 2004, Einar-Jon et al. 2011). There is an elevated risk for ototoxicity with increasing cumulative doses of cisplatin (Bertolini et al. 2004, Li et al. 2004, Schell et al. 1989). Genetics may also have an influence on individual chemosensitivity and consequently on the likelihood of ototoxicity (Dolan et al. 2004). Irradiation increases the risk for auditory complications in an evident manner with a dose greater than 30 Gy to the temporal lobe or posterior fossa area (Whelan et al. 2011), and its impact is emphasized when irradiation is combined with cisplatin chemotherapy (Schell et al. 1989).

2.2.4 Psychiatric late-effects

The diagnosis of cancer with its potential threat to life and a strenous treatment protocol may itself be a traumatic experience for the patient. Late-effects may remind the BT survivor of the detrimental effects of cancer on an everyday basis for years after diagnosis, making it more difficult to lead an ordinary life. During cancer treatment, the majority of parents experience significant stress especially from uncertainty of the future and a feeling of helplessness, although children's major stress may concentrate on more pragmatic issues such as missing routine daily activities (Rodriguez et al. 2012). It has been suggested that coping strategies among BT patients may not always be optimal: maladaptive coping mechanisms, such as avoidant coping, has been more common, and positive mechanisms such as active coping and seeking social support less common in patients with pituitary adenomas compared with healthy control group (Tiemensma et al. 2011).

However, a majority of childhood cancer survivors in general as well as childhood BT survivors in particular have displayed no psychological distress in studies which are based on screening instruments (Yallop et al. 2013, Zebrack et al. 2004a, Gianinazzi et al. 2013). There are several studies in which the measurement of psychological distress has been based on Brief Symptom Inventory-18 (BSI-18), which estimates the global severity index as well as subscales of depression, anxiety and somatization. Less than 15% of childhood cancer survivors are reported to cross the cut-off scores for psychological distress during adolescence (Gianinazzi et al. 2013) and adulthood (Zebrack et al. 2004a). A large CCSS-cohort based study with more than a thousand childhood BT survivors showed statistically significantly higher scores on global severity index as well as depression and somatic distress among survivors compared with siblings (Zebrack et al. 2004a). However, the absolute difference found was rather minor. The study of Brinkman et al., which evaluated the persistence of psychological symptoms among childhood cancer survivors with several years follow-up, found a frequency of 9 for depressive symptoms and 5% for anxiety (Brinkman et al. 2013). Close to 70% percent of survivors in the aforementioned study reported no depressive or anxiety symptoms at any of the time points evaluated (Brinkman et al. 2013).

Bagur et al. performed a Mini International Neuropsychiatric Interview for adult childhood cancer survivors based on DSM-IV diagnostics (Bagur et al. 2015). At the time of the study, survivors were more likely than the general population to have agoraphobia (5% vs. 2%) or psychotic disorder (2% vs. 0%), but less likely to suffer from general anxiety disorder (9% vs. 12%) (Bagur et al. 2015). When previous symptoms since cancer were also evaluated, 56% of survivors fulfilled the criteria of at least one psychiatric diagnosis with anxiety and mood disorders having the highest incidence (Bagur et al. 2015). The frequency of mood disorders at any time point after cancer diagnosis was higher than the corresponding frequency present in the general population (28% vs. 15%) (Bagur et al. 2015). The following risk factors for psychological distress were proposed by the aforementioned studies: female gender (Zebrack et al. 2004a, Gianinazzi et al. 2013), being not married/divorced (Zebrack et al. 2004a, Brinkman et al. 2013), lower educational status (Zebrack et al. 2004a), unemployment (Brinkman et al. 2013), lower income (Zebrack et al. 2004a) and health problems (Zebrack et al. 2004a, Gianinazzi et al. 2013, Brinkman et al. 2013).

A few studies based on a Danish Cancer registry and Psychiatric Central registry have investigated the risk for psychiatric hospitalization after cancer (Dalton et al. 2009, Ross et al. 2003, Lund et al. 2013). Central nervous system tumor survivors diagnosed before the age of twenty were shown to carry a slightly elevated risk for hospital contact because of anxiety (HR 1.8) or any psychotic disorder (HR 1.75) in males and emotional and behavioral disorders in both males and females (HR

1.5-1.8), as well as a distinct risk for neurodevelopmental disorders (HR 4.2-6.3) compared with population based comparison group (Lund et al. 2013). The risk for hospitalization due to uni- or bipolar depression or personality disorders was not increased (Lund et al. 2013). The study also suggested that siblings who are young at the time of tumor diagnosis were vulnerable to psychiatric problems, whereas siblings older than 15 years at diagnosis showed a decreased risk compared with the general population. In an adult BT population, an increased risk for hospital contact due to depression was seen in the first year, but not later on, after BT diagnosis (Dalton et al. 2009).

A Finnish cohort of adults with a BT showed a frequency of 10% to 16% for levels of scores indicating depression assessed with the Beck Depression Inventory during the first year following a BT diagnosis (Mainio et al. 2011). Another study using the DSM-IV criteria showed a frequency as high as 28% for major depressive disorder for adult BT patients during treatment (Wellisch et al. 2002).

A significant proportion of childhood cancer survivors as well as their parents have been reported to suffer from severe levels of post-traumatic stress symptoms both in their childhood (25-35% of childhood cancer survivors and 29-37% of their parents) (Rodriguez et al. 2012, Bruce et al. 2011) and still when they reach adulthood (childhood cancer survivors 12%) (Langeveld et al. 2004).

2.2.5 Circulatory late-effects

Some studies have shown that childhood brain tumor survivors have a slightly increased risk for elevated systolic blood pressure and an unfavourable lipid profile (Pietila et al. 2009, Heikens et al. 2000). Approximately 20% of childhood BT survivors were reported to have an increased blood pressure already at a young age (Pietila et al. 2009, Haddy et al. 2007). A large self-reporting based study showed childhood BT survivors to have an increased risk for myocardial infarction, pericardial disease, and congestive heart failure, with a hazard ratio from 2.2 to 6.1 compared with siblings (Mulrooney et al. 2009). In the particular study the median age for onset of cardiac events among all childhood cancer survivors was 25-30 years (Mulrooney et al. 2009). Shalitin et al. reported a mean of 10 years delay from cancer diagnosis to the development of hyperlipidemia (Shalitin et al. 2011). The study of Heikens et al. attempted to examine the risk of atherosclerosis among childhood BT survivors by measuring the intima-media thickness of carotid arteries (Heikens et al. 2000). They were able to detect a statistically significant difference in the thickness of the carotic bulb, but measurements combined from all carotid wall segments were similar between survivors and the healthy control group (Heikens et al. 2000). The majority of cardiotoxicity from cancer treatment is

caused by mediastinal irradiation, and the use of anthracyclines, especially with doses greater than 180-250mg/m² (Mulrooney et al. 2009, Brouwer et al. 2011). Another major risk factor for cardiovascular late-effects is young age at the time of the cancer diagnosis (Mulrooney et al. 2009). However, it has been reported that also childhood cancer survivors without any known cardiotoxic treatment as well may show abnormalities in both the structure and function of the left ventricle (Lipshultz et al. 2012), although the clinical importance of the finding is unclear (Lipshultz et al. 2012).

The physical performance capabilities of childhood BT survivors are diminished (Wolfe et al. 2012, Ness et al. 2010). It has been estimated that their peak oxygen uptake has decreased to a level comparable with elderly people or patients with a chronic heart disease (Wolfe et al. 2012, Ness et al. 2010).

Vascular complications after cranial irradiation may include cerebrovascular steno-occlusive disease, brain necrosis, moyamoya disease, mineralizing microangiopathy, cavernomas, teleangiectasias, aneurysms as well as carotid stenosis (Morris et al. 2009). Two large studies have reported an increased risk for cerebrovascular complications among BT survivors (Bowers et al. 2006, Haddy et al. 2011). Bowers et al., examined more than 1800 childhood BT survivors with a mean follow-up of 18 years and found that 6.3% of survivors reported a history of stroke (Bowers et al. 2006). A stroke had occurred after more than 5 years from cancer diagnosis in 3.4% of all survivors (Bowers et al. 2006). Haddy et al. estimated cumulative cerebrovascular mortality (e.g. including haemorrage and stroke) at 40 years to be 5.5% for those childhood BT survivors treated with irradiation (N=681) (Haddy et al. 2011). Both studies reported that the association between cerebrovascular morbidity and cranial irradiation was dose-dependent (Bowers et al. 2006, Haddy et al. 2011). When the irradiated area was taken into account, Haddy et al. found the effect of irradiation to be restricted to the area of the prepontine cistern (Haddy et al. 2011).

Combining alkylating agents with irradiation treatment may increase the risk for stroke (Bowers et al. 2006). Although the increase in risk due to irradiation is clear, the absolute risk for cerebrovascular mortality is still moderately small: 0.9 and 1.6/1000 per year for childhood cancer survivors with 30-50 Gy and more than 50 Gy to prepontine cistern, respectively (Haddy et al. 2011).

A rare late effect of cranial irradiation is stroke-like migraine attack after radiation therapy (SMART syndrome), which may resemble hemiplegic migraines (Armstrong et al. 2014).

2.2.6 Renal late-effects

Some potentially nephrotoxic chemotherapeutic agents are used in the treatment of BTs. For example, cisplatin is frequently included in medulloblastoma treatment protocols as well as in some cases with ependymomas. Carboplatin may be used for some cases of low-grade glioma, medulloblastoma, germ cell tumor or ependymoma. Ifosfamide is used to treat germ cell tumors, and cyclophosphamide in epedymomas and medulloblastomas. High dose chemotherapy as part of stem cell treatment may be used with ATRTs, or with medulloblastoma in infancy or relapsed medulloblastomas. High dose methotrexate may also be used for young patients with medulloblastoma in whom there is a wish to avoid irradiation. The kidneys may as well be affected by some scattered irradiation from craniospinal treatment.

The frequency of nephrotoxic late-effects after cancer is related to the method used to evaluate nephrotoxicity (Gronroos et al. 2008a). A study with 1122 childhood cancer survivors showed a probability of 5.4% for glomerular dysfunction (defined as GFR <90ml/min/1.73m²) at 15 years after cancer diagnosis in those survivors who had been treated with potentially nephrotoxic treatment but this value rose to 26.4% when the situation was evaluated at 35 years after cancer diagnosis (Mulder et al. 2013). In contrast, the probability for survivors without known nephrotoxic therapy was 1.7% and 6.6% at 15 and 35 years, respectively (Mulder et al. 2013). Another study with a limited sample size concentrating on childhood BT survivors, claimed that 29% of survivors treated with cisplatin were suffering from glomerular dysfunction immediately after treatment (Pietila et al. 2005). Patients with glomerular dysfunction also showed signs of tubular dysfunction and more than half had hypomagnesemia (Pietila et al. 2005).

The greatest nephrotoxicity from chemotherapy is induced by cisplatin and ifosfamide. Ifosfamide causes tubular dysfunction, which cannot be totally prevented with mesna which is used for uroprotection (Jones et al. 2008). The subclinical form of tubulopathy found on laboratory testing is common during the time of ifosfamide treatment, but also persistent nephrotoxicity seems to occur in a few per cent of cases after HD treatment (Ho et al. 1995). Mulder et al found that ifosfamide treatment was associated with permanently decreased glomerular filtration rates and a higher probability for glomerular dysfunction (Mulder et al. 2013). A cumulative dose of more than 60-100g/m² poses a significant risk for ifosfamide induced nephrotoxicity (Jones et al. 2008).

Cisplatin may cause glomerular dysfunction as well as tubulopathy (Mulder et al. 2013, Jones et al. 2008). The majority of patients have some signs of deterioration of kidney function during cisplatin treatment, which may be reversible (Jones et al. 2008). However, cisplatin has also been associated with a permanent decrease

of GFR and glomerular dysfunction (Mulder et al. 2013). The effect is dose-dependent, with high doses also the deterioration of kidney function after the acute phase is faster than with smaller doses used.

Carboplatin, HD-methotrexate and HD-cyclophosphamide have also been associated with decreased glomerular filtration rate, but the evidence and clinical impact is less prominent (Mulder et al. 2013, Jones et al. 2008, Knijnenburg et al. 2012, Grönroos et al. 2008b).

2.2.7 Musculoskeletal late-effects

A few studies have evaluated osteoporosis in childhood BT survivors. In a study with 25 patients, of whom 48% had received irradiation, 44% were considered as being osteopenic since their lumbar spine bone mineral density z –scores were less than -1.0. Every fifht had outright osteoporosis with a z -score of total body bone mineral density less than -2.5 (Odame et al. 2006). Decreased bone mineral density was more common in those treated with irradiation. Another study with 46 childhood BT survivors (33% irradiated) found 33% to have a z -score of total body bone mineral density less than -2.0 (Pietila et al. 2006). In a study by Guerney et al. which was based on patients' self-reporting, the risk for osteoporosis among childhood BT survivors was highest for those treated with multimodal therapy including surgery, irradiation and chemotherapy, with a relative risk of 3.1 compared with survivors treated with irradiation and surgery alone (Gurney et al. 2003a). Hudson et al. screened the frequency of osteoporosis among childhood cancer survivors exposed to potentially harmful treatment to the skeletal system (methotrexate, corticosteroids or irradiation to hypothalamus-pituitary axis), and found a prevalence of 9.6% (Hudson et al. 2013).

Muscle strength among childhood BT survivors appears to be decreased (Ness et al. 2010). Ness et al. found weakness in knee extension and hand grip in 55% and 21% of the survivors, compared with only the corresponding values of 12% and 0% in the population-based group (Ness et al. 2010).

2.3 Social and educational status of childhood brain tumor survivors

There are various and complex factors potentially influencing social outcome in BT survivors. The etiology of social difficulties is multifactorial and both BT-related risk and resilience factors as well as other less studied non-BT-related factors such as parental style and socioeconomic status must be evaluated (Hocking et al. 2015). Childhood BT survivors have been shown to have social difficulties, to be

more socially isolated and have fewer close friendships compared with healthy controls or children with other chronic illnesses (Vannatta et al. 1998, Carpentieri et al. 1993, Bonner et al. 2008). Schulte and Barrera reviewed twenty articles which had reported the level of social competence in childhood BT survivors (Schulte et al. 2010). Almost all of the studies reported that survivors encountered difficulties in social adjustment. The difficulties also seemed to be more pronounced than those seen in survivors with other types of childhood tumors (Barrera et al. 2005). Parents have evaluated BT survivors as having impaired social skills and deficits in non-verbal communication (Bonner et al. 2008). There is some evidence that BT survivors, especially girls who have received cranial irradiation, may have problems in face recognition, a deficit not explained merely by the IQ-level alone (Bonner et al. 2008, Willard et al. 2009). This may explain some difficulties in non-verbal communication. It has been suggested that attention deficits derived from a BT and its treatment might be independently associated with social difficulties (Moyer et al. 2012). However, as attention deficits might be related to a general decline in cognitive level and psychiatric morbidity, which may also associate with social functioning, this issue needs further clarification. The following factors have been reported to increase the risk for social difficulties: female gender (Carpentieri et al. 1993, Moyer et al. 2012), young age at diagnosis (Carpentieri et al. 1993), high risk treatment status (a treatment protocol including a higher dose of cranial irradiation) (Brinkman et al. 2012), posterior fossa syndrome (Brinkman et al. 2012), functional impairment (Carpentieri et al. 1993), disfigurement (Carpentieri et al. 1993), lower cognitive level (Moyer et al. 2012, Holmquist et al. 2002), and young age of the mother (Carpentieri et al. 1993).

A questionnaire based methodology makes it possible to investigate large cohorts and assess potential risk factors, but it also has several potentially confounding factors, especially when evaluating social interactions. Katz et al. conducted a study in which they observed survivors of ALL and same-aged healthy children when they were playing with their best friend (Katz et al. 2011). This study found that survivors were less likely to show signs of engaged behavior (e.g. engage in fantasy play) in peer play and more likely to show signs of disengagement (e.g. unable to sustain a common activity) than healthy controls. However, although a statistically significant difference was reported, the absolute differences found were small.

Childhood cancer survivors are less likely to be married or to have children than their siblings (Armstrong et al. 2009, Kirchhoff et al. 2010), and CNS tumor survivors less likely to be in long term relationship than ALL survivors (Wengenroth et al. 2014). Cranial irradiation seemed to decline the probability for marriage (Armstrong et al. 2009). A qualitative study evaluated romantic partnerships of

young adult survivors with a history of childhood cancer and found that the following themes seemed to exert a potential influence: redefined life priorities and perspective, concerns with disclosure of personal information (both cancer and non-cancer related), negative body image, and worries about fertility and health of future children (Thompson et al. 2013).

Childhood BT may also affect living arrangements in young adulthood and some BT survivors may remain living with their parents for a prolonged time. In a study of 32 medulloblastoma survivors who were at least 20 years of age, only 31% were living independently, 53% with their parents and 16% in a community home or boarding school (Frange et al. 2009). The same study showed that only 34% of survivors possessed a driving license.

The burden of a BT is not limited to the patient only, but the parents and siblings as well. In a Swedish study evaluating the impact of childhood BT on parents with a mean of 16 years after diagnosis, approximately 40% of parents still reported moderate or great impact on personal strain or financial burden (Hoven et al. 2013). Thirty-eight per cent of the parents also reported at least moderate ongoing impact on the patient's siblings. The impact of a BT on a family (e.g. personal strain, social disruption and financial burden) was significantly associated with the level of the survivor's health.

Many childhood BT survivors are confronted with significant educational difficulties. School grades for BT patients have been lower than those of their peers (Lähteenmäki 2007). BT survivors have encountered difficulties especially in learning foreign languages (Lähteenmäki 2007). In a Finnish study with 44 school-aged childhood BT survivors, 68% attended school with an ordinary syllabus, whereas 32% were receiving some special education (Pietila et al. 2012). The need for special education seems to be higher with embryonal tumor survivors, with approximately three out of every four attending some special education classes (Frange et al. 2009, Ribi et al. 2005). Other survivor groups especially at risk for academic decline are girls (Lähteenmäki 2007), young children diagnosed before seven years of age, and children with mutism (Ris et al. 2013). In a study based on a CCSS cohort, siblings were more likely to graduate from college and be currently employed than childhood CNS tumor survivors (Armstrong et al. 2009). The frequencies of health-related unemployment have been estimated; they are 25% for CNS tumor survivors, 6-13% for survivors of other cancer survivors but only 1.8% for their siblings (Kirchhoff et al. 2010). A similar pattern is seen in the frequency of people unemployed but seeking work, with corresponding values being 10%, 3-6% and 2.7%. For some BT survivors, some kind of protected employment or volunteer work may be an option (Frange et al. 2009). Factors found to be associated with unemployment of BT survivors are cranial irradiation ≥25Gy, female gender, increasing time since diagnosis, recurrence and secondary cancer (Kirchhoff et al.

2010). In Sweden, where the social security system resembles that of Finland, 14% of young adults with a history of childhood BT were in receipt of a handicap allowance and 22.8% were being paid a disability pension (Hjern et al. 2007). The corresponding frequencies among the age matched general population are 0.6% and 2.5%. In a recent study from Finland, 19.7% of childhood BT survivors were retired compared with only 1.7% in an age-matched control group (Ahomäki et al. 2016).

2.4 Quality of life

2.4.1 Concept of quality of life

The concept of quality of life is not completely unambiguous, and several attempts have been made to define it. The frequently cited definition by The World Health Organization (WHO) describes QOL in a comprehensive way 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. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment" (The World Health Organization 1995). Health defined by WHO is "a state of complete physical, mental, and social well-being not merely the absence of disease or infirmity" (Preamble to the Constitution of the World Health Organization 1946).

Health-Related Quality of Life (HRQOL) is also a multidimensional concept, but more concise than QOL, as it is used to measure the QOL related to the health and disease state of an individual and their impact on functioning. HRQOL also lacks a straightforward definition. The most commonly used conceptual models of HRQOL are those issued by WHO, Wilson and Cleary and its revised version by Ferrans et al. (Bakas et al. 2012, Ferrans et al. 2005, Wilson et al. 1995, World Health Organization 2007). The most frequently cited model by Wilson and Cleary consist of five concepts, which are biological and physiological factors, symptoms, functioning, general health perceptions and overall QOL (Wilson et al. 1995). Ferrans et al. revised this version by adding a description that biological function may be influenced by individual and environmental factors (Ferrans et al. 2005).

In 1984, KC Calman presented a hypothesis that QOL is the difference between individual's present experiences and his/her expectations, and emphasized the individual's own perception (Calman 1984). Thus improving one's QOL could be done by improving life conditions or by changing the expectations to be more realistic (Calman 1984). Calman claimed that because QOL is constructed from

many aspects, improving some aspect might enable the QOL to stay stable even although some aspects were declining (for example, a decline of physical condition) but at the same time there may be an improvement of the social network or personal growth. Calman also highlighted the importance of identifying the individual's own priorities to be able to measure and improve the QOL.

In 1995, Felce & Perry who reviewed the QOL definition related literature divided QOL into five categories: physical well-being, material well-being, social well-being, emotional well-being, and development and activity (Felce et al. 1995). It has been discussed whether measurement should be based merely on an individual's own perception and satisfaction on their life conditions (Calman 1984) or should objective measures be taken into account as well (Felce et al. 1995). Probably the best alternative is to take into account objective conditions of life, the individual's satisfaction with these conditions and also the individual's personal values and expectations (Felce et al. 1995).

2.4.2 Measurement

QOL and HRQOL may be evaluated by a structured interview or a questionnaire based method. Quantitative methods are often preferred because they are straighforward to carry out and the results can more easily be compared with other studies. However, there is a risk of excessive simplifying of the QOL and the results may not capture the actual general QOL of an individual. Some of the questionnaires concentrate on objectively measured concerns whereas others emphasize the individual's subjective perception. Furthermore, the correlation between the results from separate QOL questionnaires may be poor (Sundberg et al. 2010). It has been discussed that especially data from questionnaires concentrating on health status and HRQOL should not be unconditionally compared with data from QOL based on respondents' actual self perception (Sundberg et al. 2010). Despite the advantages of questionnaires and interviews based on participants own values and subjective perception these may carry chances of bias. A potential risk is that the answer may be affected too strongly by short-term events in an individual's life (Felce et al. 1995). Its feasibility may also be limited in assessing the influence of interventions, as it is affected by the level of the individual's expectations, which may vary greatly between respondents (Felce et al. 1995).

There are generic QOL-questionnaires as well as specific questionnaires targeted for specific populations with a certain illness or a symptom. QOL-instruments may be further classified as health profiles or preference based measures (Feeny et al. 2013). Generic QOL-scales enable a comparison with population norms, but may not be sensitive enough in identifying problems of a certain group of patients.

However, the areas nominated as the most important for QOL seem to be similar for the survivors and the healthy controls: family life, relations to other people, work/career, interests/leisure activities, own health and relationship to a partner (Sundberg et al. 2010). There are a dozen QOL-instruments which have been developed specifically for self-reporting of childhood cancer patients and survivors (Anthony et al. 2014, Klassen et al. 2010). Two of them have been developed especially for brain tumor survivors. The level of psychometric testing used in the development of these instruments has varied (Klassen et al. 2010).

In an optimal situation, assessment of QOL is based on self-reporting, but especially in children, this is not always possible. Thus, parental reporting based-evaluations have been used as well. However, there is a risk that the values, concerns, expectations and psychological state of the parent may influence the evaluation. Significantly different results between self- and proxy-evaluations have been shown (Wengenroth et al. 2015, Aarsen et al. 2006, Fluchel et al. 2008). In general, cancer survivors tend to evaluate their QOL as better than their parents (Wengenroth et al. 2015).

A specific risk related to measurement of QOL, especially with a questionnaire based method, when assessing individuals with cognitive and verbal limitations is insufficient comprehension of the questions. People with mental retardation are known to have a tendency to give affirmative answers irrespective of the construct of the question (Felce et al. 1995).

Table 3. The ways that different QOL instruments categorize different aspects

Categorization	Subcategories	Example of an instrument
The way of data gathering	1. Interview 2. Questionnaire	
The source of data	1. Self-reporting 2. By-proxy (parents)	
Objectivity/self perception	1. Health profile 2. Preference based	e.g. Short-Form-36 (Ware et al. 1992) e.g. Health Utilities Index 2 and 3 (Torrance et al. 1996, Feeny et al. 2002) and 15D (Sintonen 1994, Sintonen 2001)
Target population	1. Generic 2. Population specific	e.g. Short-Form-36 (Ware et al. 1992) Childhood cancer patients and survivors: e.g. Minneapolis-Manchester Quality of Life Instrument (Bhatia et al. 2004) and Pediatric Quality of Life Inventory-Cancer Module (Varni et al. 2002) Childhood brain tumor patients and survivors: the Pediatric Quality of Life Inventory-Brain Tumor Module (PedsQL Brain Tumor Module) (Palmer et al. 2007) and the Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivor (PedsFACT-Brs) (Lai et al. 2007)

2.4.3 Quality of life among childhood BT survivors

The majority of studies focusing on HRQOL of childhood cancer survivors have found comparable (Wengenroth et al. 2015, Sundberg et al. 2010, Mertens et al. 2014) or only marginal decline in the level of HRQOL in comparison with population norms or siblings (Chan et al. 2014, Yagci-Kupeli et al. 2012). There is one exception; Badr et al. reported a significantly decreased level in multiple areas of HRQOL (Badr et al. 2013). Tumor location in the CNS has been repeatedly shown to be an independent risk factor for poorer HRQOL among childhood cancer survivors (Wengenroth et al. 2015, Mertens et al. 2014, Chan et al. 2014, Yagci-Kupeli et al. 2012, Badr et al. 2013, Perez-Campdepadros et al. 2015, Meeske et al. 2004), and childhood BT survivors have shown decreased QOL compared with the normal population (Aukema et al. 2013, Aarsen et al. 2006). A significant association for decreased QOL among childhood cancer survivors has been shown with a relapse (Wengenroth et al. 2015, Aarsen et al. 2006), female gender (Mertens et al. 2014, Chan et al. 2014, Yagci-Kupeli et al. 2012, Badr et al. 2013, Perez-Campdepadros et al. 2015, Meeske et al. 2004), and parental psychiatric symptoms (Yagci-Kupeli et al. 2012). Results concerning the effect of diagnostic age have not been totally consistent. Mertens et al. reported increased figures of poor HRQOL with children diagnosed at the age of 2-4 years compared with children diagnosed earlier (Mertens et al. 2014). In the study of Reimers et al., a younger age at diagnosis was associated subsequently with a decreased level of social functioning (Reimers et al. 2009). There are reports showing that HRQOL may decrease, at least in some of the survivors, in the longer follow-up (Chan et al. 2014, Perez-Campdepadros et al. 2015, Duckworth et al. 2015). Even though the results on this issue have not been concordant in all studies (Wengenroth et al. 2015), it would not be surprising when one considers the increasing number of medical late-effects (Gurney et al. 2003a, King et al. 2016). Meeske et al. showed a changing trend with an improvement of physical and psychosocial health during the first year after the end of the BT treatment, but a decline after that time (Meeske et al. 2004).

The areas of HRQOL that have been reported as being affected in BT survivors have included comprehensively different areas of HRQOL (Wengenroth et al. 2015, Aukema et al. 2013, Aarsen et al. 2006, Badr et al. 2013, Perez-Campdepadros et al. 2015, Bhat et al. 2005). In particular, physical well-being (Wengenroth et al. 2015, Aukema et al. 2013, Aarsen et al. 2006, Badr et al. 2013, Perez-Campdepadros et al. 2015, Bhat et al. 2005), psychological well-being (Wengenroth et al. 2015, Aukema et al. 2013, Bhat et al. 2005), and peer relationships/social support (Wengenroth et al. 2015, Aarsen et al. 2006, Perez-Campdepadros et al. 2015, Bhat et al. 2005) have been shown to be significantly affected in several studies. Children with low-grade gliomas seem to have a superior HRQOL compared with children with other BT types (Bhat et al. 2005), while survivors of germ

cell tumors, oligodendrogliomas, mixed/unspecific gliomas and medulloblastomas/PNETs have been considered to fare more poorly (Boman et al. 2009). Comparison between survivors of low-grade astrocytoma and the normal population has shown variable results, from a decline of HRQOL among survivors in several areas (Aarsen et al. 2006), to comparable or even better results (Zuzak et al. 2008). With respect to the treatment variables, at least irradiation seems to negatively affect HRQOL (Yagci-Kupeli et al. 2012, Reimers et al. 2009, Bhat et al. 2005, Sands et al. 2001) whereas there is no explicit proof that chemotherapy exerts any significant effect. The location of a BT has not been shown to have an impact on survivor's HRQOL (Aarsen et al. 2006, Meeske et al. 2004, Bhat et al. 2005). Data concerning the influence of a shunt have been inconsistent (Reimers et al. 2009, Bhat et al. 2005).

In the past few years, qualitative studies aiming to describe the experiences of childhood cancer survivors more profoundly and with the survivors' own words have been published (Doukkali et al. 2013, Enskar et al. 2010, Hobbie et al. 2016). A study of 41 young childhood BT survivors living with their families, revealed the great importance of support from the family (Hobbie et al. 2016). With BT survivors, family had a great significance, e.g. endowing the survivors with an appreciation that their existence mattered to someone (Hobbie et al. 2016). Among the survivors, neurocognitive functioning had a clear effect on their everyday functioning and they all suffered from loneliness (Hobbie et al. 2016). In contrast to the results of a study concentrating on other childhood cancer survivors (Enskar et al. 2010) in which the positive impacts of cancer experience seemed to be able to compensate for its negative effects, when Hobbie et al. investigated BT survivors, it was observed that their the coping was more negatively oriented and the survivors were described to have a pervasive sense of loss due to their cancer (Hobbie et al. 2016).

The positive impact of cancer described by Enskär et al. (Enskar et al. 2010) has also been shown among childhood cancer survivors in other studies (Zebrack et al. 2012, Castellano-Tejedor et al. 2015). Based on one, study it seems that younger age at diagnosis, increased time since diagnosis and certain cancer diagnoses such as a BT diagnosis, however, seem to decrease the putative positive effects (Zebrack et al. 2012).

3 AIMS OF THE STUDY

This study aimed to gather data on late morbidity and quality of life of young onset BT survivors to obtain knowledge of special needs among this population.

The specific aims of this study were:

1. To evaluate late morbidity (at least 5 years from BT diagnosis) of BT survivors diagnosed at the age of 0-15 years, and to evaluate the effect of sex, age at diagnosis, treatment era, tumor histology and irradiation treatment for morbidity.

2. To examine late morbidity (at least 5 years from diagnosis) of BT survivors diagnosed at the age of 16-24 years, and to investigate the effect of sex, treatment era and irradiation treatment for morbidity.

3. To assess the use of neurological and endocrinological medication among BT survivors diagnosed at the age of 0-24 years, and to evaluate the effect of sex, birth year, age at diagnosis and irradiation for use of medication.

4. To determine the quality of life among survivors of childhood ependymoma, primitive neuroectodermal tumor and medulloblastoma with both quantitative and qualitative methods.

4 MATERIALS AND METHODS

4.1 Study cohorts (Studies I-IV)

Studies I-III: All the patients diagnosed with a neuroepithelial BT at the age of 0-24 years between 1970 and 2004 were identified from the Finnish Cancer Registry (FCR). Late morbidity was assessed within the 5-year survivors. Data on survivors diagnosed at 0-15 years were included in Study I (N=740) and that of the survivors diagnosed at 16-24 years in study II (N=315). For study III, all 5-year survivors diagnosed between 1988 and 2004 were included (N=602).

A control group in studies I and II consisted of the siblings of each BT patient (regardless of the patients' survivor status) diagnosed before the age of 25 years between 1970 and 2004 (N=3615). In study III, the siblings of BT patients (regardless of their survivor status) diagnosed between 1988 and 2004 were used as a comparison group (N=2392). However, siblings born before 1968 were excluded in Study III, because there were no BT survivors born before that time point. Siblings of the BT patients were identified via their common parents by linkage to the Population Register Centre (Väestörekisterikeskus) using the unique identification number of each resident in Finland. Siblings with cancer at an early age (<35 years) were excluded.

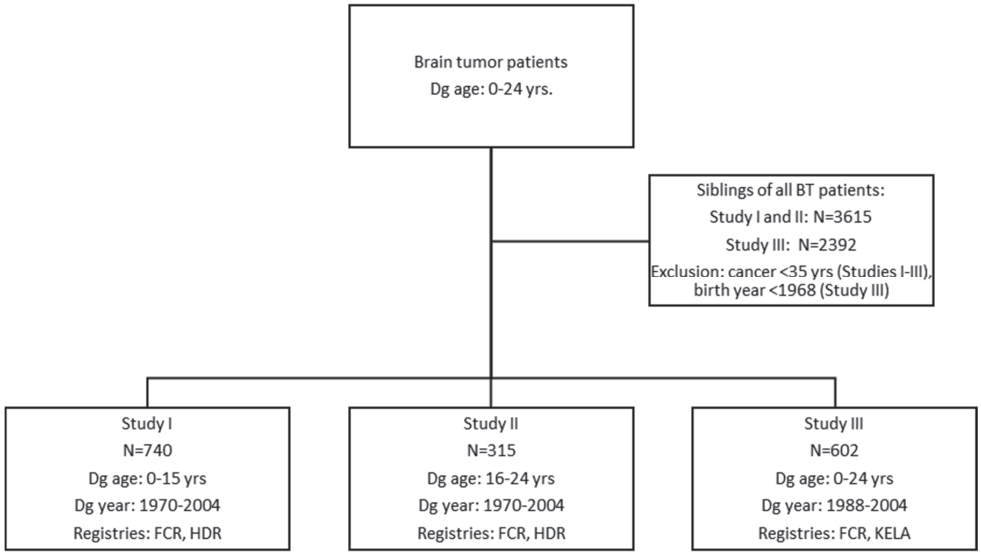

Figure 3. Participants in Studies I-III. (Gunn et al. 2014, Gunn et al. 2015, Gunn et al. 2016a)

For the study IV, the inclusion criteria were as follows:

- Year of birth between 1975 and 2000
- Histological diagnosis of ependymoma, medulloblastoma or primitive neuroectodermal tumor (PNET) of the brain
- BT diagnosis made before age of 16 years
- Diagnosis made ≥ 5 years before the beginning of the study (2010).

Patients were identified via the FCR and the five University Hospitals in Finland.

One hundred and seventy patients were identified, of whom seventy-three were alive at the beginning of the study. Altogether eight survivors were excluded. The criteria for exclusion were missing address data (N=2), major morbidity not related to BT which was assessed to have a significant influence on the QOL (N=2), and physical condition or level of cognitive limitation determined to prevent the participation (N=4). All eligible 5-year survivors (N=65) were invited to an interview via an invitation letter. The survivors who did not answer in 4 weeks from first contact were contacted the second time either via another letter or a telephone call. Twenty-one survivors participated (participation rate of 32%) and provided written consent before the study. In case of underage study subjects (N=3), written consent from a parent was requested. Hospital records from University Hospitals of all the patients filling the inclusion criteria were reviewed to gather medical data.

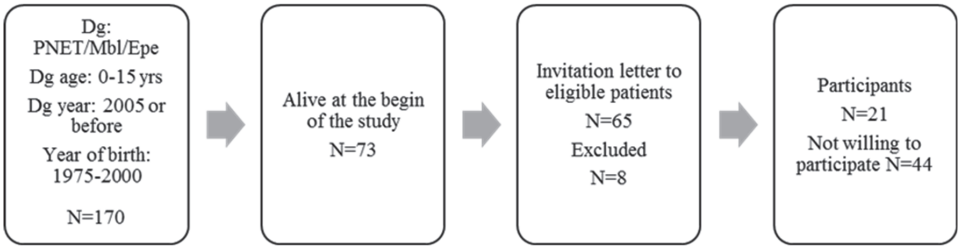

Figure 4. Participants in Study IV. Epe= ependymoma. (Gunn et al. 2016b)

4.2 Characteristics of study participants (Studies I-IV)

The characteristics of study participants in studies I-IV are shown in table 4.

Study I: The median follow-up time for the survivors after 5-year survival was 12.0 years (range, 0-33 years).

Table 4. Characteristics of study participants in Studies I-IV. Modified from Gunn et al. 2014, Gunn et al. 2015, Gunn et al. 2016a, Gunn et al. 2016b.

	Study I	Study II	Study III	Study IV
N (%)	740 (100)	315 (100)	602 (100)	21 (100)
Sex				
Female	340 (46.0)	144 (45.7)	281 (46.7)	7 (33.3)
Male	400 (54.1)	171 (54.3)	321 (53.3)	14 (66.7)
Age at diagnosis				
0-5	313 (42.3)	0 (0.0)	N/A	9 (42.9)
0-7	N/A	0 (0.0)	240 (39.9)	N/A
6-10	213 (28.8)	0 (0.0)	N/A	6 (28.6)
8-15	N/A	0 (0.0)	192 (31.9)	N/A
11-15	214 (28.9)	0 (0.0)	N/A	6 (28.6)
16-24	0 (0.0)	315 (100)	170 (28.2)	0 (0.0)
Year of diagnosis				
1970-1979	134 (18.1)	65 (20.6)	N/A	N/A
1980-1989 (1975-1989 for study IV)	223 (30.1)	99 (30.4)	N/A	4(19.0)
1990-1999	270 (36.5)	109 (34.6)	N/A	11 (52.4)
2000-2004	113 (15.3)	42 (13.3)	N/A	6 (28.6)
Diagnosis				
Astrocytic tumor	415 (56.1)	175 (55.6)	347 (57.6)	0 (0.0)
Other glioma	79 (10.7)	48 (15.2)	50 (8.3)	0 (0.0)
Embryonal tumor	79(10.7)	11 (3.5)	56 (9.3)	11 (52.4)
Ependymal tumor	61 (8.2)	17 (5.4)	44 (7.3)	10 (47.6)
Other specified tumor/ Tumor NOS	106 (14.3)	64 (20.3)	105 (17.4)	0 (0.0)
Treatment				
Surgery	644 (87.0)	275 (87.3)	536 (89.0)	21 (100.0)
Irradiation	254 (34.3)	126 (40.0)	176 (29.2)	17 (81.0)
Chemotherapy	N/A	N/A	N/A	18 (85.7)
No data available	39 (5.3.)	16 (5.1)	36 (6.0)	0 (0.0)

Study II: The median age of the participants at cancer diagnosis was 20.5 years (range, 16-24.9), and the median age at the time that the follow-up ended was 35.7 years (range, 21.7–62.9 y). The median follow-up time for the survivors after 5 year survival was 11.5 years (range, 0.1–33.9 y).

Study III: The median age of the participants at the end of the follow-up was 22.4 years (range 6.6-42.2). The median follow-up after 5 year survival was 8.8 years (range 0.0-18.0).

Study IV: The participants were interviewed at the age of 14 to 35 years (median 24 years). Four of the participants (19%) were younger than 18 years of age the time of the interview. The median lag time from a diagnosis to the interview was 17.0 years (range 8.1-25.7 years). There was no significant difference in distribution of sex, tumor histology, age at diagnosis, treatment era, follow-up time, the rate of recurrence, treatment method or the medical late-effects between the study participants and eligible survivors, who did not participate.

4.3 Registry data (Studies I-IV)

The Finnish Cancer Registry (FCR) (Studies I-IV) is an institution which has collected data on all the cancers diagnosed in Finland since 1953 (Teppo et al. 1994, Suomen Syöpärekisteri). FCR receives data from multiple sources which ensures a good coverage. For malignant tumors of CNS, the coverage is estimated to be over 98%. With benign CNS tumors, there may be some under registration, with an estimated 80.6% coverage. At present, coding of FRC is based on International Classification of Diseases for Oncology, third edition (ICD-O-3) (Fritz et al. 2000). Because of the changes made for classification in the past, the correctness of astrocytoma and glioma coding was rechecked from the original pathology reports. (Table 2)

The following data from FCR were collected: personal identification code (PIC), date of birth, sex, date of diagnosis, tumor morphology, primary site of a tumor, malignancy, primary treatment, possible emigration date, possible date of death, and underlying cause of death. Treatment data were used on the basic level: surgical treatment (yes/no), and radiation treatment (yes/no). Data on specific chemotherapy protocols or irradiation doses were not systematically available. For analysis in studies I and II, histological diagnoses were grouped as follows: astrocytic tumors, other glial tumors (oligodendroglial and oligoastrocytic tumors), ependymal tumors, embryonal tumors, other specified neuroepithelial tumors (neuronal, mixed neuronal-glial tumors, and tumors of pineal region), and brain tumors not otherwise specified (NOS).

The Hospital Discharge Registry (HDR) (Studies I-II) contains data on principal diagnoses of patients treated in hospitals in Finland (Sund 2012). The registry is maintained by National Institute for Health and Welfare in Finland (Terveyden ja Hyvinvoinnin Laitos). Data on diagnoses from hospital inpatients have been collected since 1975 in electronic form and data on outpatients treated in specialized health care settings have been added since 1994. Data on HDR are gathered in the format of the International Classification of Diseases (ICD). Diagnoses coded according to older versions (ICD-8 or ICD-9) were transformed into the ICD-10 format. The quality of the HDR data has varied from satisfactory to very good (Sund 2012).

The diagnoses gained from HDR were divided into eight main categories: endocrine diseases (Studies I-II), psychiatric disorders (Studies I-II), cognitive and developmental disorders (Study I only), neurological diseases (Study I-II), disorders of vision/hearing (Studies I-II), diseases of circulatory system (Studies I-II), disorders of the musculoskeletal system/connective tissue (Studies I-II), and diseases of the kidney (Studies I-II). Infectious diseases and diseases/conditions primarily treated in primary health care were excluded from analysis. For studies I and II, data from FCR and HDR were linked to obtain data on morbidity for 5-year BT survivors.

Table 5. Diagnoses gathered from HDR and included in the eight main outcome groups analyzed. Cognitive and developmental disorders were evaluated only from participants in Study I. Modified from Gunn et al. 2014.

Main outcomes studied	Diagnoses included in the categories	ICD-10 codes
Endocrine diseases	Hypothyroidism	(E01, E03, E89.0)
	Insulin-dependent diabetes mellitus	(E10)
	Disorders of pituitary gland	(E22.0-E23.7, E89.3)
	Disorders of adrenal gland	(E26.0-E27.9)
	Other endocrine disorder caused by dysfunction in CNS	(E28, E30, E34.3, E34.4, E89.4).
Psychiatric disorders	Mental and behavioral disorders due to psychoactive substance use	(F10.0-F19.9)
	Schizophrenia/schizotypal/delusional disorders	(F20.0-F29)
	Mood disorders	(F30.0-F39)
	Neurotic/stress-related/somatoform disorders /Organic mental disorders/personality or behavioral/emotional disorders/eating disorders or other unspecified disorder	(F40.0-F48.9) (F06.0-F09, F50, F60.0-F69, F90.0-F99)
Cognitive and developmental disorders (Included only in study I)	Mental retardation or pervasive developmental disorders	(F70.0-F79.9, F84)
	Minor disorders of psychological development (motor, speech/language or scholastic skills)	(F80.0-F82, R47)
	Mixed specific developmental disorders/other/ unspecified disorders of psychological development	(F83, F88, F89)
Neurological diseases	Demyelinating diseases	(G35.0-G37.9)
	Epilepsy	(G40.0-G41.9)
	Migraine or other headache syndromes	(G43.0-G44.8)
	Sleep apnea	(G47.3)
	Nerve, nerve root and plexus disorders	(G50-G59.8)
	Cerebral palsy and other paralytic syndromes	(G80.0-G83.9)
	Other disorders of the brain or nervous system (excluding hydrocephalus)	(G93-G94, G97-G99)
	Intracranial injury	(S06)
	Systemic atrophies affecting the CNS and extrapyramidal and movement disorders were not included because of the very small number of cases.	
Disorders of vision or hearing loss	Disorders of lens	(H25.0-H28.8)
	Disorders of retina	(H31, H33.0-H36.8)
	Disorders of optic nerve and visual pathways	(H46.0-H48.8)
	Strabismus	(H49.0-H50.9)
	Visual disturbances and blindness	(H53.0-H54.9)
	Hearing loss	(H90.0-H91.9)
Diseases of circulatory system	Ischemic heart diseases	(I20.0-I25.9)
	Cardiac arrhythmias	(I47.0-I49.9)
	Cardiomyopathy/heart failure	(I42, I50)
	Intracranial non-traumatic hemorrhage /Transient cerebral ischemic attack/ cerebral infarction/ occlusion/stenosis of precerebral arteries and other cerebrovascular diseases including sequelae of cerebrovascular diseases	(I60.0-I62.9) (G45, I63, I65-I67, I69)
Diseases of musculoskeletal system and connective tissue	Arthrosis	(M15.0-M19.9)
	Deforming dorsopathies	(M40.0-M43.9)
	Spondylopathies and intervertebral disc disorders	(M45.0-M51.9)
	Disorders of bone density and structure or diagnosed fracture of forearm, wrist/hand, femur or lower leg	(M80.0-M85.9, S52, S62, S72, S82)
	Other osteopathies and chondropathies	(M86.0-94.9)
Diseases of the kidney	Glomerular diseases and renal tubule-interstitial diseases (excluding obstructive and reflux uropathy)	(N00.0-N08.8, N10.0-N12, N14.0-N16.8)
	Renal failure	(N17.0-N19)

The Social Insurance Institution of Finland (KELA) (Study III) collects a registry which contains data on every prescription drug purchase made in Finland (Lääke-ostotiedot). Data collection in the registry started from 1993. Following data included in the registry were used in Study III: personal identification number, Anatomical Therapeutic Chemical (ATC)-classification (WHO Collaborating Center for Drug Statistics Methodology) code of a purchased drug and the date for a drug purchase. Categories of drugs which were included were:

Endocrinological medication:

- diabetes drugs (A10)
- lipid modifying agents (C10)
- hormonal contraceptives (G03A, hormonal contraceptives for systemic use; G03HB01, cyprosterone and estrogen)
- androgens (G03B)
- estrogens (G03C)
- progestogens (G03D)
- progestogens and estrogens in combination (G03F)
- gonadotropins and other ovulation stimulants (G03G)
- growth hormone (H01AC01)
- desmopressin (H01BA02)
- mineralocorticoids (H02AA)
- hydrocortisone for systemic use (H02AB09)
- thyroid hormones (H03A)
- bisphosphonates (M05BA, M05BB)

Neurological medication:

- antiepileptics (N03)
- anti-parkinson drugs (N04)
- methylphenidate (N06BA04).

The first purchase from each drug category was included in the analyses.

4.4 Questionnaires (Study IV)

Beck Depression Inventory-II (BDI) is a globally used screening tool based on self-reporting. It is used to evaluate risk for depression in adults and adolescents (Beck et al. 1996). The questionnaire has 21 questions, each one of which can have 0 to 3 points. In study IV, following cut-off scores were used: 0-13 minimal, 14-19 mild, 20-28 moderate, 29-63 severe indication of depression.

15D is a generic preference-based HRQOL tool which is primarily designed for self-reporting, but may also be used as a proxy-instrument (Sintonen 2001). It covers 15 dimensions: moving, seeing, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. The respondents score each dimension from 1 to 5. Prior to the analyses conducted in study IV, the missing values were imputed according to recommendations (Sintonen 2001). Population-based utility weights were used to calculate a total score index. A value of one indicates the best possible overall HRQOL and zero is the worst possible HRQOL. As a comparison, a randomly selected population control group (N=327) collected from the Finnish Population Registry for a previous study (Mort et al. 2011) was used.

The participants filled a questionnaire for background data which included questions concerning their health and life style: height (cm), body weight (kg), educational level, need for special support at school, attending military service, owning a driving license, exercise frequency, frequency of meeting friends, sexual activity level, attempts of pregnancy, frequency of contacts with a medical doctor during past two years and need for hospital treatment. Body mass index was calculated as body weight (kilograms) divided by the square of height (meters).

The participants were asked to fill out the questionnaires (BDI, 15D and background data) only after the interviews, so that they would not interfere wth the topics that would come up during the interview. Participants filled out the questionnaires themselves whenever possible, but were assisted by the interviewer or the parent if needed (N=3).

4.5 Qualitative interview (Study IV)

Interviews aiming to define the quality of life of childhood BT survivors and the aspects which may have an impact on the QOL, were designed based on phenomenological methodology. Phenomenological orientation in qualitative research

means approaching the area of interest from the view of several individual's experience of a phenomenom and is, thus, trying to capture the universal essence of the phenomenom (Creswell 2007).

The questions of main interest were: 1. how did the survivors experience having had a BT in childhood, and 2. how did they experience their QOL over the long term? The interviews were based on a semistructured format (Table 6.). Main questions planned in advance were asked from all the participants. Literature concerning QOL often include the following aspects of QOL in some form: general, physical, mental, social, view of life. In the case a participant did not respond to all these aspects, specifying questions were asked (examples of which are presented in Table 6.). Participants were encouraged to add aspects they felt important for the subject, although not separately asked. The questions were posed in an open-ended manner whenever possible. The interviews were continued as long as new issues/ideas came up. The duration of interviews varied from 8 to 86 minutes (mean 38 minutes). All the interviews were recorded with the participants' permission. Later, the audiotapes were transcribed verbatim. Interviews were gone through in detail to separate significant codes from the text. Codes were further categorized to form themes and subthemes, which would best describe the experience of having had a childhood BT and the QOL after that incident. Revision of the themes was made to confirm the internal homogeneity and external heterogeneity of the themes.

The interviews took place either at the nearest hospital, participant's own residence or at school, where ever was the most convenient for the study participant. The presence of a parent was allowed, if a participant him/herself wished for it. Nevertheless, it was emphasized that interviews were meant to capture the personal opinions of the participants, and the parents were asked not to interfere if possible.

Table 6. Basic structure of QOL interviews in Study IV (interviews were modified during the interview whenever needed). Data not shown in original publication.

Main questions	**Specifying questions**
How do you feel about/have you experienced having a brain tumor in childhood/adolescence?	What kind of thoughts does it bring to you afterwards? How did you feel when you heard about the brain tumor diagnosis? How did the diagnosis affected your life back then? Did the ideas you first had about having a brain tumor correlate with how it has actually been? What do you think about it (having a brain tumor in childhood) now?
In which way has having a brain tumor in childhood affected your life? (specified with questions concerning physical, mental, social and world view issues, if not otherwise discussed)	Do you think your life would be different if you would not have had a brain tumor? If yes, can you describe how you think it would be different? <u>Physical dimension:</u> How do you feel about your health? Do you have some physical restrictions in your life because of your prior brain tumor? Do you need help with any daily activities? What are your living arrangements like? Are you currently working or studying/at school? If yes, how does it go? Are you able to do any sports? <u>Mental dimension:</u> Has the prior brain tumor influenced how you are as a person? If yes, can you describe how? Are there other more important things that have influenced the way you have become? How is your mood generally? Has the prior brain tumor affected your mood now? <u>Social dimension:</u> Please, tell me about your family and your relationship with them. Have your brain tumor affected your relationships with your family? If yes, how? Have you other close relationships (friends, partner)? How do you feel about making contacts with other people (for example, with neighbours/work mates/teachers/people you don't know)? Has your brain tumor affected this? How does your brain tumor diagnosis affect your relationships? <u>World view:</u> Are you religious/spiritual? How do you feel about religion? Does it have some meaning for you? Has your brain tumor affected your spirituality? If yes, would you tell me how?
What things have affected your experience of having a brain tumor (for example certain people or situations)?	
Have some things had a positive or negative effect on your experience?	
How is your quality of life in your own opinion?	Are you mainly satisfied or unsatisfied with our life? Do you feel happy? Is there anything you would like to change in your life?
What things have affected/affect your quality of life and how?	What are the most important things in life to yourself? Does your former illness still have an impact on your life?
Do you think that by changing something in the health care system, your quality of life could have been better supported? (This does not need to be seen as a criticism. If we think there is always a way to improve things, what do you think it could it be?)	

4.6 Ethics

The Ethical Committee of the Hospital District of Southwest Finland has approved the study protocol (register number 18/180/2010, date 20.04.2010). The permission for use of the registry data from the FCR and the HDR was obtained from National Institute for Health and Welfare (register number THL/531/5.05.00/2010, date 12.10.2010).

4.7 Statistical methods (Studies I-IV)

Statistical methods used in Studies I-IV are presented in Table 7 and study time lines for Studies I-III in Figures 5 and 6.

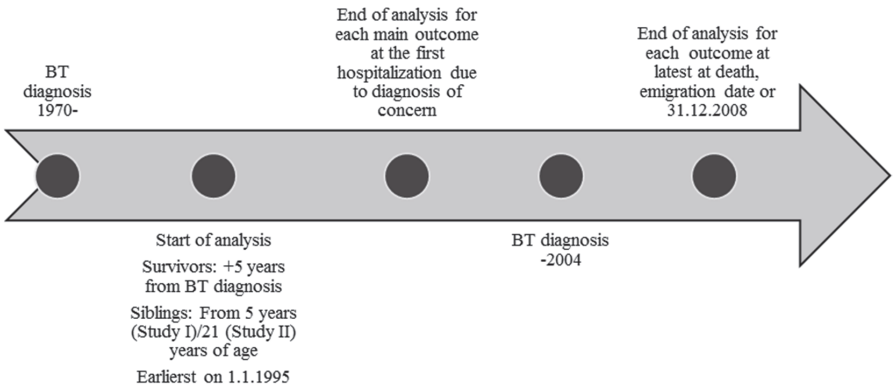

Figure 5. Follow-up period in Studies I and II (Gunn et al. 2014 and Gunn et al. 2015).

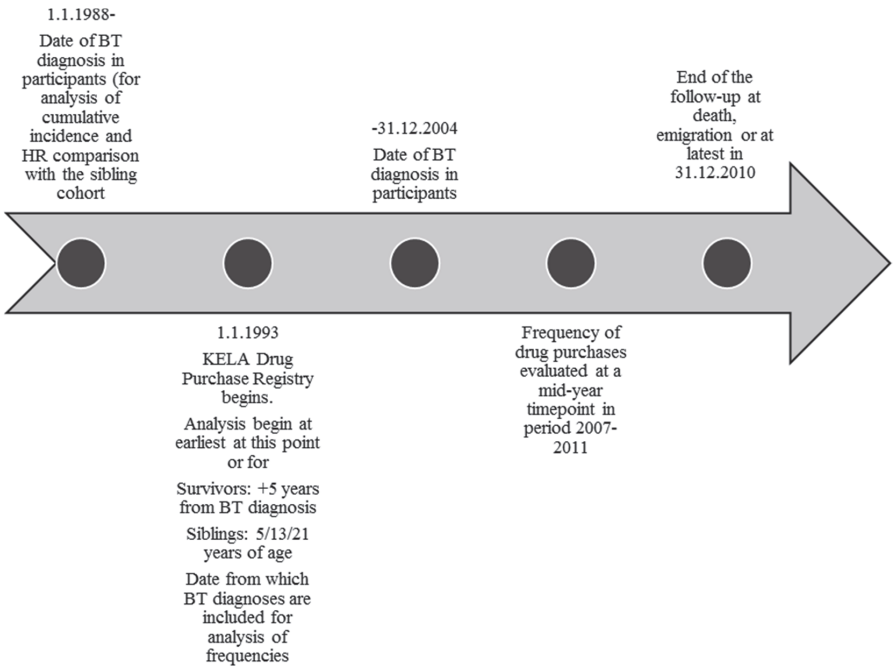

Figure 6. Period of drug purchases analyzed in Study III (Gunn et al. 2016a).

Table 7. Statistical methods used in Studies I-IV. Adapted from Gunn et al. 2014, Gunn et al. 2015, Gunn et al. 2016a and Gunn et al. 2016b.

No.	Study cohort	Outcomes studied	Methods
I	Study group: 5-year BT survivors diagnosed at 0-15 years of age (N=740) Control group: Siblings of all BT patients diagnosed at 0-24 years of age (N=3615)	Eight main outcomes (Table 5) and common separate diagnoses	Comparison between the survivors and the control group: Cox regression (results shown as hazard ratios (HR) and 95% confidence interval).
		Effect of sex and treatment era on main outcomes	Comparison between the survivors and the control group: see above. Comparison between treatment eras: Cox regression, contrasts. Predictors: treatment era (1970-1979,1980-1989,1990-2004), birth year cohort (1959 or before, 1960-1969, 1970-1979, 1980-1989, 1990 or after), sex and interaction between sex and previous cancer status (survivor/sibling)
		Effect of histology on main outcomes	Comparison between separate histology groups (astrocytic tumors and other gliomas, N=494; embryonal tumors, N=79; ependymomas, N=61) and the control group: see above. Analyzes were adjusted for sex and birth year cohort.
		Effect of irradiation on main outcomes	Comparison between the irradiated survivors and the non-irradiated survivors: see above. Analyzes were adjusted for sex and birth year cohort.
		Effect of age at diagnosis on main outcomes	The survivors diagnosed at 6-10 years or 11-15 years of age were compared with those diagnosed at 0-5 years of age: see above. Analyzes were adjusted for sex and birth year cohort.
		The age specific cumulative prevalence for main outcomes	BT survivors analyzed at 5, 10, 20 and 30 years from cancer diagnosis. A percentage (%) evaluated as survivors who had been diagnosed by the end of each period divided by the survivors alive at the end of that period. Comparison between the survivors and the control group: Fisher's exact test. Mean age of the survivors at every evaluation point was the age at which the control group was evaluated for comparison.
II	Study group: 5-year BT survivors diagnosed at 16-24 years of age (N=315) Control group: Siblings of all BT patients diagnosed at 0-24 years of age (N=3615)	Seven main outcomes (Table 5) and common separate diagnoses	Comparison between survivors and the control group: Cox regression (results shown as hazard ratios (HR) and 95% confidence interval).
		Combined effect of sex and cancer status on main outcomes	Comparison between the survivors and the control group: see above. Predictors used: birth year cohort (1959 or earlier, 1960-1969, 1970, 1979, 1980-1989, 1990 or later), sex, and relationship between sex and cancer status (survivor/sibling).
		Effect of treatment era on main outcomes	Comparison between treatment eras (1970-1979, 1980-1989, 1990-2004): Cox regression, contrasts.
		Effect of irradiation on main outcomes	Comparison between the irradiated survivors and the non-irradiated survivors and the control group. Comparison between non-irradiated survivors and the control group: Cox regression (results shown as HRs and 95% confidence interval). Analyzes were adjusted for sex and birth year cohort.
		The age specific cumulative prevalence for main outcomes	See Study I

No.	Study cohort	Outcomes studied	Methods
III	Study group: 5-year BT survivors diagnosed at the age of 0-24 years (N=420 for frequency figures, N=602 for other analyses) Control Group: Siblings of all BT patients diagnosed at the age of 0-24 years (siblings born before 1968 excluded) (N=2188-2392 depending on the analysis)	Frequency of drug purchases by the time of 5-year survival	Frequency (%) of 5-year BT survivors having purchased a drug by 5-year survival.
		Frequency of drug purchases in the middle of time period 2007-2010	Frequency (%) of the survivors alive and the the control group having purchased a drug by certain time points during the follow-up. As the difference between frequencies in separate time points was scarce, only the frequency in the middle of the latest period (2007-2010) was presented.
		The cumulative incidence of purchasing certain drugs	Cumulative incidence was estimated from 5 years since BT diagnosis in survivors. Survivors diagnosed at different ages (0-7, 8-15 and 16-24 years) were evaluated separately. In siblings, the follow-up started from the ages of 5, 13 and 21 years with death as a competing risk.
		Comparison between the survivors and the control group for purchasing certain drugs	The Fine and Gray proportional subdistribution hazards method {{202}}. Analyses were adjusted for birth year, difference between cases and siblings in age at the start of follow-up, age group at the start of follow-up and sex.
		Effect of irradiation, age at diagnosis, birth year and sex on drug purchases	Effect of different variables in the survivor group: irradiation (yes/no), age at diagnosis (8-15 years and 16-24 years compared with 0-7 years), birth year and sex: HRs.
IV	Childhood ependymoma/ medulloblastoma survivors (N=21) Control group (15D): General population (N=327) from previous study	15D – total score and dimensions	The differences between the participants and the control group: a chi-square-test (dimensions), a generalized linear model (total score). Age- and sex-adjusted OR's: logistic regression.
		Qualitative QOL interview	Phenomenological method
The significance level was defined as a p-value of <0.05 in all the analyses. Statistical analyses were performed using SAS, version 9.3.			

5 RESULTS

5.1 Morbidity and medication after young onset brain tumor (Studies I-III)

5.1.1 Endocrinological morbidity and medication (Studies I-III)

Study I-II: The HR for endocrinological morbidity among childhood and AYA survivors compared with the sibling cohort was 14.7 and 2.9, respectively (Table 8). For childhood BT survivors, the HR for hypothyroidism was 186.9 (95% CI 22.0–1584.7), and 223.9 (95% CI 52.7–952.3) for disorders of the pituitary gland. The HR for endocrinological morbidity among childhood BT survivors was greatest for patients with a history of an embryonal tumor (HR 70.1; 95% CI 36.1–136.0), although a clear risk was seen as well among ependymal tumors (HR 26.2; 95% CI 11.4–60.0) and astrocytomas/gliomas (HR 10.1; 6.0–16.9) as compared with the control group.

Study III: Medication for endocrinological morbidity was common with young onset BT patients at five years after diagnosis; especially systemic hydrocortisone (18.3%), sex hormones in females (17.6%), thyroid hormones (11.2%) and growth hormone (10.0%) were in rather extensive use (Table 9). The frequencies seemed to increase at later time points with respect to all endocrinological medication except for mineralocorticoids. However, the actual changes in percentage points were low. In female AYA survivors, a plateau curve was seen for cumulative incidence of purchases of new endorinological medication before ten years of follow-up (Study III). In childhood survivors instead, new purchases for thyroid hormones were also seen after ten years from BT diagnosis. The greatest increase of HR compared with the control group after 5 year survival was for growth hormone, although an increase was also found for thyroid hormones, estrogens and androgens (Table 10). Irradiation treatment increased the risk for all of the aforementioned medications. Age at cancer diagnosis affected the HR for the need of new growth hormone medication, but not for the other endocrinological medications. Female sex seemed to increase the risk for requiring thyroid medication, whereas the risk for growth hormone medication was comparable in males and females.

Table 8. Comparison of morbidity between BT survivors and the sibling cohort. Hazard ratios (HR) for different new diagnoses in 5-year BT survivors compared with the sibling cohort and the impact of irradiation treatment among the survivors. Analyzes are adjusted with sex and birth year cohort. Modified from Gunn et al. 2014 and Gunn et al. 2015.

	Study I: Survivors diagnosed at 0-15 years of age					**Study II: Survivors diagnosed at 16-24 years of age.**				
	Survivors vs. the control group, N=740			**Irradiated vs. non-irradiated survivors**		**Survivors vs. the control group, N=315**			**Irradiated vs. non-irradiated survivors**	
Outcome	**N**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**N**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
Endocrine diseases	52	14.7	(9.5-22.6)	6.2	(3.3-11.7)	6	2.9	(1.1-8.0)	0.8	(0.1-4.9)
Psychiatric disorders	58	1.8	(1.4-2.5)	0.9	(0.5-1.6)	20	2.0	(1.2-3.2)	1.4	(0.5-3.8)
Cognitive and developmental disorders	27	16.6	(9.1-30.1)	1.9	(0.8-4.1)	N/A	N/A	N/A	N/A	N/A
Diseases of nervous system	87	9.8	(7.3-13.2)	1.8	(1.2-2.8)	47	9.6	(6.6-14.0)	3.3	(1.8-6.2)
Disorders of vision or hearing loss	48	10.5	(6.9-16.0)	2.1	(1.2-3.9)	7	3.6	(1.5-8.5)	0.7	(0.1-3.8)
Diseases of circulatory system	15	2.7	(1.5-5.0)	2.2	(0.8-6.3)	22	4.9	(2.9-8.1)	1.8	(0.8-4.3)
Disorders of musculoskeletal system or connective tissue	38	1.4	(1.0-1.9)	0.9	(0.4-1.8)	19	1.4	(0.9-2.3)	1.3	(0.5-3.4)
Diseases of the kidney	7	2.1	(0.9-5.1)	3.6	(0.7-19.7)	8	5.9	(2.5-14.1)	0.8	(0.2-3.3)

Table 9. Frequency (%) of 5-year survivors with a drug purchase at 5-year survival, and frequency (%) of the BT survivors and the sibling cohort with a drug purchase at the latest mid-year time point (period 2007-2011). [a] Female survivors, [b] Male survivors, [c] Only purchases made before age of 7 years are analyzed (All 5-year survivors, N=412) (Gunn et al. 2016a), Published with permission from © Springer Science+Business Media New York 2016.

	Frequency (%) of the 5-year survivors with a drug purchase at 5 year survival	**Frequency (%) of the 5-year survivors and siblings with a drug purchase at mid-year time point in the period 2007-2011**	
Medication	**Survivors N=420 (Female, N=193; Male, N=227)**	**Survivors N=392 (Female, N=179; Male, N=213)**	**Siblings N=2392 (Female, N=1181; Male, N=1211)**
Thyroid hormones	11.2	14.5	1.1
Growth hormone	10.0	12.2	0.0
Hydrocortisone for systemic use	18.3	18.6	0.2
Mineralocorticoids	0.7	0.5	0.0
Desmopressin[c]	2.4	3.6	0.7
Diabetes	0.7	2.0	1.4
Lipid modifying agents	0.5	1.0	0.7
Estrogens[a]	3.6	5.0	1.5
Progestogens[a]	11.4	16.2	11.5
Progestogens and estrogens in combination	3.1	5.0	0.9
Hormonal contraceptives for systemic use	4.1	7.8	12.2
Gonadotropins and other ovulation stimulants	0.2	1.0	1.2
All sex hormones-females	17.6	24.0	21.9
Androgens[b]	2.6	6.1	0.2
Bisphosphonates	0.7	1.3	0.1
Any endocrinologic medication – females	33.2	39.1	24.9
Any endocrinologic medication – males[b]	29.1	31.0	3.3
Antiepileptics	44.8	47.5	3.9
Anti-parkinson drugs	0.7	0.8	0.2
Methylphenidate	0.2	0.5	0.3

Table 10. The Hazard ratios (HR) for a drug purchase more than 5-years after BT diagnosis (1988-2004) compared with a sibling cohort, and effect of irradiation, age at diagnosis, birth year and sex of the survivors on the HR of purchasing a drug. [a]Any endocinologic medication in females, [b]Any endocrinological medication in males (Gunn et al. 2016a). Published with permission from © Springer Science+Business Media New York 2016.

Variable			Effects of background variables for the drug purchase of the 5-year survivors									
			Irradiation		Age at cancer diagnosis - years						Sex	
	Survivors vs. siblings		Yes vs. No		8-15 vs. 0-7		16-24 vs. 0-7		Birth Year		Female vs. Male	
Medication	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Thyroid hormones	10.6	(5.1, 21.4)	6.5	(3.4, 12.7)	0.7	(0.3, 1.6)	0.6	(0.2, 1.9)	1.0	(1.0, 1.1)	2.0	(1,1, 3.8)
Growth hormone	345.5	(61.2, 6507. 8)	5.6	(2.3, 14.0)	0.1	(0.0, 0.4)	0.0	NA	1.0	(0.9, 1.1)	0.9	(0.3, 2.0)
Estrogens/females	8.0	(2.1, 25.7)	5.4	(1.6, 21.0)	0.8	(0.2, 4.2)	0.5	(0.0, 5.9)	1.0	(0.9, 1.1)	NA	NA
Androgens/males	63.3	(8.2, 1310.4)	3.9	(1.2, 14.8)	1.8	(0.3, 8.5)	1.2	(0.0, 22.2)	1.1	(1.0, 1.3)	NA	NA
Endocrinologic/ females[a]	2.0	(1.1, 3.6)	2.4	(1.2, 4.7)	1.1	(0.5, 2.6)	1.0	(0.3, 3.3)	1.0	(0.9, 1.0)	NA	NA
Endocrinologic–males[b]	3.5	(1.0, 10.0)	1.6	(0.5, 4.1)	0.2	(0.0, 0.8)	0.1	(0.0, 1.0)	0.9	(0.8, 1.1)	NA	NA
Antiepileptics	6.3	(3.4, 11.2)	1.5	(0.9, 2.5)	1.0	(0.5, 2.1)	0.7	(0.2, 2.2)	1.0	(0.9, 1.0)	1.5	(0.9, 2.4)

5.1.2 Psychiatric morbidity (Studies I-II)

The HR for psychiatric disorders among childhood and AYA survivors was similar as the value in the control group. A significant increase was seen for following diagnostic groups separately among childhood BT survivors: schizophrenia/delusional disorders (N=13; HR 2.2; 95% CI 1.1–4.1), mood disorders (N=28; HR 2.3; 95% CI 1.5-3.6) and neurotic/somatoform disorders (N=19; HR 1.9; 95% CI 1.1-3.2), but not for psychoactive substance use (N=19; HR 1.5; 95% CI 0.9-2.4). Among AYA survivors, no specific diagnostic groups reached a statistically significant difference as compared with the appropriate control group. The psychiatric disorders in AYA BT survivors included cases of psychoactive substance use (N=5; HR 0.8; 95% CI, 0.3–1.9), schizophrenia/delusional disorders (N=2; HR 1.1; 95% CI, 0.3–4.7), mood disorders (N=9; HR 1.7; 95% CI, 0.8–3.4), and neurotic/somatoform disorders (N=4; HR, 1.3; 95% CI, 0.5–3.8). Childhood ependymal tumor survivors had no single case of psychiatric disorders, whereas the HR for embryonal tumors (N=4; HR 1.6; 95% CI 0.6–4.4) and astrocytic tumors/gliomas (N=46; HR 2.1; 95% CI 1.5–2.9) was of the same magnitude, although only the HR for the last-mentioned reached a statistically significant difference.

5.1.3 Cognitive and developmental disorders (Study I)

Childhood BT survivors with a history of an embryonal tumor had a higher HR (N=5; HR 32.3; 95% CI 11.9–87.2) than the survivors with ependymal (N=1; HR 6.5; 95% CI 0.9–48.4) or astrocytic tumors/gliomas (N=17; HR 15.5; 95% CI 7.9–30.6) compared with the control group for cognitive and developmental disorders at least 5 years after a BT diagnosis.

5.1.4 Neurological morbidity and medication (Studies I-III)

Studies I-II: Compared with controls, the HR for neurological diseases among survivors of childhood (HR 9.8, 95% CI 7.3-13.2) and AYA BT (HR 9.6, 95% CI 6.6-14.0) after 5 years' survival were similar. Irradiation increased the risk somewhat (Table 8). The risk of epilepsy was significant in both diagnostic age groups studied, with HRs of 23.3 (95% CI 14.8–36.5) and 37.1 (95% CI 20.7- 66.6) among childhood and AYA survivors, respectively. In childhood BT survivors, HR for cerebral palsy/paralytic syndrome was 49.4 (95% CI 20.9-116.8, N=25). Among AYA BT survivors, mononeuropathy/nerve root compression (N=9), other disorders of the brain (N=6) and hemiplegia (N=4) were the most common neurological diagnoses after epilepsy. Among childhood BT survivors the differences between

separate BT diagnostic groups were small: astrocytic tumors/gliomas HR 9.2 (N=62, 95% CI 6.6-12.7), embryonal tumors HR 8.8 (N=6, 95% CI 3.8-20.3) and ependymal tumors HR 14.1 (N=8; 95% CI 6.8-29.2).

Study III: Almost half of the BT survivors had needed epilepsy medication at some point (Table 9), and purchases of new epilepsy medication were still seen more than ten years from diagnosis among childhood BT survivors (Study III). Irradiation treatment, age at cancer diagnosis or sex showed no effect on use of antiepileptics after 5 year survival (Table 10).

5.1.5 Morbidity related to vision and hearing (Studies I-II)

Childhood BT survivors had a HR of 10.5 compared with a control group for diseases of vision or hearing loss at least five years from diagnosis. The comparable figure for AYA survivors was 3.6. Irradiation had a modest effect of increasing the risk only with survivors diagnosed in their childhood. The risk for separate diagnostic groups in childhood BT survivors compared with a control group were as follows: astrocytic tumors/gliomas HR 10.7 (N=35; 95% CI 6.8-16.9), embryonal tumors HR 14.2 (N=5; 95% CI 5.6-36.4) and ependymal tumors HR 8.1 (N=3; 95% CI 2.5-26.3).

5.1.6 Cardiovascular morbidity (Studies I-II)

The risk for cardiovascular morbidity (see Table 8 for figures for cardiovascular morbidity in general), especially cerebrovascular diseases, was increased in both childhood (HR 7.9; 95% CI; 3.8-16.4, N=9) and AYA (HR 9.3; 95% CI 4.9-17.7; N=30) BT survivors. The risk for late cardiovascular morbidity was found in survivors with childhood astrocytic tumors/gliomas (HR 2.8; 95% CI 1.4–5.4, N=11) and embryonal tumors (HR 6.1; 95% CI 1.4-25.6; N=2), but not with ependymal tumors (HR 2.6; 95% CI 0.4-19.4; N=1). Irradiation had no effect on the risk in either childhood or AYA survivors (Table 8).

5.1.7 Morbidity of musculoskeletal system and connective tissue (Studies I-II)

Among AYA BT survivors there was a small increase in the risk for late emerging disorders of the bone (HR 2.0; 95% CI 1.1–3.7). However, this was not seen in childhood BT survivors. In general, no increase was found in the risk for disorders of musculoskeletal system or connective tissue (Table 8).

Table 11. The age specific cumulative prevalence of main outcomes for all brain tumour survivors at points of time 5, 10, 20 and 30 years after cancer diagnosis compared with the outcome of the sibling cohort. The mean age of the survivors at each point of time is used as the age in which the sibling cohort is evaluated. [a] Study I, [b] Study II. Modified from Gunn et al. 2014 and Gunn et al. 2015.

	The age-specific cumulative prevalence (%)											
	5 years			10 years			20 years			30 years		
Outcome	Survivors N=740[a]/315[b]	Siblings N=3204[b]/2207[b]	p	Survivors N=559[a]/219[b]	Siblings N=2887[a]/1738[b]	p	Survivors N=270[a]/111[b]	Siblings N=1982[a]/959[b]	p	Survivors N=81[a]/31[b]	Siblings N=1178[a]/356[b]	p
Endocrine diseases												
Dg age 0-15	10.1	0.4	<0.001	13.4	0.8	<0.001	12.2	0.9	<0.001	4.9	1.3	0.029
Dg age 16-24	1.9	0.8	0.109	1.8	1.0	0.283	4.5	1.4	0.031	6.5	1.7	0.126
Psychiatric disorders												
Dg age 0-15	3.7	0.7	<0.001	5.6	1.6	<0.001	9.6	4.4	<0.001	11.1	6.4	0.106
Dg age 16-24	6.7	4.1	0.054	9.1	5.4	0.032	12.6	6.6	0.030	9.7	5.9	0.426
Diseases of nervous system												
Dg age 0-15	25.5	1.1	<0.001	30.4	1.2	<0.001	32.6	2.0	<0.001	32.1	3.1	<0.001
Dg age 16-24	25.4	1.7	<0.001	28.8	2.5	<0.001	31.5	3.2	<0.001	25.8	3.9	<0.001
Disorders of vision or hearing loss												
Dg age 0-15	10.0	1.4	<0.001	11.8	1.5	<0.001	14.4	2.0	<0.001	12.4	1.7	<0.001
Dg age 16-24	5.4	1.8	<0.001	8.2	1.8	<0.001	6.3	1.5	0.004	9.7	1.1	0.013
Diseases of circulatory system												
Dg age 0-15	2.4	0.0	<0.001	2.5	0.0	<0.001	4.8	0.6	<0.001	3.7	0.9	0.056
Dg age 16-24	2.2	0.5	0.003	3.7	0.7	<0.001	5.4	1.4	0.009	16.1	3.7	0.010
Disorders of musculoskeletal system or connective tissue												
Dg age 0-15	3.2	1.3	<0.001	4.5	2.7	0.030	5.2	3.9	0.321	13.6	5.1	0.004
Dg age 16-24	5.4	4.2	0.375	5.9	4.4	0.301	8.1	5.8	0.398	9.7	8.4	0.739
Diseases of the kidney												
Dg age 0-15	0.7	0.2	0.025	0.7	0.2	0.064	0.7	0.5	0.632	0.0	0.3	1.000
Dg age 16-24	0.0	0.5	0.382	0.0	0.5	0.609	2.7	0.5	0.041	9.7	1.1	0.013

5.1.8 Renal morbidity (Studies I-II)

An increased risk for late renal morbidity was seen in the AYA survivors (HR 5.9; 95% CI 2.5-14.1). In childhood survivors the risk was found only in the survivors of embryonal tumors (HR 8.5; 95% CI 1.9–37.7).

5.1.9 Impact of age at diagnosis on morbidity (Study I)

Among childhood BT survivors the effect of age at diagnosis was assessed separately, but no significant effect was found (Table 12).

Table 12. The impact of age at diagnosis for late morbidity among childhood BT survivors. Morbidity of survivors diagnosed at age of 6-10 years or 11-15 years compared with survivors diagnosed at the age of 0-5 years. Adapted from Gunn et al. 2014.

	6-10 vs. 0-5 years		11-15 vs. 0-5 years	
Outcome	**HR**	**95% CI**	**HR**	**95% CI**
Endocrine diseases	0.5	(0.2-1.1)	1.4	(0.5-3.8)
Psychiatric disorders	1.2	(0.6-2.3)	1.4	(0.7-2.8)
Cognitive and developmental disorders	0.7	(0.2-2.3)	0.0	(0.0-2.5)
Diseases of nervous system	0.8	(0.5-1.4)	0.9	(0.5-1.9)
Disorders of vision or hearing loss	0.7	(0.3-1.4)	0.8	(0.4-1.9)
Diseases of circulatory system	0.6	(0.1-3.7)	3.9	(0.8-20.2)
Disorders of musculoskeletal system or connective tissue	1.5	(0.6-4.1)	1.4	(0.4-4.1)
Diseases of the kidney	0.0	(0.0-1.1)	1.2	(0.2-7.7)

5.1.10 Impact of sex and treatment era on morbidity (Studies I-II)

The interaction between sex and cancer status (survivor/sibling) was assessed to see whether cancer and its treatments would affect males and females differently, while disregarding the baseline difference between the morbidity in the two genders. In childhood BT survivors, the risk of females developing disorders of vision or hearing loss compared with female siblings was higher than the risk for males. The AYA female survivors also experienced an elevated risk (HR, 2.7; 95% CI, 1.0–7.3) for disorders of the musculoskeletal system than males when compared with healthy siblings of the same sex, although the confidence interval was at the threshold of statistical significance.

Treatment era was not associated with a risk of morbidity in AYA survivors and in only few areas with childhood BT survivors. Among childhood survivors, the following effects were seen: disorders of vision or hearing loss were more common in 1980's (HR 2.8; 95% CI 1.3–6.4) and 1990– 2004 versus the 1970's (HR 3.2; 95% CI 1.3–8.1), and endocrine diseases were more common in 1990– 2004 versus 1970's (HR, 2.8; 95% CI, 1.1–7.2).

5.2 Quality of Life after Young Onset Brain Tumor (Study IV)

5.2.1 Life style characteristics of the participants

Educational, functional, and social characteristics and use of health care of the participants in study IV are presented in Table 13. Mean self-reported heights of male and female participants ≥18 years of age at the time of the interview were 167cm (range 146-181 cm) and 158 cm (range 145-170 cm), respectively. Survivors' mean weight was 76 kg (range 53-99 kg) for males and 60 kg (range 41-98 kg) for females, and a body mass index (BMI) was 25 kg/m2 (range 18-41 kg/m2) for both sexes combined.

Table 13. Life style details of the participants (N=21) in Study IV. [a]Supported employment included. Volunteer work excluded. [b]Exercise that makes a participant sweat or breathless. Modified from Gunn et al. 2016b. Part of the data not shown in the original publication.

Characteristics	N	(%)
Level of education		
Comprehensive school, at least 6 years	3	(14.3)
Comprehensive school, at least 9 years	6	(28.6)
Vocational school	10	(47.6)
Upper secondary school	1	(4.8)
University of applied sciences	1	(4.8)
Need for special education	12	(57.1)
Military service, males ≥18 years (N=10)	4	(40.0)
Driving licence (currently valid)	9	(42.9)
Exercise at least 20min at a time[b] (N=20)		
0 time/week	4	(20.0)
1-2 times/week	7	(35.0)
≥3 times/week	9	(45.0)
Frequency of meeting friends (N=20)		
Everyday	7	(35.0)
Once a week, at least	10	(50.0)
Less frequently	3	(15.0)
Sexual activity (currently or previously)	10	(47.6)
(Attempt of) a pregnancy (oneself or a partner) (N=10)	0	(0.0)
Number of contacts with a doctor within previous 2 years time (N=19)		
<5 times	11	(57.9)
5-10 times	6	(31.6)
>10 times	2	(10.5)
Need for treatment in a hospital ward within the previous 2 years	5	(23.8)

5.2.2 The results from Beck Depression Inventory

Based on BDI, the majority of BT survivors showed no signs of depression. The total score fell below the cut-off level (≤13 points) in 95.2% of the survivors. One participant (4.8%) had a total score indicative for severe depression.

5.2.3 The results from 15D-questionnaire on HRQOL

HRQOL results of the participants assessed with 15D are presented in Table 14. The total scores for the survivors and the control group were 0.90 and 0.94, respectively (estimated difference -0.04, 95% CI -0.07, -0.01) (Gunn et al. 2016). There were significantly lower mean scores among the survivors for mobility (0.92 vs. 1.00, p<0.01), vision (0.93 vs. 0.98, p<0.001), hearing (0.91 vs. 0.99, p<0.001), eating (0.96 vs. 1.00, p<0.001), speech (0.84 vs. 0.99, p<0.001), usual activities (0.82 vs. 0.97, p<0.001), mental function (0.82 vs. 0.93, p<0.05), and sexual activity (0.90 vs. 0.96, p<0.01) compared with the control group. No significant differences were found in the following dimensions: breathing, excretion, discomfort and symptoms, depression, distress, and vitality. The survivors had higher scores in the dimension of sleeping than the controls (p<0.05). Adjustment for age and sex did not affect the results.

Table 14. The results from 15D questionnaires (only the survivors ≥16 years of age at the time of an QOL-interview, N=19). Adj. OR= Age and sex adjusted odds ratio. (Gunn et al. 2016b)

	The survivors		The control group				
Variable	**Mean**	**(SD)**	**Mean**	**(SD)**	**p**	**Adj. OR**	**(95% CI)**
Mobility	0.92	(0.21)	1.00	(0.02)	0.009	21.4	(1.6, 235.1)
Vision	0.93	(0.10)	0.98	(0.07)	<0.001	8.9	(2.6, 28.9)
Hearing	0.91	(0.16)	0.99	(0.05)	<0.001	14.7	(4.3, 49.9)
Breathing	0.91	(0.16)	0.95	(0.12)	0.065	2.9	(0.8, 8.7)
Sleeping	0.95	(0.13)	0.85	(0.18)	0.033	0.3	(0.1, 0.8)
Eating	0.96	(0.11)	1.00	(0.02)	<0.001	62.4	(6.8, 800.0)
Speech	0.84	(0.15)	0.99	(0.07)	<0.001	29.1	(9.5, 96.5)
Excretion	0.96	(0.19)	0.95	(0.12)	0.267	0.3	(0.0, 1.7)
Usual activities	0.82	(0.25)	0.97	(0.10)	<0.001	8.0	(2.7, 22.7)
Mental function	0.82	(0.21)	0.93	(0.15)	0.010	3.6	(1.3, 9.5)
Discomfort and symptoms	0.89	(0.15)	0.83	(0.17)	0.230	0.5	(0.2, 1.4)
Depression	0.91	(0.21)	0.88	(0.17)	0.627	0.8	(0.2, 2.1)
Distress	0.93	(0.18)	0.87	(0.18)	0.091	0.3	(0.1, 1.1)
Vitality	0.88	(0.21)	0.88	(0.17)	0.993	1.0	(0.4, 2.6)
Sexual activity	0.90	(0.14)	0.96	(0.11)	0.008	4.8	(1.5, 14.2)
Total	0.90	(0.09)	0.94	(0.06)	0.008	-0.04[e]	(-0.07,-0.01)

5.2.4 Results from qualitative QOL interviews

The participants were asked which factors had affected their QOL. The following issues were mentioned most commonly in order of declining frequency: social relationships, health and physical symptoms, activities and independence. Two thirds of the survivors described their mood in a positive way. Two survivors told

they were suffering from depression, and one had previously had visual and auditory hallucinations. Based on the qualitative interviews, eight main themes and several subthemes were created. The themes, subthemes and examples of the quotes which were used as the basis of the themes are presented in table 15.

Table 15. Themes, subthemes and examples of data extracts used in creating them. Adapted from Gunn at el. 2016b. Part of the data not shown in original publication.

Themes and subthemes	Examples of quotes
Positive growth stimulated by cancer	
General expanding of worldview and change in values	*"Well, I don't even know whether I would like to forget, or not… I wouldn't want to forget that thing (cancer), because it taught me so many things, and made me wiser. It made me stronger, …and gave me self-confidence." (male, 14 years)*
An increased approval of difference in others	*"..it has had a positive side that I have learnt to appreciate also different kinds of people and in a way to see also positive things, so… And after all I'm alive and things could be much worse." (female, 19 years)*
Positive attitude: Learning a more positive attitude	*"At least I have learned to value smaller things and to live one day at a time." (female, 30 years)*
Gratitude for survival	*"I am pretty satisfied that I have survived, and there's nothing else left basically than the scars" (male, 28 years)*
Negative conceptions concerning illness	
Negative experience of being different – A need for "normality"	*"It always feels like people look at me with pity, and think that, because I got this (cancer) I must be somehow weaker than others, or something." (female, 21 years)* *"..writing and other things were much slower. - - but I just tried to do my best and go on. -- I never talked about that to a teacher. Maybe I was just so shy that I did not want to differ in any way. (male, 28 years)*
Bitterness and disappointements concerning the cancer and the health care system	*"Every now and then, or actually quite often, it feels pretty unfair, that why was it me who got ill. Afterwards, I have felt that it has only caused discomfort. Again and again there comes something else because of that (cancer) and I haven't been able to live a normal life like any other adolescent." (female, 19 years)*
Living in the moment	*"Because of me having a brain tumor as a child, we are practically living in the moment or along with the situation." (male, 28 years)*
Young age at diagnosis and time past diminish the effect of cancer	
The cancer has no more significant meaning to life	*"But I have coped well. With medication I don't have seizures and so I can live a normal life." (female, 35 years)* *"I do recognize it (an effect of cancer) and every now and then, it comes to my mind in some instances, so it does have some role in some situations, but it is not a big thing." (female, 20 years)*
Young age at diagnosis affecting the experience of cancer	*"I don't know much about it [getting cancer] myself. I was so little then that I don't know what's been done and what has it caused" (male, 28 years)*
Social relationships have a major role in experience of survival	
Difficulties in friendships and remedial effect of good friendships	*"At school, I couldn't get friends. I think it was because of the illness (cancer)." (male, 28 years)* *"Of course they talked at school and said hello and so on, but when I couldn't go out with them more, so it just passed, and the distance between us became bigger and bigger." (male, 33 years)*

Themes and subthemes	Examples of quotes
	"Of course when you're different, when you are in smaller school class, you'll be thrown into a corner?. So, then I was maybe a little.. what is it.. a little discriminated. But then again in the classroom I had good friends, and a couple of good friends with whom I could spend time and do things. So, basically I did not need any other friends then. (male, 28 years)
The essential impact of family	*"It was of huge significance that my mother was kind of my mainstay. Sometimes I felt that no, I wouldn't have had enough strength without my mum." (female, 30 years)*
Bullying	*"It was in the comprehensive school. I was so lonely when I was called names so much." (tearful) (female, 19 years)* *"The children of one family living at the house harassed me. They shouted me behind the window and called names. - - That made me feel pretty unsafe." (female, 30 years)*
Learning disabilities and limitations in vocational selection	*"It has been frustrating that when I've read a lot for exams and yet they haven't went very well.. those exams.." (female, 20 years)* *"Cramming books and such doesn't go too well. I think it's partially a motivational problem. I don't know how much it could have affected that I have a lemon-sized hole in my head. I guess it could somehow affect the learning and memory - -" (male, 22 years)* *"Basically, what there is left (from the cancer) is serious dyslexia, which affects vocational selection and so on" (male, 28 years)* *"It would be nice of course that I could also work someplace else, but it is quite impossible. But otherwise I've been happy and it's really important to me that there's a place to go. Being just inside four walls would probably make me crazy." (working in sheltered workplace, female, 30 years)*
Limitations in independent life	*"I guess that in some things I need a lot of help e.g. in cooking.." (female, 19 years)*
Understanding of a term"health" is being modified	
Defining oneself as healthy	*"I do feel that I am healthy at the moment. That my physical and mental health are reallyalright and I have energy to do anything. Well of course, -- I have type 2 diabetes, so I need to think what I eat and how much I do sports and that. But I am healthy, my treatments are all finished and so."(female, 19 years)*
Physical aspects affecting health: Increased fatigue and need of sleep Epilepsy restrains life An appearance that tells of prior cancer	*" A subconscious fear remained that if the seizure starts I don't ever want to be sitting in a place in middle in public. I always want that there is a way out. "(female, 35 years)* *"I've noticed that small kids stare at me a lot. - - Sometimes I feel that they shouldn't do that and I feel a bit annoyed" (female, 19 years)*
Minor limitations on motility: The impaired balance restricts doing sports The sports have a major positive impact on life	*"Balance of course, ..although many people say that it is good, but it is worse than others'.." (male, 24 years)* *"The enthusiasm for sports and health which started from it (having a brain tumor),.. through that, when I had done sports and got some feelings of success, so through that, I gained self-confidence and so on. - - Actually after the enthusiasm for sports when I had got self-confidence I got quite a bunch of new friends" (male, 22 years)*

Fifty-two per cent of the survivors felt they had received at least some positive impact from their cancer. Some even felt the impact of cancer had been positive overall. One of the positive impacts that the survivors described that they had gained from cancer was that they felt they could experience the world differently, more comprehensively and from a different view, and for some it had given them strength. Some of the survivors felt they had become more tolerant for differences in others, and they had learnt to appreciate people with disabilities. The survivors also described learning more positive attitude because of the cancer experience.

One issue that the survivors sometimes faced was the feeling of being treated differently by others because of their prior illness. Sometimes minimizing their own problems seemed to be caused by this unwillingness to be different from others. Some young men also felt displeased by their disqualification from military service, as in Finland military service is mandatory for males.

For some of the survivors having a serious life threatening illness meant that they did not make any plans for the future, but lived one day at a time.

Many years after the BT diagnosis, nearly 40% of the participants no longer felt any significant effect of cancer on their everyday life, although some late-effects might have existed. If they had been diagnosed at a very young age, it was impossible for a child that young to understand the severity of the diagnosis and afterwards the memories on the treatments had faded. For those diagnosed in their early years, they might not be able to make a comparison of how life was before the diagnosis or the possible late-effects because they could not recall the time before the diagnosis.

The importance of social relationships were emphasized by many of the survivors. One third of the participants described difficulties in making friendships. Especially survivors with medulloblastoma reported social difficulties. Close to half of the participants had encountered bullying associated with their BTs. Support from close friends and family was described as important.

Most of the survivors had experienced learning difficulties and special support at school had been offered to every second survivor. Some who had not received additional support described for example motivational problems or difficulties in memory or motor functioning. Some of the survivors had participated in a one year ”training course” to support either independent living or before starting a vocational school and this was assessed as beneficial. Many of the survivors felt disturbed by the fact that they had limitations in selecting an occupation due to the prior BT or its late-effects. Some might also suffer from physical limitations making it difficult to fulfill the demands of the work. However, some have been able to find employment that they enjoyed.

Independent living and managing everyday tasks by oneself were described important.

More than half of the survivors experienced that they were healthy. Some felt they did encounter minor limitations and only a few described major health related problems. In some cases, there was a mismatch between the survivors' own impressions of their health and their health status based on medical history. The physical aspects associated with their prior cancer that the survivors described as the most important in current life were fatigue, epilepsy and their appearance.

Two thirds of the participants described some problems with their balance, poor fitness or headaches during physical exercise of which majority were mildly limiting for example, in some specific sports. Two survivors needed a wheelchair. Some male survivors reported a great positive impact on their QOL from doing sports, e.g. making new friends and improving self-confidence.

The following issues were mentioned by the interviewees a few times, but were not sufficiently frequent or coherent enough to make a theme: difficulties for siblings caused by a cancer, fertility, a wish for an intimate relationship, and peer support. A few survivors had benefitted greatly from the communal nature of peer support organized by cancer organizations, but differences in the severity of late-effects or in the age of the survivors at these meetings could have created a feeling for some that they were an outsider. Concerning the issue of intimate relationships, three of the survivors were satisfied in their relationship. Two reported that they did not have a relationship but were totally satisfied with the situation and 5 had a wish for an intimate relationship in the future. However, at least two of them found that having had a cancer was not related to their failure to enter a relationship.

6 DISCUSSION

The aim of this research was to analyze the burden of morbidity in survivors of young onset BT as well as other aspects (e.g. social factors) which affect their later quality of life. It was observed that young onset BT survivors are a group of individuals who carry a high risk for developing several chronic late effects. Neurological diseases were found in excess both in childhood and AYA BT survivors. The excess risk for endocrinological diseases, cognitive disorders and diseases of vision or hearing was very clear in childhood BT survivors, whereas among the AYA survivors, the risk was notable, especially for diseases of the kidney and the circulatory system, mostly attributable to cerebrovascular morbidity. A less prominent elevated risk was found for psychiatric disorders in both age groups studied, for endocrine and vision/hearing-related conditions in AYA survivors and for circulatory diseases in childhood BT survivors. More than 10% of 5-year survivors were using thyroid hormone, growth hormone, hydrocortisone and/or progesterones, and close to 50% of survivors needed antiepileptics. It seems clear that the young onset BT survivors carry an additional risk of morbidity, even years after their BT diagnosis. Therefore, they should be entitled to a well formulated follow-up organized by a unit with expertise in the special needs these young people have. In general, there was a doubled risk for hospitalization among survivors of young adulthood CNS tumor compared to the risk of age-matched controls (Zhang et al. 2014), but until now, there has been very limited data concerning the late morbidity of AYA BT survivors. Our study revealed valuable data to guide the planning of follow-up services.

We found extensive variation in the quality of life of the BT survivors. Social relationships were assessed as very important for the QOL by the survivors themselves. The description of health seemed to be affected by the experiences of the survivors and in some cases, differed from their medical perspective, which is an important aspect to consider when planning the follow-up. Several of the BT survivors had attained a positive mental growth after the cancer although feelings of resentment were also found still years after diagnosis. The desire and need to feel like everyone else was described by many of the survivors. Several aspects of HRQOL were found to be impaired among BT survivors based on a 15D questionnaire. The difference seemed to be clinically significant as there was at least a 0.1 point difference in mean scores of BT survivors and the control group in speech, usual activities and mental function.

6.1 Theoretical implications

Studies I-III were based on large cohort national registries. The largest volume of research on childhood cancer survivors is based on the Childhood Cancer Survivorship Study-cohort of 14,054 survivors diagnosed between 1970 and 1986 before the age of twenty-one in USA, 1818 of whom had a history of a CNS tumor (treatment data available for 1607 survivors) (Gurney et al. 2003b, Packer et al. 2003). Our nationwide cohort of 1055 BT survivors diagnosed before age of 25 years (Studies I and II) can thus be seen as remarkable from a country with a population of 5.5 million. Most of the other studies concerning childhood cancer survivors have focused on specific findings originating from small samples.

It is worth noticing that our study sample in the registry studies (Studies I-III) was still moderately young and it is possible that the difference between the BT survivors and the control group would increase during longer follow-up. This is because certain morbidities, such as the function of certain organs, decrease with normal ageing and the threshold for morbidity may be surpassed (e.g. cardiovascular and nephrological morbidity and the need for medication with lipid modifying agents). Some trends towards that could be seen in cumulative prevalence figures of AYA survivors (Study II). It is also known that the effects of chemotherapy and irradiation may continue for a long time. For example, the decline of glomerular function after nephrotoxic therapy may be persistent and worsen with time (Mulder et al. 2013).

In study III, we aimed to evaluate the actual use of endocrinological and neurological medications because diagnosed morbidity does not necessarily lead to medication (e.g. due to compliance issues, expenses of medication or concerns related to side-effects of a treatment) and medication may sometimes be used without a diagnosis (e.g. preventive epileptic medication). Practices and indications used for starting a medication may also differ between hospitals, clinicians and time periods. For example, the use of methylphenidate in our study was low. However, its use in Finland has significantly increased in the 21st century and thus it is likely that in the future, the results will probably differ from those in our current study (Study III).

The impact of age at diagnosis on late morbidity was not explicitly interpretable based on studies I-III. Childhood and AYA survivors were not statistically compared, but the risk compared with the control group seemed clearly higher for endocrine diseases and disorders of vision/hearing with childhood survivors than with AYA survivors (Studies I-II). There were very few differences for other late effects. In Study I, however, no difference was seen in any area of morbidity between children diagnosed at 0-5, 6-10 or 11-15 years of age. However, in Study III, children diagnosed before eight years of age showed an increased need for

growth hormone therapy compared with older children/young adults and young boys showed an increased risk of requiring endocrinological medication compared with older children. Thus, younger children seem to be at a greater risk, at least for endocrinological late-effects. However, it is noteworthy that for example, embryonal tumors, which typically are treated with multimodal therapy are more common in early childhood and thus the distribution of different histologies may to some degree affect the results. It is also likely that older survivors are less likely to have been tested for growth hormone deficiency compared to younger survivors.

The impact of irradiation on neurological morbidity was evaluated in studies I-III. In Study III, we could not find any evidence that irradiation was responsible for any significant effect (HR 1.5; 95% CI 0.9-2.5) on the need for new antiepileptics (Study III). However, the survivors treated with irradiation showed an increased risk for developing a neurological morbidity both in childhood (HR 1.8; 95% CI 1.2-2.8) and AYA survivor (HR 3.3; 95% CI 1.8-6.2) groups compared with non-irradiated survivors (Studies I and II). The greater risk in AYA survivors might be related to the differences in proportion of supratentorial tumors between childhood and AYA BTs (Keene et al. 1999, Molineus et al. 2013), although the location of tumors was not evaluated in our studies. Among AYA BT survivors, irradiation did not affect other areas of morbidity (Study II), whereas among childhood survivors, an increased risk was found for endocrinological as well as vision/hearing related morbidity (Study I). Irradiation also affected the number of drug purchases for endocrinological conditions (Study III). The rate of irradiated patients in our registry based studies (I-III) was low (31-40%) compared with some other studies. For example, the CCSS cohort has as high as 72% rate for cranial irradiation in BT survivors (Packer et al. 2003). Thus, it must be recognized that the number of irradiated patients in study cohorts under evaluation may explain some of the differences in morbidity figures between different studies.

The risk for endocrinological, cognitive, vision/hearing-related, circulatory and nephrological problems seemed highest among childhood BT survivors with a history of an embryonal tumor (Study I). For example, the administration of cisplatin to BT patients is known to cause nephrotoxicity (Finkel 2014). Thus, the higher frequency for morbidity among survivors found in our study is probably associated with the multimodal therapy used for treating these tumors (Landier, W. et al. 2009), but this could not be evaluated more precisely because of the limitations of the treatment data concerning our registry cohort. Some of the hazard ratios were very wide as was the variation in confidence intervals, especially concerning specific diagnoses and comparison between different histology groups. This may be explained by the small number of cases despite the large cohort size in our study. Although the results give a good overall view of the risk of morbidity, the limited number of cases should be considered when interpreting individual diseases.

The study population in the registry-based studies included patients diagnosed with a BT since 1970 in studies I-II and since 1988 in Study III. The patients diagnosed in 2005 or later were not included. The interest on late morbidity and especially its more structured follow-up has increased tremendously during this century. For this reason, diagnostics have been made more actively, which will probably affect any results obtained in the future. It is likely that there was some degree of under-diagnostics of some diseases and conditions in the past decades.

Studies assessing the quality of life have great methodological differences, and many different surveys have been used to study QOL and HRQOL. Although by its very definition, quality of life is one individual's subjective experience, self-reporting has a risk that cognitive skills or less-constructive coping mechanisms such as denial, may prevent the respondent from bringing forth true experiences; this is especially true in questionnaire based studies. Our preliminary hypothesis was that good QOL reported by some of the earlier studies could be influenced by the fact that survivors with cognitive deficits may not be allowed to participate in the questionnaire based studies, as well as by the limited capacity of some of the survivors to understand the concepts and language used in questionnaires, and/or to relate these concepts to their own condition. We believe that interviewing the participants themselves in Study IV enabled the evaluation in the most reliable manner possible. There are also studies based on parent-reporting. However, one could argue that this would require very good mentalization skills from the parent. For example, it is probable that the parent's own adaptational difficulties towards their child's illness and possible mental problems may significantly affect his/her assessment.

As discussed in Study IV, QOL and HRQOL concentrate to partly different issues, although the two concepts are often concidered as one and the same. There are inevitably some compromises when assessing HRQOL among childhood BT survivors. These physical aspects, however, showed less importance for survivors than expected in Study IV. The results of 15D revealed a decline in several physical dimensions among the BT survivors. However, there were no differences in dimensions of discomfort, symptoms or vitality. We think this may represent habituation by the survivors to their limitations. Good QOL of childhood BT survivors and differences between self- and proxy-evaluation have earlier been explained by defensiveness, denial, habituation to the limitations, lack of past comparison, restricted capability to realistically evaluate the individual's own situation and restrictions and the need for social desirability in reporting (Maddrey et al. 2005, Zuzak et al. 2008, Frange et al. 2009, Ribi et al. 2005, Cardarelli et al. 2006, Laffond et al. 2012). Our study supported at least the theory of habituation to the limitations/lack of past comparison (Study IV). In Study IV, 43% of the participants were diagnosed before the age of six and thus the BT and its late-effects have

probably been part and parcel of the life of a survivor for as long as he or she could remember. Thus, there was no possibility for comparison. Denial of problems and negative coping mechanisms, if present, may be harmful, for example for rehabilitation. On the other hand, habituation to the limitations and coping with some physical limitations is clearly a desirable target and should be supported.

As the frequency of late effects varies between histologically different BTs (Study I), the selection of patients for a QOL study can exert a significant effect on the results (Study IV). The BT survivor group evaluated in Study IV had received intensive treatments, with irradiation and chemotherapy rates of more than 80%. Medical late-effects were common among the participants, and 57% of the participants had received some special education. Thus, the participants in Study IV should not represent only the best coping survivors.

The registries used in the studies I-IV have good quality. The Finnish Cancer Registry is recognized as allowing a comprehensive nationwide research on malignancies (Teppo et al. 1994). The Social Insurance Institution of Finland for its part covers data on all purchases of prescription drugs in Finland (Gissler et al. 2004). The Hospital Discharge Registry (Sund 2012, Terveyden ja hyvinvoinnin laitos) makes it possible to undertake a systematic collection of diagnoses made in specialized health care despite some limitations which will be discussed later.

6.2 Practical implications

As could be seen from Study III most of the endocrinological and neurological medication is started already during the first five years after a BT diagnosis (Study III). However, the survivors are at a significantly elevated risk for morbidity still after that. There was a difference in endocrinological, psychiatric, cognitive, neurological, vision/hearing-related and musculoskeletal morbidity between the childhood BT survivor and the control group at 5 years from diagnosis (Study I). The difference in starting new medication stayed significant still at 30 years from BT diagnosis for others except psychiatric diseases. In AYA BT survivors, a significant difference in cumulative prevalence compared with the control group was found in neurological and circulatory diseases, as well as in disorders of vision/hearing at five years from diagnosis (Study II). In each of these group of diseases the difference for the control group stayed significant still 30 years from diagnosis.

Some of the children assessed in Studies I and III have been diagnosed with a BT already in first years of life when sex hormone substitution is not yet needed. It is, however, essential to remember the possible need for that in the follow-up as the

need may start more than ten years from diagnosis (Study III). Based on the results from Study III, it seems that ten years of active follow-up might be sufficient for AYA BT survivors. By then the survivors would have probably as well faced issues concerning independency and work life which affect their QOL (Study IV). Thus, as well the support from social services could be included in the follow-up when necessary. Expertise on possible late effects should be available when necessary after that as well. An appropriate length for follow-up with childhood BT survivors is more difficult to determine based on the results gained (Studies I, III, IV), but seems to be longer than with AYA BT survivors.

In Finland, a working group appointed by the Ministry of Social Affairs and Health has started to design a way to organize the follow-up of young onset cancer survivors, but is still lacking sufficient resources for realizing their planning (Taskinen et al.). In Northern America, there are the guidelines for long-term follow-up for survivors of childhood, adolescent, and young adult cancers published by Children's Oncology Group (Children's Oncology Group 2008). Organizing proper medical care and rehabilitation for young onset cancer survivors can be argued for purely on humane grounds. However, it should also be taken in to consideration that the survivor group of concern are adolescents and young adults and for society's percpective survivors' rehabilitaton and enabling their participation in to a work life can be presumed to be financially beneficial as well.

Childhood cancer survivors are at an increased risk for frailty phenotype which has been hypothesized to be associated with mitochondrial dysfunction, chronic inflammation and cellular senescence (Ness et al. 2015). They are at increased risk of developing chronic health conditions, poor activity and neuromuscular control, and their physiological reserve is thought to be reduced. Thus, the survivors may be more vulnerable for changes in normal ageing and might be assumed to need more intensive health care earlier than could be considered based on their age.

The core finding in Study IV was that although there was a small proportion of survivors who experienced significant physical late-effects with a notable influence on their QOL, the majority of the survivors did not describe any major impact on QOL due to some physical limitations. In some of the survivors, the physical late-effects seemed to be compensated to some extent by the positive sequlae of the cancer. This resulted in the finding that most of the survivors described their QOL positively. Parry et al. have also shown similar findings of possible positive effects of cancer on childhood survivors (Parry et al. 2005). The social aspects seemed to be more important determinants of the survivors QOL than the physical ones (Study IV). Other qualitative studies have also emphasized the importance of the social life for childhood BT survivors (Chen et al. 2008, Boydell et al. 2008). However, it should be recognized that the physical morbidity may indirectly affect

social relationships. Some of the survivors suffered from a feeling of being ”different”, which in some cases may have triggered an exaggerated need or effort to be and behave just like peers. This might lead to a risk of denial and an unwillingness to accept or seek appropriate support.

Support could help survivors to come to terms with their cancer and its late-effects; this is important to ensure a satisfactory QOL. Strauser et al. detected a positive association with the level of community integration and satisfaction with life in adult childhood BT survivors (Strauser et al. 2012). In the present study, depression was not common among the survivors (Study IV), which is in agreement with earlier results (Zebrack et al. 2004b). Negative opinions about the family were infrequent (Study IV). The survivors diagnosed with a BT in early years seemed to experience its influence as less important than participants diagnosed later. People may sometimes view good QOL as convergent of what they had or could do before their cancer diagnosis (Fox et al. 1998). In some respects, children diagnosed in their early years do not have to go through that comparison.

Achieving a satisfying life with good quality and without social exclusion should be independent goals of treatment and follow-up. Though they are strongly associated with many health related concerns, medical care cannot overlook those aspects and every medical decision made should target those goals and take into consideration that in individual cases, the means to reach them may be different. The BT survivors themselves highlighted the importance of social relationships on their QOL. On the other hand, childhood cancer survivors have been reported to experience certain limitations, for example in face recognition and social skills (Bonner et al. 2008). For this reason, interventions should be developed more actively to combat social difficulties; these should be considered as an essential part of rehabilitation.

6.3 Reliability and validity

Data stored in large national registries provide great opportunities to conduct research into diseases with low incidence such as young onset BTs. However, registry data also contain some limitations that must be remembered while interpreting the results. The FCR does not include data on the exact location of a tumor or details of the treatment such as doses of irradiation or details of chemotherapy protocols. Thus, we were not able to evaluate the impact of changes in irradiation techniques or doses, or changes in chemotherapy regimens (Studies I-III). Treatment protocols used in different eras may influence the prevalence figures as the survivor population under evaluation in early and later time points studied differs to some extent. The HDR contains data on diagnoses which are made in specialized

health care settings, and before 1994, the data cover only diagnoses from inpatient contacts (Studies I-II). In Finland, the majority of chronic pediatric diseases and conditions are treated in specialized health care settings. However, some of the diagnoses, especially in adults, are probably made in health care centers or the private sector, and thus are not registered in the HDR. Data from HDR began in 1975, and therefore a few of the earliest diagnoses may be missing from prevalence figures. However, the same also applies to the control group, and therefore the comparison of these two groups should be valid. Registry data only show diagnoses that have been made, and thus under-diagnostics of some conditions is probable. Furthermore, it is possible that some conditions are sought more actively from the survivors during their follow-up, and it is possible that there could be some under-diagnostics in siblings compared with the survivors.

Morbidity and drug purchases were analyzed for 5 year survivors and compared with siblings. For this reason, the figures do not represent the results of the whole BT patient population and in this way do not depict the "true" prevalence of morbidity related to BTs. However, the aim of Studies I-III was to provide clinically relevant data of the actual BT survivor population attending the late follow-up clinics and enable its organization in an evidence based manner.

In study IV, no significant difference in morbidity was found between BT survivors attending an interview and those who did not. Nonetheless, there is still a risk of a selection bias as it is possible that the participants had better functional capacity not shown based on medical records. One could also argue that survivors who are socially isolated or have severe mental disorders would be less likely to participate in an interview study. To decrease this risk, the possibility to conduct the interview at home or any place most appropriate for a participant was offered. Furthermore, there was a small number of survivors whose health excluded participation.

Considering the generalizability of the results in Study IV, it should be taken into account that in different cultures, there may be differences in the social security system, general attitude for physically challenged people, and in the significance of individuality, all of which may have an impact on the extent of the burden of survivorship (Study IV). In a Taiwanese study, struggling with role obligations was shown to be an important issue for cancer survivors (Chen et al. 2008). In Finnish society, the need to fulfill role obligations is probably not such a concern.

Qualitative analysis always has some risk that the opinions of a researcher might affect the results, although this can also be a problem in quantitative research (Study IV). In qualitative studies, attempts are made to minimize this bias by adopting a structured analysis process including a theme formation, reviewing

themes for internal homogeneity and external heterogeneity as well as having more than one researcher participating in the review process.

6.4 Recommendations for future research

Developing evidence based rehabilitation methods is an extremely demanding and important task for the future. There are very few studies that have assessed rehabilitation methods for childhood BT survivors and as are those concerning childhood traumatic brain injury patients. There are certain differences between BT and traumatic brain injury patients, for example in types of psychological late-effects, as BT survivors seem to have a smaller risk for externalizing symptoms and aggressiveness and to be more prone to internalizing symptoms (Poggi et al. 2005). Nonetheless, knowledge gained from brain injury research may be adapted at least to some extent until more data on BT rehabilitation have been acquired.

Butler et al. evaluated the impact of twenty weekly sessions of Cognitive Remediation Program for childhood cancer survivors who had signs of attentional problems (Butler et al. 2008). Some signs of improvement in academic achievement, metacognitive learning strategies and attention were seen, although the long-term clinical significance remained unproven. Similar results have been obtained with childhood traumatic brain injury patients, with whom six months of attention specific neuropsychological training improved significantly attention and adaptive skills compared with a control group not given any special intervention (Galbiati et al. 2009). There is also some evidence from traumatic brain injury patients that a 5-week commercially available Cogmed-training tool might improve working memory (Phillips et al. 2016).

Exercise interventions have been investigated in childhood cancer patients in general, and especially in children with ALL. There are signs that these interventions may have beneficial effects on HRQOL, muscle strength, and activity level (Baumann et al. 2013). In rodents, it has been shown that cranial irradiation at a very young age can evoke a serious loss of proliferating progenitor cells in dental gyrus of hippocampus (Naylor et al. 2008). However, this damaging effect may be remediated to some extent by exercise. In rodents, running in a training wheel has been shown to increase the number of stem cells and to promote neurogenesis in hippocampus (Naylor et al. 2008). Recently, Riggs et al. showed a beneficial effect of exercise in irradiated childhood BT patients with respect to the white matter fraction anisotrophy and volume of hippocampus (Riggs et al. 2016).

However, despite these promising preliminary results, far more research is needed to determine the effectiveness of the current rehabilitation methods and their most

efficient timing. Furthermore, the development of new innovative rehabilitation methods would be beneficial to ensure successful treatment for the BT survivors. It is also important to exploit resources in the most efficient way possible. In addition to physical and cognitive rehabilitation, based on our QOL interviews, it seems clear that improving social skills and offering methods to ease the survivors' participation in everyday social networks should be incorporated into in these programs. It might be interesting to create virtual support groups starting already during the cancer treatment. Based on the current literature, it seems that school reentry programs may impact positively on the attitude of teachers and peers toward the cancer patient and to assist teachers in managing any difficulties that may arise (Thompson et al. 2015a). Patients as well as parents also benefit from psychoeducation by improving their health-related locus of control and comprehension of their disease (Thompson et al. 2015b). However, more evidence of the impact of this kind of support for the patients' later psycho-social outcome could help to guarantee funding for this important part of the treatment.

There has been no properly organized structured follow-up of the late-effects of cancer survivors; in the future, it will be important to evaluate whether the frequency of certain late effects will change. It would be important to evaluate the impact of certain treatment methods on long-term late-effects, although this may be rather extremely due to the rarity of childhood BT. However, an assessment of short-term late-effects may be evaluated as a part of the current international treatment protocol studies.

7 CONCLUSIONS

The following conclusions were made based on this study:

1. Children diagnosed with a BT before the age of 16 years have an increased risk of developing later illnesses, especially for new endocrine and neurological diagnoses, cognitive disorders and problems in vision/hearing even 5 years after the initial BT diagnosis. Age at BT -diagnosis does not affect late morbidity. The impact of gender and treatment era on morbidity is small. Although irradiation treatment and histology of embryonal tumor seem to be risk factors for late-effects, they do not explain all the morbidity.

2. Adolescent and young adults aged 16 to 24 years when diagnosed with a BT are at an increased risk for developing late new neurological, nephrological, endocrinological, cardiovascular and psychiatric diagnoses as well as vision/hearing-related conditions. Irradiation treatment increases the risk for neurological problems, but not of any other type of late morbidity. The sex of the participant has only a minor influence and treatment era exert no effect on late morbidity.

3. Young onset BT survivors have a higher frequency for purchases of new types of endocrine and neurological medications still more than 5 years from the initial BT diagnosis. Females have a higher risk than males for requiring thyroid hormones compared with males. Irradiation increases significantly the risk for endocrinological drug purchases, but not for antiepileptics. Growth hormone purchases are primarily seen in children diagnosed with a BT before the age of eight years. Birth year do not affect the need for medication.

4. There is extensive variability in QOLs of individual childhood BT survivors. Participant selection and measurement methodology may have a significant impact on the results between studies. Based on the 15D questionnaire, when compared with the general population, childhood ependymoma and medulloblastoma survivors have impairments in many areas e.g. mobility, vision, hearing, eating, speech, usual activities, mental function, and sexual activity. In qualitative interviews, most of the survivors described their QOL positively. Survivors reported that social relationships, learning difficulties, limitations in vocational opportunities and independent life, age at diagnosis as well as time since diagnosis influenced their QOL. Although negative thoughts such as resentment and feeling of being different from everyone else were described, many survivors had

also experienced positive mental growth in association with their encounter with cancer. The concept of health for childhood BT survivors may differ from that usually expected.

5. Young onset BT survivors should receive years of systematic follow-up due to potential late morbidity and risk for impaired QOL because of both somatic and psychosocial causes.

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