Tiina Remes

SIGNS OF RADIATION-INDUCED ACCELERATED AGEING IN SURVIVORS OF CHILDHOOD BRAIN TUMORS

THE INCIDENCE OF CEREBROVASCULAR DISEASE, NEUROCOGNITIVE IMPAIRMENT, SECONDARY NEOPLASMS, AND LOW BONE MINERAL DENSITY AFTER 18 YEARS OF FOLLOW-UP
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The incidence of cerebrovascular disease, neurocognitive impairment, secondary neoplasms, and low bone mineral density after 18 years of follow-up

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Abstract
Background: Childhood brain tumors (CBTs) are the most common solid tumors in childhood. CBT survivors have a high risk of several late-effects, including cerebrovascular disease (CVD), neurocognitive impairment, secondary neoplasms, and low bone mineral density; however, only a few studies have clinically investigated the late-sequelae in young-adult CBT survivors.

Aim: To determine the prevalence of CVD, neurocognitive impairment, secondary neoplasms, and bone mineral density in a national cohort of radiotherapy-treated long-term survivors of CBT.

Subjects and Methods: Radiotherapy-treated CBT survivors diagnosed between 1970–2008 were selected based on the following inclusion criteria: follow-up ≥5 years since the cessation of therapy and age of ≥16 years at the time of the study. Survivors were clinically and neuropsychologically examined, and investigated by magnetic resonance imaging (MRI), bone mineral densitometry, and laboratory analysis.

Results: We included 74 survivors after a mean follow-up time of 18.9 ± 6.1 years. The mean age at follow-up was 28.4 ± 6.8 years and at diagnosis 8.3 ± 4.3 years.

At the 20-year follow-up, the cumulative prevalence of CVD, along with small- and large-vessel disease was 52%, 38%, and 16%, respectively. Ischemic infarcts or transient ischemic attacks were diagnosed in 11% of the survivors, lacunar infarcts in 10%, and cerebral hemorrhage in 3%. White matter lesions (WMLs) were noted in 49% of the survivors. Higher blood pressure was associated with CVD, large-vessel disease, WMLs, and lacunar infarcts.

Survivors had lower cognitive performance in all neuropsychological domains than controls. Mean verbal intelligence quotient was 89 ± 14 and mean performance intelligence quotient 87 ± 19. Executive functions (Z-score -5.0 ± 5.3 SD) and processing speed (Z-score -4.3 ± 5.4 SD) were extensively impaired. Executive functions and processing speed were associated with everyday life skills.

Cumulative incidence of secondary meningiomas was 10.2% at the 25-year follow-up using the clinical data, and that of secondary neoplasms was 2.4% using the Finnish Cancer Registry data. We observed low bone mineral density in 23.6% of the survivors, which was associated with fractures in long bones.

Conclusions: Young adult CBT survivors experienced late-consequences typically associated with ageing.

Keywords: bone mineral density, cerebrovascular disease, childhood brain tumor, executive function, neuropsychology, processing speed, radiotherapy, secondary neoplasm, stroke
Remes, Tiina, Sädehoidon aiheuttama ennenaikainen vanhentuminen lapsuusiän aivokasvaimen jälkeen. Aivoverisuonisairaudet, kognitiiviset ongelmat, sekundaariset tuumorit ja luuston hauraus 18 vuoden seuranta-ajan jälkeen nuorilla aikuisilla
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala; Kuopion yliopistollinen sairaala; Turun yliopistollinen keskussairaala; Tampereen yliopistollinen sairaala; Helsingin yliopistollinen sairaala
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Tiivistelmä
Taustaa: Suomessa sairastuu vuosittain 46-60 lasta aivokasvaimen sairauteen, joka on lapsuusiän yleisin, kiinteä kasvain. Selviytneillä on todettu lisääntyneen hoitojen myöhäisvaikutusten riski. Kuitenkin nuorten aikuisten haittaaikaan keskuskohdassa ei ole tehty suicientoja.


Tulokset: Tutkimukseemme osallistujia oli 74 nuorta aikuisaa 18,9 ± 6,1 vuotta hoitojen päättymisen jälkeen. Tutkimusjärjestelmiä oli 28,4 ± 6,8-yli-vuotiaita osallistujia, ja 8,3 ± 4,3-yli-vuotiaita diagnosointihetkellä.

Aivoverisuonisairaus todettiin 52% tutkimukseen osallistuneilla 20 vuoden seurannan jälkeen, pienentynyt vuoteen 38%:lla ja suuret suuntien taidot 16%:lla. Aivoinfarktiin oli sairastunut 9% tutkimusten, lukuainainfarktiin 10% ja aivoverenhevonten 3% tutkimuksessa. Valkean aivoaineen puolustus todettiin 49%:lla magneettikuvauksessa. Korkea verenpaine lisäsi aivoverisuonisairauden, suuret suuntien taudien, valkoisen aivoaineen puolustusten sekä lukuainainfarktiin riskiä.

Selviytynyt keskimääräinen kielettävä liikekäyntiä olisi 89 ± 14 ja ei-kielettävä liikekäyntiä 87 ± 19. Suurimmat vaikeudet todettiin toiminnanjohtajayksessa (Z-luku -5,0 ± 5,3 SD) ja prosessointinopeudessa (Z-luku -4,3 ± 5,4 SD). Toiminnanjohtajan ja prosessointinopeuden vaikeudet olivat yhteydessä arkielämän haasteisiin.

Sekundaarisen aivokalvokasvaimen kumulaatiivinen esiintyvyys oli 25 vuoden seuranta-aikana 10,2% kliinisessä tutkimuksessa ja sekundaarisen kasvaimen 2,4% Syöpärekisteriaineistossa. Matala luustontiheys todettiin 23,6%:lla selviytyniistä.

Johtopäätökset: Nuorilla aikuisilla, jotka ovat lapsena aivokasvaimen vuoksi saaneet sädehoidon, esiintyy useita sellaisia jälkiheittoja, jotka yleensä liittyvät ikääntymiseen.

Asiakas: aivoinfarkti, aivoverenhevonta, aivoverisuonisairaus, lasten aivokasvaimet, luustontiheys, neuropsykologia, prosessointinopeus, sekundaariset tuumorit, sädehoido, toiminnanohjaus
To My Family and Friends
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Oulu 22.11.2019

Tiina Remes
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
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<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
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<tr>
<td>AT/RT</td>
<td>Atypical teratoid rhabdoid tumor</td>
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<tr>
<td>BDI</td>
<td>Beck’s depression inventory</td>
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<tr>
<td>BMD</td>
<td>Bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CBT</td>
<td>Childhood brain tumor</td>
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<tr>
<td>CCSS</td>
<td>Childhood Cancer Survivor Study</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COG</td>
<td>The Children’s Oncology Group</td>
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<tr>
<td>CT</td>
<td>Computer tomography</td>
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<tr>
<td>CVD</td>
<td>Cerebrovascular disease</td>
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<tr>
<td>DTI</td>
<td>Diffusion-tensor imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion-weighted imaging</td>
</tr>
<tr>
<td>DXA</td>
<td>Dual x-ray absorptiometry</td>
</tr>
<tr>
<td>FCR</td>
<td>Finnish Cancer Registry</td>
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<tr>
<td>FHD</td>
<td>Focal hemosiderin deposit</td>
</tr>
<tr>
<td>FSIQ</td>
<td>Full-scale intelligence quotient</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<tr>
<td>GH</td>
<td>Growth hormone</td>
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<tr>
<td>HP</td>
<td>Hypothalamic-pituitary</td>
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<tr>
<td>IGF1</td>
<td>Insulin-like growth factor 1</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>Insulin-like growth factor binding protein 3</td>
</tr>
<tr>
<td>IS</td>
<td>Ischemic infarcts</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing hormone</td>
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<tr>
<td>LVD</td>
<td>Large-vessel disease</td>
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<tr>
<td>MCA</td>
<td>Middle cerebral artery</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic resonance angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PIQ</td>
<td>Performance intelligence quotient</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PNET</td>
<td>Primitive neuroectodermal tumor</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Spin-echo</td>
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<tr>
<td>SEER</td>
<td>the Surveillance, Epidemiology and End Results</td>
</tr>
<tr>
<td>SHH</td>
<td>Sonic hedgehog</td>
</tr>
<tr>
<td>SIOP</td>
<td>International Society of Pediatric Oncology</td>
</tr>
<tr>
<td>SJLIFE</td>
<td>St Jude Lifetime Cohort</td>
</tr>
<tr>
<td>SN</td>
<td>Secondary neoplasm</td>
</tr>
<tr>
<td>SVD</td>
<td>Small-vessel disease</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>VCIND</td>
<td>Vascular cognitive impairment not demented</td>
</tr>
<tr>
<td>VIQ</td>
<td>Verbal intelligence quotient</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WML</td>
<td>White matter lesions</td>
</tr>
<tr>
<td>WNT</td>
<td>Wingless</td>
</tr>
<tr>
<td>95 %CI</td>
<td>95 % confidence interval</td>
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List of Original Publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


*Authors contributed equally to the manuscript.
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1 Introduction

In Finland, approximately 46–60 children are annually diagnosed with brain tumor (Laronninge, 2013). Childhood brain tumors (CBTs) are the most common solid tumors and the primary etiological factor responsible for cancer-related deaths in childhood (McKean-Cowdin et al., 2013). CBTs are histologically heterogeneous and have both benign and malignant presentations (Jukich, McCarthy, Surawicz, Freels, & Davis, 2001). Overall survival rate has improved over the years; however, that of the patients with malignant CBTs has remained relatively constant in Finland (Madanat-Harjuoja, Pokhrel, Kivivuori, & Saarinen-Pihkala, 2014).

Radiotherapy is an important treatment modality of malignant CBTs, and is considered as the standard of care in numerous treatment protocols (Jairam, Roberts, & Yu, 2013; Merchant, Pollack, & Loeffler, 2010; Wells & Packer, 2015; Mueller & Chang, 2009). The use of radiotherapy has gradually declined in the past few decades, due to the high incidence of late-effects (Jairam et al., 2013; Wells & Packer, 2015). Radiotherapy-treated CBT survivors are at a high risk of experiencing of tumor- and its treatment-associated late-effects, including cerebrovascular disease (CVD), neurocognitive impairment, secondary neoplasms (SNs), low bone mineral density (BMD), hormonal dysfunction, and metabolic disease (Campen et al., 2012; de Ruiter, van Mourik, Schouten-van Meeteren, Grootenhuis, & Oosterlaan, 2013; Cai, Cao, Bao, & Xie, 2012; Odame et al., 2006; Chemaitilly et al., 2018; Pietila et al., 2009). Only a small number of studies have investigated and systematically screened the effects of radiotherapy treatment in young-adult CBT survivors (Neu et al., 2018; Brinkman et al., 2012; Schmiegelow et al., 2000).

Therefore, we selected a Finnish national cohort of consecutive CBT survivors, who were treated with radiotherapy during childhood (n = 74) to investigate for the presence of CVD, neurocognitive late-effects, SNs, and BMD using systematic screening. Considering the increase in the number of radiotherapy-treated CBT survivors, knowledge and information regarding the associated long-term late-effects has become a subject of paramount importance.
2 Review of the Literature

2.1 Incidence of Brain Tumors

Brain tumors are the most common solid tumors in childhood, accounting for approximately 25% of all childhood cancers (McKean-Cowdin et al., 2013; Arora et al., 2009). Approximately 7–9% of all brain tumors occur in children aged 0–19 years (Jukich et al., 2001; Darlix et al., 2017; Hoffman, Propp, & McCarthy, 2006).

Age-adjusted incidence rates for all brain tumors vary between 0.5 and 6.2 per 100,000 children aged 0–14 years (McKean-Cowdin et al., 2013; Leece et al., 2017; Schmidt et al., 2011; Aarimaa, Arola, & Salmi, 1997). The highest incidence rates of CBTs have been reported in Northern, Eastern, and Southern Europe; Central Asia; Canada, and the United States (Leece et al., 2017). In Finland, the overall reported CBT incidence varies between 4.0 and 6.2 among 100,000 children (Äärimaa, Arola, & Salmi, 1997; Schmidt et al., 2011). A total of 46–60 children younger than 20 years of age have been annually diagnosed with CBT in Finland (Larssoninge, 2013).

Surveillance, Epidemiology, and End Results (SEER) data revealed that CBT incidence was relatively stable between 1973 and 1982 (McKean-Cowdin et al., 2013). However, between 1983 and 1986, there was a significant increase in the incidence, which subsequently stabilized from 1987 to 2009 (McKean-Cowdin et al., 2013). The increase could be attributed to the introduction of novel diagnostic imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), which could identify low-grade gliomas or oligodendrogliomas that were previously undetected by CT (McKean-Cowdin et al., 2013). Furthermore, there was a significant increase in the incidence of pilocytic astrocytomas between 1985 and 1994 (Jukich et al., 2001). In addition, because most posterior fossa pilocytic tumors are symptomatic at diagnosis and the incidence of astrocytomas was stable according to the SEER data, it was unclear whether the overall increase in brain tumor incidence could be explained by the improved imaging (McKean-Cowdin et al., 2013). In the Nordic countries, the incidence rate of CBTs had been relatively stable between 1985 and 2006 (Schmidt et al., 2011).

A slightly higher incidence of brain tumors was reported in patients aged 0–14 years than in adolescents and young adults (aged 15–24 years), who demonstrated lowest CBT incidence (Arora et al., 2009). After the age of 25 years, the ageing population demonstrated a remarkable increase in the incidence (Arora et al., 2009),
which eventually plateaued between the ages of 75 and 79 years, after which there was a decrease in CBT incidence (Arora et al., 2009). Figure 1 represents age-specific incidence rate of primary brain tumors in the Nordic countries.

![Age-specific incidence rates of primary brain tumors in Nordic countries during 2012–2016 (Engholm et al., 2010).](image)

### 2.2 Histology of Brain Tumors

The most frequent histological groups of brain tumors are different in children and adults (Jukich et al., 2001; Arora et al., 2009). Children most commonly demonstrated astrocytic tumors, followed by medulloblastomas and other embryonal tumors (Leece et al., 2017; Schmidt et al., 2011).

The new classification system of central nervous system (CNS) tumors released by the World Health Organization (WHO) in 2016, used molecular parameters with histology to define several tumor entities (Louis et al., 2016). Diagnosis of CNS tumor included its histopathological name, followed by its genetic features (Louis et al., 2016). The WHO classification contains the following groups of brain tumors: diffuse astrocytic and oligodendroglial tumors, other astrocytic tumors, ependymal tumors, other gliomas, choroid plexus tumors, neuronal and mixed neuronal-glial tumors, tumors of pineal region, embryonal tumors, tumors of cranial and paraspinal nerves, meningiomas, germ cell tumors,
and tumors of the sellar region (Louis et al., 2016). According to the WHO classification system, pilocytic astrocytomas were grouped to other astrocytic tumors, medulloblastomas to embryonal tumors, ependymomas to ependymomal tumors, and germinomas to germ cell tumors (Louis et al., 2016). However, the new WHO classification had restructured diffuse gliomas, medulloblastomas, and other embryonal tumors according to their genetic entity, and inserted new entities, including glioblastoma, IDH-wildtype and glioblastoma, IDH-mutant; diffuse midline glioma, H3 K27M-mutant; RELA fusion-positive ependymoma; medulloblastoma; WNT-activated and medulloblastoma, SHH-activated; and embryonal tumor with multilayered rosettes (Louis et al., 2016). In 2016, it was discovered that primitive neuroectodermal tumors (PNETs), which was previously difficult to diagnose and histopathologically distinguish from other brain tumors, was molecularly associated with other well-defined CNS tumor entities (Sturm et al., 2016). This finding lead to changes in the WHO 2016 classification, and the former term “PNET” was eliminated from the current classification system (Louis et al., 2016). Considering the fact that the study population of the current study has been diagnosed before the advent of the molecular era, concepts of the previous WHO classification have been discussed in the following section.

Table 1 shows the histological distribution of the most common histological groups of CBTs (Jukich et al., 2001; McKean-Cowdin et al., 2013; Rickert & Paulus, 2001; Arora et al., 2009). Among the astrocytomas, pilocytic astrocytomas were the most common subtype in children and accounted for 24–28 % of the tumors (McKean-Cowdin et al., 2013; Rickert & Paulus, 2001; Hoffman et al., 2006). Low-grade gliomas in childhood rarely progress to high-grade gliomas (Wells & Packer, 2015). In adults, the largest histological groups include glioblastomas (23–27 %), astrocytomas (12–17 %) and meningiomas (17–22 %) (Jukich et al., 2001; Arora et al., 2009; Hoffman et al., 2006). Differences in the histological subtypes between children and adults explain the difference in the overall survival of patients with brain tumors, which is discussed later in the present study (Merchant et al., 2010).

Medulloblastoma incidence demonstrate two peaks, i.e., between the age of 3 and 4 years, and between the age of 6 and 11 years (Wells & Packer, 2015; Rickert & Paulus, 2001). Atypical teratoid rhabdoid tumors (AT/RTs) have typically been diagnosed in infants and young children (Wells & Packer, 2015). Most cases of ependymomas have been diagnosed in children before the age of 2–4 years (Wells & Packer, 2015; Rickert & Paulus, 2001; Schmidt et al., 2011). Incidence of astrocytomas shows two peaks in children: the higher peak is observed at the age
of approximately 4 years and the lower peak at 12 years (Schmidt et al., 2011). Medulloblastomas and ependymomas are typically rare in adulthood and represent only <1% and <2% of adult brain tumors cases (Merchant et al., 2010).

Table 1. Histology of childhood brain tumors (Jukich et al., 2001; McKean-Cowdin et al., 2013; Rickert & Paulus, 2001; Arora et al., 2009; Ramanan & Chaseling, 2012; Schmidt et al., 2011).

<table>
<thead>
<tr>
<th>Histology</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytomas</td>
<td>36–47</td>
</tr>
<tr>
<td>Medulloblastomas</td>
<td>12–18</td>
</tr>
<tr>
<td>Gliomas NOS¹</td>
<td>8–18</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>6–10</td>
</tr>
<tr>
<td>Glioblastomas</td>
<td>3–7</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>2–5</td>
</tr>
<tr>
<td>Primitive neuroectodermal tumors</td>
<td>2–5</td>
</tr>
<tr>
<td>Oligodendrogiomas</td>
<td>0.5–4</td>
</tr>
</tbody>
</table>

¹ not otherwise specified

2.3 Diagnosis and treatment of the childhood brain tumors

Treatment of CBTs is based on tumor histology, location in the brain, age of the child, and effect of the treatment on the developing brain (Packer, 1999). Advancements in radiotherapy techniques, chemotherapy protocols, surgery, and imaging techniques along with a deeper understanding of the biological behavior of the tumor have significantly contributed to improvement in the survival rate of patients (Jairam et al., 2013; Wells & Packer, 2015; Merchant et al., 2010; Packer, 1999, 2008).

2.3.1 Imaging techniques

In the beginning of the 20th century, X-rays were used to diagnose brain tumors (Castillo, 2014). Several intracranial tumors, including oligodendrogiomas, astrocytomas, meningiomas, choroid plexus neoplasia, and pituitary tumors, could be diagnosed owing to the presence of calcification on radiography (Castillo, 2014). In 1918–1919, a neurosurgeon named Walter E. Dandy developed the techniques of pneumoencephalography and ventriculography (Castillo, 2014). Pneumoencephalography was used to observe the lateral and midline displacement of the ventricles in the presence of gliomas (Castillo, 2014).
The diagnostic strategies to identify brain tumors have dramatically changed since the introduction of CT and MRI in the 1970s and 1980s, respectively (Jukich et al., 2001). Furthermore, a new gadolinium bolus-based technique was introduced in 2003 (Castillo, 2014). It provides a quantitative map of cerebral blood flow, and measures microvascular perfusion, which may be used to differentiate low-grade and high-grade gliomas (Castillo, 2014). Improved MRI technique, such as diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) imaging, and diffusion tensor imaging (DTI), can be helpful for analyzing the grading and behavior of tumors (Castillo, 2014). In addition, positron emission tomography (PET) can be used to provide information regarding the extent, grade, activity, and type of tumor (Castillo, 2014). Functional MRI may significantly influence strategies of tumor resection (Castillo, 2014). Currently, the usefulness of perioperative MRI is being evaluated (Castillo, 2014).

### 2.3.2 Neurosurgery

Surgery is crucial to ensure patient survival in most CBT cases (Wells & Packer, 2015; Mueller & Chang, 2009; Merchant et al., 2010). In medulloblastoma without dissemination, the residual tumor volume of < 1.5 cm² has been associated with an improved 5-year progression-free survival of 20–24 % compared to those with larger residual tumors (Albright et al., 1996; Grill et al., 2005; Zeltzer et al., 1999). Total macroscopic tumor removal in ependymomas has been associated with improved progression-free survival (83 % total macroscopic removal vs 39 % residual tumor) (Timmermann et al., 2000).

The treatment of astrocytomas is aimed at gross total resection (Mueller & Chang, 2009). Complete resection of low-grade astrocytomas is typically curative (Pollack, Claassen, al-Shboul, Janosky, & Deutsch, 1995). Although, tumor resection is essential to treat high-grade gliomas, prognosis of the disease remains poor (Mueller & Chang, 2009). Surgical intervention cannot be used to manage diffuse brain stem gliomas; however, biopsies are performed in certain cases to obtain biological material to identify potential therapeutic targets in these patients demonstrating poor disease prognosis (Mueller & Chang, 2009; Wells & Packer, 2015).
2.3.3 Radiotherapy

Radiotherapy treatment has traditionally been delivered through photons (Gibbs, Tuamokumo, & Yock, 2006). High-energy photons both directly and indirectly damage DNA, which induces tumor cell death (Gibbs et al., 2006).

In 1919, Harvey Cushing introduced radiotherapy as a treatment modality for medulloblastomas (Thorp, 2013). Since the 1950s, it has become evident that craniospinal radiotherapy is essential to control medulloblastomas (Thorp, 2013). Concurrently, medulloblastoma patients did not survive (Thorp, 2013; Oeffinger & Robison, 2007). Evaluation of the first survivors revealed that the patients were cured, particularly after radiotherapy, albeit with the presence of late-consequences (Oeffinger & Robison, 2007). Immature organ systems in children are prone to injury after radiotherapy, and certain late-effects, particularly radiotherapy-associated neurocognitive impairment, could be immediately recognized (Oeffinger & Robison, 2007). Other late-effects developed over decades after completing the treatment (Oeffinger & Robison, 2007). It is interesting to note that, awareness regarding the late-effects of cancer treatment increased during the 1970s (Meadows & D’Angio, 1974).

The various late-effects of radiotherapy have led to efforts to reduce its use (Wells & Packer, 2015; Merchant et al., 2010). In fact, between 1973 and 2008, the use of radiotherapy for the treatment of CBTs has declined from 70% to 39% according to the SEER9 database (Jairam et al., 2013). This decline mainly resulted from the diminished use of radiotherapy for grade 1–2 astrocytomas (Jairam et al., 2013).

Decreased radiotherapy doses and reduced treatment field sizes to attenuate the late-effects have been successful in average-risk medulloblastoma patients (Wells & Packer, 2015; Merchant et al., 2010). The International Society of Pediatric Oncology (SIOP) protocol PNET5, which is currently used to treat medulloblastomas in Finland, has reduced the craniospinal radiation dose from 23.4 Gy to 18.0 Gy in the low-risk group (Heyman, Juhlin, & Taskinen, 2018; Universitätsklinikum Hamburg-Eppendorf, 2017). Aggravated late-effects in younger children have been the primary reason to avoid radiotherapy in children under the age of 3–5 years (Thorp, 2013; Huynh et al., 2018; Wells & Packer, 2015). According to the current HIT-MED protocol for medulloblastoma, children under the age of 3–5 years are first treated with intensified chemotherapy without radiotherapy, which is also performed to treat cases of tumor recurrence or measurable residual tumors (Universitätsklinikum Hamburg-Eppendorf, 2017a).
Ependymomas have limited sensitivity to radiotherapy, and a local dose of $\geq 45$ Gy is needed for their treatment (Combs et al., 2008). In the current ependymoma treatment protocols, radiotherapy is administered at a dose of $> 54$ Gy (Universitätsklinikum Hamburg-Eppendorf, 2017b). After a limited volume radiotherapy, even children younger than 3 years, showed a stable intelligence quotient in the follow-up (Merchant et al., 2004). Radiotherapy did not improve the survival rates of patients with astrocytoma who underwent incomplete tumor resection (Pollack et al., 1995). Therefore, radiotherapy has played an important role, and is still considered as a standard of care to treat medulloblastomas, germ cell tumors, primitive neuroectodermal tumors (PNETs), ependymomas, and high-grade gliomas (Jairam et al., 2013; Merchant et al., 2010; Wells & Packer, 2015; Mueller & Chang, 2009).

Protons are positively charged particles that can stop, and similar to photons, by inducing cell death by introducing DNA damage (Huynh et al., 2018; Gibbs et al., 2006). Biologically, protons are more effective than photons, due to which current techniques have converted the prescribed photon dose into an equivalent proton dose (Ladra et al., 2018). In the proton beam radiotherapy, the energy deposition and penetration depth remarkably increase to a sharp peak at the end of their range, demonstrating no notable exit dose beyond the maximum peak (Schulz-Ertner & Tsujii, 2007). Introduction of proton beam radiotherapy has been an improvement in the radiotherapy era that has allowed physicians to increase radiation dose to the critical subregions while simultaneously limiting the doses to the target volume margins (Merchant, 2009). Use of proton beam radiotherapy on CBT survivors may result in a better quality of life by reducing the late-effects (Merchant, 2009). Proton beam radiotherapy may be superior to photon radiotherapy, particularly in patients with ependymoma, astrocytoma, medulloblastoma, and craniopharyngioma (Merchant, 2009). The American Society for Radiation Oncology currently recommends the use of proton beam radiotherapy for malignant or benign central nervous system (CNS) tumors (ASTRO Model Policies, 2017). In the Nordic countries, children have been treated with proton beams, since 2015 in Scandion clinic, Uppsala (Heyman et al., 2018). Several Finnish children have been treated with proton beam radiotherapy in the Essen Proton Center (Heyman et al., 2018).
2.3.4 Chemotherapy

Chemotherapy is a supplemental treatment for most tumor types and it may be used to delay radiotherapy in extremely young patients, decrease radiation doses, or be concomitantly used with radiotherapy, thereby improving the outcomes of the patients with specific tumor types (Merchant et al., 2010).

Various chemotherapy protocols have been used to treat CBTs. The “eight-in-one” protocol was developed to prevent mutation-to-resistance and myelosuppression (Pendergrass et al., 1987). The “eight-in-one” protocol was used to treat medulloblastomas, PNETs, ependymomas, anaplastic astrocytomas, and glioblastomas (Pendergrass et al., 1987). In this protocol, methylprednisolone, vincristine, lomustine, procarbazine, hydroxyurea, cisplatin, cytarabine, and cyclophosphamide were administered within a period of 24 hours for 8 times. Cyclophosphamide, which was previously used to treat medulloblastomas, ependymomas and PNETs, was replaced by dacarbazine to treat anaplastic astrocytomas and glioblastomas (Pendergrass et al., 1987). The “eight-in-one” protocol resulted in a 2-year absolute survival of 71% in patients with medulloblastoma and PNET, and of 13% in patients with anaplastic astrocytoma and glioblastoma patients (Pendergrass et al., 1987). The “eight-in-one” treatment group demonstrated better survival rates than the historical control group in Finland between 1986 and 1993 (Ilveskoski, Saarinen et al., 1996). Despite the improvement in survival rates, this treatment modality was abandoned considering the high incidence of acute toxicity and late-effects (Ilveskoski et al., 1996; Ilveskoski, Pihko et al., 1996).

Roger Packer et al. (1994) introduced a treatment protocol for medulloblastomas and PNETs between the years 1983 and 1989. Radiotherapy was initiated within 28 days after surgery with weekly injections of vincristine during the course of radiotherapy (Packer, et al., 1994). Chemotherapy was initiated six weeks after the end of radiotherapy, using lomustine and cisplatin administration every 6 weeks, and vincristine was administered weekly for 3 consecutive weeks (Packer, et al., 1994). The 5-year progression-free survival rate improved to 85% (Packer et al., 1994). Owing to the toxicity of the protocol, there was a need to modify the medication in most of the patients (Packer et al., 1994). Current treatment strategies for average-risk medulloblastomas primarily focus on reducing the dose of chemotherapy to decrease the late-effects in survivors (Wells & Packer, 2015). In the current PNET5-protocol for medulloblastomas, maintenance chemotherapy includes alternating cycles of cisplatin, lomustine and vincristine,
and cycles of cyclophosphamide and vincristine (Universitätsklinikum Hamburg-Eppendorf, 2017a). In the low-risk group, reduced-intensity maintenance therapy that consists of 6 cycles, contrary to the standard-risk group maintenance therapy consists of 8 cycles of chemotherapy (Universitätsklinikum Hamburg-Eppendorf, 2017a).

Chemotherapy is recommended in the treatment of low-grade gliomas, in cases of incomplete tumor resection or disease progression (Mueller & Chang, 2009). Typically, vincristine is used with or without carboplatin or another option is vinblastine monotherapy (Mueller & Chang, 2009; Heyman et al., 2018). However, the benefit of treating ependymomas using chemotherapy remains unproven (Mueller & Chang, 2009).

2.3.5 Histology and genetic subtypes

Development in the biological understanding of brain tumors has dramatically advanced the classification and the treatment of brain tumors (DeWitt, Mock, & Louis, 2017; Kram et al., 2018). In the new World Health Organization (WHO) 2016 classification system for CNS tumors, the presence or absence of gene mutations has been integrated as a part of the histological diagnosis (DeWitt et al., 2017).

Classification of embryonal tumors has significantly changed in the current WHO classification (DeWitt et al., 2017; Kram et al., 2018). Medulloblastomas can be genetically divided into five subtypes: wingless (WNT)-activated, sonic hedgehog (SHH) -activated and TP53-mutant, SHH-activated and TP53-wildtype, group 3 and group 4 medulloblastomas (DeWitt et al., 2017). However, medulloblastoma subgroups have been further divided into three different risk groups according to MYC-amplification, presence of metastasis at diagnosis, or loss of chromosome 11 (Table 2) (Kram et al., 2018). Seven different risk groups have been identified (Kram et al., 2018). β-catenin nuclear immune-positivity indicates the presence of WNT-activated medulloblastomas (Wells & Packer, 2015). The non-medulloblastoma embryonal tumor group includes AT/RTs and embryonal tumors with multilayered rosettes (Kram et al., 2018; DeWitt et al., 2017). The latter includes groups of ependymoblastomas and most medulloepitheliomas from the previous WHO classifications (Kram et al., 2018; DeWitt et al., 2017).

According to the current WHO 2016 classification, ependymal tumors are restructured into subependymomas; myxopapillary ependymomas; ependymomas; ependymomas, RELA fusion positive; and anaplastic ependymomas (Louis et al.,
2016). Ependymomas can be further classified as papillary, clear cell, and tanycytic subtypes (Louis et al., 2016). Molecular classification may be used to divide ependymomal tumors into nine molecular subgroups (Pajtler et al., 2015). Molecular subtypes are histologically subependymomas, anaplastic ependymomas, or myxopapillary ependymomas (Pajtler et al., 2015). Furthermore, these molecular subtypes can be observed in distinct anatomical locations (Pajtler et al. 2015); however, molecular grouping has not been incorporated in the current WHO classification (Louis et al., 2016). Although the new classification system can better classify prognostic subgroups, it has not yet been implemented in the current ependymoma treatment protocol (Godfraind et al., 2012; Universitätsklinikum Hamburg-Eppendorf, 2017b).

2.3.6 Molecular targeting therapies

Advances in genomic technology have provided new targeted therapies to treat several brain tumors that are currently under diligent investigations (Kram et al., 2018). It is possible to avail targeted therapeutic alternatives to address both SHH-subgroups of medulloblastomas, and MYC-driven medulloblastomas (Kram et al., 2018). However, several tumor types have demonstrated resistance to targeted therapies in the long-term (Kram et al., 2018). These targeted therapies are also currently being evaluated in the ependymoma trials (Merchant et al., 2010). There has been no final breakthrough associated with the novel targeted therapeutic modalities (Kram et al., 2018).

2.4 Prognosis of childhood brain tumors

Brain tumors are the most common cause of cancer-related deaths in childhood (McKean-Cowdin et al., 2013). In an international population-based registry study of 71 countries, the age-standardized 5-year net survival varied between 40 % and 80 % for patients with CBT and between 20 % and 40 % for those with adult brain tumors (Allemani et al., 2018). In the four Nordic countries, the age-standardized 5-year net survival for patients with CBTs was 79.8 % in Sweden, 79.5 % in Denmark, 75.6 % in Finland, and 74.3 % in Norway (Allemani et al., 2018).

The prognosis of CBT depends on the histology (Ramanan & Chaseling, 2012). Figure 2 shows the survival probability in Sweden during 1984-2010 (Gustafsson, 2013).
Tumors, such as medulloblastomas, have traditionally been further divided into the average- and high-risk groups according to their prognosis (Gajjar et al., 2006). The average-risk patients demonstrate a residual tumor $\leq 1.5$ cm$^2$ without metastatic presentation at the time of the diagnosis (Gajjar et al., 2006). Advances in molecular technology have further increased the understanding of disease prognosis, and have facilitated the identification of seven medulloblastoma risk groups (Schwalbe et al., 2017). Table 2 shows the new risk groups of medulloblastoma, their survival, and the factors that are used to classify the risk groups.
Table 2. Risk groups of medulloblastoma, their survival, and the factors that are used to classify the risk groups (Schwalbe et al., 2017).

<table>
<thead>
<tr>
<th>Risk-Group</th>
<th>Total</th>
<th>Infants (&lt; 3 years) (%)</th>
<th>Age (years)</th>
<th>Histology</th>
<th>Mutation</th>
<th>10-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>WNT</td>
<td>33</td>
<td>0</td>
<td>≥ 4.3</td>
<td>Large-cell Anaplastic</td>
<td>TP53 mutation, MYCN</td>
<td>72% (66-100)</td>
</tr>
<tr>
<td>SHH-Child</td>
<td>38</td>
<td>5</td>
<td>≥ 4.3</td>
<td>Desmoplastic or Nodular</td>
<td>SUFU mutation</td>
<td>48% (29-80)</td>
</tr>
<tr>
<td>SHH-Infant</td>
<td>65</td>
<td>78</td>
<td>&lt; 4.3</td>
<td>SUFU mutation</td>
<td></td>
<td>58% (46-75)</td>
</tr>
<tr>
<td>Group 3-LR1</td>
<td>50</td>
<td>54</td>
<td>&lt; 3</td>
<td>MYC mutation</td>
<td></td>
<td>69% (55-87)</td>
</tr>
<tr>
<td>Group 3-HR2</td>
<td>65</td>
<td>17</td>
<td>Large-cell Anaplastic</td>
<td>MYCN, GFI1 mutation</td>
<td></td>
<td>22% (10-46)</td>
</tr>
<tr>
<td>Group 4-LR</td>
<td>73</td>
<td>3</td>
<td>MYCN</td>
<td></td>
<td></td>
<td>72% (59-88)</td>
</tr>
<tr>
<td>Group 4-HR</td>
<td>85</td>
<td>5</td>
<td>i17q</td>
<td></td>
<td></td>
<td>36% (22-59)</td>
</tr>
</tbody>
</table>

1 low risk, 2 high risk, 3 TP53 mutation, 4 MYCN amplification, 5 SUFU mutation, 6 MYC mutation, 7 GFI1 mutation, 8 i17q mutation, 9 (95% CI)
In an international study on cancer survival, Finland demonstrated one of the highest 5-year net survival rates for most cancers; the 5-years survival rate for CBTs was 76% in the patients treated between 2010 and 2014 (Allemani et al., 2018). The age-adjusted 5-year survival of patients with CBTs improved from 70% in 1981–1990 to 79% in 2001–2010 in Finland (Madanat-Harjuoja et al., 2014). The most notable improvement was an increase from approximately 50% to 70% between the time periods of 1971–1980 and 1981–1990, respectively (Madanat-Harjuoja et al., 2014). However, the survival of patients with malignant brain tumors showed no improvement since 1991 (Madanat-Harjuoja et al., 2014).

Among the 5-year survivors of CBT, the risk of death was 13 times higher than that in their peers (Perkins, Fei, Mitra, & Shinohara, 2013). Ependymoma and medulloblastoma/PNET survivors had the highest risk of death (31- and 23-fold, respectively) (Perkins et al., 2013). Inclusion of radiotherapy increased the risk of death by 17-fold (Perkins et al., 2013). Recurrent tumors were the most common cause of death even after 5 years of survival (Perkins et al., 2013).

2.5 Late-effects

Improvements in survival rates and increasing population of CBT survivors have highlighted the importance of the patients’ quality of life, along with the late-effects of tumors and their treatment. In the Childhood Cancer Survivor Study (CCSS), adult survivors of CBT reported the second highest incidence of adverse health effects in all domains, with the highest observed in survivors of bone tumors (Hudson et al., 2003). Radiotherapy of head or brain increased the incidence of reporting at least one adverse health effect (Hudson et al., 2003). Adult CBT survivors had relative a risk of 12.6 for severe or life-threatening health conditions compared to their siblings (Oeffinger et al., 2006).

Secondary tumors and strokes are serious late-effects of CBT and are associated with increased mortality (Cai et al., 2012; Peterson, Shao, McCarter, MacDonald, & Byrne, 2006; Packer, Zhou, Holmes, Vezina, & Gajjar, 2013; Campen et al., 2012; Bowers et al., 2006; Mueller et al., 2013; Haddy et al., 2011). Late-endocrinological effects and osteoporosis are typically observed, particularly in those treated with radiotherapy (Petraroli et al., 2007; Odame et al., 2006; Darzy & Shalet, 2009; Gunn et al., 2016). Incidence of obesity, hypercholesterolemia, and hypertension are increased in CBT survivors treated with radiotherapy (Pietilä et al., 2009). Epilepsy, psychiatric disorders, and kidney, circulatory, vision, and
hearing problems were observed after CBT treatment (Gunn et al., 2015; Gunn et al., 2016).

CBT survivors, particularly those treated with radiotherapy, experienced neurocognitive impairment (de Ruiter et al., 2013; Ris et al., 2013; Palmer et al., 2001; Schreiber et al., 2014; Ris, Packer, Goldwein, Jones-Wallace, Boyett, 2001). Survivors have poorer academic achievement at the end of the comprehensive school than their healthy peers (Lähteenmäki et al., 2007). CBT affects the activities of everyday life through adulthood. Socially, CBT survivors demonstrate higher risk of remaining unmarried and unemployed than the general population (Janson et al., 2009; de Boer, Verbeek, & van Dijk, 2006).

### 2.5.1 Cerebrovascular disease

Radiotherapy has several effects on the brain vasculature (Warrington et al., 2013). The direct effects of radiation on endothelial cells of the vessel walls lead to disrupted structural integrity of the endothelial layer during follow-up (Warrington et al., 2013; Morris et al., 2009). The delayed disruption is further maintained through chronic inflammatory or oxidative stress response (Morris et al., 2009). Furthermore, intimal fibrosis and foam cell accumulation caused by the disrupted endothelial layer can lead to narrowing of the lumen and thrombus formation (Morris et al., 2009).

Survivors of CBT, particularly those treated with radiotherapy, have an increased risk of stroke and stroke recurrence (Campen et al., 2012; Noje, Cohen, & Jordan, 2013; Bowers et al., 2006; Fullerton et al., 2015). MRI findings of small-vessel disease (SVD), such as lacunar infarcts, microbleeds, and cavernomas, may appear at a young age (Fouladi et al., 2000; Passos et al., 2017; Neu et al., 2018; Wardlaw et al., 2013). Radiotherapy also induces large-vessel vasculopathy (stenosis, occlusion, and moyamoya disease) (Kralik et al., 2017; Omura, Aida, Sekido, Kakehi, & Matsubara, 1997; Desai, Paulino, Mai, & Teh, 2006). Table 3 shows the incidence of vascular pathology in CBT survivors treated with radiotherapy.
Table 3. Cerebrovascular findings in survivors of childhood brain tumors treated with radiotherapy.

<table>
<thead>
<tr>
<th>Cerebrovascular finding</th>
<th>Median follow-up time (years)</th>
<th>Prevalence (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic infarct</td>
<td>6.5</td>
<td>2.6</td>
<td>Campen et al., 2012</td>
</tr>
<tr>
<td>TIA</td>
<td>6.5</td>
<td>3.8</td>
<td>Campen et al., 2012</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>2.01^1</td>
<td>5.9</td>
<td>Fouladi et al., 2000</td>
</tr>
<tr>
<td>Focal hemosiderin deposit</td>
<td>11.1</td>
<td>41.6</td>
<td>Passos et al., 2017</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>3.6</td>
<td>45.5</td>
<td>Roddy et al., 2016</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>13.5^2</td>
<td>90.0</td>
<td>Neu et al., 2018</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>19.8</td>
<td>91.6</td>
<td>Miura et al., 2017</td>
</tr>
<tr>
<td>Large-vessel vasculopathy</td>
<td>1.5</td>
<td>6.7</td>
<td>Kralik et al., 2017</td>
</tr>
<tr>
<td>Large-vessel vasculopathy</td>
<td>5.2</td>
<td>18.8</td>
<td>Omura et al., 1997</td>
</tr>
</tbody>
</table>

1 Longitudinal study, median follow-up time to first lacunar infarcts. 2 Mean follow-up time

**Strokes**

The risk of stroke in survivors of CBT is 29–100 times than that observed in the general population (Campen et al., 2012; Bowers et al., 2006). Administration of cranial radiotherapy has increased the risk of stroke by 8–8.5-fold than those not treated with radiotherapy (Campen et al., 2012; El-Fayech et al., 2017). The risk of the same was significantly higher upon the inclusion of the circle of Willis in the radiation fields (Campen et al., 2012; El-Fayech et al., 2017). Hypertension increased the risk of stroke in the CCSS (Mueller & Chang, 2009).

**Focal hemosiderin deposits**

Focal hemosiderin deposits (FHDs), including microbleeds and cavernomas, are common signs of SVD in CBT survivors (Passos et al., 2017). FHDs have been diagnosed in 42% of survivors after a median follow-up of 11 years (Passos et al., 2017). Susceptibility-weighted imaging (SWI) or gradient-echo T2*-weighted MRI sequences are especially sensitive in detecting microbleeds (Lin, Filippi, Steever, & Zimmerman, 2001; Wardlaw et al., 2013). These methods have revealed microbleeds in 90–92% in radiotherapy-treated CBT survivors (Neu et al., 2018; Miura et al., 2017). The presence of microbleeds on MRI has been associated with impaired performance of executive functions in survivors (Roddy et al., 2016).
**Lacunar infarcts**

Lacunar infarct is a previous, acute, small, deep brain infarct or hemorrhage in one of the perforating arterioles (Wardlaw et al., 2013). Lacunar infarcts in CBT survivors are poorly studied. These infarcts have been noted in survivors treated with radiotherapy, but not in those treated with surgery alone; furthermore, the number and the size of lacunar infarcts significantly increased during follow-up (Fouladi et al., 2000). In CBT survivors with lacunar infarcts, the mean decline in the intelligence quotient was similar to that of patients without lacunar infarcts (Fouladi et al., 2000).

**White matter lesions**

The etiology and natural history of white matter lesions (WMLs), which indicates the presence of SVD among the elderly, is not typically straightforward in survivors of CBT treated with radiotherapy (Wardlaw et al., 2013; Fouladi et al., 2004). Most WMLs that appeared during the treatment could not be detected on MRI after a median onset of 6 months (Fouladi et al., 2000). The etiology of WMLs is multifactorial and is influenced by the effects of radiation on oligodendrocytes, microvascular injury, and inflammation (Fouladi et al., 2004). After whole-brain radiotherapy, the WMLs were more common in adult patients with hypertension than those without (Szerlip et al., 2011). Because of the multifactorial etiology of WMLs, they cannot be considered as a sign of SVD in CBT survivors.

WMLs are associated with cognitive problems in CBT survivors (Jacola et al., 2014; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006; Fouladi et al., 2004). Most CBT survivors who were treated with radiotherapy (64%) had diffuse and/or circumscribed WMLs after a mean follow-up time of 5 years (Dietrich et al., 2001). Additionally, ventriculoperitoneal shunts and supratentorial tumors were associated with the presence of WMLs (Dietrich et al., 2001).

**Cerebrovascular disease in the general elderly population**

The current research on CBT survivors has focused on the incidence of the signs of CVD. Few studies have investigated the clinical importance of the signs, primarily neuropsychological outcomes (Fouladi et al., 2000; Roddy et al., 2016). CVD is actively studied in the general population due to its causative association with cognitive impairment, morbidity, mortality, and high costs to the health care system.
Therefore, to understand the clinical significance of CVD, the CVD on general population is discussed herein.

Table 4 shows the reported incidence of ischemic infarcts (ISs), lacunar infarcts, microbleeds, and WMLs in the general population with a mean age of 59–75 years. WMLs are more common in the aging population; they have been found in 11–21% of the otherwise healthy elderly population with a mean age of 64 years and in 38–88% of the same with a mean age of 80–82 years (Ylikoski et al., 1995; Garde, Mortensen, Krabbe, Rostrup, & Larsson, 2000).

<table>
<thead>
<tr>
<th>MRI Findings of CVD</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Infarcts</td>
<td>3–6</td>
</tr>
<tr>
<td>Lacunar Infarcts</td>
<td>6–9</td>
</tr>
<tr>
<td>White Matter Lesions</td>
<td>11–21</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>15–24</td>
</tr>
</tbody>
</table>

CVD in the general population is a whole brain disease with significant clinical importance; however, it can be asymptomatic over several years after the development of the vascular pathology (Debette et al., 2019; Xu et al., 2015; Debette & Markus, 2010; Akoudad et al., 2014). Microbleeds and WMLs in the adult population are associated with a decline in cognitive functions, dementia, and Alzheimer disease (Debette & Markus, 2010; Akoudad et al., 2016; Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987; Garde et al., 2000; Debette et al., 2019). A recent meta-analysis revealed that lacunar infarcts did not influence cognition (Debette et al., 2019). In addition, WMLs, lacunar infarcts, and microbleeds have been associated with stroke, both intracerebral hemorrhage and ischemic stroke, and death (Debette & Markus, 2010; Kaffashian, Tzourio, Zhu, Mazoyer, & Debette, 2016; Kuller et al., 2004; Debette et al., 2019). A previous study has reported that the general population demonstrated a coexistence of microbleeds and lacunar infarcts (Akoudad et al., 2014).

Stroke is a particularly heterogeneous disorder, without well-defined risk factors (Schulz & Rothwell, 2003). In a meta-analysis, the male sex, previous TIA,
and smoking were risk factors for large-vessel disease (LVD) (Schulz & Rothwell, 2003). Hypertension was associated with stroke caused by SVD due to a significant observation in one of the four studies included in the meta-analysis (Schulz & Rothwell, 2003). In a large Caucasian cohort, hypertension, diabetes, and smoking were associated with both SVD and LVD, whereas hypercholesterolemia was associated with LVD (Khan, Porteous, Hassan, & Markus, 2007).

### 2.5.2 Neurocognitive late-effects

Among all survivors of childhood cancer, survivors of CBT treated with radiotherapy have the highest risk of cognitive impairment (de Ruiter et al., 2013). The full-scale intelligence quotient (FSIQ), verbal (VIQ), and performance intelligence quotient (PIQ) were lower in CBT survivors than in the general population (de Ruiter et al., 2013). Furthermore, the PIQ is impaired to a greater degree than the VIQ (de Ruiter et al., 2013). Radiotherapy is a strong predictor of poor cognitive functioning (de Ruiter et al., 2013).

CBT patients demonstrated cognitive impairment at the time of diagnosis (Margelisch et al., 2015). Verbal working memory, attention, verbal learning, delayed verbal recall, and recognition of words and stories were affected (Margelisch et al., 2015). White matter tracts are displaced by the tumors, and fast-growing tumors may infiltrate the tracts, thereby causing injury, which may increase during surgery (Na et al., 2018). Cerebellar mutism is observed in 23.5 % and cerebellar mutism syndrome in 6.5 % of the patients after removing the posterior fossa tumor (Renne et al., 2019). The mechanism of the cerebellar mutism is yet unknown, but its relationship with poorer cognitive function has been recognized (Renne et al., 2019; Palmer et al., 2010).

Radiotherapy causes neuroinflammation and reductions in neurogenesis, which may last for decades (Burns, Awad, Li, & Grant, 2016). Radiation-induced neuroinflammation and reduction in neurogenesis are most prominent in the hippocampus (Burns et al., 2016). Progressive white matter injury is a well-known marker of radiation-induced brain injury in the survivors (Burns et al., 2016). Axons in CNS white matter tracts are highly dependent on myelin for function and survival (Burns et al., 2016). Radiation-induced vascular brain injury has a major role in the development of the CNS injury (Greene-Schloesser et al., 2012). Radiation-induced CNS injury leads to progressive cognitive impairment in the survivors (Burns et al., 2016).
Whole-brain radiotherapy, compared to local radiotherapy, and higher doses delivered to the whole brain area, are associated with a lower intelligence quotient (Grill et al., 1999; Silber et al., 1992). After cranial radiotherapy for CBT, the FSIQ declined by 1.1–4.3 points per year for the first 3–12 years of follow-up (Ris et al., 2013; Ris et al., 2001; Palmer et al., 2001; Kahalley et al., 2016; Mulhern et al., 2005). Although a decline in the FSIQ has been observed in survivors, it was due to the inability to learn new skills at the same rate as their healthy peers, and not because of the loss of acquired skills (Palmer et al., 2001). Survivors treated with proton beam radiotherapy did not demonstrate a decline in FSIQ in a follow-up study (Kahalley et al., 2016). There was no notable difference in the intelligence quotient slopes between the patients undergoing proton beam therapy and modern photon radiotherapy (Kahalley et al., 2016). Adult survivors of CBT had a stable FSIQ, but declining working memory even after a median of 15 years since diagnosis (Edelstein et al., 2011).

Adult survivors of medulloblastoma had lower than expected scores in almost all areas of cognitive function than the reference population (Edelstein et al., 2011; Brinkman et al., 2012). The highest degree of impairment was observed in executive functions, motor dexterity, speed, and working memory (Edelstein et al., 2011; Brinkman et al., 2012).

Survivors that underwent treatment for a longer time or who were younger at the diagnosis had higher risk of impaired cognition (de Ruiter et al., 2013; Silber et al., 1992; Fay-McClymont et al., 2017; Schreiber et al., 2014). A meta-analysis showed lower cognitive function related to chemotherapy (de Ruiter et al., 2013). However, a favorable cognitive function was found in children who were not diagnosed with neurofibromatosis I and who underwent chemotherapy alone; their FSIQ was in the normal range in 87.5% (Lacaze et al., 2003). Patients are rarely treated with chemotherapy alone; chemotherapy is usually combined with radiotherapy to treat CBTs (Merchant et al., 2010; Wells & Packer, 2015). This contradiction in the results may suggest that in the meta-analysis, the effect of chemotherapy is indicative of the influence of radiotherapy on cognitive functions or that the combination of radiotherapy and chemotherapy is even more damaging than radiotherapy alone (de Ruiter et al., 2013).

2.5.3 Psychosocial late-effects

Concomitant presentation of cognitive impairment and other late-effects may lead to problems in the functional domain. Problems in executive functions, especially
lower levels of response consistency, have been associated with poorer skills in social functioning, considering the fact that CBT survivors have a high risk of remaining unmarried (Wolfe et al., 2013, Janson et al., 2009; Syse, 2008). Additionally, the late-effects of CBT such as short stature, poor self-reported physical functioning, problems with task efficiency, problems with organization, and problems with memory, have been associated with remaining unmarried (Janson et al., 2009). However, married survivors of CBT did not divorce more often than their healthy peers (Janson et al., 2009). Grades at the end of comprehensive school were lower in survivors of CBT than their healthy peers, the highest difference was noted in the foreign languages (Lähteenmäki et al., 2007). Finnish survivors of CBT demonstrated lower educational level, early retirement, and compulsory exemption from military service more often than their healthy peers (Ahomäki, Harila-Saari, Matomäki, & Lähteenmäki, 2017; Ahomäki, Harila-Saari, Parkkola, Matomäki, & Lähteenmäki, 2017).

2.5.4 Secondary tumors

All childhood cancer survivors have an increased risk of secondary tumors, along with the presence of SNs (Armstrong et al., 2011; Bhatia et al., 1996; Hijiya et al., 2007; Kok et al., 2018; Neglia et al., 1991; Armstrong et al., 2009; Neglia et al., 2006). Survivors of Hodgkin lymphoma, CNS tumors, and sarcomas demonstrated the highest risk of secondary tumors (Meadows et al., 2009; Inskip & Curtis, 2007). Radiotherapy characteristically increased the incidence of secondary tumors (Kok et al., 2018; Neglia et al., 2006; Taylor et al., 2010). Table 5 shows the observed-to-expected ratios of secondary cancers in childhood cancer survivors by their primary cancer diagnosis from the SEER databases.

Survivors of CBT have 4.8 times the risk of subsequent neoplasms during follow-up (Cai et al., 2012). The reported cumulative incidence at the 25-year follow-up has was 10.7 % for all SNs and 3.3 % for benign meningiomas (Armstrong et al., 2009). The cumulative incidence at 25 years was 7.1 % for SNs after cranial radiotherapy and 1.0 % if the brain tumor was treated without radiotherapy (Armstrong et al., 2009). Primary tumor histology influenced the risk of SNs and the highest risk was observed in the survivors of ependymoma or embryonal tumors and lowest risk in astrocytoma survivors (Cai et al., 2012).

Ionizing radiation has carcinogenic potential and exposing tissues to the same damages DNA via direct and indirect mechanisms (Kumar, 2012, Godlewski, Drummond, & Kaye, 2012). Carcinogenic effects of radiation are mainly observed
in the cells that were not killed by radiation (Godlewski et al., 2012). Therefore, the areas demonstrating lower radiation doses, where the cells are not predominantly killed by radiation, are particularly prone to radiation-induced tumors (Galloway et al., 2012). However, several studies have demonstrated that the incidence of SNs increases with higher total doses of radiotherapy (Kok et al., 2018; Armstrong et al., 2009; Taylor et al., 2010).

Table 5. Observed-to-expected ratios of the secondary cancers among the common childhood cancers according to the SEER database (diagnosis between the age of 0 and 17 years (Inskip & Curtis, 2007).

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>Observed-to-expected ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types of first cancer</td>
<td>5.9</td>
</tr>
<tr>
<td>All leukemia</td>
<td>5.0</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>9.7</td>
</tr>
<tr>
<td>All CNS cancer</td>
<td>6.3</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>6.3</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>4.3</td>
</tr>
<tr>
<td>PNET, brain CNS(^1)</td>
<td>14.6</td>
</tr>
<tr>
<td>All bone cancer</td>
<td>7.2</td>
</tr>
</tbody>
</table>

\(^1\) central nervous system

The epipodophyllotoxins, such as etoposide and teniposide, and alkylating agents, have mutagenic effects on DNA (Hawkins et al., 1992; Packer et al., 2013). Several studies have reported that chemotherapy treatment or alkylating agents administration increased the risk of SNs in childhood cancer survivors, contrary to other studies (Bhatia et al., 1996; Hijiya et al., 2007; Neglia et al., 1991; Banerjee et al., 2009). The most common secondary brain tumors in childhood cancer survivors are gliomas and meningiomas (Neglia et al., 2006; Taylor et al., 2010). Radiation-induced gliomas tended to appear 5–10 years after radiation exposure, but the risk diminished after 15–20 years of follow-up (Neglia et al., 2006). Although meningiomas appeared later, their incidence sharply increased during follow-up (Neglia et al., 2006; Banerjee et al., 2009). The risk of gliomas and meningiomas was the highest at radiation doses of 30–44.9 Gy in childhood cancer survivors (Neglia et al., 2006). Intrathecal methotrexate and carboplatin use have been associated with a higher incidence of meningiomas (Taylor et al., 2010; Kok et al., 2018). True incidence of meningiomas was one-third higher than that reported by the Finnish Cancer Registry (FCR) (Larjavaara, Haapasalo, Sankila, Helen, &
This estimation was based on the number of the meningiomas cases found in the clinical data sources from a hospital’s neurosurgical clinic, pathology database, hospital discharge database, and autopsy database compared to those reported in the FCR (Larjavaara et al., 2008).

Previous MRI screening studies revealed that the crude incidence of radiation-induced meningioma typically varied between 14% and 22% in survivors of childhood leukemia and childhood cancer after a median follow-up of 21–25 years (Banerjee et al., 2009; Goshen et al., 2007; Felicetti et al., 2015; Sabin et al., 2014). The cumulative incidence at the 20-year follow-up was 15% for meningiomas in leukemia survivors (Goshen et al., 2007). In screening studies, most meningiomas were asymptomatic, and their presence raises an important question about whether early detection of meningiomas would lead to successful total resection (Goshen et al., 2007; Felicetti et al., 2015; Sabin et al., 2014, Banerjee et al., 2009). Current consensus guidelines of the Children’s Oncology Group (COG) do not support MRI screening for asymptomatic survivors treated with cranial radiotherapy without a prior diagnosis of neurofibromatosis (Children's Oncology Group, 2018).

The role of growth hormone (GH), considering its mitogenic and carcinogenic effects, with regard to the risk of secondary tumors has been discussed over the years (Sklar et al., 2002; Ergun-Longmire et al., 2006; Jostel, Mukherjee, Hulse, & Shalet, 2005). Meningiomas and gliomas express GH and insulin-like growth factor 1 (IGF1) receptors (Swerdlow et al., 2018; Indini et al., 2017). However, concerns regarding the safety of GH treatment have declined, as recent data support that the risk of recurrence, SNs, and death is not increased with GH treatment (Sklar et al., 2002; Ergun-Longmire et al., 2006; Indini et al., 2017; Swerdlow et al., 2000; Shen, Sun, Li, Liu, & Zhou, 2015). Furthermore, the risk of meningiomas is not associated with the mean daily dose of GH, duration of GH treatment, or cumulative dose of GH after cranial radiotherapy (Swerdlow et al., 2018).

### 2.5.5 Endocrinological late-effects

The exposure to radiotherapy or alkylating agents predisposes childhood cancer survivors to endocrinological late-effects (Chemaitilly & Cohen, 2017). CBT survivors demonstrate a 14.7-fold increased risk of hormonal disease than their siblings (Gunn et al., 2015). An even higher risk (70.1-fold) has been reported in survivors of embryonal tumors (Gunn et al., 2015). CBT treatment may cause both central and peripheral endocrinopathies, owing to the effects of radiation on the
hypothalamus and administration to the peripheral endocrine glands, respectively (Rose et al., 2016; Chemaitilly & Cohen, 2017; Chemaitilly et al., 2018).

The radiation dose to the hypothalamus demonstrated a better correlation with the endocrinopathies, compared with the radiation dose to the pituitary with endocrinopathies, since the neurons in the hypothalamus are the most sensitive to the effects of radiation (Rose et al., 2016; Merchant et al., 2011). The dose delivered to the hypothalamus in whole-brain radiotherapy is minimum 18 Gy in current treatment protocols (Universitätsklinikum Hamburg-Eppendorf, 2017a). The scattering of the photon radiotherapy beams leads to administration of doses regions outside the target area (Rose et al., 2016; Merchant et al., 2011). The hypothalamus may be present in the radiation field of patients undergoing local radiotherapy to other parts of the brain or the doses delivered to the hypothalamus may subsequently increase due to the local boost to the tumor bed in patients treated with whole-brain radiotherapy (Rose et al., 2016; Merchant et al., 2011). Spinal radiotherapy may damage ovarian function, but typically does not affect testicular functions (Rose et al., 2016; Cuny et al., 2011). Radiation therapy to the neck area increases the risk of thyroid complications, as well as hyperparathyroidism (Chemaitilly & Cohen, 2017; Rose et al., 2016). Proton beam radiotherapy demonstrates limited radiation dose scattering, which decreases the risk of endocrinopathies (Merchant, 2009).

Hypothalamic-pituitary axis

Hypothalamic-pituitary (HP) axis dysfunction usually occurs after radiotherapy, but not after conventional chemotherapy (Chemaitilly & Cohen, 2017; Chemaitilly et al., 2018). Injury to the tissues may be observed at months to several decades after radiotherapy (Chemaitilly et al., 2018; Chemaitilly & Cohen, 2017; Rose et al., 2016). Radiation-induced endocrinopathies usually appear over an extended period of time (Chemaitilly & Cohen, 2017). In contrast, HP injury after tumor invasion or after surgery usually appears with multiple endocrinopathies in a short period of time (Chemaitilly & Cohen, 2017). The HP axis injury may cause GH deficiency, central precocious puberty, luteinizing hormone (LH) or follicle-stimulating hormone (FSH) deficiencies (hypogonadotropic hypogonadism), thyroid-stimulating hormone (TSH) deficiency (central hypothyroidism), adrenocorticotropic hormone (ACTH) deficiency, hyperprolactinemia, and diabetes insipidus (Chemaitilly & Cohen, 2017; Chemaitilly et al., 2018). Incidence of HP deficiency has been associated with radiotherapy, younger age at diagnosis,
longer follow-up time, and hydrocephalus at diagnosis in survivors of CBT (Clement et al., 2016). Table 6 shows the 5-year cumulative incidence of HP axis deficiencies in survivors of CBT.

Table 6. The 5-year cumulative incidence of HP axis deficiencies in survivors of CBT (Clement et al., 2016).

<table>
<thead>
<tr>
<th>Hormonal deficiency</th>
<th>5-year cumulative incidence (%) (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>11.1 (6.2 to 17.4)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>7.2 (3.0 to 13.9)</td>
</tr>
<tr>
<td>Adrenocorticoid hormone</td>
<td>2.9 (0.4 to 10.6)</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>4.0 (0.9 to 11.1)</td>
</tr>
<tr>
<td>Luteinizing/ follicle stimulating hormones</td>
<td>1.7 (0.0 to 11.1)</td>
</tr>
<tr>
<td>Antidiuretic hormone</td>
<td>1.0 (0.0 to 11.2)</td>
</tr>
</tbody>
</table>

**Growth hormone**

GH deficiency is the most common radiation-induced HP axis deficiency, reported in 47 % of the childhood cancer survivors treated with radiotherapy and 80 % of the survivors of CBT (Chemaitilly & Cohen, 2017; Chemaitilly et al., 2018; Chemaitilly et al., 2015; Schmiegelow et al., 2000). Childhood cancer survivors were evaluated using IGF1 levels and CBT survivors with the insulin-tolerance test or arginine test; therefore, the incidence in cancer survivors may be underestimated (Chemaitilly et al., 2015; Schmiegelow et al., 2000). The follow-up time was longer in cancer survivors than in CBT survivors (Schmiegelow et al., 2000; Chemaitilly et al., 2015).

A total radiation dose of 22–22.9 Gy was associated with a higher risk of GH deficiency (Chemaitilly et al., 2015). A cumulative radiotherapy dose of 16.1 Gy to the hypothalamus had a 50 % risk of GH deficiency at 5 years (Merchant et al., 2011). Survivors of CBT treated with radiotherapy had a 79-fold risk to develop GH deficiency than those who were not treated with radiotherapy (Clement et al., 2016). The incidence of GH deficiency has increased with higher doses of radiation to the hypothalamus, longer follow-up time, and presence of a ventriculoperitoneal shunt (Merchant et al., 2010). Subjects treated with a lower radiation doses developed GH deficiency later than those treated with higher radiation doses (Merchant et al., 2011).

GH deficiency causes growth impairment in children and adolescents, abnormal body composition, altered energy metabolism, poor overall health, and
diminished quality of life (Merchant et al., 2011). Even though the incidence of GH deficiency is common, it is not well recognized or adequately treated in adult survivors (Chemaitilly et al., 2015). According to the St Jude Lifetime Cohort (SJLIFE) study, 60.9% of the cancer survivors diagnosed with GH deficiency were not diagnosed with GH deficiency prior to the study (Chemaitilly et al., 2015). Additionally, only 12% of the CBT survivors received GH replacement therapy in the Finnish register-based study (Gunn et al., 2016).

**Thyroid function**

Central hypothyroidism has been reported in 7.5% of childhood cancer survivors treated with cranial radiotherapy, and in 9.1% of survivors of CBT (Chemaitilly et al., 2015; Clement et al., 2016). The estimated cumulative incidence at 40 years from cancer therapy was 11.6% in childhood cancer survivors treated with radiotherapy (Chemaitilly et al., 2015). The risk of central hypothyroidism was associated with the male sex, suprasellar and infratentorial tumors, and radiotherapy (Chemaitilly et al., 2015). The total dose of ≥ 30 Gy of radiotherapy was associated with a risk of central hypothyroidism (Chemaitilly et al., 2015).

Hypothyroidism is among the most common endocrine late-effects in childhood cancer survivors (Chemaitilly & Cohen, 2017). Disorders affecting the thyroid gland were observed in 13.8% of childhood cancer survivors, and in 5.8% of CBT survivors (Hudson et al., 2013; Clement et al., 2016). The incidence of hypothyroidism was particularly high in survivors of medulloblastoma treated with craniospinal radiotherapy, at 57.1% (Clement et al., 2016). The cumulative incidence of hypothyroidism at the 5-year follow-up was 5.4% in CBT survivors (Clement et al., 2016). In addition to radiotherapy, some chemotherapeutic agents, such as busulfan and cyclophosphamide, may cause hypothyroidism, but it is often transient and mild (Chemaitilly et al., 2018). Hyperthyroidism is a less common consequence of neck or craniospinal radiotherapy compared with hypothyroidism (Chemaitilly et al., 2018).

Symptoms of both central and peripheral hypothyroidism include fatigue, growth failure, and abnormal weight gain (Chemaitilly et al., 2018; Chemaitilly & Cohen, 2017). Thyroid replacement therapy has been reported in 14.5% of CBT survivors in Finland (Gunn et al., 2016). The risk of replacement therapy was higher among female survivors and after radiotherapy (Gunn et al., 2016).
Sex hormones

The HP axis has previously been associated with the development of central precocious puberty and LH/FSH deficiency (Chemaitilly & Cohen, 2017; Chemaitilly et al., 2018). The early activation of the HP axis causes the central precocious puberty, i.e. the onset of puberty before the age of 8 years in girls and before 9 years in boys (Chemaitilly et al., 2018). LH/FSH deficiency leads to low or no secretion of the peripheral sex hormones (Chemaitilly et al., 2018). This deficiency may lead to the absence of pubertal development, arrested puberty, menstrual cycle failure, or symptoms of low estrogen and testosterone (Chemaitilly et al., 2018).

The LH/FSH deficiency was observed in 10.8 % of adult survivors of childhood cancer treated with radiotherapy, and in 4.2 % of survivors of CBT (Chemaitilly et al., 2015; Clement et al., 2016). Precocious puberty was observed in 12.2 % of CBT survivors (Clement et al., 2016). LH/FSH deficiency has been associated with the total dose of radiation ≥ 22 Gy (Chemaitilly et al., 2015).

Peripheral sex hormone deficiencies are associated with spinal radiotherapy, and gonadotoxic chemotherapy, such as alkylating agents in female patients (Cuny et al., 2011; Chemaitilly & Cohen, 2017). Chemotherapy rarely affects Leydig cell function resulting in androgen insufficiency (Jahnukainen, Ehmcke, Hou, & Schlatt, 2011; Chemaitilly & Cohen, 2017). Spinal radiotherapy is not associated with testicular damage (Cuny et al., 2011). Hypergonadotropic hypogonadism was reported in 4.0 % of survivors of CBT with a 5-year cumulative incidence of 3.5 % (Clement et al., 2016). Predisposing factors for hypergonadotropic hypogonadism were noted in older patients at the time of primary cancer diagnosis, high-dose chemotherapy, and craniospinal radiotherapy (Clement et al., 2016).

Replacement therapy of all sex hormones in women and testosterone in men were reported in 24.0 % and 6.1 % of CBT survivors, respectively (Gunn et al., 2016). Radiotherapy increased the risk of both estrogen and androgen replacement therapy (Gunn et al., 2016).

Fertility

Testes have two distinct functions with very different sensitivities to cancer treatments (Chemaitilly & Cohen, 2017). Chemotherapeutic agents and even low doses of radiation are particularly toxic to germ cells (Jahnukainen et al., 2011). However, craniospinal radiotherapy should not cause infertility in men.
(Schmiegelow et al., 2001). Since FSH regulates spermatogenesis, and its secretion may be reduced after cranial radiotherapy, spermatogenesis may be affected after cranial radiotherapy alone (Ballester et al., 2004; Chemaitilly & Cohen, 2017). However, a combination of chemotherapy and radiotherapy was reportedly more damaging to the Sertoli cells and germ cells (Schmiegelow et al., 2001).

Estrogen deficiency in women is associated with expected impairment in fertility (Chemaitilly & Cohen, 2017). Chemotherapeutic agents, along with cranial and spinal radiotherapy, may develop infertility in female CBT survivors (Cuny et al., 2011; Chemaitilly & Cohen, 2017). Approximately 32% of survivors treated for medulloblastoma or ependymoma do not attain puberty, subsequently preventing menstruation (Cuny et al., 2011).

**Adrenocorticotropic hormone**

ACTH deficiency leads to insufficient cortisol secretion from the adrenal glands. (Rose et al., 2016). In specific physical illnesses, patients are predisposed to the risk of adrenal crisis (Chemaitilly et al., 2018). Other symptoms may include fatigue, weight loss, and low blood glucose levels (Chemaitilly et al., 2018). ACTH deficiency has been reported in 4.3% of CBT survivors (Clement et al., 2016). A total dose of ≥30 Gy radiotherapy was associated with ACTH deficiency in childhood cancer survivors (Chemaitilly et al., 2015). ACTH deficiency may typically develop early during follow-up (Chemaitilly et al., 2015). Hydrocortisone replacement therapy was used in 18.6% of CBT survivors (Gunn et al., 2016). Therefore, it is apparent that patients with ACTH deficiency usually are well-recognized, according to the SJLIFE study; furthermore, only one new diagnosis was identified through ACTH stimulation testing (Chemaitilly et al., 2015).

### 2.5.6 Bone mineral density

Childhood cancer survivors demonstrate an increased risk of low BMD (Arikoski et al., 1999) (Arikoski et al., 1998; Bilariki et al., 2010). Low BMD was common in CBT survivors who underwent radiotherapy, and these survivors may have multiple endocrinological deficiencies, which may additionally affect the bones (Odame et al., 2006; Petraroli et al., 2007).

Osteopenia was diagnosed in 44% of CBT survivors and in 67% of those treated with radiotherapy after a mean follow-up of 7 years (Odame et al., 2006).
Craniospinal radiotherapy was associated with a lower BMD, unlike cranial radiotherapy (Pietila et al., 2006).

BMD was higher in survivors who were younger at diagnosis and with a longer follow-up time (Cohen et al., 2012). The analysis of hormonal deficiencies considering BMD revealed contradictory results. Several studies did not report any association between GH deficiency and BMD; however, Cohen et al. (2012) reported that higher BMD levels in those treated for GH deficiency (Petraroli et al., 2007; Pietilä et al., 2006; Morris et al., 2008; Kang et al., 2012). Hypogonadism was associated with low BMD levels in a select group of studies, but not in others (Petraroli et al., 2007; Pietilä et al., 2006; Krishnamoorthy, Freeman, Bernstein, Lawrence, & Rodd, 2004; Morris et al., 2008; Kang et al., 2012; Cohen et al., 2012; Holmer et al., 2011). Contrary to the findings in the general population, lower BMD has been observed in male CBT survivors (Marshall, Johnell, & Wedel, 1996; Krishnamoorthy et al., 2004). Although the association between low BMD and the risk of fractures has been well established in the general population, little is known regarding the risk of fracture in survivors of CBT (Marshall et al., 1996).
3 Aims of the study

The present PhD project is a part of a larger study on late-effects of radiotherapy in Finnish young adult CBT survivors that underwent treatment during their childhood. The aims of the present study were as follows:

1. To investigate the prevalence and risk factors of CVD by using MRI screening and laboratory testing.
2. To assess the neuropsychological outcomes, tumor- and treatment-related risk factors for neuropsychological impairment, and their effects of the impairment on everyday life.
3. To evaluate the incidence of secondary tumors in a clinical study with MRI screening and compare the results with the data retrieved from the FCR.
4. To investigate BMD and hormonal, tumor-related, and treatment-related risk factors for low BMD.
4 Patients and methods

4.1 Study design

We invited a Finnish national cohort of consecutive survivors of CBT who were previously treated with radiotherapy to participate in the present study. The participants were identified from local registries of five university hospitals at Oulu, Kuopio, Turku, Tampere, and Helsinki. The inclusion criteria for the study were as follows:

1. Patients diagnosed with a brain tumor at the age of < 16 years
2. Radiotherapy was a part of tumor treatment
3. Patient age at the time of the study was ≥ 16 years
4. Follow-up time since cessation of tumor therapy was ≥ 5 years
5. No known progressive brain tumor at enrollment

The patients were treated between 1970 and 2008. The study was conducted between 2010 and 2015.

4.2 Patients

A total of 74 survivors of the 127 eligible survivors (58 %) participated in the study. Table 7 enlists the number of participating survivors according to the specific study parameters. Forty survivors declined to participate in the entire study, and 13 did not follow-up. Table 8 shows the patient, tumor, and treatment characteristics of the participants. There were no significant differences between the non-participants and participants (Remes et al., 2018).

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for not participating</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniospinal MRI</td>
<td>Vagus nerve stimulator</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Claustrophobia</td>
<td>1</td>
</tr>
<tr>
<td>Neuropsychological examination</td>
<td>Severe visual impairment</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe cognitive impairment</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory samples</td>
<td>Could not be collected</td>
<td>1</td>
</tr>
<tr>
<td>Reason for not participating</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Metabolic blood samples</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Could not be collected</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not fasted</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Right femoral neck</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Right side not imaged</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Left femoral neck</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Left side hip prosthesis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Refusal</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Patient, tumor, and treatment characteristics of the study participants.

<table>
<thead>
<tr>
<th>Patient, tumor, and treatment characteristics</th>
<th>n = 74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/female), n (%)</td>
<td>47(64) / 27(36)</td>
</tr>
<tr>
<td>Age at diagnosis in years, mean (SD)</td>
<td>8.3 (4.3)</td>
</tr>
<tr>
<td>Follow-up time in years, mean (SD)</td>
<td>18.9 (6.1)</td>
</tr>
<tr>
<td>Age at follow-up visit in years, mean (SD)</td>
<td>28.4 (6.8)</td>
</tr>
<tr>
<td>Location of the tumor, n (%)</td>
<td></td>
</tr>
<tr>
<td>Infratentorial</td>
<td>38 (51)</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>36 (49)</td>
</tr>
<tr>
<td>Histology of the tumor, n (%)</td>
<td></td>
</tr>
<tr>
<td>Glial cell tumors</td>
<td>25 (34)</td>
</tr>
<tr>
<td>Embryonal tumors</td>
<td>22 (30)</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Pituitary tumors</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Not known</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Total dose of radiotherapy in Gy, mean (SD)</td>
<td>51.3 (5.2)</td>
</tr>
<tr>
<td>Radiotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>39 (53)</td>
</tr>
<tr>
<td>Cranial</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Craniospinal</td>
<td>30 (40)</td>
</tr>
<tr>
<td>Stereotactic</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Chemotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (64)</td>
</tr>
<tr>
<td>No</td>
<td>27 (36)</td>
</tr>
</tbody>
</table>
Patient, tumor, and treatment characteristics n = 74

<table>
<thead>
<tr>
<th>Surgery, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial resection</td>
<td>32 (43)</td>
</tr>
<tr>
<td>Total resection</td>
<td>29 (39)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>10 (14)</td>
</tr>
<tr>
<td>No operation</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reoperation, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>19 (26)</td>
</tr>
<tr>
<td>No</td>
<td>52 (70)</td>
</tr>
<tr>
<td>Not known</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ventriculoperitoneal Shunt, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>44 (59)</td>
</tr>
<tr>
<td>No</td>
<td>30 (41)</td>
</tr>
</tbody>
</table>

1 Follow-up time since the end of tumor therapy

Participants had a mean age of 28.4 ± 6.8 years at the time of the study. The mean age at diagnosis was 8.3 ± 4.3 years and the mean follow-up time since cessation of tumor therapy was 18.9 ± 6.1 years. The most of the participants were men (64%). One participant was diagnosed with type 1 neurofibromatosis.

4.3 Tumor treatments

4.3.1 Surgery

Most participants underwent surgery to treat the primary tumor (96%). According to the patient files, total resection was observed in 39% and partial resection in 43% of the survivors; additionally, 14% of the tumors were biopsied. Re-operation was performed in 19 survivors, of whom seven underwent multiple re-operations (1–5 times; Table 8). Although we attempted to reanalyze the histological samples from operated or biopsied tumors, we were unable to review histological characteristics for most survivors; therefore, we used the original diagnosis.

4.3.2 Radiotherapy

All participants underwent photon-based radiotherapy. Half of the subjects were treated with local radiotherapy (local radiotherapy in 39 participants and stereotactic radiotherapy in 2). Whole-brain radiotherapy was performed in 33 participants with (n = 30) and without (n = 3) spinal radiotherapy. Radiotherapy
was re-administered in one survivor. Table 9 shows the treatment characteristics of the local and whole-brain radiotherapy groups.

Table 9. Patient-, tumor- and treatment characteristics in survivors treated with local or whole-brain radiotherapy participating in neuropsychological examination

<table>
<thead>
<tr>
<th></th>
<th>Local (n = 39)</th>
<th>Whole-brain (n = 32)</th>
<th>Mean Diff. (95 % CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>8.2 (4.4)</td>
<td>8.4 (4.3)</td>
<td>-0.2 (-2.3 to 1.9)</td>
<td>0.890</td>
</tr>
<tr>
<td>At follow-up</td>
<td>30.2 (5.9)</td>
<td>25.6 (6.8)</td>
<td>4.5 (1.5 to 7.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>21.1 (5.0)</td>
<td>16.9 (6.3)</td>
<td>4.2 (1.6 to 6.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Total dose of radiotherapy</td>
<td>51.7 (5.5)</td>
<td>50.6 (5.2)</td>
<td>1.1 (-1.4 to 3.6)</td>
<td>0.402</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 46)</td>
<td>22 (56)</td>
<td>24 (75)</td>
<td></td>
<td>0.136</td>
</tr>
<tr>
<td>Female (n = 25)</td>
<td>17 (44)</td>
<td>8 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes (n = 45)</td>
<td>17 (44)</td>
<td>28 (88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 26)</td>
<td>22 (56)</td>
<td>4 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventriculoperitoneal shunt, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Yes (n = 44)</td>
<td>24 (62)</td>
<td>20 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 267)</td>
<td>15 (38)</td>
<td>12 (37)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Mean (SD), 2 Student's t-test, 3 Chi square exact test, 4 Significant level is 0.05

4.3.3 Chemotherapy

Chemotherapy was administered as a part of the treatment in 64 % of the participants (Table 8). The chemotherapy protocols varied according to tumor histology and time period of treatment. The most commonly used chemotherapy protocols were the “eight-in-one” protocol and another protocol that included administration of cisplatin, vincristine, and lomustine (Geyer, Pendergrass, Milstein, & Bleyer, 1988; Pendergrass et al., 1987; Packer et al., 1994; Packer et al., 1991). Six participants with medulloblastoma, three with ependymoma, one with PNET, and four with astrocytoma were treated with the “eight-in-one” protocol and seven participants with medulloblastoma were treated with the second chemotherapy protocol that involved cisplatin, vincristine, and lomustine administration.
4.3.4 Glucocorticoid treatment

Among the included participant only 10 had not been treated with glucocorticoids while undergoing treatment for brain tumor. Data regarding the glucocorticoid treatment of two survivors could not be found in the patient files. At the time of the study, eight survivors were receiving hydrocortisone treatment for adrenal insufficiency. Dexamethasone was administered throughout the period in which the 62 participants were undergoing tumor operations and radiotherapy, considering the fact that it was the most commonly used glucocorticoid during treatment. The mean cumulative dose of dexamethasone was 250 ± 316 mg/m² in all survivors and the mean duration of dexamethasone treatment was 42 ± 67 days. The “eight-in-one” protocol included a total dose of 300 mg/m² methylprednisolone per course (Geyer et al., 1988; Pendergrass et al., 1987). The mean cumulative dose of methylprednisolone was 6.5 ± 3.6 g/m² in 11 participants who were treated with the “eight-in-one” chemotherapy protocol. Two participants were excluded from the analysis, since one was treated with three courses of the “eight-in-one” protocol along with actinomycin D and vincristine and VP-16 administration, and another was treated with two courses of the “eight-in-one” protocol. In all survivors, the mean cumulative dose of glucocorticoids, calculated as g/m² of prednisolone, was 4.1 ± 5.2 g/m².

4.3.5 Hydrocephalus

Among the 74 survivors, 44 (59 %) were treated with ventriculoperitoneal shunt for hydrocephalus (Table 8), of which half required shunt revision. The number of shunt revisions varied between 1 (n = 9) and 14 (n = 1). The shunt was removed in 11 patients, and was replaced in four survivors after removal.

4.4 Methods

4.4.1 Medical records, questionnaires and medical examination

Patient, tumor, and treatment characteristics were collected from clinical files prior to the study visit. All the tumors have been treated in university hospitals; therefore, the treatment-related data were gathered accurately from the patient files. However, the time period of treatment influenced the accuracy of documenting treatment details with the early years being less precise. The total doses of chemotherapy and
glucocorticoid treatment were recorded as accurately as possible from the patient files. The data on hormonal deficiencies, the date of replacement therapy initiation, diagnosis of previous secondary malignancies, and the date of strokes were retrieved from the files. Information regarding brain tumors, their treatment or late-effects of the treatment was obtained from the other hospitals as needed.

Study participation required a two-day visit to the hospitals. During this visit, a questionnaire was used to collect information about education, marital status, functional life, current follow-up, atherosclerotic risk factors, and knowledge about the brain tumor and its treatment. The parents, caregivers, and researchers assisted the participants to complete the questionnaire. Information from the questionnaire was subsequently gathered from all participants. A questionnaire about the patients’ quality of life (Rand 36-Item Health Survey), and the Beck depression inventory (BDI) were also given to the survivors during the visit. These questionnaires were particularly difficult for the participants with severe cognitive problems; therefore, Rand-36 could not be collected from three survivors and BDI from six survivors due to cognitive impairment. In addition, six Rand-36 questionnaires and six BDI questionnaires were not gathered owing to errors on the behalf of the researcher.

The height, weight, height of the sitting participant, along with waist and head circumference were measured. Physical and neurological examinations were performed and the results documented with a questionnaire in all participants. Systolic and diastolic blood pressure (BP) was measured.

### 4.4.2 Craniospinal magnetic resonance imaging

Craniospinal MRI was performed using the following scanners: a Magnetom Espree 1.5T scanner (Siemens Healthcare GmbH, Erlangen, Germany) in Oulu, an Ingenia 1.5T scanner (Phillips Healthcare, Amsterdam, the Netherlands) in Turku, and Avanto 1.5T scanners (Siemens Healthcare GMbH) in Helsinki, Kuopio, and Tampere. The following pulse sequences were included in the brain MRI and magnetic resonance angiography (MRA) protocols: T1-weighted spin-echo (SE) sagittal, T2-weighted SE axial, T2-weighted fluid-attenuated inversion recovery SE coronal, axial diffusion-weighted imaging (DWI), and three-dimensional time-of-flight MRA. After administering gadolinium as the contrast agent (Dotarem 0.2 mL/kg, Guerbet, Villepinte, France), T1-weighted SE axial and T1-weighted SE coronal sequences were obtained. Contrast-enhanced T1-weighted turbo spin echo (TSE) and T2-weighted TSE sagittal sequences were performed for spinal MRI.
MRI and MRA scans were evaluated by using viewing applications for diagnostic radiology, including the picture archiving and communication systems or the digital imaging and communications in medicine (DICOM) format; neaView (Neagen, Helsinki, Finland) in Oulu, Sectra Workstation IDS7, version 19.1.10.3584 (Sectra AB, Linköping, Sweden) in Kuopio and Agfa Impax, version 6.6.1.551 2017 (Agfa Healthcare N.V., Mortsel, Belgium) in Helsinki. Radiologists Maria Suo-Palosaari, Anna Sutela, Päivi Koskenkorva and Sanna Toiviainen-Salo assessed the scans. Maria Suo-Palosaari re-assessed all the MRI and MRA scans.

4.4.3 Classification criteria for cerebrovascular disease

CVD definition included information regarding the history of transient ischemic attack (TIA) or cerebral hemorrhage verified from the patient files, or any imaging finding of CVD, excluding WMLs, that was detected on MRI or MRA.

LVD was defined by previous IS on MRI, a history of TIA, or vascular pathology diagnosed on brain MRA. SVD was diagnosed on the based on the presence of lacunar infarcts and FHDs on MRI (Wardlaw et al., 2013).

The American Heart Association and America Stroke Association (AHA/ASA) consensus criteria for IS were used, defined cerebral, spinal cord, or retinal cell death which was attributable to ischemia, based on imaging evidence of cerebral, spinal cord, or retinal focal ischemic injury, respectively, in a defined vascular distribution (Sacco et al., 2013). TIA diagnosis was made according to the following American Academy of Neurology consensus definition: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction (Easton et al., 2009). The AHA/ASA definition for stroke caused by intracerebral hemorrhage excluded all hemorrhages caused by traumas, along with subdural hemorrhages; however, it is possible that subdural hemorrhages spontaneously occur (Sacco et al., 2013).

The neuroimaging standards for research into SVD were used to diagnose lacunar infarcts, microbleeds, and WMLs (Wardlaw et al., 2013). An international consensus considered lacunar infarcts as round or ovoid, subcortical fluid-filled cavities (diameter ranging from 3 to 15 mm) that are consistent with previous acute small subcortical infarcts or hemorrhages in a perforating arteriole (Wardlaw et al., 2013). Cerebral microbleeds are small areas (diameter ranging from 2 to 5 mm and occasionally 10 mm) of signal voids with associated blooming artefacts observed on gradient echo MRI sequences that were sensitive to susceptibility effects, according to the International Consensus Criteria (Wardlaw et al., 2013). Here,
FHDs were diagnosed on low B-value DWI sequences, owing to the absence of SWI or T* sequences. Although WMLs were not classified as CVD or SVD in the present study, the International Consensus criteria were used to define white matter hyperintensity signal abnormalities of variable sizes of white matter that show hyperintensity on T2-weighted images without cavitations (Wardlaw et al., 2013). The Fazekas scale was used to classify the size and distribution of the periventricular and deep white matter hyperintensities (Fazekas et al., 1987). Figure 3 shows the MRI scans of participants classified according to the Fazekas scale. Mineralizing microangiopathy was diagnosed with the presence of calcifications on MRI.

![Fazekas scale](image)

Fig. 3. Representative MRI scans of the participants according to the Fazekas scale. Periventricular hyperintensities (PVH) grade was defined as 0 = absence, 1 = “caps” or pencil-thin lining, 2 = smooth “halo”, 3 = irregular PVH extending into the deep white matter. Deep white matter hyperintense signals are graded as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci and 3 = large confluent areas (Fazekas et al., 1987). Images were selected and compiled by radiologist Maria Suo-Palosaari and have been published here with her kind permission.
4.4.4 Characteristics of secondary tumors

Meningiomas were characterized as extra-axial dural-based circumscribed masses that demonstrated an intensity similar to that of the gray matter on T1- and T2-weighted images. This enhancement was homogenous and intense on using gadolinium as the contrast agent.

4.4.5 Neuropsychological examination

Most neuropsychological examinations were performed by psychologist Heli Pohjaniemi, whereas psychologist Heli Korkiakoski kindly helped us examine the remaining patients. We included 45 healthy subjects (20 men) in the control group (Harila, Winqvist, Lanning, Bloigu, & Harila-Saari, 2009). The controls were selected for a previous study from the local population registry (Harila et al., 2009).

The Wechsler Adult Intelligence Scale III was used to assess the VIQ and PIQ (Wechsler, 1955). The selected subtests were similarities, arithmetic, digit span, information, picture completion, coding, and block design (Wechsler, 1955). The similarities subtest measured logical thinking, verbal concept formation, and verbal abstract reasoning (Wechsler, 1955). Numerical accuracy, reasoning, and mental arithmetic ability were examined through the arithmetic subtest (Wechsler, 1955). The digit span subtest was used to measure short-term auditory memory and attention (Wechsler, 1955). The information subtest was used to investigate general cultural knowledge, long-term memory, and acquired facts (Wechsler, 1955). The subject’s ability to recognize familiar items and identify missing parts was measured by using the picture completion subtest (Wechsler, 1955). The coding subtest investigated visual-motor dexterity, associative non-verbal learning, and non-verbal short-term memory (Wechsler, 1955). Spatial visualization and analysis, simultaneous processing, visual-motor coordination, dexterity, and non-verbal concept formation were measured by using the block design subtest (Wechsler, 1955). Normal scores for the Finnish population have been used to scoring the results.

Regarding the intelligence quotient, the mean value of 100 and the standard deviation (SD) of 15 were used to calculate the Z-scores of the test result to compare the results and normal values of the general population (Wechsler, 1955). In the subtests, the mean value of 10 and the SD of 3 were used (Wechsler, 1955).

The trail making A test was used to measure visual scanning, graphomotor speed, and processing speed and the trail making B test was used to measure
executive functions, such as working memory and inhibition control (Llinas-Regla et al., 2017). In the absence of test norms, we used the scores of the normal population from a Canadian study to calculate the Z-scores for the participants (Tombaugh, 2004). The mean ± SD score was 22.93 ± 6.87 seconds in the age group of 18–24 years, 24.40 ± 8.71 seconds in the age group of 25-34 years, and 28.54 ± 10.09 seconds in the age group of 35-44 years for the Trail making A test (Tombaugh, 2004). The mean ± SD score for the trail making B test was 48.97 ± 12.69 seconds in the age group of 18–24 years, 50.68 ± 12.36 seconds in the age group of 25–34 years, and 58.46 ± 16.41 seconds in the age group of 35–44 years (Tombaugh, 2004).

The Wechsler Memory Scale III was used to measure memory functions (Wechsler, 1945). The logical memory I subtest assessed narrative memory and the logical memory II assessed long-term narrative memory (Wechsler, 1945). The verbal paired associates I test was selected to measure verbal memory, and the verbal paired associates II test was used to measure long-term recall for verbally paired information with cued recall and recognition tasks (Wechsler, 1945). The test included a free recall task (Wechsler, 1945). The logical memory I and the verbal paired associates I subtests were used to calculate the immediate auditory memory index (Wechsler, 1945). The general auditory memory index was calculated using the logical memory II and verbal paired associates II subtests (Wechsler, 1945).

The digit span backwards subtest of the Wechsler Adult Intelligence Scale III was used to assess the working memory (Wechsler, 1955).

In all subtests, the mean value of 10 and SD of 3 were used to calculate the Z-scores (Wechsler, 1955). In the memory indexes, the mean value of 20 and the SD of 6 were used (Wechsler, 1945).

The Benton C test modified by Vilkki (1989) was used to assess visual perception, memory, and visuoconstructive abilities. In the absence of the normative values, we used the mean and the SD of the control group to calculate the Z-scores.

The Rey-Osterrieth complex figure test was used to assess visuospatial construction; visuospatial abilities, visuographic memory, attention, and a number of aspects associated with planning and executive functions (Fastenau, Denburg, & Hufford, 1999). In the absence of the normative values, we used normative values from an American study (32.83 ± 3.10) (Fastenau et al., 1999). These normative values were of a population aged 30–50 years, but in the absence of the values of the younger population, we used the values for survivors aged 16–29 years.
4.4.6 The Finnish Cancer Registry data

We retrieved data on secondary tumors from the FCR. The FCR is a population-based nationwide registry that collects data on all cancers diagnosed in Finland. Although it has adequate information regarding solid cancers, the FCR registry does not completely include the same for CNS benign neoplasms (Teppo, Pukkala, & Lehtonen, 1994). The FCR population in the present study was included using the following criteria:

1. Brain tumor diagnosed at the age of \( \leq 16 \) years between 1963 and 2010
2. Radiotherapy registered as a part of the primary tumor treatment

Data were retrieved from the FCR by using International Classification of Disease (version 10) codes C70–72, D32–33, and D42–43. The date of the diagnosis of primary brain tumors, presence of chemotherapy as a treatment modality for primary tumors, the date of the diagnosis and the diagnostic information regarding the secondary neoplasm, and the date of death were retrieved from the registry.

4.4.7 Bone mineral density

The BMD was measured in the lumbar spine and four femoral sites using dual X-ray absorptiometry (DXA). The bone densitometries used were Lunar Prodigy DXA bone densitometry in Oulu, Lunar Prodigy Advance DXA bone densitometry in Kuopio, Lunar iDXA DXA densitometry in Tampere (Lunar Corporation, General Electric Madison, WI, USA), Hologic Discover A DXA in Helsinki, and Hologic QDR 4500C DXA densitometry in Turku (Hologic Inc., Bedford, MA, USA). The age- and sex-normalized Z-scores provided by manufacturers were used in the analysis of the results.

4.4.8 Laboratory testing

Table 10 enlists the laboratory tests used. The samples were collected after ensuring that the participants had fasted overnight. To minimize the effects of the circadian rhythm, samples were collected between 7:30 AM and 10:00 AM. All the samples were analyzed at Nordlab, Oulu University Hospital. However, the samples could not be collected for one survivor, and another one had not fasted, due to which these samples were excluded from the metabolic analysis. Results of a number of samples were missing due to transportation issues or problems in the laboratory. Clinical
chemistry system analysis was carried out with Advia 1800 (Siemens Healthcare GmbH), chemiluminescent immunoassay with Advia Centaus XP (Siemens Healthcare GmbH), immunoassay with Immulite 1000 Immunoassay (Siemens Healthcare GmbH, Munich, Germany), and liquid chromatographymass spectrometry with Agilent 6410 Triple Quad LC/MS (Agilent Technologies, Santa Clara, CA, USA) systems.

**Table 10. The laboratory tests.**

<table>
<thead>
<tr>
<th>Analysis method</th>
<th>Laboratory test</th>
<th>n (missing samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemiluminescence</td>
<td>Luteinizing hormone</td>
<td>73 (1)</td>
</tr>
<tr>
<td></td>
<td>Follicle stimulating hormone</td>
<td>73 (1)</td>
</tr>
<tr>
<td></td>
<td>Estradiol in females</td>
<td>24 (3)</td>
</tr>
<tr>
<td></td>
<td>Thyroid-stimulating hormone</td>
<td>73 (1)</td>
</tr>
<tr>
<td></td>
<td>Free thyroxine</td>
<td>72 (2)</td>
</tr>
<tr>
<td>Liquid chromatographymass spectrometry</td>
<td>Testosterone in males</td>
<td>47</td>
</tr>
<tr>
<td>Immunoassay</td>
<td>IGF1</td>
<td>73 (2)</td>
</tr>
<tr>
<td></td>
<td>IGFBP3(^1)</td>
<td>73 (2)</td>
</tr>
<tr>
<td><strong>Metabolic analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical chemistry</td>
<td>Cholesterol</td>
<td>71 (3)</td>
</tr>
<tr>
<td></td>
<td>Low-density lipoprotein</td>
<td>71 (3)</td>
</tr>
<tr>
<td></td>
<td>High-density lipoprotein</td>
<td>71 (3)</td>
</tr>
<tr>
<td></td>
<td>Plasma glucose</td>
<td>69 (5)</td>
</tr>
<tr>
<td></td>
<td>Glycosylated hemoglobin 1Ac</td>
<td>70 (4)</td>
</tr>
<tr>
<td>Chemiluminescent immunoassay</td>
<td>Serum insulin</td>
<td>71 (3)</td>
</tr>
</tbody>
</table>

\(^1\) Insulin-like growth factor binding protein 3

### 4.4.9 Radiation dose distribution analysis

Medical physicists Vesa-Pekka Heikkilä, Jan Seppälä, Mika Kapanen, Antti Vanhanen, Hannele Niiniviita, and Liisa Porra analyzed the patient’s charts, treatment plans, and radiation field images to measure the radiation doses (expressed in Gy) administered to the different parts of the brain. Radiation field images and treatment plans of nine patients were unavailable. The doses delivered to the area of the secondary tumor were analyzed.
4.4.10 Statistical analyses

The statistical analyses were performed by using IBM SPSS Statistics for Windows version 24.0 (IBM Corp, Armonk, NY, USA), StatsDirect Statistical software version3 (StatsDirect Ltd 2013, England), and Stata Statistical Software: Release 13 (StatCorp LP, StataCorp.2013 College Station, TX, USA). The chi-square exact test was used to evaluate the relationship between the categorical variables. Differences between two proportions were compared using the standardized normal deviate test. Student’s T test and Mann Whitney U test were used to compare the difference in the mean and median values of two continuous variables for two categorical groups. The Kaplan-Meier estimator was used to assess cumulative incidences. Regarding FCR data, which represented death as a competing risk, the cumulative incidence function was estimated using the Fine-Gray method. With regard to CVDs, since only the time before the occurrence of the event was known and the interval-censored survival analysis with EMICM algorithm was used to calculate cumulative prevalence. The association between the two continuous variables were evaluated with linear regression analyses, and their respective results were presented as $\beta$ coefficients and their 95% confidence intervals (95% CIs).

The association between secondary tumors and a set of explanatory variables was estimated via a multivariate logistic regression model using an enter methods. A multivariate linear regression model with forward stepwise variable was used to identify the variables that best predicted the BMD in Z-scores. A logistic regression model was used to estimate the influence of reduction in BMD SD value by 1 with regard to the Z-scores on the fractures. To calculate the influence of the atherosclerotic risk factors and MRI markers on stroke and CVD, a logistic regression analysis was used. These results were presented as odds ratios (ORs) with their 95% CI.

4.4.11 Ethics

All enrolled participants or their legal guardians signed a written informed consent form for this study. The Institutional Review Boards of the Oulu, Kuopio, Turku, Tampere and Helsinki University Hospital approved the current study. The research was conducted according to the principles of the Declaration of Helsinki. Permission to retrieve the FCR data was approved by the National Institute of Health and Welfare.
5 Results

5.1 Cerebrovascular disease in adult survivors of childhood brain tumor (Study I)

A total of 70 survivors participated in the part of the study on CVD. Two survivors treated with stereotactic radiotherapy participating the MRI study were excluded from the analysis. The participants had a median age of 27.1 years at the time of the study (range 16.2–43.8 years). Type 1 neurofibromatosis was diagnosed in one participant.

MRI and patient files revealed CVD in 64 % (45/70) of the survivors. CVD was defined as the history of cerebral hemorrhage or TIA and any marker of CVD on MRI, excluding WMLs. The cumulative prevalence of CVD at 20 years after radiotherapy treatment was 52 % (95 % CI, 39 % to 66 %) (Figure 4.). Table 11 shows the prevalence of the CVD findings and WMLs on survivors of CBT.

Table 11. Prevalence of MRI findings of cerebrovascular disease and white matter lesions in survivors of CBT treated with radiotherapy.

<table>
<thead>
<tr>
<th>CVD findings</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic strokes</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Large-vessel vasculopathy</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Focal hemosiderin deposits</td>
<td>23 (33)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Mineralizing microangiopathy</td>
<td>21 (30)</td>
</tr>
<tr>
<td>White matter lesions</td>
<td>34 (49)</td>
</tr>
</tbody>
</table>

Fazekas scale

- Periventricular hyperintensity
  - Grade 0: 50 (72)
  - Grade 1: 12 (17)
  - Grade 2: 7 (10)
  - Grade 3: 1 (1)

- Deep white matter hyperintensity
  - Grade 0: 45 (64)
  - Grade 1: 13 (19)
  - Grade 2: 9 (13)
  - Grade 3: 3 (4)
Fig. 4. Cumulative prevalence of cerebrovascular disease.
5.1.1 Small-vessel disease

SVD, defined as the presence of FHDs or lacunar infarcts in MRI, was diagnosed in 27/70 (39%) of the survivors. The cumulative prevalence at 20 years of follow-up was 38% (95% CI, 27% to 51%) (Figure 4).

FHDs, such as cavernomas and microbleeds, were diagnosed in 33% of the subjects. Cavernomas were found in 11 and microbleeds in 16 of the 70 survivors. The 20-year cumulative prevalence of FHDs was 33% (95% CI, 23% to 46%). Lacunar infarcts were found in 10% of the participants with a cumulative prevalence of 13% (95% CI, 7% to 23%) at 20-year follow-up (Figure 4).

5.1.2 Large-vessel disease

LVD demonstrated lower frequencies of occurrence than SVD, and was diagnosed in nearly 19% of the survivors. The cumulative prevalence at the 20-year follow-up was 16% (95% CI, 9% to 28%). MRI examination revealed ischemic infarcts in 8% of the survivors, with two ischemic infarcts each in two survivors. Patient files confirmed TIAs in two survivors. Cumulative incidence of ischemic infarcts or TIA at the 20-year follow-up was 10% (95% CI, 5% to 21%) (Figure 4).

Large-vessel vasculopathy was diagnosed in six subjects. We used MRA to detect stenotic caliber changes in the right middle cerebral artery (MCA) (n = 1), vasculopathy in the right MCA (n = 1), and stenosis in the left posterior cerebral artery (n = 1), and in the left vertebral artery (n = 1). Large-vessel vasculopathy was observed in one survivor with IS and in one with lacunar infarct. In one survivor, the right MCA and the anterior cerebral arteries could not be visualized on MRA. Surgery for left frontal arteriovenous malformation was performed in one participant after radiotherapy.

5.1.3 Cerebral hemorrhage

Cerebral hemorrhage had been previously diagnosed in two of the 70 survivors (3%), each demonstrating intraparenchymal hemorrhage. In addition, three traumatic hemorrhages and two subdural hemorrhages have been diagnosed. All hemorrhages had occurred more than 1 year after the cessation of radiotherapy. The diagnosed traumatic hemorrhages were subdural (n = 2), and contusion hematomas (n = 1). One survivor was simultaneously diagnosed with a subdural hematoma and
IS. Only one of the survivors with cerebral hemorrhage did not have other CVD pathologies or WMLs.

### 5.1.4 Mineralizing microangiopathy

Mineralizing microangiopathy, which was diagnosed by the presence of calcifications on MRI, was observed in 30% of the survivors. The cumulative prevalence at the 20-year follow-up was 25% (95% CI, 16% to 39%) (Figure 4).

### 5.1.5 White matter lesions

WMLs were detected in almost half of the survivors. Deep white matter hyperintensity was detected in 36% of the survivors, and periventricular hyperintensity in 28% classified with the Fazekas scale. WMLs appeared after 10 years of follow-up. The cumulative prevalence at 20 years was 42% (95% CI, 29% to 57%) (Figure 4).

### 5.1.6 Cerebrovascular burden

The survivors had multiple, coincidental CVD findings and WMLs, also called CVD burden. Different types of lesions or WMLs were detected in 44% of the survivors (Table 12).

**Table 12. Cerebrovascular burden and WMLs in the Survivors of CBT treated with radiotherapy.**

<table>
<thead>
<tr>
<th>Cerebrovascular burden</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16 (23)</td>
</tr>
<tr>
<td>1</td>
<td>23 (33)</td>
</tr>
<tr>
<td>2</td>
<td>17 (24)</td>
</tr>
<tr>
<td>3</td>
<td>9 (13)</td>
</tr>
<tr>
<td>4</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

### 5.1.7 Tumor- and treatment-related risk factors

The presence of large-vessel disease and WMLs increased with increasing age at follow-up visit. Small-vessel disease, and particularly FHDs associated with ventriculoperitoneal shunt. Survivors with supratentorial tumors were more likely
to have FHDs as survivors with infratentorial tumors. Mineralizing microangiopathy was more frequent in survivors who had received higher radiation doses. Most MRI findings of CVD were detected in the high-dose radiation areas (≥ 30 Gy dose). Most of the FHDs were detected in the 30–49.9 Gy dose area. Only 3% of the findings were outside the radiation field.

**5.1.8 Magnetic resonance imaging findings as risk factors**

We observed no associations between WMLs, FHDs or mineralizing microangiopathy, and strokes. It is remarkable that 5 out of the 6 survivors with IS, both TIA survivors, both participants with cerebral hemorrhage, and all survivors with lacunar infarcts demonstrated other signs of CVD.

**5.1.9 Atherosclerotic risk factors**

Blood pressure were associated with CVD, large-vessel disease, lacunar infarcts, and WMLs. An increase in systolic blood pressure by 1 mmHg, demonstrated 1.03 and 1.05 times increase in the risk of CVD and LVD, respectively. The LVD risk increased by a factor of 1.07 and that of lacunar infarct by 1.08 for every 1 mmHg increase in the diastolic blood pressure. High-density lipoprotein levels and lacunar infarcts demonstrated a significant association (OR 0.01; p < 0.05). Total cholesterol and low-density lipoprotein levels associated with ischemic infarcts and TIsAs. Higher total cholesterol levels increased the risk of WMLs by 1.83-fold. The presence of WMLs was associated both with systolic and diastolic blood pressure.

**5.2 Neuropsychological late-effects (Study II)**

We investigated neuropsychological late-effects in 71 survivors. They performed significantly worse in the cognitive examinations than the healthy controls. Mean VIQ was 88.8 ± 14.0 and mean PIQ was 86.9 ± 18.5 in the survivors. Figure 5 shows the neurocognitive profile of the survivors and Table 13 shows the distribution of the VIQ and PIQ levels in the survivors.
Fig. 5. Neuropsychological profile of the survivors considering the Z-scores. Abbreviations: VIQ = verbal intelligence quotient, PIQ = performance intelligence quotient. Lower lines represent -1.5 SD, which has been classified according to the degree of the relevant impairment. Z-scores are calculated using mean ± SD with 100 ± 15 for VIQ and PIQ and of 10 ± 3 for the subtests of Wechsler Adult Intelligence scale. The Z-scores for executive functions and processing speed are calculated using age-specific means and SDs of time used considering the Canadian population. Immediate and General auditory memory Z-scores are calculated by using mean ± SD of 20 ± 6. Z-scores of visuospatial constructions using a mean ± SD value of 32.83 ± 3.10 of an American population. Visual memory Z-score are calculated by using mean and SD of the control population from the present study (Wechsler, 1955; Tombaugh, 2004; Wechsler, 1945; Fastenau et al., 1999).
Table 13. IQ classification in the survivors.

<table>
<thead>
<tr>
<th>The classification IQ</th>
<th>Definition of the classification</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average or higher</td>
<td>≥ 90</td>
<td>37 (53)</td>
</tr>
<tr>
<td>Low average</td>
<td>80–89</td>
<td>17 (24)</td>
</tr>
<tr>
<td>Borderline</td>
<td>70–79</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Extremely low</td>
<td>≤ 69</td>
<td>7 (10)</td>
</tr>
<tr>
<td>PIQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average or higher</td>
<td>≥ 90</td>
<td>35 (49)</td>
</tr>
<tr>
<td>Low average</td>
<td>80–89</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Borderline</td>
<td>70–79</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Extremely low</td>
<td>≤ 69</td>
<td>12 (17)</td>
</tr>
</tbody>
</table>

Primarily the executive functions were the most impaired functions among the survivors with a mean Z-score of -5.0 ± 5.3 SD, and relevant impairment in 74 %. Among those demonstrating a relevant impairment, 85 % were classified as severely impaired. A similar degree of impairment was noted in the processing speed with a mean Z-score of -4.3 ± 5.4 SD, and relevant impairment in 70 %. Among the survivors with relevant impairment in processing speed, 67 % were severely impaired. There was a significant but relatively milder impairment in the memory functions; the mean Z-scores were -1.37 ± 1.1 SD for immediate auditive memory, -1.21 ± 1.1 SD for general auditive memory, -3.3 ± 3.4 SD for visual memory, and -1.40 ± 0.7 SD for working memory. The relevant impairment in memory functions was recognized in 49 % of the survivors with regard to immediate auditive memory, in 42 % considering general auditive memory, 58 % considering visual memory, and in 40 % considering working memory. A severe impairment in memory functions was observed in 45 % considering immediate auditive memory, 32 % considering general auditive memory, 90 % considering visual memory, and 21 % considering working memory of the survivors with relevant impairment in memory functions. However, it is imperative to note that only 60 survivors were capable of finishing the general auditive memory tasks. The mean Z-score considering visuospatial construction was -2.50 ± 2.9 SD. A total of 54 % of the survivors demonstrated relevant impairment considering visuospatial construction, and among them 72 % of the survivors presented with severe impairment.
5.2.1 Patient, tumor and treatment characteristics

Participants with infratentorial tumors were associated with poorer PIQ performance than those with supratentorial tumors. Survivors with a ventriculoperitoneal shunt had a higher impairment in the PIQ, processing speed, and immediate and general auditory memory, and visual memory 19 years after the cessation of tumor therapy.

Younger participants at the time of diagnosis demonstrated poorer in the VIQ, PIQ, processing speed, executive functions, and working memory. Among survivors treated with whole-brain radiotherapy, VIQ, immediate and general auditory memory, and working memory were negatively associated with the follow-up time.

5.2.2 Neurocognitive impairment and everyday life

The highest educational qualifications of the survivors were distributed as follows: comprehensive school in 29 %, secondary degree in 61 %, and higher degree in 10 %. VIQ, PIQ, processing speed and attention, executive functions, and visuospatial construction were all associated with the educational level; the highest degree of impairment was noted in survivors with comprehensive school as their highest educational qualification.

Among the survivors, 27 % were students, 39 % were employed, and 34 % were either unemployed or retired. There was a significantly higher degree of impairment in PIQ, executive functions, visuospatial construction, along with immediate and general auditory memory among the unemployed or retired survivors.

A total of 65 % of the survivors were not in an intimate relationship and showed poorer performance in the processing speed and executive functions than those in an intimate relationship. A total of 38 % of the survivors were not living independently at the time of the study. They demonstrated significantly poorer performance in PIQ, processing speed, executive functions, and working memory. Approximately 42 % of the survivors did not have a driving license, which was associated with poorer performance with regard to in the VIQ, PIQ, processing speed, executive functions, working memory, visual memory, and visuospatial construction.
5.3 Secondary tumors (Study III)

5.3.1 Secondary tumors in the clinical data

This portion of the study included 73 participants. MRI analysis was performed for 72 participants, the remaining one participant had visited a clinic to follow-up for secondary tumors; therefore, his results were included in the analysis. We noted type 1 neurofibromatosis in one participant, and another was diagnosed with vestibular schwannoma and multiple meningiomas, type 2 neurofibromatosis was suspected in the same.

Secondary tumors were diagnosed in 6 of the 73 participants (8.2 %). All survivors with secondary tumors had meningiomas. Multiple meningiomas were noted in three participants. One patient with three secondary meningiomas also demonstrated vestibular Schwannoma. Cumulative incidence of secondary tumors was 10.2 % (95 % CI, 3.9 % to 25.1 %) at the 25-year follow-up.

Although tumor- and treatment-related factors were not associated with secondary tumors, GH deficiency was significantly more common in the survivors with secondary meningiomas. IGF1 levels were lower in the participants with secondary meningiomas than in others demonstrating borderline significance (p = 0.076).

Radiation field charts were available for four participants with six meningiomas. All six meningiomas were detected outside the primary target volume area considering the prescribed treatment dose. Four meningiomas were situated in the whole-brain volume, and two in the field border area.

Multivariate regression analysis, including the following explanatory variables: age at the diagnosis, follow-up time since diagnosis of the primary tumor, radiation dose in Gy, measured levels of IGF1 in nmol/l, body mass index in kg/m², sex, mode of radiotherapy (local or whole-brain), total radiation dose (OR 1.43; p < 0.05), and whole-brain radiotherapy (OR 43.3; p < 0.05) associated with meningiomas.

5.3.2 The Finnish Cancer Registry data

We analyzed the FCR data for SNs in 596 registered-cases diagnosed with CBT and those registered for radiotherapeutic treatment. At the time of the data collection, 194 (34 %) cases were alive. The mean age at which the primary tumor was diagnosed was 7.6 ± 4.2 years, and was 33.5 ± 10.1 years at the end of the
follow-up. Mean follow-up time since the diagnosis of the primary tumors was 11.8 ± 12.9 years. A total of 194 (34 %) cases were registered for chemotherapeutic treatment of the primary tumor.

A total of 18 SNs were found in the registry, with a crude incidence of 3.2 %. There were only two secondary brain tumors, no meningiomas, one ganglioneuroma or ganglioneuroblastoma of posterior fossa, and one grade 3 PNET. SNs in the FCR resulted in high mortality rates, since 56 % of the cases with SNs had died by the time the relevant data was collected. The cumulative incidence of SNs at 25-year follow-up was 2.4 % (95 % CI, 1.3 % to 4.1 %). Table 14 shows the SN diagnoses in the FCR population.

<table>
<thead>
<tr>
<th>Secondary neoplasm</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal cell tumor</td>
<td>5</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>4</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>2</td>
</tr>
<tr>
<td>Ovarian tumors</td>
<td>1</td>
</tr>
<tr>
<td>Endocrinological epithelial tumor of the Fallopian tube</td>
<td>1</td>
</tr>
<tr>
<td>Papillary adenocarcinoma of the thyroid</td>
<td>1</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
</tr>
<tr>
<td>Neurilemmoma of autonomic nervous system</td>
<td>1</td>
</tr>
</tbody>
</table>

**5.4 Bone mineral density (Study IV)**

A total of 73 survivors participated in the part of the study that investigated BMD. One survivor demonstrated a left side hip prosthesis, and in one subject underwent analysis for only the left side femoral neck and spine due to a research error. Therefore, the spine was analyzed in 73 survivors, and both femoral necks and total hip analysis was performed in 72 survivors.

Sex- and age-normalized Z-scores were below the expected range (Z-score ≤ -2.0) in 24 % of the participants. Mean BMD considering Z-scores was -0.91 SD for the right femoral neck, -0.82 SD for the left femoral neck, -0.77 SD for the right total hip, -0.69 SD for the left total hip, and -0.83 SD for the lumbar spine. Male survivors had a significantly lower BMD with regard to the Z-scores of the femoral necks and lumbar spine in comparison with the female survivors.

BMI demonstrated a significantly positive association with BMD in all measured areas. A younger age at diagnosis was associated with a lower BMD in
the femoral necks. Similarly, the age at the follow-up visit and the follow-up time were positively associated with BMD in the lumbar spine.

Patients with a ventriculoperitoneal shunt had a significantly lower BMD in the femoral necks and total hips of the participants. Multivariate regression analysis with forward stepwise variable selection (using the candidate variables of ventriculoperitoneal shunt, cranial radiotherapy with or without spinal radiotherapy, chemotherapy, tumor location (supratentorial or infratentorial tumor), BMI, dose of radiotherapy to the thalamic area, and total dose of corticosteroids during the tumor treatment), revealed that ventriculoperitoneal shunt and BMI were significantly associated with BMD in the femoral necks and total hips. Furthermore, there was a significant association between BMD and BMI in the lumbar spine.

In female survivors, there was a negative association between FSH and BMD in femoral necks and left total hip, as well as between LH and BMD in the lumbar spine. High level of free thyroxine was associated with a low BMD in the left femoral neck, total hips, and lumbar spine. Multivariate analysis, after adjusting BMI in the analysis, demonstrated that the otherwise significant association between FSH and BMD was absent, and a significantly negative association was noted only between FSH and BMD in the left femoral neck. Multivariate analysis of peripheral hormones and BMI demonstrated that BMI was positively associated with BMD in all measured areas in female survivors. In the male survivors, BMI and testosterone were positively associated with BMD in the left femoral neck and both total hips.

A total of 40% of the participants reported previous fractures, with 22% of those present in the long bones. Reduction in the SD value by 1 with regard to BMD, considering Z-scores, increased the risk of fractures in long bones to 2.0-fold in the right femoral neck, to 1.9-fold in the right total hip, to 1.8-fold in the left total hip, and to 1.7-fold in the lumbar spine.
6 Discussion

In the present study, we examined the late-effects of CBT treated with radiotherapy, and demonstrated that the survivors had a very high prevalence of CVD (64 %) and severe impairment in the neurocognitive function among the young-adult survivors. CVD may potentially cause increased morbidity, progressive decline of cognitive function, and late-mortality (Debette et al., 2019; Haddy et al., 2011; Staals et al., 2014; Roddy et al., 2016). Cognitive impairment had a large-scale impact on everyday life in the survivors.

Secondary meningiomas occurred in 8.2 % of the survivors in the clinical study, and according to the FCR data, 3.2 % had SNs. Multiple meningiomas were common, and occurred in three of the six survivors with meningiomas. According to the FCR data, SNs were also associated with high rates of mortality. It had previously been reported that 10 % of the late-mortality cases in survivors of CBT were causatively associated with SNs (Perkins et al., 2013). BMD was below the expected range in 24 % of the survivors and was associated with fractures in long bones. Secondary meningiomas and osteoporosis may particularly increase the morbidity and impair the survivors’ quality of life.

Cancer therapy causes early ageing of cells (Scuric et al., 2017). Furthermore, treatment-associated accelerated ageing is suggested to lead to the occurrence of late-effects (Scuric et al., 2017). Studies have reported that a decline in working memory, hearing impairment, second cancer, diabetes, hypertension, and endocrine deficiencies have been suggested to be clinical signs of early ageing among the survivors (Edelstein et al., 2011). Our results pertaining to the prevalence of CVD, slow processing speed, decreased performance in the executive functions, incidence of secondary meningiomas, and low BMD correspond with the phenomenon of accelerated ageing (Debette et al., 2019; Tombaugh, 2004; Dolecek et al., 2015; Marshall et al., 1996). Here, the term “accelerated ageing” has been used to describe the presence of similar changes and diseases that are typically present in the elderly populations.

6.1 Cerebrovascular disease (Study I)

Radiotherapy-treated young adult survivors of CBT had an alarming cumulative prevalence of CVD; 52 % developed CVD at the 20-year follow-up. The general elderly population in their 70s had a lower or similar rate of IS, microbleeds, lacunar infarcts, and cerebral hemorrhage than those in the present study, who had
a mean age of 28 years (de Bruijn et al., 2014; Kaffashian et al., 2016; Kuller et al., 2004). Radiotherapy-treated CBT survivors appeared to develop an aggressive version of CVD during follow-up. Few other studies have demonstrated an increase in lacunar infarcts and microbleeds during follow-up; however, the overall CVD progression and its clinical significance over a very long-term follow-up period require further investigation (Roddy et al., 2016; Fouladi et al., 2000; Kralik et al., 2018).

The risk of stroke has increased in survivors of both childhood cancer and CBT (Campen et al., 2012; Mueller et al., 2013; Noje et al., 2013; Bowers et al., 2006). Typically, stroke is rare in the general young adult population, but CBT survivors demonstrate a 29- to 100-fold increase in the risk of incidence (Campen et al., 2012; Bowers et al., 2006). Here, the prevalence of IS was 9 % at a young age, whereas in the same-aged Finnish population, the incidence was between 5.4 and 25.8 per 100 000 people (Sipilä, Posti, Ruuskanen, Rautava, & Kytö, 2018). Since IS has been associated with stroke recurrence and cerebrovascular sequelae related to high mortality rate, the future of the survivors remains unclear (Haddy et al., 2011; Fullerton et al., 2015). Radiotherapy-treated childhood cancer survivors demonstrate increased CVD mortality rates compared to the general population; however, CVD primarily comprised of only 0.9 % of late-causes of death in the long-term survivors of CBT (Haddy et al., 2011; Perkins et al., 2013). Tumor recurrence remains the most common cause of death (Perkins et al., 2013). Additionally, stroke prevention has been poorly studied in the survivors.

Other findings of CVD, including microbleeds, lacunar infarcts, and WMLs are much more common in the general elderly population compared to IS, and their relationship with cognitive impairment has been well established (Akoudad et al., 2016; Debette et al., 2019; Debette & Markus, 2010; de Bruijn et al., 2014; Kaffashian et al., 2016; Kuller et al., 2004). The results reported in this study are in line with those of earlier studies on the CBT survivors and the general population, all of which demonstrated that the incidence microbleeds and WMLs exceeded that of IS (Neu et al., 2018; Passos et al., 2017; Roddy et al., 2016).

Here, among the survivors that were treated with whole-brain radiotherapy, the VIQ, working memory, and immediate and general auditory memory were associated with follow-up time. Microbleeds and WMLs disrupt the fronto-subcortical pathways, which has been considered as the mechanism behind the neuropsychological impairment in SVD (Vasquez & Zakzanis, 2015). Nevertheless, very little is known about the clinical importance of MRI markers of CVD in CBT survivors; however, the results of a previous study have reported that CVD has an
impact on cognitive outcomes (Roddy et al., 2016). The declining working memory reported in adult survivors of medulloblastoma is a common symptom of normal ageing that has also been associated with vascular pathology in the elderly (Edelstein et al., 2011; Kessels, van den Berg, Ruis, & Brands, 2008; Vasquez & Zakzanis, 2015). Our results on cognitive impairment could be attributed to a more harmful treatment modality administered in those who were treated a longer time ago; however, in a situation associated with a true decline in cognitive functions, vascular pathology is one of the most plausible explanations for the same.

Neuropsychological analysis revealed a number of elements that may suggest the vascular involvement in neurocognitive impairment, which includes severe impairment in the processing speed and executive functions, and a relatively milder impairment in the working memory (Vasquez & Zakzanis, 2015). Vascular cognitive impairment not demented (VCIND) is a term used in the elderly with vascular cognitive impairment in whom cognitive symptoms are not associated with significant functional impairment (Vasquez & Zakzanis, 2015). A meta-analysis demonstrated a relationship between VCIND and poorer performance in all cognitive domains in comparison with healthy controls demonstrating the highest degree of impairment in processing speed and lowest in working memory (Vasquez & Zakzanis, 2015). Comparing the results with non-vascular mild cognitive impairment, the elderly people with VCIND performed worse, considering their processing speed and executive functions (Vasquez & Zakzanis, 2015). In contrast to elderly people with VCIND, our survivors that demonstrated impaired executive functions and processing speed experienced relatively higher degree of difficulties in their everyday life. The survivors have not been able to become fully independent while performing their daily activities during the maturation, considering the fact that they are not able to achieve similar cognitive capacity as their healthy peers; furthermore, impairment in executive functions and processing speed may prevent them from learning the skills necessary to allow them to live independently (de Ruiter et al., 2013; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004). Elderly people with VCIND have been able to live with independency, which may indicate that the skills of everyday life may be easier to maintain (Vasquez & Zakzanis, 2015). In the present study, CBT survivors demonstrated faster processing speed than the general elderly with VCIND in an Italian study (59 s vs. 67 s), but had higher degrees of impairment with regard to executive functions (114 s vs 104 s) (Giorgio et al., 2019). Here, both executive functions and processing speed were important in everyday life skills. The neurocognitive impairment in the survivors of CBT treated with radiotherapy has
multifactorial etiology, with vascular pathology having a potential role (de Ruiter et al., 2013; Roddy et al., 2016).

A good cognitive reserve is protective against the vascular dementia after stroke (Pendlebury, Rothwell, & Oxford Vascular Study, 2019). A higher level of education has been associated with more severe cortical thinning in imaging (Jung et al., 2018). Since the patients with a higher level of education and thinner cortex performed similarly on neuropsychological tests than those with a lower education, researchers have suggested compensatory effects of education on cognition (Jung et al., 2018). Furthermore, cognitive reserve has been proposed to be the ability to optimize and maximize performance through differential recruitment of the brain networks, which may perhaps reflect the use of alternative cognitive strategies (Opdebeecka, Martyrb, & Clareb, 2016). CBT survivors are likely to have suboptimal cognitive reserve considering the direct effects of brain tumor and its treatment on brain tissue, and owing to the lower levels of education (de Ruiter et al., 2013). This possible suboptimal cognitive reserve in survivors may present itself with a higher influence of CVD on cognition, this pathological outcome may be considerably more harmful for survivors than those in the general elderly population. Our results indicate that there is an extensive impairment of executive functions and processing speed, which may support the theory that radiation-induced CVD injury leads to an even a higher impairment in survivors compared to CVD in the general elderly population.

Signs of SVD in the general population, such as WMLs, lacunar infarcts and cerebral microbleeds, have been associated with higher risk of ischemic stroke, intracerebral hemorrhage, and death (Debette et al., 2019). We could not find a significant association between strokes and WMLs, FHDs or mineralizing microangiopathy. Even with an absence of significant associations, it is remarkable that coincidental findings of CVD were noted in most of the survivors with IS, TIA, cerebral hemorrhage or lacunar infarct.

The impact of radiotherapy has obvious ramifications in the development of CVD. Previous studies demonstrated higher rates of CVD in survivors treated with radiotherapy than those treated without (Campen et al., 2012; Passos et al., 2017; Roddy et al., 2016; Fouladi et al., 2000). In the present study, CVD occurred approximately 40 years earlier than that observed in the general elderly population (de Bruijn et al., 2014; Kaffashian et al., 2016; Kuller et al., 2004). The rate of CVD was similar in survivors that were treated with local or whole-brain radiotherapy, and most of the imaging markers of CVD were observed in the high-dose radiation field. Previously, radiation dose to the circle of Willis area has been associated with
a significant risk of stroke (Campen et al., 2012; El-Fayech et al., 2017). The current treatment strategies aimed to reduce the use and dosage of radiation, along with the size of the radiation field, may be beneficial for reducing the risk of CVD. The risk of stroke increased with higher doses of radiotherapy, and whole-brain radiotherapy increased the total count of microbleeds and the risk of FHDs than local radiotherapy (Mueller et al., 2013; Bowers et al., 2006; Neu et al., 2018). However, any form of cranial radiotherapeutic procedure may affect the brain vasculature (Campen et al., 2012; Passos et al., 2017; Fouladi et al., 2000). In the present study, we noted a small number of microbleeds outside the radiation field. During stereotactic radiotherapy, there was a notable reduction in the cerebral flow in the surrounding tissue, which may explain the presence of vascular issues outside the field of radiation (Taki et al., 2002).

Our results demonstrated that the survivors treated with local radiotherapy had a similar prevalence of CVD than those treated with whole-brain radiotherapy. It is possible that proton beam radiotherapy may be superior to photon radiotherapy due to its better tumor targeting and lesser late-effects; however, the long-term effects of proton beam therapy on brain vasculature require further investigation. Radiation-induced large-vessel vasculopathy was noted in 5 of the 75 patients (7%) after a mean follow-up of 1.5 years with four cases of acute infarcts (Kralik et al., 2017). Furthermore, after more than 5 years of follow-up, microbleeds were observed in 81% of the survivors treated with proton beam radiotherapy with most microbleeds found in the \( \geq 30 \text{ Gy} \) radiation field (Kralik et al., 2018). The current study findings were similar to those of Kralik et al. (2018), which suggested that most microbleeds were situated in > 30 Gy radiation field. Studies involving proton beam therapy supported the concept that vascular injury may occur even after proton beam radiotherapy, and that proton beam therapy may not be superior to photon radiotherapy (Kralik et al., 2017; Kralik et al., 2018). There is a need to investigate if the radiation areas outside the radiation field are affected by CVD.

Previous studies have focused on stroke, microbleeds, lacunar infarcts, and large-vessel vasculopathy separately, but to our knowledge, the current study is the first to evaluate each of these aspects of CVD in survivors of CBT treated with radiotherapy (Campen et al., 2012; Passos et al., 2017; Neu et al., 2018; Roddy et al., 2016; Fouladi et al., 2000; Kralik et al., 2017; Omura et al., 1997). Accordingly, as radiotherapy is an essential part of the treatment protocols in a number of brain tumors, but there is a need to urgently investigate and determine the clinical significance and prevention of CVD in patients treated with radiotherapy (Wells & Packer, 2015; Merchant et al., 2010).
6.2 White matter lesions

Radiotherapy causes diffuse white matter changes that are divided in scattered focal and confluent WMLs, later involving a greater portion of the periventricular or hemispheric white matter (Dietrich et al., 2001). Fouladi et al. (2004) found both abnormal or increased signal intensity on T2-weighted images and contrast enhancement on T1-weighted images in all patients who developed WMLs at a median of 7.8 months after the start of radiotherapy. WMLs resolved in 73% of the patients (Fouladi et al., 2004). We analyzed confluent WMLs according to the Fazekas scale and found that WMLs first appeared in the survivors with follow-up time > 10 years (Fazekas et al., 1987). In the general population, age, previous stroke, TIA, myocardial infarction, and claudication have been associated with WMLs (Basile et al., 2006; Longstreth et al., 1996). We noted that WMLs were associated with an increase in the systolic and diastolic BP, which was supported by the findings of previous studies in the general elderly population (Longstreth et al., 1996). In adult patients who were treated with whole-brain radiotherapy, WMLs accumulated at a higher rate in those with hypertension (Szerlip et al., 2011). However, vascular pathology is not the only factor that is causatively associated with WMLs; direct effects of radiotherapy and radiation-induced neuroinflammation have an important role in WML development (Greene-Schloesser et al., 2012).

We found WMLs according to the Fazekas scale in survivors followed-up for longer than 10 years. Radiation-induced injury has been categorized into acute, early-delayed, and late-delayed based on the duration of clinical expression (Greene-Schloesser et al., 2012). Transient demyelination which was previously described was a part of the early-delayed brain injury (Greene-Schloesser et al., 2012). Late-delayed brain injury included vascular abnormalities, demyelination, and white matter necrosis that are observed typically > 6 months following radiotherapy (Greene-Schloesser et al., 2012). Progressive WMLs originate after the damage of radiosensitive oligodendrocytes, microvascular injury, and the failure of neural stem cells and oligodendrocyte progenitor-cell repairing mechanisms (Burns et al., 2016). Radiation induces microglial cells, which lead to prolonged neuroinflammation that may last for decades (Burns et al., 2016). However, it is possible that neuroinflammation may be associated with decreased hippocampal neurogenesis; however, recent studies in rodents and imaging studies on brain tumor survivors treated with radiotherapy suggest that neuroinflammation is involved with WMLs after radiotherapy (Burns et al., 2016; Andrews et al., 2017;
Belliveau, Bauman, Tay, Ho, & Menon, 2017). However, the main mechanism has been suggested to be vascular (Fouladi et al., 2004). The association between BP and WMLs, and the presence of WMLs in the survivors with ≥ 10 years of follow-up in the present study, suggest the vascular involvement in the development of WMLs (Andrews et al., 2017).

Tsuruda et al. (1987) have reported that periventricular WMLs after radiotherapy or chemotherapy results from demyelination, gliosis, edema and coagulation necrosis. Whereas mechanism of deep white matter hyperintensity is more likely to be ischemic (Mamlouk, Handwerker, Ospina, & Hasso, 2013). However, our results could not validate these previous findings.

In the present study, the survivors showed extensive impairment in executive functions, attention, and processing speed, along with impairment in working memory. The association between WMLs and cognitive impairment is well-established both in the general population and in CBT survivors (Debette et al., 2019; Fouladi et al., 2004; Mabbott et al., 2011). Injury in the fronto-subcortical pathways manifesting as WMLs has been associated with impairment in processing speed, attention, and executive functions in the general elderly population (Vasquez & Zakzanis, 2015). In adult CBT survivors treated with radiation, these cognitive domains have been the most impaired, and the relation between reduced white matter integrity has been correlated with poorer performance in executive functions in the survivors (Edelstein et al., 2011; Brinkman et al., 2012). Normal appearing white matter volume has been associated with working memory function (Jacola et al., 2014). Future research should focus on the association between vascular pathologies and neurocognitive profiles, as well as in the follow-up of neurocognition in ageing survivors.

6.3 Treatment options for cerebrovascular disease and white matter lesions

MRI markers of CVD are typically incidental findings that are detected on MRI (Debette et al., 2019). However, it is not known, how to treat people in the presence of such findings even in the general population (Debette et al., 2019). CVD is a heterogeneous group of disorders with poorly understood risk factors (Schulz & Rothwell, 2003). The preventive effect of antihypertensive medication is dose-dependent on stroke, even in high-risk patients, and has been well demonstrated (Bohm et al., 2017; Xu et al., 2017). The progression of WMLs has been slower in those treated with antihypertensive medication and with lower BP (Godin, Tzourio,
Maillard, Mazoyer, & Dufouil, 2011). A previous study by Mueller et al. (2013) and the present study outcomes support the general consensus of the careful antihypertensive treatment in the survivors (Bohm et al., 2017; Xu et al., 2017). However, the studies lack sufficient evidence regarding the importance of antihypertensive medication for CVD in CBT survivors.

The preventive effect of antihypertensive medication on cognitive functions and dementia has demonstrated contradictory results in the general population (Zonneveld et al., 2018; McGuinness, Todd, Passmore, & Bullock, 2009; Levi Marpillat, Macquin-Mavier, Tropeano, Bachoud-Levi, & Maison, 2013). In one meta-analysis, a positive effect of antihypertensive medication was observed in overall cognition, executive functions, immediate memory, episodic memory, and attention (Levi Marpillat et al., 2013). Angiotensin II receptor blockers were superior compared to other antihypertensive medication (Levi Marpillat et al., 2013). Three meta-analyses did not show the effect of antihypertensive medication on dementia (Zonneveld et al., 2018; Levi Marpillat et al., 2013; McGuinness et al., 2009). Angiotensin-converting enzyme (ACE) inhibitors prevented whole-brain radiation-induced impairment in the perirhinal cortex-dependent cognitive function of novel object recognition in rats (Lee et al., 2012). The association between CVD and cognition in survivors of CBT remains unclear, but studies about preventing of stroke and CVD are urgently needed. Antihypertensive medication could potentially protect cognitive abilities in survivors of CBT.

Treating cholesterol requires concomitant management of increased risk of both ischemic stroke in those with high cholesterol and the hemorrhagic stroke in those with low cholesterol (Wang, Dong, Qi, Huang, & Hou, 2013; Iso, Jacobs, Wentworth, Neaton, & Cohen, 1989; Leppälä, Virtamo, Fogelholm, Albanes, & Heinonen, 1999). Survivors are prone to both ischemic and hemorrhagic strokes owing to radiation-induced vascular fragility, early atherosclerosis, and CVD findings on MRI, which are associated with both the risk of ischemic stroke and intracerebral hemorrhage in the general population (Campen et al., 2012; Passos et al., 2017; Neu et al., 2018; Fouladi et al., 2000, 2004; Debette et al., 2019). Multiple CVD findings, and the association between lacunar infarcts, ischemic infarcts and TIA, WMLs and cholesterol levels supported the need to monitor cholesterol in survivors. However, evidence about the advantages and disadvantages of cholesterol treatment in survivors of CBT treated with radiotherapy need further investigation. A balance between the low and high values of cholesterol might be even more sensitive in survivors of CBT compared to that in the general population.
6.4 Neuropsychological late-effects (Study II)

Due to the increasing survival rates of CBTs, focus of tumor therapy planning includes both further increasing survival and limiting the late-effects (Wells & Packer, 2015; Merchant et al., 2010). Neurocognition is among the most examined late-effects in survivors of CBT (Ris et al., 2001, 2013; Palmer et al., 2001; Edelstein et al., 2011; Brinkman et al., 2012).

Decreased FSIQ which was attributed to a slower rate of learning new skills after radiotherapy is a well-known effect of radiotherapy (Ris et al., 2001, 2013; Palmer et al., 2001). After a median follow-up of 15 years since diagnosis, the survivors performed poorer than expected in all cognitive domains, but the difficulties were the highest in the executive functions, motor dexterity, and speed (Edelstein et al., 2011). Working memory continued to decline, which was suggested to be a common sign of ageing (Edelstein et al., 2011). Our study findings are similar to those of Edelstein et al. (2010); survivors performed poorer than healthy controls in all domains, but the highest impairment was noted in executive functions (mean Z-score – 5.0 SD), and attention and processing speed (mean Z-score –4.3 SD).

Whole-brain radiotherapy is a major risk factor for cognitive impairment with a dose-dependent manner (Grill et al., 1999). In the current study, there was no difference in cognitive skills between the survivors treated with local and those treated with whole-brain radiotherapy. A younger age at the follow-up visit, and in particular, the shorter follow-up time in the whole-brain group may explain these results in the current study, as we showed that the follow-up time was inversely associated with cognitive performance if treated with whole-brain radiotherapy. It is unclear if the association is due to the true worsening of the cognitive skills during the follow-up, or because of the more intensive treatment in the survivors treated a longer time ago or both.

In the present study, the survivors demonstrated extensive impairment in executive functions (a mean Z-score of -5.0). The executive functions in the healthy population develop along with progressive neuronal myelination during childhood and adolescence (Wolfe et al., 2013). Sensitivity of oligodendrocytes to radiation and radiation-induced microvascular injury resulted in delayed white matter injury (Burns et al., 2016). White matter radial diffusivity, which reflects myelin-specific abnormalities, in the frontal lobes has been shown to be associated with a significantly shorter shifting attention, and cognitive flexibility (Brinkman et al., 2012). Fractional anisotrophy, which measured a higher degree of myelination and
density, or white matter integrity, in the parietal lobe have been associated with working memory (Brinkman et al., 2012). We found WMLs in 47% of the survivors. Cerebral small-vessel disease, found in 38% of the survivors in this cohort, has been associated with problems of executive functions in the elderly populations (Vasquez & Zakzanis, 2015). Previously, a decrease of 1 SD in executive functions was noted in CBT survivors treated with radiotherapy (Spiegler et al., 2004). It is unclear how long the decline continues. In our cohort, the executive functions were more impaired than those reported by Edelstein et al. (2011) in their study of medulloblastoma patients (mean Z-score -3.39 SD). Edelstein et al. (2011) had a shorter follow-up time and a more homogenous group of patients. The decline in executive function during follow-up, and the more harmful treatment protocols used a longer time ago may explain the difference in the results between these two studies.

Processing speed was also highly affected in the survivors, similar to executive functions. White matter also plays a key role in the processing speed function (Aukema et al., 2009). Similar to executive functions, our results on processing speed and attention were lower compared to that reported in the study by Edelstein et al. (-4.3 SD vs. -2.4 SD) (Edelstein et al., 2011). In one meta-analysis, the greatest impairment in elderly people with SVD was found in the processing speed (Vasquez & Zakzanis, 2015). We observed an increase in the prevalence of SVD after a follow-up time of 15 years, which could theoretically be involved with higher impairment in processing speed in the present study. In addition, heterogeneity in our cohort may have resulted in the difference.

A decline in working memory was suggested to be a part of the early ageing in survivors of medulloblastoma (Edelstein et al., 2011). Diffuse white matter degeneration is known to be associated with problems with working memory (Burns et al., 2016). Our results were relatively similar to that of Edelstein et al. (2011) considering the results of working memory (-1.4 SD vs. -1.2 SD). In our study, the working memory was associated with the follow-up time in survivors treated with whole-brain radiotherapy. In the elderly population SVD, the working memory was significantly less impaired than in processing speed similar to our findings (Vasquez & Zakzanis, 2015).

Here, the survivors presented with issues in immediate and general auditory memory, and visual memory. The hippocampal cells are prone to both radiation-induced neuroinflammatory effect and apoptosis of neuroproliferative cells (Burns et al., 2016; Thotala et al., 2015). The hippocampus is responsible for learning and memory (Thotala et al., 2015). Radiation doses to the temporal regions have been
associated with memory impairment (Armstrong et al., 2010). In the current study, immediate and general auditory memory and visual memory were associated with the follow-up time in survivors treated with whole-brain radiotherapy, which could be explained by the newer treatment strategies in those followed-up for a shorter time.

In the present study, the mean Z-scores of visuospatial construction were low (-2.5 SD). Previously, problems in visuospatial construction have been reported in survivors of childhood cerebellar tumors (Starowicz-Filip, Chrobak, Milczarek, & Kwiatkowski, 2017; Maddrey et al., 2005). In the present study, the impairment in visuospatial construction was not higher in the survivors with infratentorial tumor. However, the Rey-Osterrieth complex figure test has been proven to be sensitive to various non-cerebellar brain pathologies, including vascular pathology (Fastenau et al., 1999; Graham, Emery, & Hodges, 2004). The reported impairment rate in medulloblastoma survivors was as high as 85% (Maddrey et al., 2005).

In the present study, radiation-induced cognitive impairment was recognized in the majority of the survivors with relevant impairment in the executive functions and processing speed. On the basis of the current literature, efforts have been already made to reduce CNS radiation toxicity and related cognitive late-effects by reducing the use of radiotherapy, diminishing the doses delivered, and avoiding radiotherapy in very young patients (Grill et al., 1999; Silber et al., 1992). The results on proton beam radiotherapy are encouraging in considering the effect on cognitive function (Kahalley et al., 2016). The intelligence quotient did not decline in the survivors treated with proton beam radiotherapy (Kahalley et al., 2016). However, no difference could be observed between the intelligence quotient slopes in those treated with proton beam radiotherapy and those treated with conventional radiotherapy, which may also indicate the development of the associated techniques (Kahalley et al., 2016).

Radiotherapy is still essential to treat some brain tumors (Wells & Packer, 2015; Merchant et al., 2010). Survivors in our study had severe cognitive impairment, which was associated with challenges in everyday life. Therefore, new treatment strategies are needed to protect survivors from radiation-induced brain injury. In the juvenile rat brain, lithium reduced radiation-induced progenitor-cell death in the hippocampus, and ameliorated radiation-induced neurogenesis and astrogensis (Zhou et al., 2017). Lithium may reduce free radical damage, which may reduce the efficacy of radiotherapy on tumor cells (Khasraw, Ashley, Wheeler, & Berk, 2012). In both cell culture and animal models, valproic acid has prevented hippocampal neuronal injury and acted as a radiosensitizer in brain tumor cells.
ACE inhibitors administration has protected microglial cells from activation and novel object recognition task function related to perirhinal cortex activation in young adult male rats (Lee et al., 2012). As described in previous section, antihypertensive treatment has positively been associated with overall cognition, executive functions, immediate memory, episodic memory, and attention in the elderly population (Levi Marpillat et al., 2013). These are considerably the early steps on the protection of the brain from radiation-induced injury, and it is still far from being included in the treatment protocols.

In the current study, infratentorial tumors were associated with a lower performance intelligence quotient. In patients with posterior fossa tumors, the injured posterolateral hemispheres are associated with cognitive problems (Cantelmi, Schweizer, & Cusimano, 2008). The cerebellum and cerebral cortex are well connected, which may explain why patients with injury to the cerebellum may have deficits similar to patients with injury to the cerebral cortex (Cantelmi et al., 2008). The anatomical circuits pass via the cerebellum, which modulates cognitive functions (Cantelmi et al., 2008). Functional MRI has revealed the important role of the cerebellum in working memory, short-term and long-term name recollection, sensory discrimination, speech perception, and spatial orientation and judgment tasks (Cantelmi et al., 2008). Our results of poorer cognitive function in the survivors with infratentorial tumors are well explained by the pathology of the cerebellum (Cantelmi et al., 2008; Palmer et al., 2013). Previously, survivors with infratentorial tumors had a higher impairment in attention, working memory, reading and spelling compared to those with supratentorial tumors (Patel, Mullins, O'Neil, & Wilson, 2011). Cerebellar mutism has been associated with even poorer cognitive function (Renne et al., 2019; Palmer et al., 2010). Unfortunately, the occurrence of cerebral mutism was not adequately recorded in the patient files and therefore, its significance was not assessed in this cohort.

Hydrocephalus is present at the time of diagnosis of CBT in many patients. In the present study, ventriculoperitoneal shunts had been inserted in 63% of the survivors who underwent neuropsychological examination. The survivors with ventriculoperitoneal shunts had lower scores in the PIQ, attention and processing speed, and immediate auditory and general auditory memories, and visual memory. A high intracranial pressure may disturb the supratentorial grey and white matter by stretching the axons and compressing the white and grey matter, including the cortical neurons (Lindquist, Persson, Uvebrant, & Carlsson, 2008; Cantelmi et al., 2008). This leads to damage to the periventricular white matter and possible axonal degeneration (Krishnamurthy & Li, 2014). The cognitive functions, especially
executive functions, are dependent on long distance connections in the white matter (Griffanti et al., 2018; de Groot et al., 2000). Children with meningomyelocele and shunted hydrocephalus have showed problems in learning, memory, executive functions, working memory and processing speed (Boyer, Yeates, & Enrile, 2006; Lindquist et al., 2008). Other pathologies affecting long distance connections in the periventricular area, such as periventricular leukomalacia in preterm children and periventricular leukoaraiosis in elderly people, were significantly associated with overall cognitive tasks, psychomotor speed, and impaired working memory (Griffanti et al., 2018; de Groot et al., 2000; Choi, Rha, & Park, 2016). In preterm children, problems are higher in the PIQ than in the VIQ, similar to that observed in the present study (Choi et al., 2016). The results of the present study are in line with the finding of previous studies on hydrocephalus and other pathologies affecting the long-distance tracts.

The results of the current study showed that neurocognitive injury has a wide impact on life of survivors, and rehabilitation should be considered to help them. However, neuropsychological rehabilitation has not been widely studied in survivors of CBT treated with radiotherapy. In a previous study, medulloblastoma patients were randomized to computer-based training and standard treatment groups who were receiving active radiotherapy treatment, and results did not show any benefit in reading scores (Palmer et al., 2014). Patients had difficulties in completing the required intervention dosage (Palmer et al., 2014). Exercise training increased white matter fractional anisotrophy in radiotherapy-treated CBT survivors, as well as increased hippocampal volume and improved reaction time in a group setting (Riggs et al., 2017). A carryover effect was observed at 12 weeks after training (Riggs et al., 2017). The timing and method of rehabilitation should be further investigated. Thus, exercise could be beneficial for cognition, and it has other beneficial effects on overall health.

Cognitive impairment is a result of multiple causes. In survivors whom radiotherapy cannot be avoided, new treatment strategies are urgently needed. More information is warranted on the cognitive profile during ageing. As cognitive impairment results from multiple causes, multiple, coincidental treatment strategies, e.g. medication to treat vascular pathology and neuroinflammation, rehabilitation and exercise training, may lead to better results compared to single treatment options alone.
6.5 Cognitive functions and everyday life

Both neurocognitive impairment and problems in everyday life are late-effects of CBT (de Ruiter et al., 2013). Attention, working memory, and executive functions are foundational skills of higher-level cognitive functions (Raghubar et al., 2017; Brinkman et al., 2012; Jacobson, Mahone, Yeates, & Ris, 2018).

Impairment in executive functions results in problems in shifting attention, working memory, cognitive fluency, cognitive flexibility, planning, and organization (Brinkman et al., 2012). Executive functions were associated with educational level, employment status, intimate relationship status, living situation and driving license in the present study. These results present, how executive function skills are necessary in everyday life. In the elderly population with mild cognitive impairment, executive functions were associated with problems in complex finances, complex cooking and remembering events (Mansbach & Mace, 2018).

Processing speed and attention are important skills in learning new information, especially in academic settings (Palmer et al., 2013; Raghubar et al., 2017). In the present study, associations were found between processing speed and having an intimate relationship, living independently and having a driving license. The processing speed was not associated with the educational level and employment situation in the present study. The educational degree and employment rate were low in survivors; only 10% had a higher degree education and 39% were employed. The overall processing speed was extremely low, indicating that there were no differences between the groups.

Working memory stores and manipulates information that is necessary for complex cognitive tasks, language comprehension, problem-solving, reasoning and learning (Raghubar et al., 2017). Survivors of CBT treated with radiotherapy who were not living independently or had no driving license had a worse working memory compared to the other survivors in the present study. Working memory and processing speed are linked with executive functions, which may explain why no association was found with education and employment (Lindquist, Persson, Fernell, & Uvebrant, 2011).

In the present study, the VIQ and PIQ were associated with the educational level, and memory function was associated with employment. Survivors with a lower PIQ were more likely to not live independently. The VIQ and PIQ were associated with having a driving license. Intellectual functioning is a predictor of academic achievement (de Ruiter et al., 2013). The PIQ tests are dependent on...
motor functions, visuomotor integration, visual attention, abstract reasoning, and working memory; all the skills that are needed for driving (de Ruiter et al., 2013).

Cognitive impairment has a wide impact on everyday life of the survivors of CBT treated with radiotherapy. Of 71 % of the survivors who attained a higher education than comprehensive school, only 54 % (28/52) of the survivors who were not studying at the time of the study, were employed; hence the survivors had an urgent need for a well-supported labor market. It is important to investigate the treatment and rehabilitation of neurocognition, especially executive functions, processing speed, working memory and nonverbal skills, as it may lead to a more independent life and better quality of life for survivors of CBT treated with radiotherapy.

6.6 Secondary tumors (Study III)

Secondary tumors are the second most common cause of late-mortality after recurrence of the primary tumor (Ning, Perkins, Dewees, & Shinohara, 2015; Perkins et al., 2013; Armstrong et al., 2009). On FCR data, the secondary tumors were associated with high mortality of 56 %.

In the present clinical study, meningiomas were found in all six survivors with SNs. Meningiomas are the most common secondary brain tumors on MRI screening studies and in self-reported studies (Banerjee et al., 2009; Armstrong et al., 2009; Goshen et al., 2007; Felicetti et al., 2015; Sabin et al., 2014). In register-based studies, including our study on FCR cases, meningiomas did not represent the highest proportion of SNs or secondary brain tumors (Cai et al., 2012; Peterson et al., 2006). The low incidence of secondary meningiomas in register-based studies has most likely resulted from poor registration of the meningiomas, thereby leading to underestimation of radiation-induced secondary cancers and secondary brain tumors (Larjavaara et al., 2008). We found no meningiomas in the FCR data, even though the good coverage has been proven for other solid tumors (Teppo et al., 1994).

In the present study, multiple or recurrent meningiomas developed in three of the six survivors with secondary meningiomas. In earlier studies on leukemia, Hodgkin lymphoma and childhood cancer survivors treated with cranial radiotherapy, the occurrence of multiple or recurrent meningiomas has varied between 13 % and 45 % (Banerjee et al., 2009; Goshen et al., 2007; Felicetti et al., 2015). Although the doses of radiation, intrathecal methotrexate and carboplatin have been associated with an increased risk of meningiomas, the occurrence of
multiple and recurrent meningiomas may suggest genetic predisposition to cancer (Kok et al., 2018; Taylor et al., 2010).

Meningiomas rarely occur in children, adolescents and young adults in the general population, but the incidence increases with age (Dolecek et al., 2015). In the present study, the crude meningioma incidence was 8.2 %, and the cumulative incidence was 10.2 % at the 25-year follow-up, both of which are high. The cumulative incidence of meningiomas was 14.8 % at the 20-year follow-up since cranial radiotherapy for leukemia or lymphoma, suggesting that leukemia and lymphoma survivors may be at a higher risk of developing meningiomas compared to survivors of CBT treated with radiotherapy (Goshen et al., 2007). A higher crude incidence of meningiomas has been reported while screening of leukemia survivors compared to that observed in the present study (Banerjee et al., 2009; Goshen et al., 2007; Sabin et al., 2014). However, in register-based studies, the risk of meningiomas has been higher in survivors of CBT (Taylor et al., 2010; Neglia et al., 2006). This may be explained by the poor registration of meningiomas in registries, and by the possibility of more frequent imaging for the CBT survivors (Larjavaara et al., 2008).

Screening studies have revealed asymptomatic giant meningiomas in childhood cancer survivors (Felicetti et al., 2015; Sabin et al., 2014). The occurrence of these giant meningiomas has raised a question about whether the screening of meningiomas would result for better surgical outcome (Felicetti et al., 2015; Sabin et al., 2014). The current studies or the current guidelines do not support screening (Felicetti et al., 2015; Children's Oncology Group, 2018).

The clinical and register-based studies revealed different types of secondary neoplasms in the survivors. Meningiomas were asymptomatic in the survivors, and thus detected only in the MRI screening. In the register-base study, the secondary neoplasms other than basal cell tumors had a high mortality. The clinical study focused on secondary brain tumors because of the uncertainty to reveal other secondary neoplasms, especially basal cell tumors, treated outside the university hospitals.

The most common location of secondary tumors was the whole-brain field in the present study and in the study of Galloway et al. (2012). These findings support the theory that the highest incidence of radiation-induced tumors occurs at the edge of the radiation field where non-lethal doses are usually delivered (Galloway et al., 2012; Godlewski et al., 2012). Reducing the radiation dose to the whole-brain area should be beneficial in reducing the risk of secondary meningiomas, as a higher total dose has been associated with an increased risk of secondary meningiomas.
(Kok et al., 2018; Taylor et al., 2010). However, a higher incidence of secondary meningiomas has been reported in survivors of leukemia and lymphoma, in whom the doses of cranial radiotherapy are usually lower compared to that in patients with brain tumors (Banerjee et al., 2009; Goshen et al., 2007; Sabin et al., 2014). The use of intrathecal methotrexate, which is rarely used for CBT patients, may explain the higher incidence in the leukemia survivors (Taylor et al., 2010). The ability of proton beams to precisely target the planned radiation field has been suggested to reduce the risk of SNs (Merchant, 2009).

Current evidence has reduced concerns about the potential risk of GH in increasing the risk of recurrence of primary tumor or the development of secondary tumors and meningiomas (Sklar et al., 2002; Swerdlow et al., 2000, 2018; Indini et al., 2017; Shen et al., 2015). In fact, GH replacement therapy has been shown to be safe considering the risk of disease recurrence, secondary malignancies, and meningiomas (Sklar et al., 2002; Swerdlow et al., 2000, 2018; Indini et al., 2017; Shen et al., 2015). The association between GH deficiency and meningiomas in the present study may be explained by the fact that both the risk of meningiomas and GH deficiency increased with higher doses of radiation and longer follow-up time (Kok et al., 2018; Taylor et al., 2010; Merchant et al., 2011; Schmiegelow et al., 2000). Future studies with a higher number of patients should evaluate whether a true association exists.

6.7 Bone mineral density (Study IV)

Low BMD is a common late-effect of CBT treated with radiotherapy, and it was found in 24% of the survivors in the present study (Petraroli et al., 2007; Odame et al., 2006; Barr et al., 1998; Pietila et al., 2006; Cohen et al., 2012). A low BMD is associated with fractures after minimal trauma in the general population, and the findings of the current study are in line with those obtained in previous studies that showed that a low BMD was associated with fractures in long bones (Marshall et al., 1996). Screening is not recommended in the general population, and its benefit has not been studied in survivors of CBT treated with radiotherapy (Marshall et al., 1996).

Male survivors had lower Z-scores in BMD measurements compared to female survivors in the present study. Male gender has been a risk factor for low BMD in earlier studies on survivors of CBT, whereas female gender is a risk factor for low BMD in the general population (Krishnamoorthy et al., 2004; Kang et al., 2012; Marshall et al., 1996; Rachner, Khosla, & Hofbauer, 2011).
Survivors with a low BMI had a lower BMD. In the adult population, weight increases the BMD by increasing mechanical loading, converting androgens to estrogens in the adipose tissue, and augmenting bone mass in adulthood owing to earlier puberty in obese children (Dimitri, Bishop, Walsh, & Eastell, 2011; Taaffe et al., 2001; Pluijm et al., 2001). However, being overweight is a common problem among survivors of CBT treated with radiotherapy (Pietila et al., 2009).

Hormonal dysfunctions, such as GH and sex hormones dysfunctions, may affect BMD, but the results are contradictory in survivors of CBT (Petraroli et al., 2007; Barr et al., 1998; Pietila et al., 2006; Morris et al., 2008; Kang et al., 2012; Cohen et al., 2012; Holmer et al., 2011). In the present study, an increased level of follicle stimulating hormone, a marker of the ovarian dysfunction, had a negative impact on BMD in women (Tabatabai, Bloom, Stewart, & Sellmeyer, 2016). In men, testosterone levels were associated with BMD in the femoral necks and total hips. Androgens stimulate osteoblast differentiation and proliferation, and reduce bone resorption (Dimitri et al., 2011). Free thyroxine had negative association with BMD. As the hormonal deficiencies increase over time after radiotherapy treatment, and because hormonal deficiencies may have an impact on BMD, careful monitoring of hormones is encouraged (Chemaitilly et al., 2015; Merchant et al., 2011). Replacement therapy for thyroid dysfunction should be moderate, and overcorrection should be avoided.

The fracture risk in long bones increased by 1.7–2.0-fold to every decrease of 1 SDs in BMD considering Z-scores. In the general population, the risk is 1.5-1.6-fold for all fractures (Marshall et al., 1996). Survivors of CBT might be more even vulnerable for fractures compared to the general population owing to the impairment in moving, balance, vision, and hearing and the risk of epilepsy (Gunn et al., 2015).

6.8 Strengths and study limitations

We investigated a national cohort of consecutive survivors of CBT treated with radiotherapy. The participation rate was reasonable (58 %) and comparable to those of previous studies (Schmiegelow et al., 2000; Neu et al., 2018; Copeland, deMoor, Moore, & Ater, 1999). The group was very homogenous considering the radiotherapy treatment doses, but chemotherapy protocols varied according to histology of the tumors and time period of treatment.

The limitations of the study are owing to its cross-sectional design and lack of follow-up, and the strength is the use of screening with MRI, and DEXA, as well
as performing laboratory, and neuropsychological examinations. One limitation was associated with the absence of controls in studies I, III and IV, but the protocol was very demanding regarding the time and funding. In part I of the study, the absence of SWI sequences may have underestimate the incidence of microbleeds in the study population (Lin et al., 2001). In study about secondary tumors, the small number of tumors limited the statistical analysis. In the neuropsychological examination, the strength of the study was the inclusion of healthy controls for the analysis, although the controls were younger than the survivors were. However, when analyzing the neuropsychological test results, the difference would not have been significant, as in normal population, the results would be similar at the ages of 25 and 28 years (Wechsler, 1945, 1955; Tombaugh, 2004).
7 Summary and conclusions

In the present study, the young adult survivors of CBTs experienced late-effects of tumor treatment, such as CVD, impaired executive functions, slow processing speed, working memory issues, meningiomas, and low BMD, all of which generally are associated with problems in an ageing population (Debette et al., 2019; Tombaugh, 2004; Mok, O'Donoghue, Myers, Drazich, & Nobre, 2019; Dolecek et al., 2015; Marshall et al., 1996). Early ageing after cancer therapy has previously been found at the cellular level, e.g. higher levels of DNA damage and lower telomerase activity (Scuric et al., 2017). Early ageing may occur in the survivors of CBT treated with radiotherapy. Previously, it has been suggested that declining working memory, hearing impairment, second cancer, diabetes, hypertension, and endocrine deficiencies are clinical signs of early ageing in survivors of medulloblastoma (Edelstein et al., 2011). Some of the consequences are possible causes of increased morbidity and mortality (Debette et al., 2019; Marshall et al., 1996; Corell et al., 2019).

We found a very high prevalence of CVD, strokes and WMLs in the survivors. Previous studies have contradictory results regarding the impact of cerebrovascular MRI findings on cognition; microbleeds were associated with executive functions, but lacunar infarcts did not show a significant association with cognition (Roddy et al., 2016; Fouladi et al., 2000). The role of WMLs in cognitive functions has been well established after radiotherapy for CBT (Fouladi et al., 2004; Jacola et al., 2014; Brinkman et al., 2012). The neurocognitive profile of survivors is similar to that of the VCIND; the highest impairment was found in the processing speed, attention and executive functions (Vasquez & Zakzanis, 2015). However, vascular neurocognitive impairment might be difficult to differentiate from non-vascular mild cognitive impairment in the general population (Vasquez & Zakzanis, 2015). In addition, in the current study, neurocognitive impairment was relevant, even severe, in most of the survivors. As nearly half of the survivors had coincidental vascular findings, the vascular burden may play a more important role in neuropsychological functioning than one vascular pathology alone. The survivors had potentially a low cognitive reserve, which may not protect the brain from vascular cognitive injury (Pendlebury et al., 2019). Future research should investigate the impact of CVD on cognition in survivors of CBT treated with radiotherapy.

The high prevalence of strokes and cerebrovascular MRI findings in young adult survivors is alarming. The survivors presented a similar or higher prevalence
of CVD findings compared to the general population in their 70s (de Bruijn et al., 2014; Kaffashian et al., 2016; Kuller et al., 2004). It is currently unknown how vascular pathology evolves during the follow-up period; therefore, the longitudinal survey studies are urgently needed. As the findings of SVD are associated with increased risk of ischemic infarcts, hemorrhagic strokes and mortality in the general population, and because a high incidence of strokes was observed in the CBT survivors, the aggressive efforts are needed to investigate possible prevention strategies. The proper treatment for hypertension should be included in the treatment of survivors and its effect on the development of CVD should be investigated (Mueller et al., 2013; Bohm et al., 2017). Survivors should be actively supported to live healthy and to have active lifestyle to decrease atherosclerotic risk factors. Radiation is such a strong risk factor for CVD that prevention by reducing atherosclerotic risk factors by healthy lifestyle may not be sufficient, and other prevention possibilities are urgently needed. However, the progression of CVD in survivors, and the clinical significance of CVD are not currently well-known.

As there are multiple etiological factors behind the neurocognitive impairment, several coincidental strategies are needed for the prevention and treatment. The mechanical damage caused by the tumor itself and by hydrocephalus can be difficult to manage, but early detection of the tumor may be beneficial (Margelisch et al., 2015; Cantelmi et al., 2008). The vascular and neuroinflammatory components of radiation-induced injury may require medication, but currently there is no evidence regarding such a treatment (Greene-Schloesser et al., 2012). Large-scale studies are needed on benefits of rehabilitation, and active living with regular exercise is supported by the current literature (Riggs et al., 2017). In my opinion rehabilitation should be carefully chosen to those who benefit from it. Generally speaking, usually those who are less impaired benefit the most from the rehabilitation, but actually we do not know, who benefits and who does not. A high impairment in the cognitive skills, especially in executive functions and processing speed, had major effects on everyday life. To actively search survivors with impairment in the cognitive skills and support them early at school and in daily living should be organized by regular follow-up visits. The results of executive functions and processing speed suggest accelerated ageing, as the mean results were similar to those observed in the 70–84- year old general elderly population (Tombaugh, 2004). Hence, better neurocognitive outcomes could offer better quality of life and might require smaller need for supportive services.
In the present study on secondary meningiomas, the main findings were the presence of secondary meningiomas in some survivors in the clinical study, the low cumulative incidence of SNs with a high mortality due to SNs in the FCR data, and the poor registration of secondary meningiomas to the FCR. Hence, to reveal the true incidence of SNs both register-based and MRI screening studies should be performed as part of studies, as clinical studies do not report the incidence of SNs in patients who died and register-based studies poorly report the incidence of meningiomas. In addition, it is unclear whether MRI screening is beneficial for treating of secondary meningiomas.

Survivors of CBT treated with radiotherapy need regular follow-up for years, possibly even for decades after the cessation of the tumor therapy. Survivors should be followed-up by a multi-professional team, including oncologists, neurologists, endocrinologists and neuropsychologists with good knowledge of the late-effects of CBTs and its treatment. Beyond the medical treatment, the support of social workers and employment officers who understand the special needs of the CBT population should be encouraged.

Early ageing is the term used in the literature for the clinical late-consequences of cancer treatment and to describe the cellular findings after cancer treatment related to ageing in the general population (Edelstein et al., 2011; Scuric et al., 2017). It is my understanding that ageing is the process of growing older and gathering experiences, and it is not absolutely related to disease or morbidity. Certainly, it is too early to have CVD, problems in executive functions and processing speed, meningiomas, and low BMD at the mean age of 28 years. In conclusion, childhood brain tumor survivors suffer from radiation-induced accelerated ageing, which initiates several decades too early. Accelerated ageing is a pathological process, that is not a part of normal ageing, but it occurs early. Longitudinal follow-up studies are needed to investigate, how the ageing advances in the different individuals. With the current knowledge, it is important to actively search for late-effects, to encourage survivors to live healthy and have regular exercise, and to support life-long those who are not able to achieve normal milestones in education, working life and independent living.
References


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List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


*Authors contributed equally to the manuscript.

The original publications have been reprinted here with the kind permission of the copyright holders; Journal of Adolescent and Young Adult Oncology and the publisher: Mary Ann Liebert, Inc., New Rochelle, NY, and Acta Oncologica and the publisher: Taylor & Francis, Abingdon, UK. Original publications are not included in the electronic version of the dissertation.
1530. Sirniö, Kai (2019) Distal radius fractures : Epidemiology, seasonal variation and results of palmar plate fixation
1536. Terho, Henri (2019) Electrocardiographic risk markers for cardiac events in middle-aged population
1538. Ylönen, Susanna (2019) Genetic risk factors for movement disorders in Finland
1541. Tiri, Hannu (2019) Comorbidities and mortality of hidradenitis suppurativa in Finland
1542. Hynynen, Johanna (2019) Status epilepticus in mitochondrial diseases and the role of POLG1 variants in the valproic-acid induced hepatotoxicity
1543. Urpilainen, Elina (2019) The role of metformin and statins in ovarian and breast cancer in women with type 2 diabetes

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SIGNS OF RADIATION-INDUCED ACCELERATED AGEING IN SURVIVORS OF CHILDHOOD BRAIN TUMORS

THE INCIDENCE OF CEREBROVASCULAR DISEASE, NEUROCOGNITIVE IMPAIRMENT, SECONDARY NEOPLASMS, AND LOW BONE MINERAL DENSITY AFTER 18 YEARS OF FOLLOW-UP