Brain tumors in children

Intervening with the aftermath: relapse and long term side effects

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“Outside of a dog, a book is a man's best friend. Inside of a dog it's too dark to read”

— Groucho Marx

To Susanne, Axel and Ivan

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ABSTRACT

After completing primary treatment, childhood brain tumor patients enter a follow-up phase. Follow-up is needed for two main reasons; to detect relapse and to diagnose late side effects. The overall aims of this thesis were; 1) To describe and analyze the pattern of relapse after treatment for medulloblastoma – the most common malignant brain tumor in childhood – with the aim to find potentially successful relapse treatment and; 2) To investigate ways to lessen the side effects of brain tumor treatment, especially the cognitive side effects.

Methods: The long-term outcome of 338 medulloblastoma patients enrolled in the HIT-SIOP-PNET4 trial was investigated, with a focus on relapse diagnosis, pattern of relapse, and treatment of relapse. In a separate randomized, single-center, single-blinded, pseudo crossover study, the potential benefit of physically active video gaming in childhood brain tumor survivors was investigated. Thirteen children, all previously treated with cranial radiotherapy, were randomized to either active video gaming (with weekly internet-based coaching sessions) followed by a waiting list period, or these periods in reverse order. They were assessed before and after each period, with measures of cognition, motor function and activities of daily living (ADL). Finally, in a rodent model the potentially protective effect of post-irradiation hypothermia on the neurogenic areas of the brain – the subventricular zone (SVZ) and the granule cell layer (GCL) of the hippocampus – was examined. Young rats were randomized to either normothermia or hypothermia for eight hours post-irradiation, or a control group. Their brains were examined one week later, measuring the SVZ and GCL areas, and counting the number of proliferating cells and microglia.

Results and conclusions: The ultimately grim prognosis for patients with recurrent medulloblastoma, irrespective of treatment, is confirmed. Surgery for histological diagnosis and research should be encouraged, and can in selected cases prolong survival, but new treatment options are needed. Active video gaming improves body coordination and the execution of ADL. Positive effects on cognition is a possibility, although not confirmed in this pilot study. Hypothermia after irradiation of the brain has a protective effect on the SVZ, but not the GCL, one week post-irradiation. The long term and functional effect of this finding needs further exploration, together with studies of the effect of hypothermia on brain tumors.

Keywords: medulloblastoma, relapse, radiotherapy, cognition, exercise therapy, video games, hypothermia, pediatric, brain tumor **ISBN:** 978-91-629-0131-8

SAMMANFATTNING PÅ SVENSKA

När barn med hjärntumör är färdigbehandlade påbörjas en uppföljningsfas, av två viktiga skäl: för att upptäcka eventuella återfall och för att upptäcka sena biverkningar. Målsättningen med denna avhandling var dels att beskriva och analysera återfall av medulloblastom, den vanligaste elakartade hjärntumören hos barn, dels att undersöka sätt att mildra de långsiktiga (kognitiva) biverkningarna som barn med hjärntumör ofta drabbas av.

I avhandlingen presenteras resultat avseende överlevnad hos 338 patienter som behandlats för medulloblastom i studien HIT-SIOP-PNET4. Hos de 72 patienter som fick återfall beskrivs diagnostik, återfallsmönster, behandling och prognos. I en separat studie av 13 barn som fått strålbehandling för en hjärntumör undersöktes om regelbundet spelande av fysiskt aktiverande dataspel (Nintendo Wii) kunde påverka motorik, kognition, aktiviteter i dagliga livet (ADL) och aktivitetsnivåer. I denna randomiserade singelblindade studie fick barnen antingen börja med fysiskt aktivt dataspelande (med veckovis internetbaserat coachningstöd) följt av en ”vänteperiod”, eller det omvända. De utvärderades före och efter varje period med hjälp av kognitiva och motoriska tester samt test avseende ADL-förmåga. Slutligen undersöktes i en djurmodell om generell nedkylning (hypotermi) kunde skydda de nervcellsbildande (neurogena) områdena i den unga hjärnan från att skadas av joniserande strålning. Unga råttor randomiserades till tre grupper, normal kroppstemperatur alternativt nedkylning under åtta timmar efter en stråldos mot vänster hjärnhalva, eller till en kontrollgrupp. En vecka senare undersöktes de neurogena områdena i hjärnan, den subventrikulära zonen (SVZ) och den subgranulära zonen i korncellslagret (eng: granule cell layer, GCL) i hippocampus. Områdenas areor mättes och antalet celler i celldelning samt antalet inflammatoriska celler (mikroglia) räknades.

Slutsatser: Återfallsrisken efter behandling för medulloblastom är ca 20 %. Återfall medför en mycket dålig prognos, trots ibland intensiva behandlingsförsök. I utvalda fall kan kirurgi förlänga överlevnaden. Nya läkemedel eller angreppssätt behövs. Fysisk aktiverande dataspel förbättrar kroppskoordinationen samt ADL-förmågan hos barn som behandlats för hjärntumör. Positiva kognitiva effekter är en möjlighet men kunde inte säkert påvisas i denna pilotstudie. Hypotermi efter strålning skyddar cellerna i SVZ men inte i GCL, en vecka efter strålningen. Betydelsen av detta för den kognitiva förmågan, liksom effekten av hypotermi på tumörer behöver studeras ytterligare i framtida studier.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Sabel M, Fleischhack G, Tippelt S, Gustafsson G, Doz F, Kortmann R, Massimino M, Navajas A, von Hoff K, Rutkowski S, Warmuth-Metz M, Clifford, S C, Pietsch T, Pizer B, Lannering B. **Relapse patterns and outcome after relapse in standard risk medulloblastoma: a report from the HIT-SIOP-PNET4 study**. *J. Neurooncol.* 2016;129(3):515-524.

II. Sabel M, Sjölund A, Broeren J, Arvidsson D, Saury J. M, Blomgren K, Lannering B, Emanuelson I. **Active video gaming improves body coordination in survivors of childhood brain tumours**. *Disabil Rehabil*. 2016;38 (21):2073–2084.

III. Sabel M, Sjölund A, Broeren J, Arvidsson D, Saury J-M, Gillenstrand J, Emanuelson I, Blomgren K, Lannering B **Effects of physically active video gaming on cognition and activities of daily living in childhood brain tumor survivors: a randomized pilot study**. *Neuro-Oncology Practice* Epub August 29, 2016; doi: 10.1093/nop/npw020

IV. Sabel M, Kalm M, Björk-Eriksson T, Lannering B, Blomgren K. **Hypothermia after cranial irradiation protects neural progenitor cells in the subventricular zone but not in the hippocampus**. *International Journal of Radiation Biology*, accepted for publication April 13, 2017. doi:10.1080/09553002.2017.1321810

CONTENTS

ABBREVIATIONS

ACT	Auditory Consonant Trigrams
ADD	Attention deficit disorder
ADL	Activities of daily living
AMPS	Assessment of Motor and Process Skills
AT/RT	Atypical Teratoid/Rhabdoid Tumor
AVG	Active video gaming
BDNF	Brain-derived neurotrophic factor
BOT-2	Bruininks–Osteretsky Test of Motor Performance, 2nd Edition
CCNU	Lomustine
CCR	Continuous complete remission
Chr	Chromosome
CI	Confidence interval
COWAT	Controlled Oral Word Association Test
CPT II	Conners' Continuous Performance Test II
CSF	Cerebrospinal fluid
CSI	Craniospinal irradiation
CTNNB1	Catenin (cadherin-associated protein), beta 1
D-KEFS	Delis-Kaplan Executive Function System
DNMB	Desmoplastic/nodular medulloblastoma
EFS	Event free survival
EE	Energy expenditure
FSIQ	Full-Scale Intelligence Quotient
ETMR	Embryonal Tumor with Multi-layered Rosettes
GTR	Gross total resection
Gy	Grey
HDSCR	High dose chemotherapy with stem cell rescue
HFRT	Hyperfractionated radiotherapy
Iba1	Ionized calcium-binding adapter molecule 1
IHC	Immunohistochemistry
i.t.	Intrathecal
MBEN	Medulloblastoma with Extensive Nodularity
MET	Metabolic Equivalent of Task
MID	Minimal important difference
MRI	Magnetic resonance imaging

Mtx	Methotrexate
MVPA	Moderate and vigorous physical activity
MYC	V-MYC avian myelocytomatosis viral oncogene homolog
MYCN	V-MYC avian myelocytomatosis viral oncogene neuroblastoma-derived homolog
NPC	Neural progenitor cell
n.s.	Non-significant
OS	Overall survival
PAAC	Physical activity across the curriculum
PBS	Phosphate-buffered saline
PF	Posterior fossa
PFS	Progression-free survival
PNET	Primitive neuroectodermal tumor
PHH3	Phosphorylated-Histone H3
QoL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
ROS	Reactive oxygen species
SD	Standard deviation
SHH	Sonic hedgehog
SMN	Second malignant neoplasm
SRM	Standardized response mean
stPNET	Supratentorial PNET
STRT	Standard radiotherapy
SVZ	Subventricular zone
SWA	SenseWear Pro2 armband
WHO	World Health Organization
WISC-IV	Wechsler Intelligence Scale for Children-version IV
WNT	Wingless-related integration site
WT	Wild type

DEFINITIONS IN SHORT

Active video gaming	Video gaming requiring physical activity (beyond that of conventional hand-controlled games), sometimes referred to as exercise gaming or exergaming
Cognition	The mental action or process of acquiring knowledge and understanding through thought, experience, and the senses (Oxford Dictionaries, 2016)
Epigenetics	Mitotically heritable changes in gene expression that are not accompanied by modifications in primary DNA sequence (Northcott et al. 2010)
Executive function	A psychological construct of the cognitive processes responsible for planning, sequencing, and controlling goal-directed behavior (Banich 2009)
Exergaming	A portmanteau of "exercise" and "gaming"
Exercise	Exercise is a subset of physical activity that is planned, structured, and repetitive with the objective of improving or maintaining physical fitness (Caspersen et al. 1985)
Physical activity	Any bodily movement produced by skeletal muscles that requires energy expenditure (WHO)
Standardized Response Mean (SRM)	Effect size measure, defined as the ratio between the mean change score and the standard deviation of that change score within the same group

1 INTRODUCTION

Every year in Sweden, around 300 children are diagnosed with a childhood cancer, and 28 % of them have a tumor in the central nervous system, CNS (Gustafsson et al. 2013). The mean annual incidence rate in the Nordic countries has been estimated to 4.2/100 000, and has remained stable for at least 20 years (Schmidt et al. 2011). The prognosis for CNS tumors has improved during the last decades, and 10 year overall survival (OS) in Sweden is now exceeding 70%, although the prognosis is highly dependent on the histopathological diagnosis and tumor location, as well as treatment (Lannering et al. 2009).

Despite the improvement in prognosis, cancer is still the major cause of death in Swedish children aged 1-14 years, with CNS tumors being the most common cancer type leading to death in this age group (Socialstyrelsen 2016). Malignant brain tumors have a worse prognosis, and curative treatment usually requires a combination of neurosurgery, chemotherapy and/or radiotherapy. For the survivors, cure often comes with a cost of long-term side effects. This means that annually in Sweden, around 50-60 children and adolescents join an increasing group of pediatric brain tumor survivors. Finding effective rehabilitation therapies that promote neural recovery, as well as preventive programs, will therefore be increasingly important.

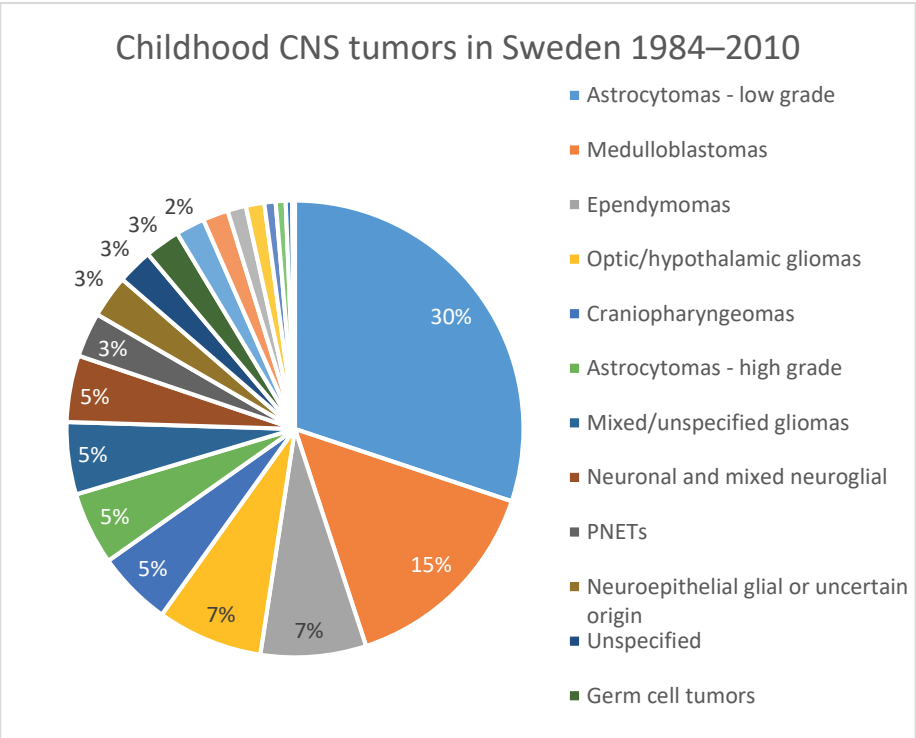
If a tumor relapses after primary treatment, chances of cure are reduced. The additional relapse treatment required, adds to the risk for late side effects (Conklin et al. 2008). The balancing of increased treatment intensity, with the aim of increasing the chance for cure, versus the risk for severe long-term side effects is a major challenge in all pediatric oncology and especially in pediatric neuro-oncology. Without cure there are no long-term side effects, but if cure is achieved at the price of a functioning brain there might be life, but of poor quality. Despite the sometimes severe impact of the neurocognitive side effects, there have been few studies of methods to remediate or prevent them, and even fewer empirically supported interventions available in clinical practice.

1.1 Brain tumors in children

A “brain tumor” is not a single entity, and children are not adults. As for many childhood cancers, the type and distribution of brain tumors differs

from those of adults (Ostrom et al. 2013). The most recent update of the WHO classification; the 2016 World Health Organization Classification of Tumors of the Central Nervous System, lists >130 different entities and variants of brain tumors. In this classification update, brain tumors are for the first time classified not only according to their histopathological features, but with the option to also incorporate molecular findings, integrating the tumors' phenotypic and genotypic features (Louis et al. 2016). The WHO classification includes a grading of the malignancy of a tumor type according to features suggesting malignancy, such as pleomorphic nuclei, high mitotic rate, and vascular invasion, ranging from I-II (non-malignant) to III and IV (malignant). The grading can be used as a means of predicting the biological behavior of a neoplasm (Louis et al. 2007). On top of this histological/molecular classification, the tumor location in the brain is a crucial factor, with implications on symptoms, treatment strategy and prognosis. Thus, a non-malignant tumor such as a pilocytic astrocytoma (WHO grade I) can have an excellent prognosis when located at a site where it is amenable to surgical removal (such as the cerebellum), and a poorer prognosis when located in a more sensitive area, such as the thalamus or basal ganglia (Gnekow et al. 2012).

Figure 1.Childhood CNS tumors in Sweden 1984-2010. (Gustafsson et al. 2013)



The childhood brain tumors (Figure 1) can be roughly divided into tumors of glial origin and those of non-glial origin (Northcott et al. 2015). Examples of glial tumors include astrocytomas, ependymomas, oligodendrogliomas, and mixed glial/neuronal tumors (e.g. gangliogliomas). Examples of non-glial tumor types are embryonal tumors, such as medulloblastomas, atypical teratoid/rhabdoid tumors (AT/RTs) and Embryonal Tumors with Multi-layered Rosettes (ETMRs), but also craniopharyngeomas, and germ cell tumors, among others. The classification is constantly evolving and changes over time, as we gain more knowledge. For example, in the current WHO classification, primitive neuroepithelial tumors (PNET) are no longer recognized as an entity and the PNET terminology is no longer used (Louis et al. 2016). This change reflects the emerging evidence, using e.g. methylation profiling, that most "PNETs" are more commonly related to other tumor types (such as glioblastomas or ependymomas), than to each other (Schwalbe et al. 2013, Danielsson et al. 2015). There are data however, suggesting the existence of a true "PNET" group of tumors (Sturm et al. 2016).

The age distribution of diagnosed childhood CNS tumors (between ages 1 to <15 years) is fairly even, without apparent age peaks (Gustafsson et al. 2013). Just over 50 % of all pediatric CNS tumors are located in the posterior fossa (PF), the majority of these are in the cerebellum (41 %), and a smaller fraction in the brainstem (10-13 %). The remainder are found in the cerebral hemispheres (21-24 %), the midbrain (13-25 %), and spinal cord (3 %). (Lannering et al. 1990b, Kaatsch et al. 2001).

1.2 Pediatric brain tumor treatment

Finding a brain tumor does not automatically mean it must be treated. Treatment decisions are based on the (presumed or histologically proven) tumor type, tumor location, symptoms and the patient´s age. In selected cases, tumor surveillance by repeated magnetic resonance imaging (MRI) can be justified (Ali et al. 2014). This option is mainly used in cases of slow-growing (low-grade) tumors in neurologically sensitive areas, such as the tectal plate (Stark et al. 2005). In the majority of brain tumor cases, treatment is necessary without further delay. The first option to consider is to surgically remove the tumor, completely if possible, partially if not. In sensitive areas of the CNS only a biopsy might be achievable. A major advantage with an initial surgical procedure is obtainment of tumor tissue, leading to a

histopathological diagnosis. The histopathological diagnosis is the foundation for further treatment decisions, together with tumor location, tumor stage (presence or absence of metastases), result of surgery, and the patient´s age.

Staging of CNS tumors is usually done by MRI of the brain and spine, together with cerebrospinal fluid (CSF) cytology. Some tumor types (germ cell tumors) secrete substances that can be detected in the CSF and/or blood, and used as diagnostic/prognostic tumor markers. If the tumor is completely resected, and is non-malignant (WHO grade I-II), no further treatment is usually required (Fisher et al. 2001), although exceptions to this rule exist. Sub-totally resected, non-malignant tumors can benefit from additional therapy, but a period of watchful waiting is often prudent (Fisher et al. 2008).

The malignant tumors (WHO grade III-IV) cannot be cured by surgery alone, even if a (macroscopically) complete resection is achieved. Malignant tumors grow in an infiltrative manner that prevents *microscopically* complete resections, without causing inacceptable neurologic damage. They also have a propensity to metastasize, usually within the CNS. Therefore they are treated with surgery together with chemotherapy and/or radiotherapy, in order to get rid of infiltrating tumor cells as well as metastases. An example of such combined therapy is the treatment for medulloblastoma.

1.3 Medulloblastoma

The term medulloblastoma was coined by Bailey and Cushing around 1925, when they described “a very cellular tumor of a peculiar kind”, usually located in the central part of the cerebellum, just over the 4th ventricle. (Bailey and Cushing 1925). Medulloblastoma is the most common *malignant* brain tumor in children, diagnosed in about 15-20 % of children with brain tumors (Kaatsch et al. 2001, Lannering et al. 2009, Ostrom et al. 2013). Most cases occur during the first decade of life, with a peak incidence between 5-9 years of age (Lannering et al. 2009, Ostrom et al. 2013), but it can also be diagnosed in infants, teenagers and young adults. Boys are more commonly affected, about 1.4-1.5 times as commonly as girls (Lannering et al. 2009, Kool et al. 2012). Metastases are present at primary diagnosis in ~24 % of all cases (Kool et al. 2012).

Histological subgroups The four histological medulloblastoma subgroups defined in the current WHO classification (and their relative frequency) are: classic medulloblastoma 70 % (CMB), desmoplastic/nodular

16 % (DNMB), medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic 10 % (LCA) (Kool et al. 2012, Louis et al. 2016). Medulloblastomas of the large cell or anaplastic histological subtype have been found to be associated with poorer survival, and these histologies are now regarded as high risk factors (Brown et al. 2000, Eberhart et al. 2002).

Age The significance of lower age (< 3 years) as an independent negative prognostic risk factor is unclear (Packer et al. 2003). In many studies, children < 3 years have a worse prognosis compared to older children (Evans et al. 1990, Zeltzer et al. 1999, Packer et al. 2001), but comparisons are confounded by differences in therapy (e.g. no radiotherapy or lower radiotherapy dose given to the younger children), differences in M-stage between groups, and the inclusion of (poor prognostic) AT/RTs, in studies of the earlier era – before this diagnosis was described (Rorke et al. 1996). Younger children have a greater risk for cognitive impairment after radiotherapy, as discussed below. Looking solely at younger children treated without radiotherapy, the DNMB/MBEN histological subtypes have a better prognosis (Rutkowski et al. 2010).

Table 1. Chang staging classification for metastasis in medulloblastoma

Stage	Definition
Metastasis	
M_0	No evidence of gross subarachnoid or hematogenous metastasis.
M_1	Microscopic tumor cells found in cerebrospinal fluid.
M_2	Gross nodular seeding demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M_3	Gross nodular seeding in spinal subarachnoid space
M_4	Extraneural metastasis

Table derived from Chang et al. 1969

Stage and risk stratification A staging classification (Table 1) was developed by Chang et al. in the 1960s (Chang et al. 1969), and risk group stratification according to Chang M-stage and other clinical biomarkers, (i.e. age at diagnosis, extent of surgical resection), has been used since the 1990s (Gottardo et al. 2014). The average or standard risk group, has been defined by: age >3 years, gross total resection (GTR) of the tumor, (or a tumor residual of ≤ 1.5 cm^2), no evidence of metastatic disease (= Chang stage M0), and no other high risk factors present (Ellison et al. 2003).

Molecular subgroups Based on the almost identical appearance (determined by light microscopy and immunohistochemical techniques) of tumors originating in different parts of the CNS, the concept of PNET was formed, suggesting that medulloblastomas were a subgroup of PNETs located in the cerebellum (Becker and Hinton 1983, Rorke 1983). This concept remained controversial however, especially since different responses to therapy (and prognosis) were seen for PNETs in different areas of the brain (Rorke et al. 1997). Using gene expression data, Pomeroy et al. showed that PNETs from different areas of the brain had different gene expression profiles, and that medulloblastomas could be separated from supratentorial PNETs and AT/RTs using the molecular profile (Pomeroy et al. 2002). They also described a subgroup of medulloblastomas (mainly of the desmoplastic histological subtype) with a distinct gene expression profile characterized by activation of the sonic hedgehog (SHH) signaling pathway, and showed that gene expression data could be used as a prognostic tool (Pomeroy et al. 2002).

In time, several molecular subgroups of medulloblastoma were identified by different researchers (Thompson et al. 2006, Kool et al. 2008, Fattet et al. 2009, Cho et al. 2011, Northcott et al. 2011), and in a consensus statement 2012, the four principal molecular medulloblastoma subgroups were described and named: Wnt, Shh, Group 3, and Group 4 (Taylor et al. 2012). In the revised WHO classification from 2016 medulloblastomas can now, in addition to the histologically defined variant, also be genetically or epigenetically defined as either WNT-activated medulloblastomas, SHH-activated medulloblastomas (TP-53 mutant or TP-53 wildtype) and non-WNT/non-SHH medulloblastomas (i.e. Group 3 and group 4 medulloblastomas) (Louis et al. 2016).

Molecular subgroups together with other molecular risk factors are now used in on-going clinical trials, and will be increasingly important in both diagnosis and treatment stratification in future studies (Gajjar et al. 2004, Pfister et al. 2009). The clinical and biological risk factors used so far, will need to be validated in the context of medulloblastoma subgroups. In this new era, metastatic status and medulloblastoma subgroup seem to be strong predictive biomarkers. Previously reported biological prognostic biomarkers are sometimes subgroup driven (e.g. chr6 loss in WNT medulloblastomas), and sometimes only relevant in a given subgroup (Zhukova et al. 2013, Shih et al. 2014). A new proposal on risk factor stratification for clinical trials, combining traditional clinical risk factors with subgroups and molecular/genetic factors, was recently published (Ramaswamy et al. 2016b), Table 2.

Table 2. Proposed risk stratification for non-infant childhood medulloblastoma, (Ramaswamy et al. 2016a)

	WNT	SHH	Group 3	Group 4
Low risk	< 16 years			
Standard risk		TP53 wt (somatic or germline) No MYCN amplification Non-metastatic	All of the following: No MYCN-amplification Non-metastatic	All of the following: Non-metastatic Chr.11 loss
High risk		One or both: Metastatic MYCN amplification		Metastatic
Very high risk		TP53 mutation (metastatic or non-metastatic)	Metastatic	
Unknown	Metastatic		Non-metastatic with MYC amplification Anaplasia Isochromosome 17q	Anaplasia

1.3.1 Medulloblastoma treatment

Neurosurgical treatment for medulloblastoma was pioneered by Harvey Cushing and it was soon recognized that more extensive surgery rather than a biopsy could prolong survival, but only for a limited time (from 6 to 17 months) (Cushing 1930). It was also early noted that radiotherapy prolonged survival (Bailey and Cushing 1925), and Bailey suggested that craniospinal irradiation (CSI) was necessary to counter the tumor's propensity to recur distally in the CNS, far from the original site (Bailey 1930). In an early Swedish report, Olivecrona and Lysholm described the treatment of various gliomas with surgery and irradiation, including an 11 year old boy with a very cellular tumor "closely resembling a type of gliomatous tumor

designated by Bailey and Cushing as medulloblastoma" (Olivecrona and Lysholm 1926).

For decades to follow, medulloblastoma was a fatal disease for all but a few patients (Ingraham et al. 1948), but improvements in radiotherapy technique, surgical and anesthetics procedures continued. The numbers of medulloblastoma survivors started to increase in the 1960-70s (Bloom et al. 1969). New imaging techniques with computerized tomography (CT) and MRI also became available, improving diagnosis as well as tumor staging and risk grouping (Zimmerman et al. 1978, Kramer et al. 1991). Assigning patients to risk groups and the addition of adjuvant chemotherapy were also important steps.

Evans and coworkers were among the first to demonstrate a survival benefit of radiotherapy and adjuvant chemotherapy in the treatment of high (poor) risk medulloblastoma (Evans et al. 1990). They reported an event free survival of 49 % in the chemotherapy group versus 0 % in the radiotherapy-only group ($p=0.006$), although no benefit from chemotherapy was found in patients with less advanced disease. In a single-institution trial, the addition of chemotherapy to radiotherapy was found to significantly improve survival in poor-risk patients, compared to historical controls (Packer et al. 1991). Expanding on these encouraging results, a larger, three-institution trial, was conducted. Patients with high risk medulloblastoma received a combination of radiotherapy and chemotherapy, resulting in a 5-year progression-free survival (PFS) of 85% (Packer et al. 1994). The study also included some younger patients (<5 years) without high-risk disease, who received a lower dose of CSI (23.4 Gy) with promising results (Packer et al. 1994).

Alarming reports of severe cognitive side effects from radiotherapy (discussed below) triggered research to find less toxic therapies, without jeopardizing the chance of cure. The POG 8631/CCG 923 study randomized standard risk medulloblastoma patients between "reduced-dose" CSI (23.4 Gy) and "standard-dose" CSI (36 Gy) – both in combination with a posterior fossa boost up to 54 Gy – but found the reduced CSI dose to be inferior regarding survival (8-year EFS 52% vs 67%, $p=0.080$) (Thomas et al. 2000).

However, another study in standard risk medulloblastoma also used reduced-dose CSI (23.4 Gy, with a PF boost up to 54 Gy), but in combination with chemotherapy, and presented better survival with a 5-year PFS of 79% (Packer et al. 1999). The shift towards the current, lower "standard dose" for standard risk medulloblastoma of 23.4 Gy CSI had thus begun. The positive results of combining chemotherapy with the lower dose of 23.4 Gy CSI were

later confirmed in two large trials. The COG9961 study which used 23.4 Gy CSI and randomized between two different chemotherapy arms, resulted in a 5-year EFS of 81% (irrespective of randomization arm) (Packer et al. 2006). Also the HIT-SIOP PNET4 trial, described below, demonstrated similar results (Lannering et al. 2012). In a retrospective study, the addition of chemotherapy to radiotherapy improved local control (100% for the combined-therapy group vs 75% in the group with radiotherapy only) (Christopherson et al. 2014). Although the significance of adding chemotherapy to radiotherapy has not been convincingly proven in randomized controlled trials (Michiels et al. 2015), there are several studies indicating a benefit of adding chemotherapy.

In order to avoid the detrimental effects of radiotherapy there has been a consensus within the medical community to avoid radiation therapy in younger children, (below 3-5 years of age), and to treat these children with chemotherapy alone (± high dose chemotherapy with stem cell rescue, HDSCR) (Grill et al. 2005, von Bueren et al. 2011, Cohen et al. 2015). For a subset of infants (i.e. with DNMB/MBEN histology) this strategy has been successful (Rutkowski et al. 2010).

1.3.2 HIT-SIOP PNET4

The HIT-SIOP PNET4 trial (2001-2006) was a multinational collaborative European study with patients from 120 centers in Germany, France, Italy, UK, Austria, Spain, The Netherlands, Sweden, Norway and Denmark. It included 338 patients (211 male, 127 female), aged 4 to 21 years, with a non-metastatic medulloblastoma (i.e. no metastases on craniospinal MRI and negative CSF cytology). A postoperative residual tumor was allowed, but second surgery was recommended if it was >1.5 cm^2. After an amendment in 2003, patients with large-cell/anaplastic histology tumors were no longer included, due to reports of inferior outcome in these patients with standard-risk therapy (Eberhart et al. 2002).

Patients were randomized to either standard radiotherapy (STRT, n=169) (23.4 Gy to the craniospinal axis and 54 Gy to the whole posterior fossa over 42 days, in 30 fractions of 1.8 Gy, one fraction per day) or hyperfractionated radiotherapy (HFRT, n=169) (1 Gy/fraction, two fractions per day up to 36 Gy to the craniospinal axis, 60 Gy to the posterior fossa, and an additional boost to a total of 68 Gy to the tumor bed). Patients in both randomization arms received concomitant chemotherapy with weekly vincristine during radiotherapy, followed by adjuvant chemotherapy (eights cycles of cisplatin-CCNU-vincristine every six weeks), starting 6 weeks after the end of

radiotherapy. Tumor histology (99.4 % centrally reviewed) identified classic medulloblastoma in 81 %, desmoplastic-nodular medulloblastoma in 14 % and large-cell/anaplastic medulloblastoma in 5 % of cases. Out of 254 assessable tumors, 58 (22.8 %) were WNT-positive medulloblastomas by β-catenin IHC, 31/195 (15.9 %) harbored *CTNNB1* activating mutations (Clifford et al. 2015). On central review of pre- and post-operative MRIs (performed in 94 % of cases), 31/338 patients (9 %) had a residual tumor >1.5 cm^2.

No difference in survival was demonstrated after HFRT compared to STRT. After a median follow up of 4.8 years after diagnosis, the 5-year-EFS for all patients was 79 %, and the 5-year OS 86 %. The 5-year EFS was 78 % for the STRT arm and 81 % for the HFRT arm (p=0.9) (Lannering et al. 2012). Features significantly associated with inferior prognosis were the presence of a post-operative tumor residue >1.5 cm^2 (n=31, p<0.01), and a delay in radiotherapy start >49 days after surgery (5-year EFS 0.67 vs 0.81, p=0.04) (Lannering et al. 2012). Patients with WNT-MB had favorable outcomes, although WNT-MB patients aged ≥16.0 years at diagnosis appeared to have a lower EFS than younger patients (p=0.058). In the true standard-risk cohort (i.e. after removal of patients with a tumor residue >1.5 cm^2), tumors with chromosome 17 imbalances/diploid background were associated with a poor outcome (<60 % 5-year EFS), but tumors with MYC/MYCN amplification or LCA histology were not (Clifford et al. 2015).

1.3.3 Medulloblastoma relapse

Several studies have shown the prognosis of recurrent medulloblastoma after standard therapy (i.e. including radiotherapy) to be dismal (Torres et al. 1994, Bouffet et al. 1998, Pizer et al. 2011). In the French study, by Bouffet et al., median survival after progression was only five months after a variety of treatments including surgery, chemotherapy, radiotherapy and high dose chemotherapy (Bouffet et al. 1998). Histological subtype was not reported. Response to salvage therapy and solitary recurrence were clinical factors associated with longer survival after relapse, but only 2/46 relapsed patients remained alive, (only one disease-free), at the writing of the report (Bouffet et al. 1998).

High dose chemotherapy with stem cell rescue (HDSCR) for recurrent brain tumors (including medulloblastoma) has been tried with some initially promising results (Finlay et al. 1996, Graham et al. 1997, Guruangan et al. 1998). These studies, together with studies that followed, indicated a benefit of HDSCR in a subgroup of patients, e.g. patients never treated with

radiotherapy as part of their primary therapy, or patients with minimal residual disease responsive to chemotherapy (Dunkel et al. 1998, Butturini et al. 2009). There is one caveat however; in many studies the recurrences were treated with surgery and/or radiotherapy in addition to HDSCR, making the prognostic impact of HDSCR difficult to evaluate (Dunkel et al. 1998, Gururangan et al. 2008). In addition, several studies enrolled patients just prior to the initiation of HDSCR, and not immediately at the diagnosis of relapse, e.g. (Dunkel et al. 2010). With such a design, patients with chemo-resistant disease or early disease progression are never enrolled and the benefit of HDSCR therefore overestimated, based on the total population of relapsing patients. This selection bias is a problem in several other studies and makes it difficult to estimate the true benefit of HDSCR, in the absence of randomized controlled trials comparing HDSCR to other therapies (Gajjar and Pizer 2010).

Only a few national studies addressing treatment with HDSCR for recurrent medulloblastoma exist, but they can give an estimate of the benefit of HDSCR when considering the entire population of patients. The UK CCLG relapsed PNET study (2000-2007) enrolled 40 patients, (35 with recurrent medulloblastoma and five with stPNET), all but one previously treated with radiotherapy (Pizer et al. 2011). The study aimed to first achieve complete or near-complete remission, and then treat with HDSCR. Of the patients enrolled, only 22/40 (55 %) proceeded to the HDSCR phase. The remainder were withdrawn from the study, either due to lack of response to induction chemotherapy or other reasons, such as toxicity. At a median follow-up of 7.4 years, only three MB patients were still alive. The 5-year EFS and OS was 8.7 % and 8.2 % years respectively (Pizer et al. 2011).

The German HIT-REZ-97 national study tested a non-randomized but stratified relapse protocol using either intensive chemotherapy with the addition of HDSCR to good responders (as a potentially curative therapy), or only oral chemotherapy as a palliative option (Bode et al. 2014). Of 72 patients (87 % medulloblastomas) selected to receive the intensive chemotherapy option, only 27 (38 %) eventually received HDSCR. The median PFS was 11.6 months for the whole cohort, and 5-year PFS 0.5 %. In the HDSCR cohort the median PFS was 8.4 months, and 5-year PFS 0.1 %. Regarding OS, the median was 21.0 months for the whole cohort, and 5-year OS 16 %. In patients treated with HDSCR, the median OS was 20.2 months, and 5-year OS 17 %. There was no difference in survival when comparing good responders who did, or did not, receive HDSCR. A treatment related mortality of 8 % was reported. Increased toxicity is an obvious risk from

intensive therapies such as HDSCR, and many studies have reported even higher toxic death rates of 10-16 % (Bouffet et al. 1998, Dunkel et al. 2010).

Oral chemotherapy regimens, e.g. with temozolomide, has been shown to provide some disease control, albeit not long-lasting. In a study by Cefalo et al., oral temozolomide gave a response rate of 42.5 %, but a disappointing 1-year PFS of 7.5 % (Cefalo et al. 2014). Oral etoposide as single therapy has also been evaluated in small series, with similar but short-lived responses, and median survival times of 5.5 months from treatment initiation (Ashley et al. 1996, Chamberlain and Kormanik 1997).

Low intensity multi-agent drug combinations, (often referred to as 'metronomic chemotherapy') have been tried in smaller series of relapsed medulloblastoma, with some promising preliminary results (Sterba et al. 2006, Peyrl et al. 2012). This approach, believed to function through anti-angiogenesis which indirectly inhibits tumor growth, is currently being evaluated in the multinational MEMMAT trial.

1.4 Long term side effects

Survivors of pediatric brain tumors often suffer long term side effects. The risk for these side effects, and their character, depend on several factors. Treatment is one, but premorbid factors as well as damage from the tumor itself, also contributes (Iuvone et al. 2011). Before discussing the cognitive late effects, some other side effects are worth mentioning. Although not a complete list, late side effects include: impaired motor performance and other neurological sequelae (Lannering et al. 1990a, Aarsen et al. 2004, Oyharcabal-Bourden et al. 2005, Ullrich 2009, Piscione et al. 2014), epilepsy (Sonderkaer et al. 2003), endocrine deficiencies and perturbed growth (Gurney et al. 2003, Oyharcabal-Bourden et al. 2005, Chemaitilly et al. 2015), impaired vision or visual field defects (Harbert et al. 2012), impaired hearing (Lannering et al. 1990a, Oyharcabal-Bourden et al. 2005), increased risk for second malignancies (Tsui et al. 2015), vasculopathy leading to increased risk for stroke (Gurney et al. 2003, Murphy et al. 2015), reduced muscle strength and fitness (Ness et al. 2010), and alopecia (Oyharcabal-Bourden et al. 2005).

Childhood brain tumor survivors often have deficits in activities of daily living (ADL) (Demers et al. 2016), and are (among childhood cancer survivors) the group most likely to report restricted abilities to perform

personal care, restricted abilities to do routine activities, restricted abilities to attend work or school, as well as performance limitations (Ness et al. 2005). In a small study (n=20) by Edelstein et al., 20 % of adult survivors of childhood medulloblastoma were dependent on caregivers for their daily care (Edelstein et al. 2011). On the other hand, 55 % were competitively employed or attended school full time. Studies of quality of life (QoL), have found radiotherapy and intelligence quotient (IQ) to be associated with lower health-related QoL (Reimers et al. 2009). In follow-up studies, brain tumor survivors were at increased risk for adverse outcomes such as unemployment, having a health condition affecting their ability to work, lower education level, lower income, and poorer health (Mostow et al. 1991, Boman et al. 2010). Still, in the study by Mostow et al., 85 % of the survivors had some employment, and 80 % described their health as excellent or good, indicating the diversities within the brain tumor group (Mostow et al. 1991). Negative social consequences for brain tumor survivors have also been reported. Adult childhood brain tumor survivors were less likely to be married or to live in a relationship, and to have children of their own, compared to controls (Langeveld et al. 2003, Reimers et al. 2009).

1.4.1 Cognitive side effects

The prevalence of cognitive dysfunction in pediatric brain tumor patients ranges from 20-70 % (Lannering et al. 1990a, Aarsen et al. 2006, Brinkman et al. 2016), up to 100 % in selected subgroups (Glauser and Packer 1991). IQ has been the most common measure of general cognitive function. Most studies have found a lowered IQ score in survivors, 1-2 standard deviations below the expected mean (Saury and Emanuelson 2011).

Intelligence quotient (IQ)

The finding of lowered IQ is perhaps not surprising, since IQ is a compound of several different abilities. IQ can be measured by different scales, e.g. the Wechsler scales, with different scales for different age groups. These scales are regularly updated. The full-version or the abbreviated version of the Wechsler scales can be used. The Full-Scale IQ score is a composite of Verbal and Performance IQ scores, each with a normative mean of 100 and a standard deviation (SD) of 15. Verbal IQ is composed of several subtests that measure verbal comprehension and knowledge. Performance IQ includes subtests that measure visual-perceptual and nonverbal skills. In childhood brain tumor survivors, the non-verbal (performance) abilities are usually more affected than the verbal abilities (Grill et al. 1999, Mulhern et al. 1999, Kieffer-Renaux et al. 2000, Carpentieri et al. 2003, Reimers et al. 2003).

After radiotherapy, the IQ score decreases at a rate between 1.7 and 5 IQ points per year in different series (Copeland et al. 1999, Palmer et al. 2001, Ris et al. 2001, Spiegler et al. 2004, Saury and Emanuelson 2011, Ris et al. 2013). Longitudinal studies suggest that IQ declines for the first 2-5 years after diagnosis, but the decline is attenuated 5-10 years after diagnosis (Palmer et al. 2003, Spiegler et al. 2004, Kieffer-Renaux et al. 2005, Edelstein et al. 2011). It seems the decline in IQ is not caused by loss of previously learnt skills, but rather a slower rate of acquiring new knowledge compared to healthy peers, so that patients lag behind more and more with time (Palmer et al. 2001). IQ scores can predict certain forms of achievement, e.g. academic achievement, and subsequently occupational and financial outcome, although this correlation only accounts for about 25 % of the variance (Strauss et al. 2006). Other individual factors, such as perseverance, interest and motivation are probably equally important in academic achievement (Neisser et al. 1996).

Specific cognitive deficits

The most common specific cognitive deficits reported in childhood brain tumor survivors involve attention, memory – especially working memory –, executive function, processing speed, visual-motor integration and visual-spatial functioning (Lannering et al. 1990a, Butler and Haser 2006, Edelstein et al. 2011, Palmer et al. 2013). Attention can be subdivided in sustained and selective attention. *Sustained attention* is the capacity to maintain focus and alertness over time; and *selective attention* (focused attention) is the ability to select target information from an array while ignoring irrelevant stimuli (Mirsky et al. 1991). *Working memory* can be described as a short-term memory buffer that allows us to hold information in our mind and mentally work with it (Cowan 2008). For example, working memory is used when baking a cake, to avoid adding the same ingredient twice, or when solving an arithmetic problem in your head. Working memory is also necessary to make sense of written or spoken language. When reading a sentence, you need to remember the beginning of the sentence when you reach the end of it, (as you hopefully just did). Working memory is distinct from short-term memory, although some consider working memory to be a part of short-term memory (Cowan 2008). The latter only requires the holding of information in mind, without manipulation (Diamond 2013). Working memory is generally divided in two types, verbal and visual-spatial.

Long-term memory can be separated into two broad forms: declarative and non-declarative (Shohamy and Turk-Browne 2013). *Declarative memory* handles long-term, conscious memories of general facts, including new word meanings (*semantic memory*), and personal events that have a specific

context in space and time (*episodic memory*). *Non-declarative memory* (procedural memory) handles the rest, e.g. nonconscious learning of skills and habits, perceptual information, and emotional and motor responses (Squire 2004). Declarative memory relies on the medial temporal lobe (including the hippocampus), whereas habit learning involves primarily the striatum, although there is interaction between these two systems (Knowlton et al. 1996).

Executive function (executive control) is a psychological construct that covers the cognitive processes responsible for planning, sequencing, and controlling goal-directed behavior (Banich 2009). These processes allow us to make a plan, initiate its execution, and persevere on the specific task until its completion, but also to quickly adapt to diverse situations as well as inhibit prepotent responses (Jurado and Rosselli 2007). Executive functions consist of at least three basic functions: shifting (between tasks or mental sets, sometimes called cognitive flexibility), updating (of working memory), and inhibition (of automatic, or prepotent responses, when necessary) (Miyake et al. 2000).

Processing speed can be described as the rate at which a person can take in a bit of new information, reach some judgment on it and then formulate a response (Fry and Hale 2000). It has been defined as the general rate at which a person can complete cognitive operations, and can be viewed as a measure of the efficiency of the system (Kail 2000). As children develop, they process information more rapidly, reflecting age-related changes in the CNS, such as myelination.

Academic achievement is directly related to the skills and knowledge children acquire at school and is an ecologically valid measure regarding psychological outcomes, reflective of their daily functioning (Mabbott et al. 2005) After radiotherapy treatment, children fall progressively behind their peers in academic skills (reading, spelling, and mathematics), due to a reduced rate of skill acquisition. Although academic achievement is correlated to IQ, the academic decline remains also when adjusting for the decline in intelligence, and it is likely that other factors (i.e. fatigue, absence from school) contribute (Mabbott et al. 2005).

1.4.2 Factors associated with cognitive dysfunction

When survival rates for medulloblastoma began to improve in the 1970s, initial reports were also optimistic regarding functional outcomes, with e.g. Bloom et al. reporting 82 % of survivors having no or mild disabilities (Bloom et al. 1969). However, a number of reports that followed described serious cognitive side effects in the survivors (Hirsch et al. 1979, Duffner et al. 1983, Silverman et al. 1984).

Radiotherapy

The most important treatment-related factor for cognitive late effects is probably cranial radiotherapy, and the negative cognitive impact of radiotherapy has been confirmed in multiple studies (Mulhern et al. 1989, Mulhern et al. 1992, Palmer et al. 2001, Brinkman et al. 2016). An early publication by Duffner et al., reported of 10 children with posterior fossa tumors treated with surgery, craniospinal radiation and chemotherapy. All children had either mental retardation, or cognitive decline, and/or learning disorders, with 40 % having IQs <70 (Duffner et al. 1983). Several subsequent studies confirmed these findings, and also found lower age (at radiotherapy) to be a risk factor for the most severe cognitive deficits (Duffner et al. 1988, Packer et al. 1989, Lannering et al. 1990a, Mulhern et al. 1998). It has also been established that the risk of cognitive deficits increases with higher radiation dose (Goldwein et al. 1996, Mulhern et al. 1998, Grill et al. 1999, Kieffer-Renaux et al. 2000, Merchant et al. 2014), larger irradiation fields, or combinations of larger doses and fields (Grill et al. 1999, Kieffer-Renaux et al. 2005, Moxon-Emre et al. 2014).

Surgery

The importance of the cerebellum also for non-motor abilities, such as language, thought modulation, emotions, and planning, has gained increased attention, but the surgical contribution to deficits found after cerebellar tumor treatment was for long less known. Several studies have demonstrated that, although patients with cerebellar tumors (treated with surgery alone) had FSIQ scores within normal range, a majority had partial cognitive deficits affecting memory, attention, visual-spatial abilities, and executive function (Levisohn et al. 2000, Riva and Giorgi 2000, Steinlin et al. 2003). Furthermore, behavioral problems were described in one third of the patients (Levisohn et al. 2000, Steinlin et al. 2003). Other studies have found a cognitive impact from isolated surgical treatment, both after surgery for cerebellar tumors; affecting sustained attention, visual-spatial function, executive function, and visual-spatial memory (Aarsen et al. 2004), and for tumors in supratentorial locations (Carpentieri et al. 2003). The impact on cognition from the tumor itself (discussed below) is difficult to disentangle from the surgical impact. Repeated surgery and perioperative complications have been associated with lower IQ in medulloblastoma patients (Kao et al. 1994), and surgical complications, e.g. cerebellar mutism, with lower Verbal and Performance IQ in both irradiated and non-irradiated patients (Grill et al. 2004, Ris et al. 2013).

Chemotherapy

Many studies that evaluated the cognitive effects of multimodal brain tumor treatment, found no significant impact on cognition from chemotherapy, at least not compared to the impact from radiotherapy (Grill et al. 1999, Palmer et al. 2001, Reimers et al. 2003). A medulloblastoma trial for young children (< 3 years) used intensive postoperative chemotherapy alone (including intraventricular methotrexate, Mtx, but without radiotherapy), and found the mean IQ score after treatment to be significantly lower compared to healthy controls, but significantly higher compared to children treated with radiotherapy, in an earlier trial, (Rutkowski et al. 2005).

Much of the data on the cognitive effects of chemotherapy alone have come from studies of children treated for leukemia (without CNS involvement), where fewer confounding variables are involved. In a study of patients treated for acute lymphatic leukemia (ALL) with a chemotherapy-only protocol, no significant differences were found in the survivors´ IQ, academic skills, learning, or memory, compared to normative expectations (Jacola et al. 2016). However, significantly more children than expected (16 %) performed below average in measures of sustained attention, and caregivers reported a greater frequency of learning problems (Jacola et al. 2016). A Nordic study found progressive deficits in Verbal and Performance IQ in ALL survivors treated with cranial irradiation, as well as significantly lower test scores in memory functions, attention and motor functions, compared to ALL patients treated with chemotherapy only, and to healthy controls (Harila et al. 2009). Although the chemotherapy-only treated group performed significantly better than the radiotherapy treated group, they had statistically significant impairments in VIQ and PIQ, sequential reasoning, working memory and information processing speed, compared to controls (Harila et al. 2009). The combination of intrathecal (i.t.) Mtx and cranial irradiation has been found to be more detrimental for cognition compared to radiotherapy alone (Iuvone et al. 2002, Riva et al. 2002, Mitby et al. 2003). The sequence of treatment seems to be important, with a more pronounced IQ decline when Mtx is given after radiotherapy, rather than before (Balsom et al. 1991).

Other factors

Although treatment often is blamed for the cognitive decline after childhood brain tumor treatment, several other factors correlate with cognitive outcome. Negative risk factors include: lower age at diagnosis (Mulhern et al. 2001), female sex (Mulhern et al. 2004b, Merchant et al. 2014), hydrocephalus (Merchant et al. 2004, Moxon-Emre et al. 2014, Brinkman et al. 2016), seizures/epilepsy (Iuvone et al. 2011, Brinkman et al. 2016), and neurologic complications (Moxon-Emre et al. 2014).

One must not forget the child´s pre-morbid abilities, but also the impact from the brain tumor itself. Several studies have found cognitive difficulties already at diagnosis (before treatment), in up to 50 % of patients, compared to norm (Iuvone et al. 2011). Comparing to norms could however be problematic, since some impairment could be due to the stressful situation, and the test results negatively affected by anxiety and physical discomfort. In an attempt to control for this, Margelisch and co-workers compared newly diagnosed pediatric brain tumor patients to children with an oncological diagnosis not involving the CNS, and found significantly impaired cognitive abilities in the brain tumor patients, involving working memory, verbal memory and attention (but no difference in perceptual reasoning, processing speed, or verbal comprehension) (Margelisch et al. 2015). Other tumor related factors include the location of the tumor (Iuvone et al. 2011), tumor size (Tonning Olsson et al. 2014), and medulloblastoma subgroup (Moxon-Emre et al. 2016).

To conclude, the cognitive impairment after treatment is most certainly caused by multiple factors, including host factors, tumor, treatment, and other factors.

1.4.3 Neurogenesis in the brain

Throughout life, human neurogenesis occurs in the brain, mainly in the dentate gyrus of the hippocampus and the lateral wall of the lateral ventricles, in the subventricular zone (SVZ) (Eriksson et al. 1998). The SVZ is the subependymal cell layer that lies directly subjacent to the ventricular ependyma. These areas contain neural stem and precursor cells, collectively known as neural progenitor cells (NPCs).

Hippocampus

In the dentate gyrus of the hippocampus, NPCs in the subgranular zone (SGZ) generate granule cells, which migrate into the granule cell layer (GCL) where they integrate into neural circuits and become functional neurons (van Praag et al. 2002). Many neurons fail to integrate, and subsequently die (Zhao et al. 2008). Hippocampal neurogenesis appears to be involved in memory formation (Shors et al. 2001), and hippocampus-dependent learning leads to increased hippocampal neurogenesis, at least in animal models (Gould et al. 1999, van Praag et al. 1999, Curlik and Shors 2011). Furthermore, selective inhibition of hippocampal neurogenesis leads to impairments in spatial memory tasks (Deng et al. 2009).

The hippocampus is important in declarative memory, something that was discovered by accident in 1953. After bilateral medial temporal lobe resections (due to intractable seizures), the patient H.M. experienced permanent severe anterograde amnesia (Scoville and Milner 1957). The amnesia manifested itself as a permanent disability in forming new episodic and semantic memories, and much knowledge has come from the study of this single patient (Corkin 2002). The hippocampus does not store memories, but rather processes and prepares incoming information before sending it back for long-term storage in the neocortex.

The hippocampus also has a role in other cognitive functions, beyond declarative memory. It has been described as a bridge between perception and decision making, implicated in imaging the future, keeping track of space and time, perception and attention as well as reward (Shohamy and Turk-Browne 2013). The hippocampus is important for the processing of spatial layouts, topographical memory, and navigation (O'Keefe and Nadel 1978, Maguire et al. 1997). An indication of this was demonstrated by the posterior hippocampi of London taxi drivers being significantly larger than those of controls, and that posterior hippocampal volume correlated positively with the number of years spent as a taxi driver (Maguire et al. 1997, Maguire et al. 2000). It is also implicated in social navigation, helping to keep track of memories of social interactions through a “social map” (Tavares et al. 2015).

Subventricular zone

Neurogenesis in the SVZ has a less clear role, at least in humans. In rodents, quiescent radial glia-like cells (B-cells) become activated and give rise to fast dividing transient amplifying cells (C-cells), which in turn generate neuroblasts (A-cells), which migrate through the rostral migratory stream (RMS) to the olfactory bulb, where they end up as interneurons (Doetsch et al. 1999a, Ming and Song 2011). Although this appears to occur also in humans (Curtis et al. 2007, Wang et al. 2011), the extent of this migration seems to be much smaller or even minimal compared to rodents, at least after the perinatal period (Wang et al. 2011, Bergmann et al. 2012). In humans, instead of supplying neurons to the olfactory bulb, evidence suggests that adult neurogenesis in the SVZ produces neurons ending up as interneurons in the striatum (Ernst et al. 2014). Apart from neurons, type B cells also give rise to oligodendrocytes and astrocytes (Chaker et al. 2016). Interestingly, SVZ neurogenesis seems to have a role also in brain repair e.g. in ischemia (Arvidsson et al. 2002, Jin et al. 2006, Osman et al. 2016), and for providing remyelinating oligodendrocytes in models of demyelinating disease (Xing et al. 2014).

Several of the studies (e.g. Bergmann et al. 2012, Ernst et al. 2014), proving (or disproving) post-natal neurogenesis in different areas of the human brain have relied on a ground-breaking birth-dating method that uses carbon-14 (^{14}C), generated by the cold war atomic bomb tests, to date neurons in human brain tissue (Spalding et al. 2005). Using this method, it was determined that cortical neurons are as old as the individual, and that neurons in the cortex are not replaced by postnatal neurogenesis (Spalding et al. 2005, Bhardwaj et al. 2006). In the cerebellum, the average age of neurons were found to be 2.9 years (after the individual´s birth), indicating neuronal cell proliferation destined for the cerebellum during the first post-natal years (Spalding et al. 2005).

1.4.4 Damaging mechanisms from radiotherapy

Radiobiology

The exact mechanisms of cell death due to ionizing radiation is still an area of active investigation, but the most important mechanism is through DNA damage. Radiation ionizes cell molecules either directly, or indirectly via free-radical intermediates formed from the radiolysis of water. The direct energy, or energy released by these free radicals, break the phosphodiester bonds in the backbone of the DNA helix and cause single- or double-strand breaks. Alterations of the DNA bases and crosslinks between DNA strands and chromosomal proteins are important reactions as well. Cells respond to DNA damage by inducing cell-cycle arrest to allow repair. If repair is unsuccessful or the damage is severe, it results in permanent cell cycle arrest, p53-mediated apoptosis, or mitotic catastrophe (Gudkov and Komarova 2003). Highly proliferating cells tend to enter apoptosis, whereas low-proliferating cells (e.g. fibroblasts) tend to enter growth arrest (Gudkov and Komarova 2003). Damaging reactions with cell membranes in e.g. endothelial cells and oligodendrocytes can also trigger apoptosis mechanisms, via sphingomyelinase-mediated release of ceramide (Kolesnick and Fuks 2003). Furthermore, irradiation causes sustained elevations of reactive oxygen species (ROS) in cells and tissues, leading to a shift in the redox homeostasis, which could alter the course of cell proliferation, cell differentiation, and affect long-term cell survival (Limoli et al. 2004).

Irradiation is damaging to neurogenesis

Animal studies have shown that when brains of young rodents are irradiated, the volume of the irradiated hippocampus is reduced corresponding to an apoptosis-induced loss of proliferating neural stem and progenitor cells, rendering the tissue incapable of normal growth (Monje et al. 2002, Fukuda et al. 2004, Rola et al. 2004). The reduction in neurogenesis leads to a

profound reduction in newborn neurons, whereas the production of newborn astrocytes or oligodendrocytes is relatively spared (Monje et al. 2002). The damage to the neurogenic regions is greater in younger animals and it is also sustained, at least until the animals become adult (Hellström et al. 2009). The reduced neurogenesis is not merely a function of reduced NPC numbers or proliferative activity, but also due to inhibitory alterations of the neurogenic microenvironment (Monje et al. 2002). One hypothesis is that chronic inflammation after radiotherapy influences NPC proliferation as well as cell fate. Radiation-induced inflammation has been demonstrated to cause neuronal progenitors to differentiate into glial cells instead of neurons, and an increase in microglia (Monje et al. 2002). In the juvenile brain neurogenesis is even more sensitive to irradiation, but there seem to be differences in the inflammatory response to irradiation compared to the adult brain (Blomstrand et al. 2014).

In contrast to the profound and long-lasting effect of irradiation, intraventricular infusion of the chemotherapeutic drug Ara-C (cytarabine) severely reduced the number of fast-dividing precursors/neuroblasts in the SVZ, but the effect was transient and the cell population was normalized within a week (Doetsch et al. 1999b, Ahn and Joyner 2005). Another study however, found a more long lasting detrimental effect on in vivo neurogenesis after treatment with BCNU or cisplatin, lasting at least six weeks (Dietrich et al. 2006).

Disrupting hippocampal neurogenesis causes decreased performance in hippocampal-dependent memory tasks and behavioral tests in rodents (Rola et al. 2004, Barlind et al. 2010, Karlsson et al. 2011). A study in humans treated with chemotherapy and cranial irradiation showed profoundly reduced hippocampal neurogenesis in combination with reported memory deficits, supporting the hypothesis that neurocognitive impairment after CNS-directed therapy to some degree is due to a hampered hippocampal neurogenesis (Monje et al. 2007). In a study correlating radiation doses to different brain regions with cognitive outcome, a higher radiation dose to the (right) hippocampus was associated with reduced reading scores (Merchant et al. 2014).

Irradiation is damaging to white matter and blood vessels

Radiation affects oligodendrocytes, and together with vascular changes, this probably contributes to white matter damage (Mulhern et al. 1999). White matter damage, (i.e. a reduction of normal appearing white matter or reduced white matter integrity on MRI), can be seen after radiotherapy, and correlates to cognitive deficits, i.e. a decrease in IQ, (Mulhern et al. 1999, Palmer et al.

2001) working memory (Jacola et al. 2014), and executive function (Brinkman et al. 2012). In the study by Mulhern et al. (1999), surgery alone did not affect the amount of normal appearing white matter. Furthermore, neither the addition of chemotherapy to radiotherapy, nor (surprisingly) treatment with a higher radiotherapy dose, decreased the amount further (Mulhern et al. 1999). Younger age at radiotherapy has been associated with less normal appearing white matter (Mulhern et al. 2001). It is possible that the white matter is more sensitive to irradiation during the rapid myelination that occurs in children and adolescents (Moore 2005). A specific form of MRI abnormality, cerebral microbleeds, has been observed on MRIs after radiotherapy. In a retrospective MRI study, cerebral microbleeds were associated with previous cranial radiation (and chemotherapy) (Roddy et al. 2016). A high number of microbleeds correlated with worse cognitive function (Roddy et al. 2016), but the contribution of these microbleeds to the cognitive decline is at present unclear. In the hippocampus, the reduction in proliferating cell numbers has been attributed to a direct effect on NPCs rather than blood vessels (Boström et al. 2013).

1.4.5 Means to mitigate the cognitive side effects

Prevention

Avoiding radiotherapy by substituting it for chemotherapy has for long been the only strategy available, and is still used especially in the more radiosensitive younger children (Rutkowski et al. 2005, Lafay-Cousin et al. 2009). With Proton beam therapy, a better delineation of the radiation field is possible, and irradiation of the hippocampi could thereby be avoided. This could potentially reduce the cognitive side effects, although it remains to be tested in a pediatric clinical trial (Blomstrand et al. 2012, Brodin et al. 2014). A study of hippocampal avoidance in whole brain radiotherapy in adults found significant (verbal) memory preservation compared to historical controls (Gondi et al. 2014). Also with conventional modern photon radiation, a reduction of the radiation field can improve cognitive outcome. In medulloblastoma treatment, the radiation boost field is nowadays restricted to the tumor bed (and not the entire posterior fossa), with positive effects on cognition (Moxon-Emre et al. 2014). As discussed previously, a lower radiation dose to the brain also reduces the cognitive late effects.

Hypothermia

Hypothermia is used in clinical pediatric practice to treat newborn infants with hypoxic-ischemic encephalopathy, and has in randomized controlled trials been reported to improve both neurological outcome and survival (Azzopardi et al. 2009, Jacobs et al. 2013). In hypoxic-ischemic

encephalopathy, post-insult hypothermia is neuroprotective through several different mechanisms that are also relevant after irradiation, including anti-apoptosis, anti-inflammation, and anti-oxidative mechanisms (Ma et al. 2012). Hypothermia has not been studied in children receiving radiotherapy. A previous rodent study indicated a possible protective effect on the neurogenic regions of the brain after irradiation, and inspired the study presented in **Paper IV**. Hyperthermia on the other hand, had detrimental effects on neurogenesis (Fukuda et al. 2005).

Cognitive training

In a small study by van´t Hooft and co-workers, children with acquired brain injury (including brain tumor patients) were randomized to regular cognitive (and metacognitive) training (daily 30-minute exercises in specific attention and memory techniques with a coach), vs control (doing a freely chosen daily interactive activity for 30 minutes). After a 17-week intervention, positive effects were found in measures of sustained and selective attention, as well as memory performance (van't Hooft et al. 2005, van't Hooft et al. 2007).

A larger randomized multi-center study examined the effects of a cognitive remediation program (20 two-hour sessions over 4-5 months), including cognitive and metacognitive training, on brain-irradiated childhood cancer patients and found a modest positive effect on academic achievement and parent-reported attention, but not in tests of selective attention, working memory or vigilance (Butler et al. 2008). A drawback was the substantial time commitment needed from all involved, with only 60% of participants in the intervention arm completing the entire program.

Computerized cognitive training

In a randomized, single-blind, waiting list controlled study, Conklin and coworkers evaluated a computerized intervention using Cogmed (http://www.cogmed.com), in 8-16 years old survivors of ALL (n=47) and childhood brain tumors (n=21) (Conklin et al. 2015). Cogmed is a computerized game-like intervention, where repetitive visual–spatial and verbal working memory exercises of graded difficulty are used. The intervention period consisted of 25 home-based sessions (30-45 min each), over 5 to 9 weeks, with weekly telephone-based coaching. Improvements from pre- to post-intervention tests were seen in measures of working memory, attention, processing speed and executive function, but not in academic fluency. (Conklin et al. 2015). Compliance was good at 88 %.

Video gaming

A large number of studies have reported improvements in various aspects of cognition from ordinary video (computer) gaming, including improvements in attention, information processing, task switching flexibility and visual processing (Powers et al. 2013). A cross-sectional study of video gaming showed that young adults who played computer games had better spatial and temporal visual attention, as well as increased visual attention capacity, compared to non-gamers (Green and Bavelier 2003). Furthermore, the non-gamers improved their visual attention capacity after training action video games for just 10 days, compared to a control group playing slower paced video games (Tetris) (Green and Bavelier 2003).

A longitudinal study in adults examined structural changes in the brain after 2 months of daily video gaming. (Kuhn et al. 2014). In this MRI-study, grey matter volume changes were observed between pre- and post-test and between experimental and control group, in the right hippocampus and right dorsolateral prefrontal cortex. Interestingly, a game with a prominent navigation component was used, and the cortical areas affected are thought to be involved in navigation. Changes were also seen in the cerebellum. Cognitive testing was however, not performed. (Kuhn et al. 2014). Another study compared different types of games and found that children playing action video games had shorter reaction times (without making more errors), compared to those playing non-action video games, and the authors concluded that action video gamers had enhanced attentional resources (Dye et al. 2009). There is however, some debate as to whether improvements seen are a result of bias due to study design flaws (e.g. differential recruitment bias in cross-sectional studies), or differential placebo effects, and also if the improvements are transferable to other tasks (Boot et al. 2008, Boot et al. 2011). Concerns also persist about whether video games foster aggression or addictive play (Calvert et al. 2017).

Active video gaming (exergaming)

In a Dutch study, children and young adults with acquired brain damage exercised using active video gaming (Nintendo Wii), for two hours per week for 12 weeks. Test results before and after were compared, and showed improvements in processing speed, attention, and response inhibition tests (de Kloet et al. 2012). A study of the effects of a single bout of physical activity studied different combinations of physical activity and cognitive engagement, and compared active video gaming to sedentary video gaming or watching a video (Best 2012). The physical activity level was found important for improving executive function, but with no added effect from increasing the cognitive engagement level (Best 2012). The authors

speculated however, that the activity chosen to deliver high physical activity but low cognitive engagement, could have been more cognitively demanding than intended. This speculation might be true, since a similar study found a significant improvement in executive function (cognitive flexibility) from cognitively engaging physical activity, compared to simple aerobic activity or control (Benzing et al. 2016). It should be noted that both studies examined the acute effects of exercise, and not the effects of long-term physical activity.

Physical activity

A positive correlation of physical exercise with better cognitive function, including executive function and memory, has been demonstrated in multiple studies, in both children and the elderly (Barnes et al. 2003, Colcombe et al. 2004, Etnier et al. 2006, Erickson et al. 2011). Some studies provide correlative evidence, others are cross-sectional studies and some are randomized intervention trials. A large cohort study on young adult men found a positive association between cardiovascular fitness and IQ, even after adjusting for relevant confounders (Åberg et al. 2009). A meta-analysis of randomized controlled trials in adults found aerobic exercise to be associated with modest improvements in attention, processing speed, executive function and memory, but not in working memory (Smith et al. 2010).

A study of pediatric brain tumor survivors investigated the relationship between cardiorespiratory fitness and executive functioning, and found a correlation between higher cardiovascular fitness and a more efficient brain activation pattern (measured with fMRI) during a working memory task (Wolfe et al. 2012). In a randomized study involving pediatric brain tumor survivors previously treated with radiotherapy, Riggs and coworkers found that aerobic exercise, (three 90-minute sessions per week for 12 consecutive weeks) increased the hippocampal volume, and specific white matter tracts (i.e. corpus callosum and cingulate gyrus) and decreased reaction times on tasks of attention, processing speed, and short-term memory (Riggs et al. 2016). Apart from the study presented in this thesis (**Paper II and III**), this is so far the only intervention study that has examined the effect of physical activity on cognition in pediatric brain tumor patients. However, several other studies have investigated the cognitive effects of physical activity in other pediatric populations.

In a study by Davis et al., sedentary overweight 7-11 year-olds (n=171) were randomized to a daily exercise program (20 or 40 min/day), or to a control group, for a duration of three months. A dose-response benefit from exercise on executive function (planning) and mathematical academic achievement

was found, but not in reading or attention (Davis et al. 2011). Schmidt and coworkers explored the impact of cognitive engagement during physical activity on cognitive outcome, by randomizing 10 to 12-year-olds to one of three different interventions. Group one performed team games with sudden rules changes (i.e. high level of physical activity + high level of cognitive engagement), group two did aerobic exercise (high level of physical activity + low level of cognitive engagement), and group three did a control activity (with low level of both physical activity and cognitive engagement) (Schmidt et al. 2015). The intervention lasted for six weeks with two exercise sessions per week. Interestingly, although the two high-level physical activities reached the same level of physical exertion, the team game group had a stronger improvement in certain aspects of executive function (shifting) but not in others (updating and inhibition), compared to the other two groups (Schmidt et al. 2015). A similar study in younger children (5-9 years old), also found a larger improvement in executive function (attention) when using a more cognitively challenging form of physical activity (Pesce et al. 2013).

A 9-year long intervention study randomized school children to either daily physical exercise in school (225 min/week, plus one hour per week of motor skills training to pupils with specific needs), or two days per week (90 min/week), and found a reduction in motor skills deficits from 47 % to 7 % and an increased proportion of pupils who qualified for upper secondary school, in the group with more physical education (Ericsson and Karlsson 2014). In a randomized controlled trial, 24 elementary schools were randomized to physical activity across the curriculum (PAAC) or control (Donnelly et al. 2009). The aim was to study the effect of exercise on body mass index (BMI), but as a secondary outcome academic achievement was also measured. The intervention consisted of 10-minute sessions of moderate to vigorous physical activity delivered intermittently throughout the school day (90 minutes per week) over three years. They found improved academic results in schools randomized to PAAC, but no effect on BMI (Donnelly et al. 2009). A randomized, primary school-based, pilot trial with healthy children, randomized between two hours per week of aerobically intense physical education vs normal physical education, and found significant improvements in tests for attention and working memory, but not for executive function (Fisher et al. 2011).

In a cross-sectional study comparing higher-fit with lower-fit children (8-10 years), the higher-fit children outperformed their lower-fit peers on a simulated real-world task: street crossing. Interestingly, the fitter children were not quicker at crossing streets than the less-fit children, but were less susceptible to distraction and made better decisions about when to cross

(Chaddock et al. 2011). In the Fitness Improves Thinking in Kids (FITKids) trial, 221 children (7-9 years old) were randomized to a 9-month after-school exercise program (for two hours each school day) or a waiting list control group (Hillman et al. 2014). Compared to the control group, the exercise group improved significantly in aerobic fitness, response accuracy, and cognitive flexibility, but not in reaction time. Improvements measured by neurophysiological changes (event-related brain potentials derived from EEGs) were also reported (Hillman et al. 2014).

Regarding the effects of physical activity on executive function, the majority of studies have been performed in the elderly, and fewer in children, adolescents and young adults (Verburgh et al. 2014). A meta-analysis of the effects of acute and chronic physical activity (chronic defined as 6-30 weeks) on executive function in children, adolescents and young adults, found a positive effect from acute exercise, but failed to find a significant overall effect from chronic exercise (Verburgh et al. 2014). However, only five (out of 24) studies evaluated chronic effects, and the authors concluded that more studies on the chronic effects of exercise were needed (Verburgh et al. 2014).

Pharmacological treatment

Methylphenidate is believed to enhance the function of the fronto-striatal attentional network, and is probably the most studied medication in pediatric attention deficit disorder (ADD) (Castellino et al. 2014). In children with ADD, methylphenidate can improve measures of vigilance, sustained attention, and reaction time (Chavez et al. 2009). There are a few studies of methylphenidate in children with brain tumors. Three of them have examined partly the same patient population: In a short-term (three weeks), randomized, double-blind, crossover trial, 40 ALL and 43 brain tumor patients received either placebo or methylphenidate in a low or moderate dose (0.3 or 0.6 mg/kg). Parents and teachers reported improvements in behavioral rating scores, and teachers (but not parents) reported improvements in social rating scores. Academic achievement was not evaluated (Mulhern et al. 2004a).

Before study entry in the three-week trial, potential patients had to demonstrate adequate medication tolerance in a separate 2-day, single-dose, double-blind, randomized, crossover trial between methylphenidate and placebo (Conklin et al. 2007). The 2-day trial included 122 children (61 brain tumor patients), and demonstrated improvement after methylphenidate in Stroop Word-Color Association Test (a measure of attention, cognitive flexibility, and processing speed) (Conklin et al. 2007). After completing the three-week trial, patients could enter a 12-month open-label trial (Conklin et

al. 2010). In this trial the control group (n=54) was recruited from cancer survivors that had been screened and found eligible for the previous trials, but either had declined participation in any medication phase, or had participated but discontinued the medication, or had been classified as non-responders (Conklin et al. 2010). Sixty-eight children and adolescents (6-18 years, 35 with malignant brain tumors, 33 with ALL) completed the 12-month treatment. The methylphenidate treated group demonstrated an improved performance in sustained attention, as well as on parent, teacher and self-report measures of attention, and also on parent report of behavior problems and social competencies. However, controls also showed improvements on parent report measures of attention, behavior problems, and social competencies. Neither group improved in IQ or academic skills (Conklin et al. 2010). A substantial rate of study termination due to medication side effects among brain tumor survivors has been reported, suggesting an increased vulnerability with methylphenidate in this patient population (Conklin et al. 2009).

A small, open-label, pilot study evaluated the feasibility, tolerance, and cognitive impact of the acetylcholinesterase inhibitor donepezil, in previously irradiated pediatric brain tumor patients, and reported improvements in tests of executive function and visual memory (Castellino et al. 2012).

Ecological

Last but not least, the child´s environment, especially in school, needs special attention in order to facilitate rehabilitation and learning. Since academic problems can appear soon after diagnosis, it is important that pedagogic interventions are instituted early after diagnosis (Mulhern and Butler 2004).

1.4.6 Effects of physical activity on cognition, potential mechanisms

Physical activity has several different effects on the brain, and the resulting positive effects on cognition are probably multifactorial. Enhanced hippocampal neurogenesis is one of the most reproducible effects of exercise in the rodent brain, resulting in improved learning in younger as well as older mice (van Praag 1999, van Praag 2005, Fabel et al. 2009). A running study in brain-irradiated mice, by Naylor et al., was the inspiration for the clinical study presented in **Paper II and III** (Naylor et al. 2008). It was found that voluntary running after brain irradiation improved hippocampal neurogenesis, with better neuronal integration of new neurons in the dentate gyrus, compared to a group of non-running mice (Naylor et al. 2008). The running mice also showed a more normal behavior compared to non-runners.

Running has been shown to increase the levels of neurotrophins (e.g. brain-derived neurotrophic factor, BDNF) in the hippocampus (Neeper et al. 1995), and also improve hippocampal blood perfusion (van Praag 2005). By using MRI-methods, an increase in cerebral blood flow in the dentate gyrus was demonstrated in humans within two weeks after exercise, seemingly corresponding to an exercise-induced increase in neurogenesis (Pereira et al. 2007). MRI measurements have also shown an increase in hippocampal size after 12 months of aerobic exercise training, in a randomized trial (walking vs stretching), involving older adults (Erickson et al. 2011). Cross-sectional MRI studies of children and adolescents have found some brain regions to be larger in higher-fit children compared to lower-fit children (Chaddock et al. 2010a, Chaddock et al. 2010b). These brain regions, the hippocampus and the striatum, are known to be important for declarative learning and habit learning and have been suggested to play a role in learning while multitasking (Foerde et al. 2006). In the previously mentioned study by Riggs et al., hippocampal size was normalized after exercise, in previously brain-irradiated children (Riggs et al. 2016).

Physical activity seems to improve long-term potentiation (i.e. give a persistent increase in synaptic strength between two neurons), and improve synaptic plasticity (Farmer et al. 2004). Evidence points to a positive effect on white matter structure from physical activity (Chaddock-Heyman et al. 2014, Riggs et al. 2016). Physical activity resulted in an increased efficiency of cognitive control networks in children, according to a cross-sectional study (Voss et al. 2011), a finding that was confirmed in a randomized longitudinal trial (Chaddock-Heyman et al. 2013). Furthermore, the combination of physical activity and cognitively challenging tasks (enriched environment) seems to have additive effects on hippocampal neurogenesis (Fabel et al. 2009).

2 AIMS

The overall aims of this thesis were twofold;

1) To describe and analyze relapses after treatment for standard risk medulloblastoma, aiming to find potentially successful treatments and to analyze the impact of clinical and biological factors on prognosis after relapse.

2) To explore ways to lessen the side effects of pediatric brain tumor treatment, especially the cognitive side effects.

3 PAPER I (MEDULLOBLASTOMA RELAPSE STUDY)

3.1 Specific aims for Paper I

The aims for **Paper I** were to:

1) Estimate the long term survival after treatment for standard risk medulloblastoma, in the HIT-SIOP PNET4 cohort.

2) Acquire detailed information on medulloblastoma relapse (diagnosis, site, and timing of relapse), relapse treatment and outcome after relapse in this cohort.

3.2 Materials and methods (Paper I)

In **Paper I**, all 338 patients in the randomized HIT-SIOP PNET4 trial (described above) were included and data collected on survival, as well as detailed information on all relapses and second malignant neoplasms (SMNs). Time of relapse was defined as the date of the MRI confirming the relapse. Central review of the MRI at relapse was performed in Germany, but in all other countries relapse was diagnosed at the treating centers. Detailed information on relapse site, reason for performing the MRI, and symptoms preceding relapse diagnosis was collected, as well as information on the treatment of relapses, intention of treatment (curative or palliative) and the date of death. Central review of tumor material was performed at the time of primary diagnosis. In addition, a series of molecular biomarkers (β-catenin nuclear accumulation, CTNNB1 exon 3 mutation, MYC and MYCN, Chromosome 17 alterations) were analyzed as part of the HIT-SIOP PNET4 study. (For further details see **Paper I**.) The study was approved by each national/institutional review board and all patients/parents/guardians had consented to participate.

3.2.1 Statistical methods

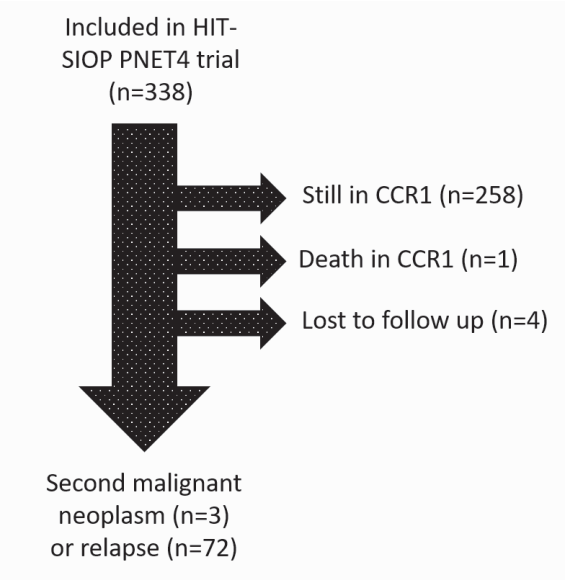
The probability of EFS and OS after relapse were estimated using the Kaplan–Meier method and differences in outcome between patients groups were tested using the Log Rank method. Relapse, SMN, death in remission, and death after relapse were defined as events. Comparisons of patient characteristics between subgroups were performed using Fisher's exact test, Chi square test or ANOVA where appropriate. Prognostic factors after

relapse were evaluated by using the Cox multivariate, proportional regression analysis. The significance level was set to p=0.05.

3.3 Results (Paper I)

Of the 338 patients in the HIT-SIOP PNET4 trial, 76 % were still in CCR1 when the database was frozen. The fate of the remaining patients is illustrated in figure 2. The 72 relapses were studied in detail.

Figure 2. The fate of patients included in the HIT-SIOP PNET4 trial. Adapted from ***Paper I***



3.3.1 Survival after primary treatment

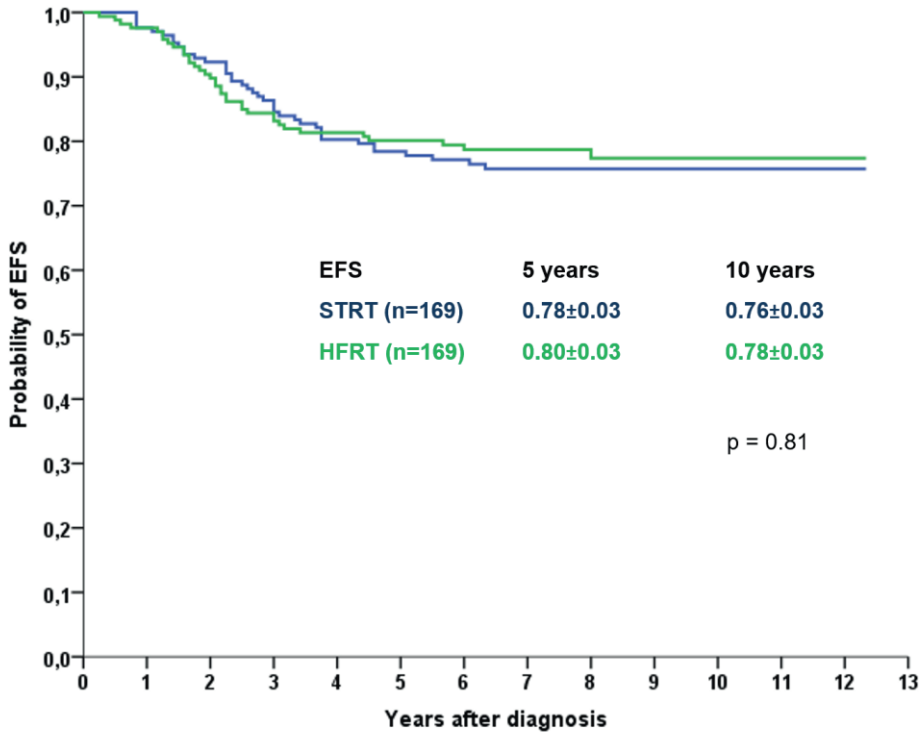
When the database was frozen, the patients in the HIT-SIOP PNET4 trial had been followed for a median 7.8 years after primary diagnosis. The 10-year probability of EFS and OS was 76 % and 78 % respectively. There was no difference in 10-year EFS between the two randomization arms (Figure 3).

3.3.2 Diagnosis of relapse

Diagnosis of relapse was made by craniospinal MRI in all 72 cases, with central review performed in 29/72 (40 %) of cases. Information on the reason for performing the MRI was available in 65 cases (90 %). In 45 patients (69 %), the relapse was diagnosed on surveillance MRI in an asymptomatic

patient. In the remaining 20 patients the MRI was preformed due to symptoms. No correlation was found between relapse diagnosis (surveillance MRI or symptoms) and histological variant, relapse pattern/site, or biological factors (MYC/MYCN, chr17 alterations, or β-catenin status). There was a trend for β-catenin nuclear positive relapses more commonly being diagnosed due to symptoms, compared to non-β-catenin positive tumors (p=0.090, Fisher´s exact test). About a quarter of recurrent tumors (17/72, 24 %), were histologically verified by biopsy or surgery.

Figure 3. Probability of event-free survival (EFS) in the two randomization arms of the HIT-SIOP PNET4 trial. STRT= standard radiotherapy, HFRT=hyperfractionated radiotherapy. From Sabel et al. 2016, ***Paper I***



3.3.3 Relapse site and timing of relapse

The majority of relapses 59/72 (82 %) were metastatic (all within the CNS), with or without involvement of the posterior fossa. Most metastatic relapses (47/59, 80 %) were multifocal, including cases with leptomeningeal dissemination. The remaining 12 metastatic cases were solitary metastases in

the brain (n=5) or spine (n=7). Thirteen patients (18 %) had an isolated local recurrence in the posterior fossa. In eighteen cases, recurrences were confined exclusively to the spine, without cranial manifestations. The majority (12/18, 67 %) of isolated spinal relapses were diagnosed by surveillance MRI, the remainder due to symptoms. Eight of the 18 MRIs (44 %) displaying an isolated spinal recurrence were centrally reviewed. Information on CSF cytology was known in 61/72 relapses (85 %), with malignant cells in 21 cases (34 %). All CSF-positive cases also had tumor manifestations visible on MRI.

The 72 relapses occurred at a mean/median of 30/26 months (range 2 to 95 months), from diagnosis. Six patients (8 %) had late recurrences, (>5 years from primary diagnosis), with one relapse occurring almost eight years after primary diagnosis. The majority of late recurrences, 5/6, were isolated relapses in PF (n=3) or spine (n=2). Regarding the anatomical distribution of early/late recurrences there was a trend for more isolated PF recurrences among the late relapses (p=0.07, Fisher's exact test). When comparing the randomization arms, there was no difference regarding the timing of relapses or relapse sites. The number of chemotherapy courses received in primary treatment ($\leq$ 4 compared to >4) had no impact on the frequency of relapses (p=0.398, Fisher's exact test).

3.3.4 Relapse in relation to histology and biology

At primary diagnosis, the tumors were classified as classic MB in 57 cases, DMB in 10, and LCA in five cases. There was no relation between histological subgroup and time in CCR1, localization of relapse, or survival after relapse. Some biological markers could be analyzed: β-catenin status by immunohistochemistry (IHC) was known in 80 % of tumors, with a nuclear positive pattern in 14 % of these. Nuclear β-catenin positive status had no impact on time in CCR1, localization, or survival after relapse. Of the eight nuclear β-catenin positive tumors that relapsed, four had other unfavorable risk factors, (such as age >16 years, delayed start of radiotherapy and/or residual primary tumor >1.5 cm^2). The status of Chr 17(im)/diploid background could be analyzed in 44 % (positive finding in 31 % of these), but was not found to be related to time in CCR1, localization, or survival after relapse. MYC/MYCN status was known in 33/72 (46 %) of cases, with only 3/33 MYCN amplified cases found (no MYC amplified).

3.3.5 Second malignant neoplasms

Three SMNs were reported as primary events. One patient had an anaplastic astrocytoma in the pons, one had a glioblastoma in the PF, and one patient

(with Li-Fraumeni syndrome) had a rhabdoid tumor in the abdomen. The SMNs occurred 61, 55 and 35 months after primary diagnosis, and all three patients died.

3.3.6 Relapse treatment

Data on treatment of the recurrent tumor was known in 71/72 cases. All but four patients received treatment for relapse. Conventional chemotherapy was used in the majority of relapses. Surgery was performed in 25 %, radiotherapy in 22 %, and HDSCR in 21 % of relapsed patients. Surgery was used more often in isolated PF relapses, but gross total resection was achieved in less than half of the procedures. HDSCR was also more commonly used in isolated PF relapses. Focal re-irradiation (20-45 Gy) was used to treat metastases located in the spine, supratentorial metastases or relapses in the PF. No patient was re-irradiated with CSI. Data on the use of intrathecal chemotherapy was available in 66/72 patients. Seventeen (26 %) received intrathecal chemotherapy. Of those with malignant cells in CSF (data known in 53/72), 9/21 (43 %) received intrathecal treatment. Five out of 32 without malignant cells in the CSF also received intrathecal therapy.

3.3.7 Survival after relapse

The 3- and 5-year OS after relapse was 20 % and 6 % respectively (Figure 4). The patients presenting with symptoms had a significantly shorter survival after relapse than those detected by surveillance MRI (median survival 12 months vs 19 months, $p< 0.01$), but the OS (after primary diagnosis) did not differ ($p= 0.21$, Log Rank test). An isolated local relapse, (i.e. in the posterior fossa), was associated with longer survival compared to all other relapse patterns ($p= 0.02$, figure 5). In Cox multivariate analysis, isolated posterior fossa relapse was associated with longer survival ($p< 0.01$), together with surgery ($p< 0.01$), but not treatment with RT ($p= 0.10$) or HDSCR ($p= 0.44$). When the data base was frozen, nine patients were still alive. The mean and median survival after relapse was 23 and 18 months respectively.

*Figure 4. Probability of survival (OS) after relapse. From **Paper I***

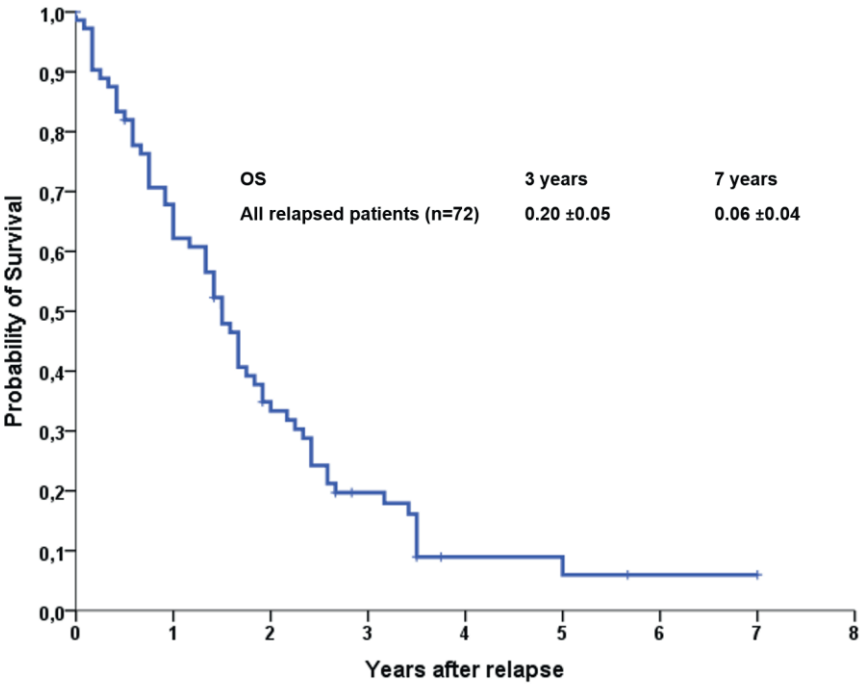
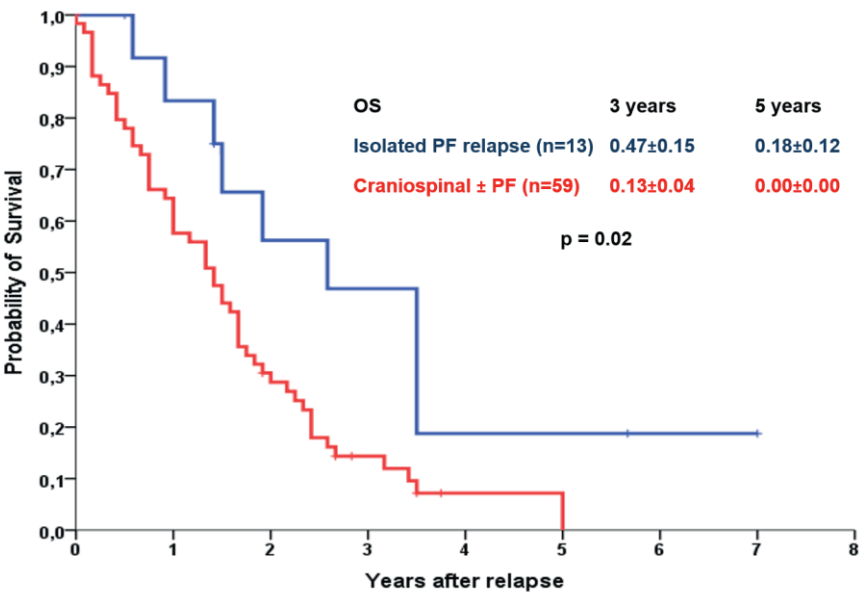


*Figure 5. Probability of survival after relapse in isolated posterior (PF) relapses and craniospinal ± PF relapses. From **Paper I***



3.4 Discussion (Paper I)

Survival after standard risk medulloblastoma

The majority of children diagnosed with standard risk medulloblastoma in the HIT-SIOP PNET4 trial are survivors, with 10-year EFS and OS around 80 %. Survival did not differ between treatment arms (STRT and HFRT), after a median follow up of 7.8 years. These results are comparable to the Children's Oncology Group (COG) A9961 study, another large randomized standard risk medulloblastoma trial, that reported a 10-year OS of 81.3 % which is very similar to the adjusted OS of 81 % in HIT-SIOP PNET4 (Packer et al. 2012). In both these studies, patients who were not optimally staged at primary diagnosis (due to incomplete/poor quality MRIs or no central review of MRIs), or had excess residual tumor (>1.5 cm^2) on review, had worse outcome. The latter observation might however be dependent on medulloblastoma subgroup. A retrospective analysis of 787 medulloblastoma patients, with radiographic central review as well as molecular subgrouping, concluded that the prognostic benefit of increased extent of resection was attenuated after MB subgroup was taken into account (Thompson et al. 2016). Only in Group 4 tumors a survival benefit from GTR was found, but not in WNT, SHH, or Group 3 tumors.

Impact of relapse site on prognosis

The majority of relapses reported in **Paper I** were metastatic within the CNS, with or without involvement of the posterior fossa, consistent with several previous reports (Bouffet et al. 1998, Pizer et al. 2011, Packer et al. 2012, Bode et al. 2014). In the paper from Bowers et al. however, a higher proportion of isolated local relapses (51 %) was reported, the remainder being metastatic (Bowers et al. 2007).

Isolated PF relapse (i.e. in the posterior fossa only) was found in 18 % of relapses and was associated with longer survival compared to all other relapse patterns. We found no difference in survival when comparing all *isolated* relapses (i.e. PF or non-PF) vs combined relapses. In contrast, Bouffet et al. found the opposite association, i.e. an isolated relapse was associated with better survival compared to a combined relapse, but a local PF relapse was not associated with longer survival compared to a distant or combined relapse (Bouffet et al. 1998). In line with our finding, Bowers et al. reported isolated PF relapse to be associated with longer survival (Bowers et al. 2007), and also Bode et al. found longer PFS in patients with localized PF

relapse compared to disseminated (Bode et al. 2014). Packer et al. found about the same frequency (20.6 %) of isolated PF relapses in the COG A9961 trial, but the prognostic impact of relapse site was not reported (Packer et al. 2012).

No extra-CNS metastases where reported neither in the HIT-SIOP PNET4 trial nor in the equally large COG-trial A9961 (Packer et al. 2012, Sabel et al. 2016). Such metastases, usually found in bone (but also in lymph nodes, liver and lungs) were reported quite frequently (in up to 18 % of relapses) when medulloblastomas were treated with surgery + radiotherapy but without chemotherapy (Kleinman et al. 1981). This relapse pattern now seem very rare, probably due to the addition of chemotherapy (Tarbell et al. 1991).

Median time to relapse and late relapses

We report in **Paper I** a median time to relapse of 26 months (mean 30 months). Bouffet et al. reported a shorter median time to relapse, 315 days from surgery (Bouffet et al. 1998). Other studies have reported a slightly longer median time to relapse, at 2.3-2.5 years (Pizer et al. 2011, Bode et al. 2014). Bowers et al. reported a *mean* interval of 1.9 years from primary diagnosis to relapse (Bowers et al. 2007).

Six of 72 (8.3 %) relapses in **Paper I** were late relapses (>5 years after primary diagnosis), which is comparable to previous reports. Others have reported 8.7 % and 10.3 % late relapses, defined as >4 or >5 years from primary diagnosis respectively (Bouffet et al. 1998, Packer et al. 2012). In the latter study a significant proportion of late relapses (57 %), were isolated relapses in the posterior fossa (Packer et al. 2012). A similar trend for late relapses more commonly being isolated posterior fossa relapses was found in the present study (**Paper I)**.

To summarize, the median time from primary diagnosis to relapse varies from 315 days to 2.5 years in different series, albeit in slightly different medulloblastoma populations. Late relapses (>4-5 years after primary diagnosis) are uncommon, but amount to 8-10 % of recurrences. A recent retrospective epidemiological study found the probability of dying from a neurological cause was <5 % eight years after medulloblastoma diagnosis, and stated that patients alive eight years after diagnosis are likely long-term survivors (Weil et al. 2017).

Survival after relapse

We report a median survival time after relapse of 1.5 years (mean 1.9 years), and a 5-year OS after relapse of 6 % (**Paper I)**. In the study by Bouffet and

coworkers, 44/46 patients died, and the median survival after relapse was only five months. The shorter survival might be explained by the inclusion of patients with high risk (metastatic) disease, and thus potentially more aggressive disease, at primary diagnosis (Bouffet et al. 1998). Others have reported a median OS of 1.6-1.8 years after relapse and a 5-year OS of 8.2 - 29.5% (Bowers et al. 2007, Pizer et al. 2011). The relatively high 5-year OS of 29.5 % in the study reported by Bowers et al, included only the 41 patients who received relapse treatment and excluded five patients that did not receive any treatment, and subsequently died shortly thereafter (Bowers et al. 2007). Furthermore, a substantial proportion of the patients had not previously received radiotherapy, which could explain the higher number of survivors (Bowers et al. 2007). Bode et al reported a median OS of 1.75 years (21.0 months) for the whole cohort (mainly recurrent medulloblastomas, but also including 12.5 % stPNET/pineoblastomas) (Bode et al. 2014).

Relapse prognosis in relation to histology and biology

The histological subgroup (at primary diagnosis) had no impact on time in first remission, relapse pattern, or survival after relapse. Since biopsy of the relapsed tumor was not performed in the majority of cases, we could only analyze histological and biological factors in the primary tumor. This is a limitation, since it has been demonstrated that significant biological changes can emerge between primary diagnosis and relapse, e.g. *MYC*-family gene amplifications or *TP53* pathway defects (Hill et al. 2015). The biological analyses were also limited by lack of remaining tumor material, and e.g. retrospective MB subgrouping could not be achieved other than the prospectively delineated WNT-MB group. It seems however, that MB subgroup remains stable between the tumor at diagnosis and at relapse (Ramaswamy et al. 2013, Hill et al. 2015).

Analysis of β-catenin status, Chr 17(im)/diploid background, and MYC/MYCN status did not reveal an impact on time in CCR1, localization of the recurrent tumor, or survival after relapse, but there was a limited number of cases in some biomarker subgroups. For example, there were only eight relapsed cases with β-catenin nuclear positive status (WNT-MB), but the prognosis after relapse was equally poor also for these tumors compared to non-WNT cases.

Diagnosis of relapse

Histological verification of the relapse diagnosis was achieved in a minority of cases. In the majority, diagnosis was based on MRI findings, sometimes together with CSF cytology. The majority of relapses (69%) were found on surveillance MRI in asymptomatic patients, and seemingly these patients had

a longer survival after relapse compared to patients diagnosed due to symptoms. This confirms findings in previous studies (Torres et al. 1994, Bouffet et al. 1998, Minn et al. 2001), but is probably due to the effect of lead time and length time bias. Eventually almost all patients died due to progressive disease, and there was no difference in OS (from primary diagnosis) between the diagnostic groups.

The role for surveillance MRI has been questioned, and especially so for spinal MRIs, since isolated spinal relapse without concurrent findings on cranial MRI has been described as rare (or absent) in previous studies (Saunders et al. 2003, Bartels et al. 2006, Perreault et al. 2014). It should be noted however, in the study by Saunders and coworkers, a spinal MRI was included in the surveillance protocol only if the patient had disseminated disease at primary diagnosis or when a recurrence was detected by cranial MRI, which might explain the absence of isolated spinal relapses (Saunders et al. 2003). Perreault and coworkers found 4/27 (14.8 %) isolated spinal relapses when reviewing the surveillance MRIs of 89 medulloblastoma patients (Perreault et al. 2014). In **Paper I**, 17 % of relapses were both asymptomatic and confined only to the spine. Six more isolated spinal relapses were diagnosed due to symptoms. A substantial number (44 %) of MRIs diagnosing these isolated spinal relapse were centrally reviewed, indicating that this relapse pattern occasionally occurs. The detection rate of isolated spinal recurrences is however low, and has been estimated to 7/1000 MRIs (Perreault et al. 2014). Considering the poor prognosis after medulloblastoma relapse, the benefit of early discovery of relapse by surveillance MRI remains unclear, but could be justified in the perspective of possible inclusion in a relapse study.

Second malignant neoplasms

The number of SMNs (n=3) in **Paper I** is somewhat lower than expected. The equally sized COG A9961 study reported fifteen cases, albeit with almost two years longer (median) follow up (Packer et al. 2012). More SMNs should therefore be expected with time. Given the fairly low frequency of tumor biopsies performed at relapse, some SMNs might have been misdiagnosed as relapses, something that also might explain the low number of SMNs in **Paper I**.

Relapse treatment

All but four patients received some form of treatment for the recurrent tumor, most commonly chemotherapy. Since there was no common relapse protocol, the treatments used in **Paper I** varied significantly. This makes it difficult to draw any firm conclusions, e.g. regarding the efficacy of specific

chemotherapy regimens, and the results should be interpreted with caution. No patients received antiangiogenic/metronomic therapy according to the currently on-going MEMMAT or COMBAT trials (Sterba et al. 2010, Peyrl et al. 2012).

There was a fairly low usage of intrathecal chemotherapy (17/66, 26 %) considering that 82 % of patients had a metastatic relapse. Different intrathecal drugs were used, and the role of intrathecal chemotherapy in recurrent medulloblastoma was difficult to evaluate. Only 43 % (9/21) of patients with positive CSF cytology received intrathecal chemotherapy.

Both HDSCR and surgery were more likely to be used in isolated PF relapses, the relapse pattern associated with the longest OS after relapse. We found no benefit of HDSCR however (used in 21 % of all cases), or focal re-irradiation (22 % of cases), whereas surgery was associated with longer OS after relapse. Even though gross total resection was obtained in < 50 % of procedures, surgery should be considered in selected cases. This in light of the positive impact on prognosis, but also due to the value of obtaining tumor tissue for diagnosis and biological studies.

Strengths and limitations

One of the strengths with the study is the long-time follow up of a large cohort of standard risk medulloblastoma patients, treated according to the same protocol in multiple centers across Europe. This reduced bias from treatment at single/few (tertiary) centers and also selection bias. The study shows the outcome of relapse treatment without the use of a common relapse protocol and gives a survival curve based on a variety of treatments to which future studies could be compared.

The study has limitations, e.g. the lack of consistent central review of MRIs at relapse. Patients were considered to have relapse or secondary tumors based on institutional determinations, less than half of MRIs were centrally reviewed. The importance of central review has been shown e.g. in the COG A9961 study, where central review after the trial found “unequivocal evidence of residual or metastatic disease” in 30/409 (7.3 %) of included patients; a misclassification that resulted in under-treatment of these high risk patients, and subsequently poorer survival (Packer et al. 2006). In **Paper I** a central review of all MRIs at relapse would have been ideal, but this was deemed not feasible given the high number of treatment centers and difficulties in retrospectively retrieving the MRIs.

Another limitation of the study is the low frequency of tumor biopsy at relapse, 24 %. This low frequency is perhaps understandable, since MRI often is considered sufficient for relapse diagnosis and a biopsy of a CNS tumor is no trivial procedure. A biopsy in a patient who is unlikely to be cured also raises ethical concerns, since (unnecessary) surgery could potentially lead to further morbidity. Furthermore, the result of the histopathological/biological analysis is not (at present) used to guide relapse treatment. On the other hand, not performing biopsies can lead to misdiagnosis of a SMN as a medulloblastoma relapse, something that could lead to incorrect therapy. Radiation necrosis, unspecific contrast enhancing nodules in the radiation field, and even infections can sometimes mimic recurrent tumor on MRI (Muscal et al. 2009, Fisher et al. 2012, Weintraub et al. 2014). MRI spectroscopy, MRI perfusion and PET can sometimes be of help in the differential diagnosis, but histological confirmation should be used more frequently. Furthermore, if targeted therapy is considered for treatment of recurrent tumors, it is vital to look for the target in the recurrent tumor, not only in the primary tumor, since the target might have disappeared during clonal evolution (Morrissy et al. 2016).

4 PAPER II AND III (ACTIVE VIDEO GAMING STUDY)

4.1 Specific aims for Paper II and III

To evaluate if regular, home-based active video gaming (AVG) (with online coaching), could be used to achieve regular, enjoyable, physical exercise in children treated for brain tumors and to:

1) Explore the effect of the intervention on physical activity levels, during gaming sessions, and overall (**Paper II**).

2) Evaluate compliance to the intervention over time, as well as the general feasibility of the method (**Paper II**).

3) Explore the effect on cognitive function (**Paper III**).

4) Investigate the effect on motor function (**Paper II**).

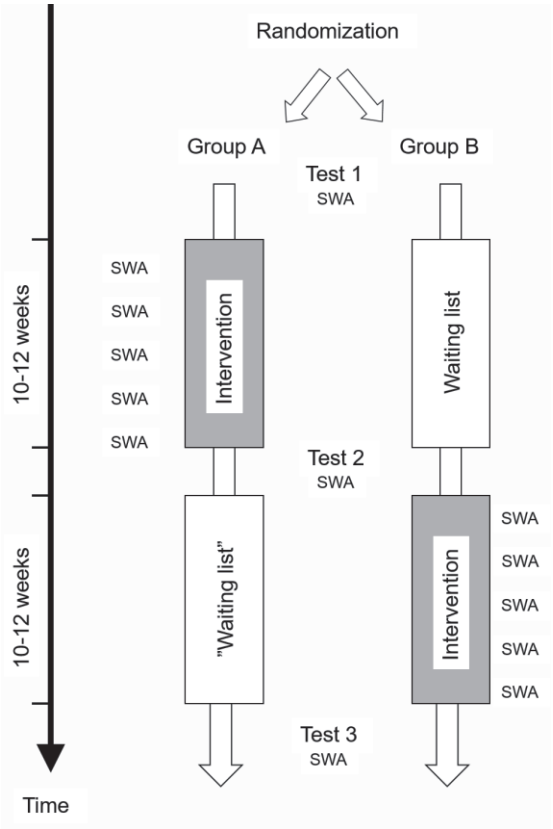
5) Investigate the effect on the performance of activities of daily living (ADL) (**Paper III**).

4.2 Material and methods (Paper II and III)

Inclusion and exclusion criteria

Children, 7-17 years old, who had completed treatment for a brain tumor between one and five years earlier, were eligible for inclusion. Previous treatment with cranial radiotherapy was mandatory, but treatment combinations including surgery and/or chemotherapy were allowed. The cut-off of one year was chosen to reduce the risk of tumor relapse occurring during the study period, and the five year cut-off was arbitrarily chosen. Patients were excluded if not in clinical remission, if they were in a medically unstable situation (e.g. tumor progression), or if they had another medical or behavioral condition making them unable to understand or complete the intervention or assessment measures, e.g. severe motor/sensory deficits. Patients with conditions that could be worsened by the intervention, such as photosensitive epilepsy, were also not allowed to participate. Participants had to speak Swedish. The study was approved by the Regional Ethical Review Board in Gothenburg.

Figure 6. Study design. (SWA: SenseWearPro2 Armband measurements for one week)



Study design

Participants were randomized to either start with the intervention period (intervention group) or a waiting list period (control group) (Figure 6). The intervention consisted of AVG for 10 weeks, aiming for a minimum of 30 minutes of AVG per day at least five days a week, and weekly coaching sessions. An extension of the period from 10 up to 12 weeks was allowed, to compensate for weeks being away or ill. During the waiting list period the participants were asked to refrain from AVG but otherwise live their life as normal. Other possible treatments, e.g. physiotherapy or occupational therapy, could continue as before during both the intervention period and the waiting list period, although this was not registered. At half-time the groups crossed over. All participants were tested at three time points, before and after each period (Figure 6). All testers were blinded to the allocated

randomization group. Tests included cognitive tests, assessments of motor function and execution of ADL. Physical activity levels were recorded continuously for one week at baseline, and every second week during the AVG period (see below).

Randomization by minimization

The minimization method was used to randomize between treatment groups (Altman and Bland 2005). With the minimization method, the randomization group allocated to the next study participant depends partly on the characteristics of those participants already enrolled, thus minimizing the imbalance between the groups across multiple factors. The groups were balanced for the following variables: sex, age at randomization, age at radiotherapy, age group (7-13 years or >13 years), and type of radiotherapy (focal vs craniospinal).

Gaming equipment and games

An off-the-shelf motion-controlled video console, the Nintendo Wii (Nintendo Co. Ltd., Kyoto, Japan), was used for active video gaming. The Wii is controlled by one or two hand-held remote controls, and requires movement to play the games. Each child received two pairs of controls, which enabled them to play with friends, and a balance board, the Wii Fit. The balance board was used for balance games, as well as some aerobic type games. The games were pre-tested by the investigators and chosen mainly to stimulate physical activity and gross body movements, but also included less physically demanding games such as balance games. Since the intensity of the games varied, participants were instructed to start every session with a physically more demanding game for at least 10 minutes, before considering switching to a slower paced game. The participant did not get access to all games from the start. Instead new games were introduced throughout the intervention period. This was done by the coach, in dialogue with the participant, to increase motivation and reduce attrition. The following games were used: Wii Sports (13/13 participants), Wii Sports Resort (13/13), Wii Fit (13/13) and Wii Fit plus (11/13). Several dance games were also used: Just Dance 1–3 (12/13) and Michael Jackson – the Experience (5/13).

Home visits were done at the start and end of the intervention period. During the first home visit, the study coach and a technician installed and tried out the equipment together with the family, and the participant performed a familiarization gaming session. The participants also created their own unique Wii avatar and were instructed not to let anyone else use it. At the end of the intervention period all equipment was collected.

Monitoring of energy expenditure and gaming time

To register energy expenditure (EE) levels, participants wore a multisensory activity monitor, the SenseWearPro2 Armband (SWA) (BodyMedia Inc., Pittsburgh, PA, USA), continuously (daytime) for one week at baseline, and every second week during the intervention period (Figure 6). The SWA is attached as an armband, with the sensor touching the skin on the backside of the upper right arm. It registers input from multiple physiological sensors (skin temperature, near-body temperature, heat flux, galvanic skin response and a biaxial accelerometer). It is powered by one AAA battery for up to 14 days and has a data storage capacity of 10 days. Since it is not water proof it cannot be worn during water-based activities.

With the assistance of the parents, registered SWA data were uploaded to a secure server at the end of each recording week. Data from these recordings, together with information on the participant´s age, sex, weight and height, were used to estimate EE levels, using the SenseWear Professional Software (version 6.1 with algorithms 2.2). The EE levels were presented as Metabolic Equivalent of Task (MET). The MET, or just metabolic equivalent, is a physiological measure of the energy cost of physical activity. It is defined as the ratio of the metabolic rate during a specific activity to the resting metabolic rate (Ridley and Olds 2008, Ainsworth et al. 2011). The metabolic rate during rest is assigned MET=1 and, e.g. an activity with the MET-value 3, would require three times the energy consumption compared to rest. To assess time spent at different EE levels, the following cut-off points were used:

- Sedentary = MET < 1.5
- Light physical activity = MET 1.5–2.9
- Moderate physical activity = MET 3.0–5.9
- Vigorous physical activity = MET > 6.0

These are cut-off points previously defined for adults, but found to be similar for physical activities in children (Ridley and Olds 2008). The amount of moderate physical activity is often combined with vigorous physical activity, and presented as MVPA (moderate and vigorous physical activity). The SWA and software have been validated for total EE in children, both for activities under controlled laboratory conditions (Arvidsson et al. 2007, Arvidsson et al. 2009b, Lee et al. 2014), and under everyday living conditions (Arvidsson et al. 2009a, Calabró et al. 2013).

The participants registered the date, start- and stop times of each gaming session in a gaming diary. In addition, the Wii console recorded how much

time was spent playing each game on any given day, and by which avatar (player). We expected that this information could replace a detailed gaming diary and used these data to compare the playing time noted by the participants in the gaming diary, to the gaming time recorded in the console. Before and after the intervention period, parents and children were interviewed about the children's leisure time activities, especially the amount of regular physical exercise.

Comment: The SWA has a "time stamp" button which we initially thought could be used to mark the start- and stop times of gaming sessions. However, there is no indication on the armband itself showing if the button has been pressed or not, which turned out to be a problem. The participant often forgot to press it, or forgot he/she had already pressed it and thus pressed it again, inadvertently indicating a session stop. Fortunately, this was quickly discovered and the "time stamp" was replaced with the gaming diary. A more detailed gaming diary, (e.g. including specific games played), would have been ideal but also more cumbersome for the participants, and we therefore settled for just start and stop times. As described above, the Wii console automatically records gaming time and games used, but this registration has several limitations. Most Wii games consist of several sub-games. These different games require varying levels of physical activity to be played. The console only records the main game inserted into the console, and gives no information on the different sub-games used. Furthermore, it records the time a specific avatar (gamer) is logged in, but if you forget to log off at the end of the session (and leave the console on), the registration continues, and logs a falsely long gaming time. To associate MET levels to specific sub-games, or extracting the active gaming time solely from console data, was therefore not possible. It could however be used to confirm that entries in the gaming diary were correct.

Coaching during the intervention period

Coaching was used during the intervention period to encourage participants, and maintain compliance, and to check that study instructions were being followed (Hayes and Kalmakis 2007). To provide some background information, participants completed two surveys before the first coaching session: one about school, friends and interests and one about how they usually spend their leisure time. Coaching was performed mainly by the same research nurse, over the Internet, using laptops with communications software (Adobe Connect Pro, Adobe Systems Inc., San Jose, CA), webcams, and headsets. During the weekly coaching sessions, the coach performed semi-structured interviews with the child regarding the past week's AVG sessions. The coach encouraged the participants to perform the AVG,

maintaining an optimistic attitude, and also challenged the child to try new games and/or to compete. No coaching was performed during the waiting list period.

Cognitive assessment

The cognitive tests were selected in close collaboration with a psychologist experienced in evaluating children with cognitive difficulties after brain tumor treatment. Tests were chosen to cover the areas most commonly affected, including IQ, attention (selective, sustained and visual), working memory (verbal and visual-spatial), memory, verbal learning, executive function, processing speed, and social ability. For a full description of tests used, including references, see Supplement table I in **Paper III**. In short, the tests were:

- **Wechsler Intelligence Scale for Children (WISC-IV).** A measure of IQ was computed from an abbreviated version of WISC-IV, using four subtests: digit span, similarities, block design, and coding B.
- **Conners' Continuous Performance Test II (CPT II)** *(Sustained Attention).*
- **Map Mission,** a subtest from the Test of Everyday Attention for children *(Selective attention).*
- **Visual Scanning**, a subtest in the Trail Making Test version of the Delis-Kaplan Executive Function System (D-KEFS) test battery of executive functions *(Visual attention).*
- The **Digit Span** subtest of the Wechsler Intelligence Scale for Children-version IV (WISC–IV) *(Verbal short-term/ working memory/general working memory).*
- **Auditory Consonant Trigrams (ACT)** *(Verbal working memory).*
- **Spatial Span,** a subtest from the Wechsler Nonverbal Scale of Abilities *(Spatial working memory).*
- **Rey Auditory Verbal Learning Test (RAVLT)** *(Immediate memory, verbal long-term memory and learning).*
- The subtest **Information** from WISC-IV *(General knowledge).*
- **Rey Complex Figure Test** *(Visual-spatial memory).*
- **Coding,** a subtest from the WISC-IV *(Processing speed and implicit learning).*
- The **Controlled Oral Word Association Test (COWAT)** *(Executive function – Verbal fluency).*

- **Stroop Test**, Victoria version *(Executive function).*
- The **Trail Making Test** from D-KEFS *(Executive function).*
- **Picture Arrangement,** a subtest from the Wechsler Nonverbal Scale of Abilities *(Social ability).*

The cognitive tests were administrated in a quiet room, usually at the hospital, by a trained psychologist. Their order of presentation was designed to facilitate the child's engagement, (with easy tests at the beginning), and to avoid the risk of interference in the period between immediate and delayed recall of Rey Auditory Verbal Learning Test and Rey Complex Figure Test. The test battery was delivered in five sets, with four small pauses, to allow the child to recover. Three tests had alternative forms available: Map Mission, Rey Auditory Verbal Learning Test and Rey Complex Figure Test. For these tests, the original form was presented at the first and third assessments whereas the alternative form was presented at the second assessment session.

Assessment of motor performance

Assessments of physical functioning were done at the hospital's physiotherapy department by an experienced physiotherapist, using the complete form of the Bruininks–Osteretsky Test of Motor Performance, Second Edition (BOT-2) (Bruininks and Bruininks 2005). BOT-2 is designed to characterize motor performance and measures fine and gross motor skills in patients, 4–21 years of age. The BOT-2 has moderate to high inter-rater and test–retest reliabilities in children (Bruininks and Bruininks 2005, Wuang and Su 2009). It has been used in studies in pediatric neurological populations as well as pediatric oncological conditions, including brain tumors (Johnson et al. 2010, Dahl and Emanuelson 2013, De Luca et al. 2013, Piscione et al. 2014).

BOT-2 has 58 items with eight subscales, which are combined into four motor area composite scores:

- **Fine Manual Control** (includes the subscales Fine Motor Precision and Fine Motor Integration),
- **Manual Coordination** (includes Manual Dexterity and Upper-Limb Coordination),
- **Body Coordination** (includes Bilateral Coordination and Balance), and
- **Strength and Agility** (includes Running Speed and Agility and Strength)

Assessment of the execution of ADL

To evaluate the ability to perform both personal and instrumental ADL we used the Assessment of Motor and Process Skills (AMPS) (Fisher and Jones 2012). The evaluations took place in each participant's home. AMPS measures the quality of a person's performance during ADL tasks. An AMPS-trained and calibrated rater (calibrated to compensate for harshness or softness in the judgment of performance) scores performance in two tasks according to explicit, specific criteria, using a 4-point ordinal scale; (1=unacceptable performance, 2=ineffective, 3=questionable, 4=competent). Tasks are selected from the AMPS collection of analyzed tasks (e.g. setting the dinner table for four, or making a fruit salad), and should be familiar to the person tested and identified by him or her as presenting problems in everyday life.

During the execution of the tasks, the rater evaluates and scores 16 motor skills and 20 process skills. Motor skills are observable actions used to move oneself and objects within a task environment, and process skills refer to the observable actions of a person to organize and adapt task actions to prevent or overcome problems while performing a functional task (e.g. searching, locating, and gathering needed objects; initiating, sequencing, and terminating actions appropriately). Raw scores are adjusted for the difficulty of the performed task and the severity of the examiner, and converted to a linear measure of motor and process skills using many-facet Rasch analysis, and are expressed as interval-scaled log-odds probability units (logits) (Fisher 1993, Linacre 1994). This was done using the AMPS software, version 2005. A higher ADL motor or ADL process ability measure indicates that the individual is more able.

AMPS has been validated for use in Sweden (Bernspång and Fisher 1995). Several studies of the psychometric properties of AMPS, in different populations, age groups and settings, suggest that it is well suited to both clinical and research applications (Fisher et al. 1992, Dickerson and Fisher 1993, Gantschnig et al. 2013).

4.2.1 Statistical methods

To detect a mean difference of 1 SD between the two randomized groups, with a power of 80 % and an alpha of 0.05, a sample size of 34 was estimated. We expected this number to be difficult to achieve, given the population base and the rarity of the underlying condition, and therefore designed an exploratory study with a pseudo crossover design. This design allowed us to evaluate all children´s performance before and after the

intervention period (within-subjects design), as well as to compare the randomized groups after the first period (parallel group analysis). Since a carry-over effect from the intervention period could not be excluded, we choose not to do a conventional crossover analysis.

As a primary analysis we performed Fisher's paired non-parametric permutation test of the change in outcome variables during the intervention period, for all individuals (Good 2000). A parallel group analysis was done as a sensitivity analysis, comparing the change in outcome variables during the first period, between the randomized groups. We used analysis of covariance (ANCOVA) to adjust for the baseline values, with randomization group and baseline scores as independent variables.

A secondary analysis, measuring the correlation between activity levels and gaming time and the change in outcome variables, was performed using Pitman´s non-parametric permutation test (Good 2000), and described with Pearson correlation coefficient. To calculate the effect sizes (in **Paper III**) we used the Standardized Response Mean (SRM), i.e. the ratio between the mean change score and the standard deviation of that change score within the same group.

To compare the distribution between the randomization groups we used unpaired t-test for continuous variables and Fisher´s exact test for categorical. Wilcoxon signed ranks test was performed to compare EE levels (METs) at baseline with measurements from the intervention period. To allow comparison of activity levels regardless of SWA wearing time, the daily duration of different activity levels were first normalized to 14 hours of SWA-wearing. This procedure was also used for comparing active video gaming time between different time periods of the intervention.

To further describe the patient group and allow comparison of BOT-2 and AMPS results to previous publications and normative data we also, post-hoc, calculated the Z scores for theses variables. For comparison with normative data we used one-sample t-test. Post-hoc analyses were done using SPSS statistics for Windows (version 20, IBM Corp., Armonk, NY, USA). All other analyses were done using SAS Software (version 9.3, SAS Institute, Cary, NC, USA). All test were two-sided, and were based on the intention to treat (ITT) population. For between-group analyses, the significance level was set to $p=0.05$, but for comparisons to normative data, the significance level was reduced to $p=0.01$ due to multiple comparisons.

4.3 Results (Paper II and III)

All patients in Western Sweden diagnosed with a brain tumor after 2003, who had received radiotherapy and were < 17 years at the start of the study (n=33), were identified through the Swedish Childhood Cancer Registry and hospital records. Six had been off treatment for more than five years, four were too young (< 7 years), four were receiving treatment for a recurrence, two could not speak Swedish and one was excluded because of autism. Sixteen patients, fulfilling all criteria, were identified. Three declined to participate.

The demographics and randomization results are presented in Table 3. Ten of 13 had been treated for high grade (malignant) tumors. The remaining three had midline supratentorial low grade astrocytomas, not amenable for surgical removal. The mean time from radiotherapy to randomization was 4.4 years (median 4.2, range 1-12.3 years), and did not differ between the groups (p=0.76). The mean IQ score was > 1 SD below the population mean, at 76.8 (median 77, range 63-90). There was no difference between groups regarding age, sex, tumor location, treatment, and baseline IQ score, or previous Wii experience (Table 3).

4.3.1 Compliance and gaming time

All included children (n=13) completed the trial. The mean gaming session lasted 47 minutes (median 38 min). The intervention period (10-12 weeks) lasted for mean 71 days (median 70 days, range 60-82), and the participants performed active video gaming on mean (=median) 51 days (72 % of available days). The preset target of active video gaming on at least five out of seven days per week was reached (or surpassed) by ten children, who were within 95 % of the target frequency (or above). Three children reached between 75-89 % of the target frequency. Compliance was generally good. The main reasons for non-compliance were illness or travel.

When splitting the intervention period in five equal parts (P1-P5) and comparing the AVG frequency, the most frequent active video gaming was seen in the first fifth of the intervention period, with AVG performed on mean 5.8 days per week. After this intense start the AVG frequency dropped significantly, to mean 4.7 days/week (p=0.01, Wilcoxon signed ranks test), but recovered during the following weeks to 5.2 days/week and remained stable for the remainder of the intervention period.

*Table 3. Demographics and randomization results. (Adapted from **Paper II** and **Paper III**)*

Characteristic	All (n=13)	Randomization group: Intervention first (n=7)	Randomization group: Waiting list first (n=6)	p-value
Age at randomization, y	12.5 (2.9)	11.9 (3.6)	13.2 (1.9)	0.43
Sex				
M/F	6/7 (46/54 %)	3/4 (43/57 %)	3/3 (50/50 %)	1.0
Tumor type		Anaplastic astrocytoma Germinoma (x2) Medulloblastoma Central Pilocytic astrocytoma (x2) ST-PNET	Choroid plexus carcinoma Germinoma Medulloblastoma (x2) Central Pilocytic astrocytoma ST-PNET	
Tumor location				
PF/ST	3/10 (23/77 %)	1/6 (14/86 %)	2/4 (33/67 %)	0.56
Type of RT				
Focal/CSI	3/10 (23/77 %)	2/5 (29/71 %)	1/5 (17/83 %)	1.0
Age at RT	8.4 (2.6)	8.0 (3.4)	8.9 (1.6)	0.53
Neurosurgery	9 (69 %)	4 (57 %)	5 (83 %)	0.56
Chemotherapy	12 (92 %)	6 (85 %)	6 (100 %)	1.0
VP shunt	4 (31 %)	2 (29 %)	2(33 %)	1.0
Baseline IQ	76.8 (8.0)	77.3 (10.2)	76.2 (5.4)	0.81
Previous Wii experience	7 (54 %)	4 (57 %)	3 (50 %)	1.0
Regular weekly physical activity	5 (38 %)	2 (29 %)	3 (50 %)	0.59

For categorical variables n (%) is presented. For continuous variables Mean (SD) is presented. CSI craniospinal irradiation, PF Posterior fossa, PNET Primitive neuroectodermal tumor, RT radiotherapy, ST Supratentorial. Continuous variables analyzed with unpaired t-test, categorical with Fisher´s exact test, both two-sided, comparing randomization groups.

4.3.2 Energy expenditure levels

The AVG frequency pattern described above (in section 4.3.1), with the most intensive active video gaming in the first fifth of the intervention, was also

evident when analyzing SWA measurements. During the initial weeks (P1), the sedentary time (MET < 1.5) decreased by 14 % compared to baseline (p=0.004 Wilcoxon signed ranks test), but slowly rose to baseline levels thereafter. There was a trend for an increase in MVPA from mean (median) 115 (110) min/day to 139 (116) min/day (p=0.099 Wilcoxon signed ranks test) during P1, but for the remainder of the intervention there was no change compared to baseline.

The overall mean daily EE level was not affected by the intervention (1.9 MET at baseline and 2.0 during AVG weeks, n.s.). The mean daily MET value increased during the intervention period (compared to baseline) in six children, was unchanged in five and decreased in two, although these changes were not statistically significant. Five children performed other types of regular physical exercise, and only one in this group increased the daily mean MET value (one decreased and three remained at the same level). In the remaining eight children, without other regular physical exercise, five increased their daily MET value, in one case it decreased and for the remaining two it did not change. The mean physical activity level during AVG sessions was of moderate intensity, at mean 3.0 MET (median 3.0, range 1.2-5.7).

4.3.3 Internet coaching and technical issues

The mean (and median) number of coaching sessions during the intervention period was 10 (range 8–11), usually once a week, with a mean duration of 18 minutes. It is our impression that weekly coaching sessions helped the participants to continue with the study, and it enabled the coach to respond quickly to signs of attrition, by e.g. introducing a new game, or to help with technical problems. The participants rated 36 % of the gaming weeks as ‘‘fun’’, 52 % as ‘‘OK’’, and 2 % as ‘‘boring’’. No enjoyment data were registered in 10 % of the gaming weeks.

The AVG equipment itself did not cause any substantial technical problems. The children managed to both play and connect to the Internet with little or no help from their parents. Most technical difficulties were related to the on-line coaching sessions but the great majority of coaching sessions (89 %) were performed as planned; however, 11 % had major technical problems. In these cases coaching was done over the telephone. When functioning as intended, coaching through video conferencing rather than over the telephone had several advantages, such as mutual facial contact and making it possible to instruct also with gestures. If the coaching would have taken place at the

participant´s home (or at the hospital), a weekly return trip to each participant would have amounted to over 1900 km of travelling per week.

4.3.4 Effects on cognitive test results

There was no significant change in cognitive test results between tests before and after the intervention period (see **Paper III** for details). There were trends for improvement in sustained attention (CPT-II omission, T-score) by mean -8.9 (lower score=better; p=0.090; 95 % CI -21.8 to 4.1) and selective attention (Map-mission) by mean 0.9 standard points, (p=0.078; 95% CI -0.02 to 1.9). The improvement in sustained attention was positively correlated to the total active video gaming time (r=0.61, p=0.047) but showed no correlation to energy expenditure (MET) parameters. No correlation was found between selective attention and active video gaming time or MET-levels.

4.3.5 Effects on physical functioning

At baseline, the participating children had significantly decreased performance (Z scores) compared to norms in the following BOT-2 composite scores:

Manual Coordination (mean Z score -1.0, 95 % CI -1.6 to -0.4, p=0.0042)

Body Coordination (mean Z score -0.9, 95 % CI -1.4 to -0.4, p=0.0006)

Strength and Agility (mean Z score -0.9, 95 % CI -1.6 to -0.3, p=0.0062)

Performance in Fine Manual Control (and the corresponding sub-tests) was normal. The reduced performance in Manual Coordination corresponded to a reduced performance in the sub-test Manual Dexterity (mean Z score -1.0, 95 % CI -1.5 to -0.6, p=0.0007), but not Upper-limb Coordination. The decreased performance in Body Coordination corresponded to a reduced Balance score (mean Z score -1.2, 95 % CI -1.9 to -0.6, p=0.002) whereas the Bilateral Coordination score was within norms (mean Z score -0.4, 95 % CI -0.8 to 0.10, p=0.11). Finally, the sub-tests making up the composite score Strength and Agility were both sub-normal, i.e. Running Speed and Agility (mean Z score -1.0, 95 % CI -1.7 to -0.3, p=0.007) and Strength (mean Z score -0.9, 95 % CI -1.4 to -0.4, p=0.003). Over the intervention period (within-subjects analysis), the Body Coordination score improved by 15 %, (mean improvement 4.55 scale score points, 95 % CI 0.45 to 8.64, p=0.021). An analysis of the sub-scores forming the Body Coordination score, revealed a statistically significant 17% improvement in the Bilateral Coordination

score over the intervention period, (mean improvement 2.18, 95 % CI 0.31 to 4.05, p=0.047), but no change in Balance score. Regarding Body Coordination, the statistical significance was lost in the parallel group analysis (mean improvement 4.13 scale score points, 95 % CI -4.06 to 12.33, p=0.28).

4.3.6 Effects on ADL performance

At baseline, the participating children had significantly reduced Z scores compared to norms in both AMPS motor score (mean Z score -1.7; 95 % CI -2.5 to -0.93, P=0.001), and AMPS process score (mean Z score -1.1; 95 % CI -1.8 to -0.45, p=0.003).

ADL motor performance

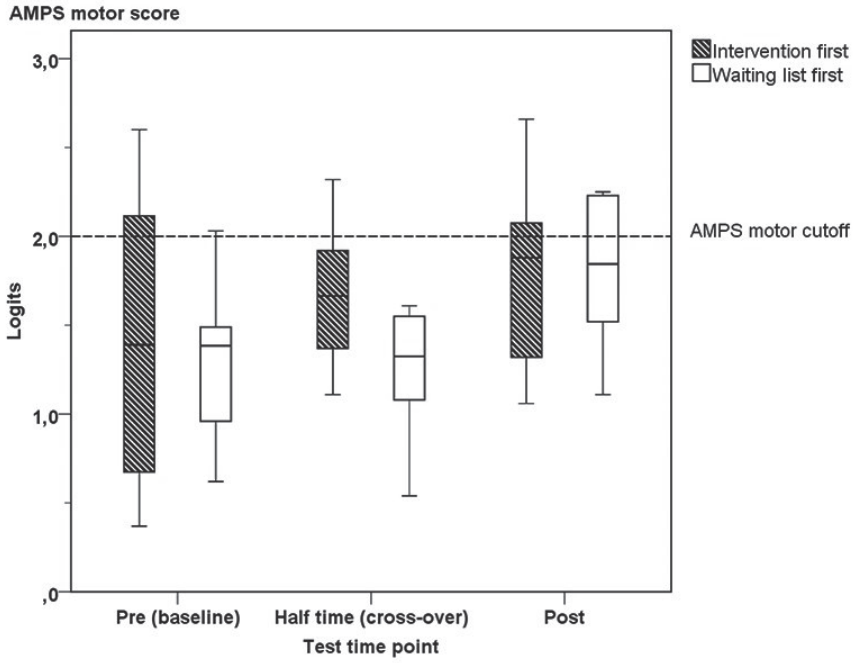
The mean motor skills score improved significantly over the intervention period (within-subjects analysis), by mean 0.51 logits (95 % CI 0.16 to 0.85, p=0.012). The motor skill Z score also improved after the intervention, but was still below the norm (mean Z score -1.1, 95 % CI -1.7 to -0.46, p=0.003). In the parallel group analysis the intervention group improved more than the control group in motor skills score, but this was not statistically significant (mean difference 0.47 logits, 95 % CI -0.02 to 0.96, p=0.059).

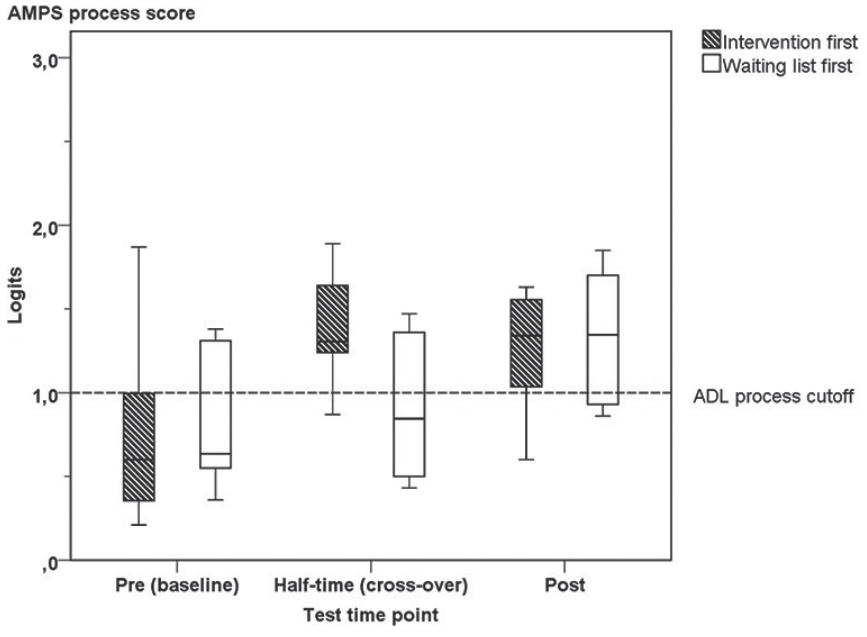
ADL process performance

The mean process skills score also improved over the intervention period (within-subjects analysis), by mean 0.50 logits (95 % CI 0.27 to 0.74, p=0.0020). Translated into Z score, the post-intervention process score reached the age-expected norm (mean Z score 0.20, 95 % CI -0.24 to 0.64, p=0.34). In the parallel group analysis, the intervention group improved by mean 0.47 logits compared to the control group (95 % CI 0.059 to 0.89), an improvement that was statistically significant (p=0.0296). No correlation was found between improvement in AMPS motor/process scores and active video gaming time or MET-levels.

When looking at the AMPS motor and process scores over time, an improvement was seen after the intervention period but not after the control period, contradicting a practice effect from multiple testing (Figure 7). Furthermore, looking at the intervention-first group, the positive effect on ADL was preserved at the follow up test, 10-12 weeks after the intervention period, indicating a sustained effect over time.

Figure 7. AMPS scores (logits) over time in the two groups. AMPS motor scores in the upper panel and process scores in the lower.





4.4 Discussion (Paper II and III)

This study was, to our knowledge, the first to report on the use of active video gaming to mitigate late side effects in childhood brain tumor survivors. AVG, stimulated by weekly online coaching was used to encourage near-daily, moderately intense, physical activity over a period of three months. The activity was perceived as fun or OK, and all enrolled participants completed the study. Coaching was probably an important factor for compliance. In the absence of a non-coached AVG group we cannot substantiate this feeling, but it is supported by the results of a randomized study that compared AVG with or without weekly coaching, and found a higher gaming participation in the coached group (Errickson et al. 2012).

There were two main reasons for using a crossover design even though a conventional crossover analysis was not performed:

1) It permitted a within-subjects analysis of the effects of the intervention, together with a parallel group comparison after the first period. A pure within-subjects trial would lose the randomization group comparison, and a pure randomization study would more likely be underpowered.
2) All children were allowed to play video games at some point; a motivational factor for participating in the trial.

Active video gaming improved body coordination and ADL performance. It is likely that the improvement in ADL was due to both motor improvement and a cognitive effect, although the specific cognitive tests failed to find any significant improvement. It has been suggested that exercise enhances the capacity to use previously encoded memories, i.e. you remember effective task strategies (Hill et al. 2011), something that might explain the positive impact of exercise on ADL performance. Since no significant changes in cognitive tests were found, the question if AVG can improve cognition remains unanswered. A full-sized randomized controlled trial should be done to answer this question. Building on the findings from this trial, as well as other exercise trials aiming to improve cognition, the cognitive assessment battery could be narrower in future trials, and focus on executive function, working memory, and attention. Tests of academic achievement have in some studies been more sensitive than cognitive (IQ) tests (Fouladi et al. 2004, Merchant et al. 2014), and could also be considered. We found statistically significant improvements in Body Coordination and Bilateral Coordination after AVG. One way of assessing if these improvements are clinically significant is by estimating the minimal important difference (MID). MID

can be defined as the smallest change in the measurement score considered to be important by using another anchor score (de Vet et al. 2006). A change greater than the MID is by definition clinically important. A study of children with intellectual disabilities explored different aspects of the BOT-2 instrument, and used the physical tasks performance scale as an anchor score (Wuang and Su 2009). They found the MID for Body coordination to be 1.65, and for Bilateral Coordination 1.11. The mean changes presented in **Paper II** were 4.55 and 2.18 respectively, which implies clinically significant improvements. Regarding ADL, the mean improvement in AMPS score after the intervention was 0.51 logits in motor score and 0.50 logits in process score. A change of 0.3 logits is considered clinically relevant (Fisher and Merritt 2012). The improvement in AMPS score can therefore be transferred to functional gains that can have an influence on the patients´ daily life. However, although the effects on ADL performance seem strong and the results are encouraging, due to the small sample size they must be interpreted with some caution.

The major limitation of the study is the small sample size, which could lead to a type II error (i.e. incorrectly retaining a false null hypothesis). There could also be other potential explanations for the lack of cognitive effects from the intervention:

1. *Physical activity levels were not increased enough*. The mean EE levels during AVG sessions reached moderate levels, which is in accordance with previous AVG studies (Howcroft et al. 2012, O'Donovan et al. 2013). Reaching higher EE levels during AVG is possible, but probably harder to achieve in a home setting compared to a laboratory setting. The intensity of AVG is more intermittent, and EE is less uniform across the gaming session in a home setting, probably contributing to lower mean intensity levels (Biddiss and Irwin 2010). Regarding the measurement of EE levels with the SenseWear Armband, there is a possibility of underestimation of the EE level during some high intensity activities. The signal from an accelerometer is integrated over a given time interval (epoch), then summed and stored. The SWA is restricted to a 1-minute epoch due to storage capacity limitations. This sampling rate may not fully capture the variability pattern of children, characterized by short, intermittent bursts of activity, and the SWA (as other activity monitors), has a tendency of underestimating EE at higher intensities (Nilsson et al. 2002, Arvidsson et al. 2007). Also, it is possible that SWA overestimates activities involving primarily upper body movements, and underestimates activities using lower body

movements. A validation study for Wii gaming using SWA would be desirable.

2. *The intervention period was too short*. Exercise intervention studies in older adults have resulted in conflicting results and it has been proposed that longer intervention periods (≥ 1 year) are necessary to get cognitive health benefits (Snowden et al. 2011). However, cognitive benefits from exercise has been found in children after interventions of similar length as our trial (Davis et al. 2011, de Kloet et al. 2012, Riggs et al. 2016).
3. *Interference from non-active video gaming during the waiting list period*. Non-active video gaming was not restricted and this could have interfered with the results. We have no way of controlling for this, as it was not measured. Furthermore, we do not know if some participants performed active video gaming also during the control period. The gaming console was retrieved and not available during the waiting list period for the majority of participants, but some children had a console of their own. Although we asked the parents to refrain the children from using it during the control period, compliance to this was not measured.
4. *Interference from other physical exercise or previous AVG experience*. Some participants (5/13, two in the intervention first group, three in the waiting list group) performed regular physical exercise (1-3 times/week) along with the trial, which potentially could have reduced the effect of the intervention. Regarding previous AVG experience, 7/13 had previous Wii experience (4 in the AVG group, 3 in the waiting list group). It is possible that higher fit children or AVG-experienced children had reduced benefit from AVG interventions, due to a ceiling effect. Unfortunately, the small trial size prevented reliable sub-analyses regarding this effect.
5. Lastly, it is possible *the intervention had no effect on cognition*. To clarify this, a larger trial is needed. A study using Nintendo Wii in a similar patient population (with acquired brain injury) found improvements in cognitive parameters after AVG, indicating a cognitive effect, although the study did not include a control group (de Kloet et al. 2012).

In conclusion, the children in the study, previously treated for brain tumors with multimodal therapy (including radiotherapy to the brain), had poor performance in several functional areas, e.g. motor functions, cognitive performance and execution of ADL. Their performance was, in some aspects, improved by the intervention, hopefully helping them to manage their everyday life better.

5 PAPER IV (HYPOTHERMIA STUDY)

5.1 Specific aim for Paper IV

The aim for **Paper IV** was to study, in a rodent model, if the radiation-induced damage to the neurogenic regions of the brain could be lessened by inducing hypothermia directly after brain irradiation.

5.2 Material and methods (Paper IV)

Postnatal day 9 (P9) Wistar rats of either sex were randomized to either a normothermia group, a hypothermia group or a control group. All subjects were anesthetized with an intraperitoneal injection of tribromoethanol, and the control animals were then returned to the dam. The two other groups received irradiation (8 Gy, single fraction) to the left brain hemisphere using a linear accelerator. After irradiation, the animals were placed in containers submerged in temperature-controlled water baths (36˚C and 30˚C respectively) for eight hours. They were then returned to the dam. Animals were kept in a 12-h light/dark schedule (lights on at 07:00 h) with food and water available *ad libitum.* All animal experimental procedures were performed in accordance with the European and Swedish animal welfare regulations and approved by the Regional Ethical Review Board of Gothenburg.

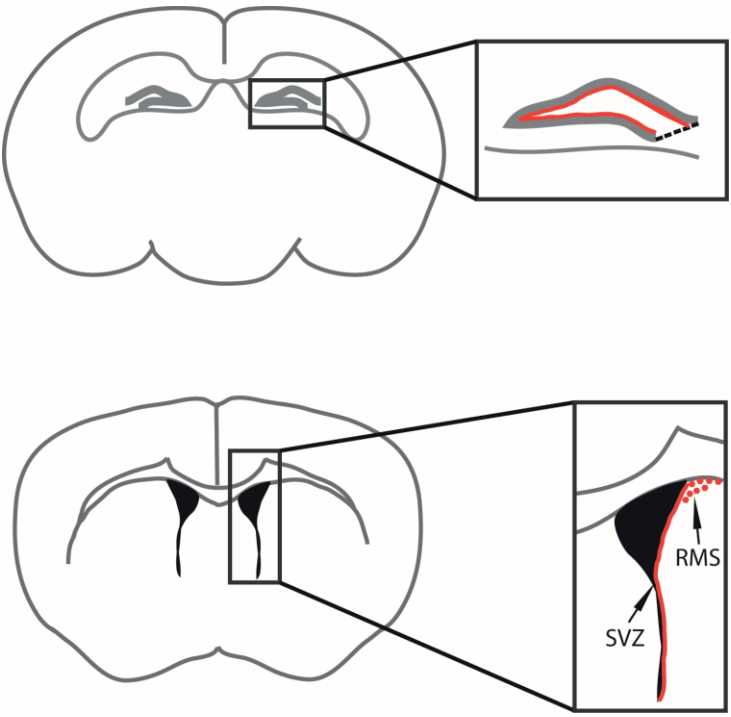
Tissue preparation and staining

Seven days after irradiation the animals were deeply anaesthetised with sodium pentothal, and transcardially perfusion-fixed with 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS). The brains were removed and fixed in formaldehyde for 24 hours. After dehydrating the brains with a graded series of ethanol and xylene, they were then embedded in paraffin. By this process, the water in the tissue was replaced by paraffin.

Coronal sections (5 μm thick) were mounted on glass slides and stained with thionin/acid fuchsin for morphological analysis. Adjacent sections were used for immunostaining. When using paraffin-embedded sections it is beneficial to perform antigen retrieval before adding the antibody. This was done by boiling the sections in 10 mM citrate buffer (pH 6.0) for 10 min. Nonspecific binding was blocked with 4% goat serum in PBS. After blocking, sections were incubated with primary antibodies (see below) for 24 hours. The following day all unbound antibody was washed off and the biotinylated

secondary antibody was added for one hour at room temperature (goat anti-rabbit biotinylated secondary antibodies). Endogenous peroxidase activity was blocked, and visualization was performed using an avidin–biotin–peroxidase solution.

Figure 8. Illustration of the rat brain (coronal section) at the level of the dentate gyrus (DG) of the hippocampus (upper panel), and the lateral ventricles (lower panel). The magnification window in the upper panel shows the different areas of the DG, the granule cell layer (GCL, in grey) and the subgranular zone (SGZ, in red). The hilus is defined as the area enclosed by the GCL and the imaginary straight (dotted) line joining the tips of the two GCL blades, not including the SGZ. The lateral ventricles are seen in the lower panel and the magnification illustrates the subventricular zone (SVZ, red line) along the lateral wall of the ventricles, and the rostral migratory stream (red dots).



Immunohistochemistry

To count the number of proliferating cells an antibody versus phosphorylated Ser10 in the tails of histone H3 (PHH3), a well-studied marker of cell mitosis, was used (Hans and Dimitrov 2001). Since neuroinflammation has been suggested to contribute to the reduced neurogenesis after radiotherapy (Monje et al. 2002), we also wanted to count the number of microglia. Microglia are the resident macrophages of the brain that serve both glial (e.g. monitoring of synapses and synapse pruning) and immune-related functions (e.g. immune surveillance, phagocytosis, removal of apoptotic and necrotic cells, regulation of inflammation) (Nimmerjahn et al. 2005, Schlegelmilch et al. 2011). They develop from embryonal yolk sac myeloid progenitors and enter into the brain very early in embryonic development (Ginhoux et al. 2010). We used the ionized calcium-binding adapter molecule 1 (Iba1) monoclonal antibody as a microglia marker. The choice of antibody dilutions was based on a separate staining experiment. Several different antibody dilutions were tested, and the optimal dilution for cell counting was chosen.

Counting was performed in two stained sections per animal, one from 5.3 mm (for the SVZ) and one from 1.6 mm (for the hippocampus) rostral to the vertical zero plane, according to an atlas of rat brain anatomy in P9 rats (Sherwood and Timiras 1970) (Figure 8). The SVZ and GCL areas (including the SGZ), as well as the length of the SGZ, in both the ipsi- and contralateral hemispheres were traced and measured using Stereo Investigator 6.0 (MBF Bioscience, VT, USA). The examiner was blinded to the randomization group. In a separate experiment we explored the effect on blood glucose levels from eight hours of fasting. P9 rats were randomized to two treatment groups and one control group. The treatment groups were anaesthetized and put in chambers submerged in temperature-controlled water baths for eight hours, replicating the conditions from the first irradiation experiment (but without being irradiated). The control animals were anaesthetized and then returned to their biological dam. The body temperature was measured after 1.5, 4, and 8 hours. After eight hours the animals were decapitated and blood was collected in a capillary tube from the neck vessels. Blood glucose was analyzed immediately in a blood analyzer. For further details regarding methods see **Paper IV**.

Comments

The brain development in P9 rats corresponds to an infant in humans (Semple et al. 2013). Since radiotherapy (especially craniospinal radiotherapy) seldom is used in children below 3-4 years of age, and practically never in newborn children, the choice of P9 rats is not ideal when translating our findings to children receiving radiotherapy. The rationale behind this choice was to make

the results comparable to the previous experiments, e.g. by Fukuda et al. (Fukuda et al. 2005). The single dose of ionizing radiation is also different from the radiotherapy practice in humans, where the total dose is delivered in multiple daily fractions, (usually every week-day, over a period of weeks). We could not replicate this however, for different practical reasons: 1) multiple procedures are more stressful for the animals, 2) the risk of introducing an infection to the animal facility increases when bringing them back and forth, 3) multiple sedations using tribromoethanol is not recommended due to its inflammatory properties.

5.2.1 Statistical analysis

One-way ANOVA followed by Sidak´s multiple comparison test was used to compare irradiated hemispheres from the normothermia and hypothermia groups with the control group. The significance level was set to p=0.05. The same analysis was used to compare the non-irradiated hemispheres between groups. GraphPad Prism version 7 for Windows (GraphPad Software, CA, USA), was used for statistical analyses.

5.3 Results (Paper IV)

5.3.1 Temperature, body weight, and blood glucose

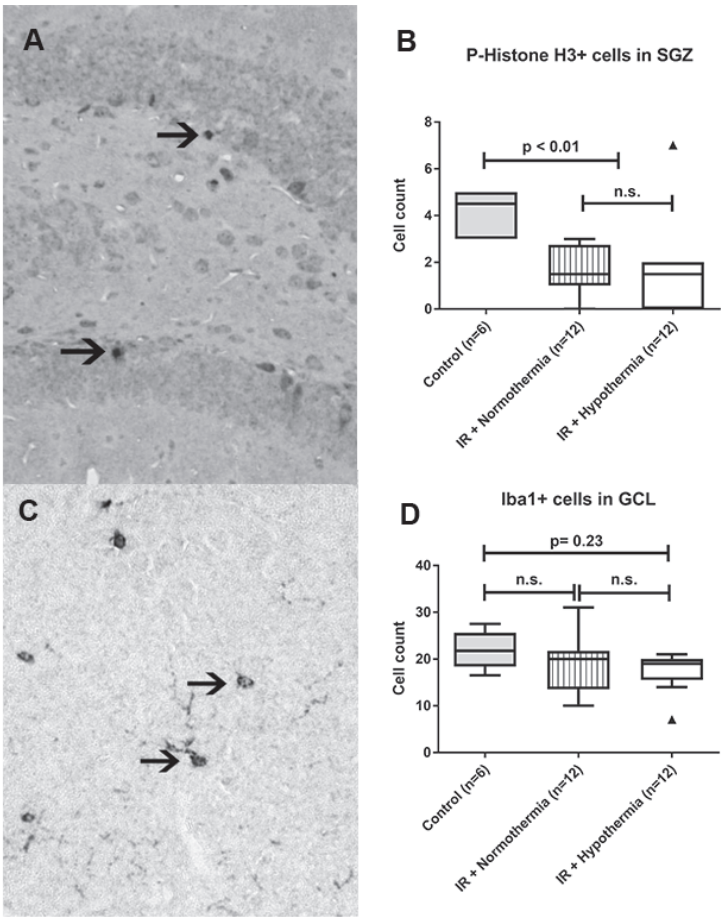
The hypothermia group had, as expected, a significantly lower body temperature (32.2°C) eight hours after irradiation, although the target rectal temperature of 30°C was not quite achieved. There was no significant difference in body temperature between the animals in the normothermia group and the non-irradiated control group. The groups did not differ significantly in body weight. The blood glucose levels decreased in the irradiated groups compared to controls, due to the eight-hour separation from the dam, but there was no significant difference between the normo- and hypothermia groups.

5.3.2 Effects on the hippocampus (GCL and SGZ)

The GCL area and SGZ length decreased significantly in all irradiated hemispheres compared to control animals, whereas the non-irradiated hemispheres were unaffected. There was no significant difference in GCL size or SGZ length between the irradiated hemispheres in the hypothermia and normothermia groups. The (absolute) number of proliferating cells (phospho-Histone H3+, Figure 9A) in the SGZ was significantly higher (x2.5) in the control group compared to the irradiated groups, but did not differ between the normo- and hypothermia groups (Figure 9B). There was a

non-significant trend towards lower relative numbers of proliferating cells (phospho-Histone H3+ cells/mm SGZ) after irradiation when comparing the control group versus the hypothermia group (p=0.053), and versus the normothermia group (p=0.075), but not between the two treatment groups (mean difference 0.04, 95 % CI -0.47 to 0.55, p=1.0, not shown). Furthermore, there was no difference in the number of microglia (Iba1+ cells, figure 9C) in the GCL, neither in absolute numbers (Figure 9D), nor in cell density (not shown), between treatment groups or compared to the control group.

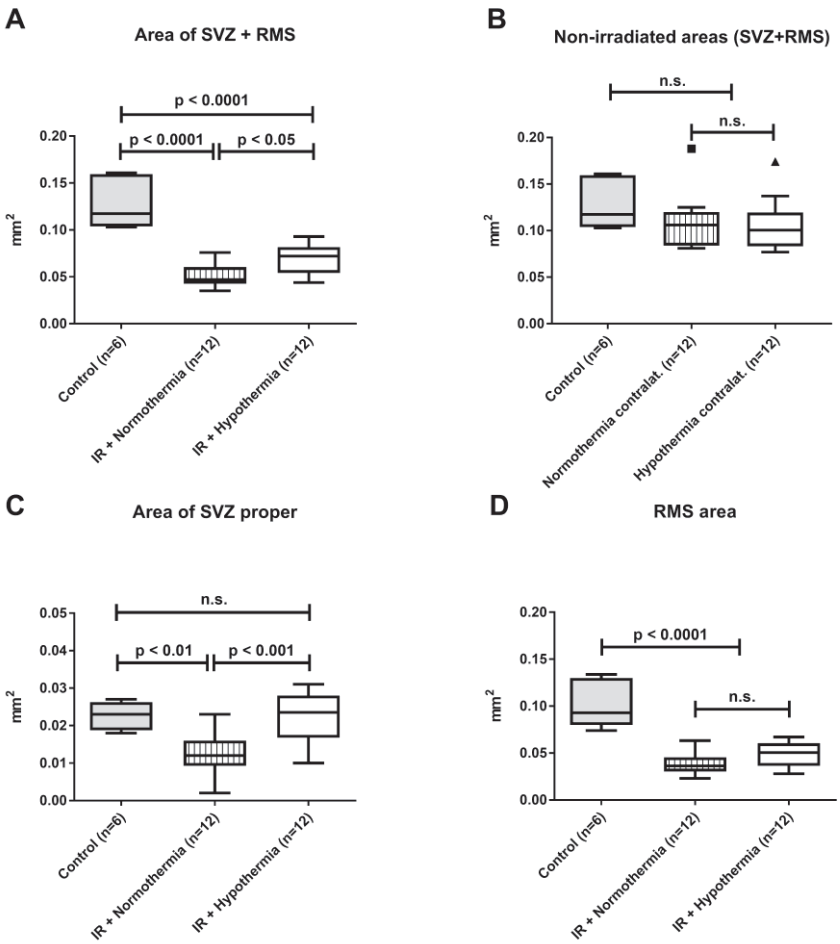
Figure 9. A) Phospho-Histone H3 positive cells (arrows) in the subgranular zone (SGZ) of the hippocampal granule cell layer (GCL). B) Proliferating (phospho-histone H3+) cells in the SGZ, in the irradiated hemispheres of treatment groups and controls. C) Iba1 positive cells (arrows) in the hippocampus. D) Microglia (Iba1+ cells) cell count in the GCL between randomization groups. Boxplots with the interquartile range (IQR) and median, and Tukey style whiskers (i.e. extended to the most extreme data point that is no more than 1.5 × IQR from the edge of the box). IR irradiated, n.s. not significant (p >0.3).



5.3.3 Effects on the subventricular zone

The combined size of the SVZ and the RMS was significantly smaller in the irradiated hemispheres of both the normothermia group and the hypothermia group, compared to the control group (Figure 10A). Furthermore, this area differed also between the normo- and the hypothermia groups, with a significantly larger size in the hypothermia group (mean 0.05 mm^2 vs 0.07 mm^2, 95 % CI 0.001 to 0.04, $p<0.05$, Figure 10A).

Figure 10. A) The combined area of the subventricular zone and the rostral migratory stream (SVZ+RMS) in the irradiated hemispheres of the treatment groups, and in controls. B) For comparison, the areas of the non-irradiated (contralateral) hemispheres were also measured. C) The SVZ proper (i.e. without the RMS), was severely reduced in the normothermia group after irradiation, but was unchanged in the hypothermia group, compared to controls. D) The RMS was reduced after irradiation, but did not differ between treatment groups

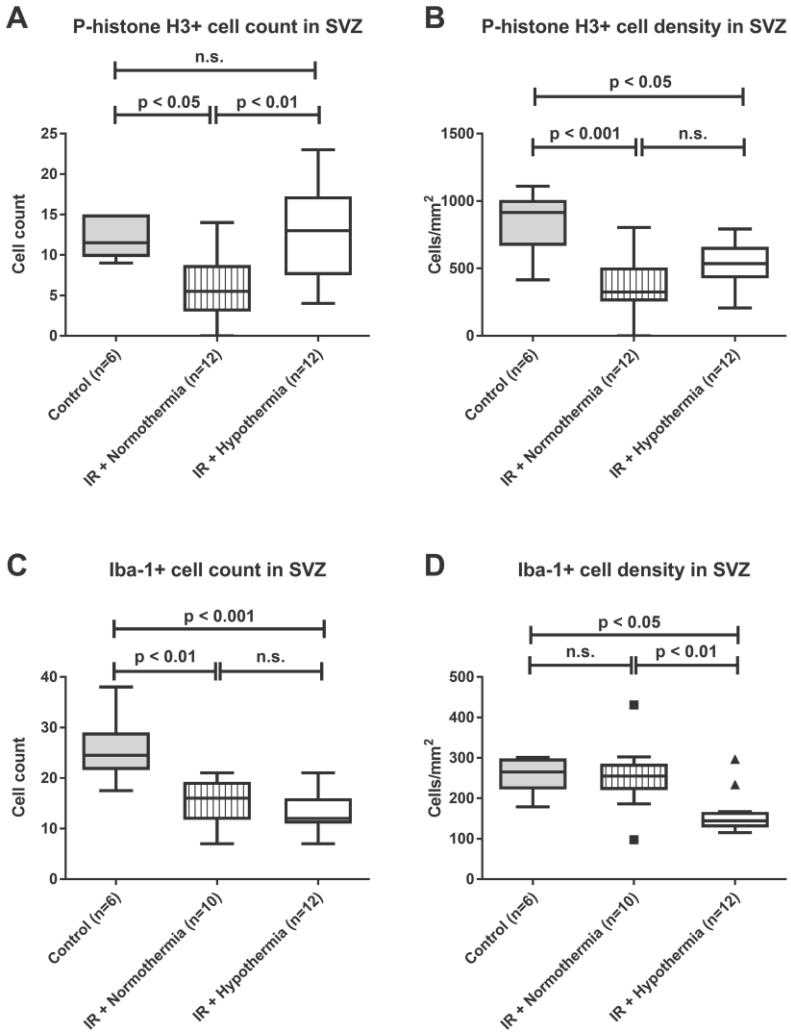


The corresponding areas in the non-irradiated hemispheres were not different in size from control areas (Figure 10B). When the SVZ was measured separately, excluding the RMS (SVZ proper), the difference between the treatment groups was even more pronounced, with a 50 % reduction in SVZ size in the normothermia group compared to controls (0.012 mm^2 vs 0.023 mm^2 , 95 % CI 0.003 to 0.02, $p<0.01$). This reduction was completely prevented in the hypothermia group (0.022 mm^2 vs 0.023 mm^2 in controls, 95% CI -0.007 to 0.008, $p=1.0$, Figure 10C). The RMS decreased to mean 43 % of controls after irradiation ($p<0.001$), but did not differ significantly between the normo- and hypothermia groups (Figure 10D).

The number of proliferating (phospho-histone H3+) cells was reduced by more than half in the irradiated normothermic SVZ, but this loss of proliferating cells was prevented in the hypothermic group (Figure 11A). Given the larger SVZ size in the irradiated hypothermia group, the cell density was however not significantly different from the irradiated normothermia group (Figure 11B).

The absolute numbers of microglia (Iba1+ cells) in the SVZ decreased in the irradiated groups compared to controls, more significantly in the hypothermia group than the normothermia group, although the difference between the treatment groups was not significant (Figure 11C). Due to the preservation of SVZ area in the hypothermia group, there was a lower density of microglia in the irradiated SVZ of the hypothermia group compared to both the normothermia group (Figure 11D), and controls.

Figure 11. A) Absolute cell count of proliferating cells (phospho-histone H3+) in the subventricular zone (SVZ), compared between randomization groups. B) Cell density of proliferating (phospho-histone H3+) cells in the SVZ proper. The cell density did not differ between normothermia and hypothermia groups, probably due to the preserved, relatively larger SVZ in the hypothermia group. C) Microglia (Iba1+) cells in the SVZ+RMS compared between groups. D) Microglia (Iba1+) cell density in the SVZ+RMS was lower in the hypothermia group, compared to both the normothermia group and controls, probably due to the preserved, relatively larger SVZ in the hypothermia group. Boxplots showing the interquartile range (IQR) and median, with Tukey style whiskers (i.e. extended to the most extreme data point that is no more than 1.5 × IQR from the edge of the box). IR irradiated, n.s. not significant (p > 0. 3)



5.4 Discussion (Paper IV)

In this animal model, young (P9) rats were randomized to a control group, or a treatment group consisting of hypo- or normothermia for eight hours immediately after a single fraction of hemi-brain irradiation. We found a protective effect from hypothermia on the SVZ area and the proliferative cell population in the SVZ, but no protection of the hippocampal dentate gyrus, one week post radiation.

The reason for this selective protection is unclear, although consistent with previous findings (Fukuda et al. 2005). It could due to different sensitivities to irradiation, or differences in cell turn-over between the regions. This is supported by previous finding of differential dynamics between the SVZ and the GCL in the juvenile rat brain after irradiation, such that the SVZ recovered with time whereas the GCL did not (Hellström et al. 2009). It is conceivable that hypothermia in some way can enhance the recovery process of the SVZ. Another speculative hypothesis is that the close proximity of the SVZ to the CSF contributes to a less toxic environment after irradiation, as discussed in **Paper IV**. It is also possible that NPCs in the hippocampus are more vulnerable to stress compared to their SVZ counterpart, and that stress from hypothermia could counter the protective effect. In a study of the effect of longer-term hypothermia (30˚C for 24 h) on neurogenesis, cell proliferation was reduced in the hippocampus but not in the SVZ, possibly mediated by a stress-induced increase in corticosteroid levels (Kanagawa et al. 2006).

Although the body temperatures in the hypothermia group reached hypothermic levels (mean body temperature 32.2˚C), the target temperature of 30˚C was not achieved. During the experiment, it was observed that the animals tended to clump together in the temperature-controlled container, something that probably helped them preserve body heat and lessened the cooling effect. We did however, reach the same hypothermic temperature as a previous study, but for twice as long, and compared to the previous study we found a more pronounced protective effect on the SVZ, post-irradiation (Fukuda et al. 2005). This indicates that hypothermia duration could be an important factor. The lower cell density of Iba1+ cells in the SVZs of the hypothermia group could indicate that hypothermia influences the inflammatory response after irradiation, leading to improved NPC survival/proliferation in the SVZ, although further studies are needed.

The RMS did not seem to benefit from hypothermia in the same way as the SVZ. Although the border between these two areas is somewhat arbitrary,

this might reflect an underlying mechanism yet to be elucidated. A hypothesis could be that although the proliferative capacity of the SVZ was benefited by hypothermia, the previously reported negative effect of irradiation on the RMS – preventing the migration of neuroblasts – was unaffected (Achanta et al. 2012).

Both irradiated groups had a lower mean blood glucose level after eight hours compared to controls, but there was no difference in blood glucose levels between the normo- and hypothermia groups that could explain the difference in SVZ areas. Furthermore, the GCL and SVZ areas in the non-irradiated (contralateral) hemispheres were not reduced compared to controls. It is therefore unlikely that blood glucose levels (or other metabolic changes due to fasting), can explain the difference in SVZ areas.

The strengths of this study is the randomized design with blinded evaluation of the effect of hypothermia on the proliferative areas of the rodent brain. A limitation of our study is that we studied the potential protective effect of hypothermia at one time point only, and that we did not characterize the proliferating cells further. However, in a stroke model using adult rats, the size of the SVZ reflected the number of proliferating cells, indicating that SVZ size could be used as a marker of SVZ precursor proliferation (Parent et al. 2002).

It may be that hypothermia delayed the detrimental effect on the SVZ area and that, over time, the area would decrease in a similar way as it did in the irradiated normothermia group. It is possible however, that hypothermia protected the NPC population in the SVZ (through anti-apoptosis, anti-oxidation, or anti-inflammatory mechanisms), leaving a greater number of viable proliferating cells to repopulate the area. The latter scenario is supported by the combined findings of a larger preserved SVZ area, together with higher numbers of proliferating cells in the hypothermia treated group. This however, needs to be confirmed in future studies.

6 FINAL CONCLUSIONS AND FUTURE PERSPECTIVES

The poor survival after medulloblastoma relapse found in **Paper I** is consistent with previous findings, and treatment for recurrent medulloblastoma continues to be a major clinical challenge. In isolated relapses, surgery can be beneficial. Surgery or biopsy should also be encouraged to verify the diagnosis of recurrent disease vs SMN or even non-malignant MRI findings. International collaborative trials for recurrent medulloblastoma are needed and should be encouraged. These should preferably be based on biological sampling of recurrent tumors, and use the results to guide therapy. Tumor biopsy in that context is less ethically problematic, since the procedure leads to an immediate benefit for the patient (guided therapy), as well as the research community (more knowledge).

Targeted therapy could be a way forward, e.g. using inhibitors of the sonic hedgehog pathway in SHH-MB, but the long term side effects of these new therapies are yet unknown. For example, the sonic hedgehog pathway is an important stimulating factor for neurogenesis the SVZ and GCL (Ahn and Joyner 2005), which raises concerns that SHH-inhibition could adversely affect normal brain function.

The best way to handle relapses is of course to prevent them from happening. Research in resistance mechanisms is therefore important. Continued research in tumor (molecular) biology will hopefully provide further insight into how tumor cells avoid being killed by therapy, and how to best close their escape routes. As an example, Lithium treatment of radioresistant *TP53* mutant medulloblastoma cell lines sensitized the tumor cells to radiation through activation of the WNT pathway (Zhukova et al. 2014). Interestingly, Lithium did not activate *WNT* signaling in normal neuronal stem cells, and consequently their sensitivity to radiation was not enhanced (Zhukova et al. 2014). In fact, evidence suggests Lithium could have a protective effect on hippocampal neurogenesis after irradiation, and reduce cognitive side effects (Zhou et al. 2017).

Finding effective ways to mitigate the long term side effects after childhood brain tumor treatment is important, since they can have a severe impact on the survivors' daily life. In addition, the number or survivors increase every year. There is growing evidence that exercise is beneficial to cognition, and exercise interventions are an interesting option for this patient group. But

there are challenges in finding interventions that are easily managed, fun to do, and can be performed on a long term basis. Interventions should probably be a combination of different activities, varying over time, to enhance participation and reduce attrition. The value of active video gaming deserves further exploration, and future research should focus on games that stimulate both physical activity and cognition, e.g. dance games. Group activities e.g. real life dance classes, could be considered, as well as methods of proven benefit, e.g. computerized working memory training with Cogmed. Inconvenience in travelling to the cancer center, e.g. after school hours, can hamper clinic-based interventions (Patel et al. 2009), and home-based interventions are therefore preferable.

Support by Internet coaching is a resource efficient way of doing studies, but perhaps not easily transferred to large-scale clinical practice. Building Internet-based communities of brain tumor survivors could however be a method to stimulate rehabilitation activities, with the added value of decreasing social isolation. In view of the rapid technical development, already available virtual reality solutions will probably soon be less expensive, and could be an interesting option to explore further.

Using hypothermia after radiotherapy to mitigate the harmful effects on neurogenesis needs further study before it can be used in a clinical setting. Both the functional and long term effects of the findings in **Paper IV** need to be investigated in animal studies, as well as the effect of hypothermia on brain tumors. Since radiotherapy is given over a period of weeks, the method has obvious practical challenges as well, although not unsurmountable provided the gain from the intervention is large enough.

6.1 Concluding remarks

In response to specific aims

I. Long term survival after treatment for standard risk medulloblastoma has improved over the years, now reaching an estimated 10-year EFS and OS of ~80 %. After a median follow up of 7.4 years there was no difference in survival between treatment arms in the HIT-SIOP PNET4 trial. The prognosis after relapse however, was very poor, with a median OS of 1.5 years after relapse and a disappointing 5-year OS of 6 %, irrespective of relapse treatment. Recurrent

tumors appeared at a median interval of 26 months from primary diagnosis, with 8 % late relapses (> 5 years after primary diagnosis). No benefit from HDSCR or radiotherapy was detected, but relapse treatments were diverse, and therefore difficult to evaluate. Patients with isolated posterior fossa relapses survived longer compared to patients with other relapse patterns. In selected cases, surgery seemed to be of benefit. The majority of relapses however, were metastatic within the CNS. The histological subgroup or biological factors (at primary diagnosis) had no impact on time in first remission, relapse pattern, or survival after relapse.

II. An intervention with active video gaming and regular on-line coaching achieved an enjoyable, near daily exercise of moderate intensity in pediatric brain tumor survivors. The method was feasible and compliance was good, but the overall physical activity levels were not significantly increased.

III. No significant improvement was found in cognitive test scores after AVG, but the evaluation was limited by the small sample size. Clinically important improvements were found in motor function (body coordination) and ADL abilities. Continued research should be encouraged.

IV. Post-irradiation moderate hypothermia for eight hours protected neurogenesis in the SVZ, but not in the hippocampus, in a rodent model. The mechanism for the protective effect and the reason for the selective effect on the neurogenic areas needs further study, as well as the effect of post-irradiation hypothermia on brain tumors.

7 ERRATA

Paper I: On page 3, the second last sentence on the page should read: "There was information on CSF cytology in 61/**72** patients."

On page 4: Surgery was performed in 18 cases and radiotherapy was given to 16 patients, as indicated in Table 1.

Paper III: In the Table 2 legend at page 8, the first row should read: "t =T-score: mean=50, SD=10; s= standard score: **mean=10, SD=3, IQ**: mean=100, SD=15"

In Table 3, page 9, the p-value for the change in motor score should be p=**0.0122**.

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APPENDIX (PAPER I-IV)