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FACULTEIT PSYCHOLOGIE EN
PEDAGOGISCHE WETENSCHAPPEN

LONG-TERM NEUROCOGNITIVE FUNCTIONING IN POSTERIOR FOSSA TUMOR SURVIVORS

A systematic literature study and follow-up cohort study

Masterproef aangeboden tot het
verkrijgen van de graad van
Master of Science in de
psychologie
Door
Lissa Maes en Ellen Turelinckx

promotor: Jurgen Lemiere
m.m.v: Charlotte Sleurs

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ABSTRACT

Background

Brain tumors are the second most prevalent form of childhood cancer, thereby succeeding leukemia. Approximately 2/3 of pediatric brain tumors are located in the posterior fossa. Different types of treatment are applied, depending on tumor type (i.e. medulloblastoma, ependymoma, astrocytoma). The differential contribution of treatment strategies to long-term impairment still remains unclear.

Purpose

This study aims to investigate long-term post-treatment neuropsychological effects of childhood posterior fossa tumors. We focused on the differential influence of possible risk factors concerning radiotherapy, surgery and timing (age at diagnosis and time since treatment) on neurocognition. Furthermore, we investigated possible risk factors for worse neurosurgical outcome.

Methods

Inclusion was based on an existing database of patients who completed treatment at UZ Leuven at least 1.5 years ago. This resulted in 21 patients (medulloblastoma n=12, ependymoma n=1, astrocytoma n=8) between 16 and 35 years old and 21 age- and gender-matched controls. Testing consisted of a comprehensive neuropsychological assessment objectifying intelligence (WAIS-IV-NL), memory (AVLT and RVDLT), attention (ANT), verbal function (COWAT and PPVT-III-NL) and self-report questionnaires assessing executive (BRIEF) and cognitive function (CFQ), health-related quality of life (PedsQL), depressive symptoms (BDI) and anxiety (STAI). Neuroimaging was used to visualize brain anatomy. Three general linear models were constructed to: (1) assess outcome differences between patients and controls, (2) identify independent treatment-related risk factors for worse outcome in patients, (3) identify treatment variables that influence cerebellar tissue proportion.

Results

Patients performed significantly worse on intelligence, memory, object naming, attention and self-reported emotion regulation and health-related quality of life (HRQoL). Craniospinal radiotherapy dose was related to worse performance concerning intelligence and attention, postoperative mutism to lower scores on intelligence and emotion regulation, and time since treatment to worse intelligence, memory and object naming. Furthermore, craniospinal radiotherapy dose and relapse were significantly associated with reduced cerebellar tissue proportion.

Conclusion

Negative effects on long-term neuropsychological outcome were found for higher craniospinal radiotherapy doses, presence of postoperative mutism and longer time since treatment. Further research integrating neurocognitive with psychomotor and psychosocial findings is recommended. In addition, the exact role of white matter damage needs to be further examined. Finally, it becomes important for future research to investigate possible interventions to improve the outcome deficiencies in brain tumor survivors.

Keywords: behavior, children, cognition, long term outcome, posterior fossa, radiotherapy, surgery, timing, tumor

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APPROACH

This thesis consists of two different sections. The first one contains a systematic literature study which gives an overview of the available research on pediatric posterior fossa tumors. PubMed was searched for articles published in the last 10 years on the general neuropsychological outcome of posterior fossa tumor survivors with an age range of 16-35 years at least 1.5 years post-treatment. This resulted in the identification of several risk factors for worse outcome in pediatric brain tumor survivors, which were implemented in our own cohort study.

The second section of this thesis contains a follow-up cohort study about the long-term cognitive, behavioral and emotional function of pediatric brain tumor patients treated at UZ Leuven. This study focuses more specifically on the influence of variables such as radiotherapy, surgery, and timing on outcome in order to detect the effects of treatment-specific risk factors on a wide range of neurocognitive functions.

Since this thesis was a concerted action, the work was divided and each of us focused on different components. In regard to the systematic literature study, all abstracts found by our search operation in PubMed were read by the both of us in order to achieve mutual agreement on the usefulness of the articles. Afterwards, each of us read half of the selected articles to identify results relevant for our research purpose. Regarding the follow-up cohort study, both of us performed testing of approximately half of our participants during data-acquisition. During data processing, Ellen focused on the statistical analyses of the data gathered during the assessment of patients and controls, while Lissa integrated the findings in the articles of the literature study after thorough examination of all of them. In regard to the report of our results, Lissa wrote the general introduction, the systematic literature study, and the methods and materials section of our follow-up cohort study. The abstract, acknowledgements, approach, procedure and results section of our follow-up cohort study, and the discussion were written by Ellen. The conclusion of this thesis was written in consideration by both of us.

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GENERAL INTRODUCTION

In 2012, the global incidence of cancer was estimated to be around 14.1 million new cancer cases a year. With 8.2 million deaths annually, cancer remains one of the most important risk factors for premature death (Cancer Research UK). When focusing on childhood cancer, it was found that pediatric brain tumors are the second most common form, comprising 17-18% of all cancers in children (Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013). Over the past few years, survival rates for all tumors have improved significantly. Because of this, the presence and impact of long-term side effects of treatment have begun to receive more and more attention. One of those possible side effects is cognitive dysfunction, which is best known sequel in brain tumors.

It has been estimated that 54-60% of brain tumors originate in the posterior fossa region (El-Ghandour, 2011). The most common types of tumors of the posterior fossa are medulloblastoma, pilocytic astrocytoma, ependymoma, atypical teratoid rhabdoid tumors, and brainstem glioma (Brandão & Young Pouissaint, 2017). These tumors typically arise in early childhood, with a peak in diagnosis when children are around 5 years old (Palmer et al., 2012). For example, the 5-year survival rate for medulloblastoma (the most malignant tumor type) is currently at 85% for medium-risk patients and at 70% for high-risk patients (Palmer & Leigh, 2009). This means that children often undergo successful treatment. Although survival rates increase, research has demonstrated a downside to the different types of treatment typically used. Hence, this thesis will first shed light on the 3 most common types of treatment and their potential neurotoxic effects. This is followed by a discussion on which short- and late-term effects were previously investigated. Finally, potential patient-related risk factors will be summarized.

NEUROTOXICITY OF CANCER TREATMENTS

After treatment with surgical resection, radiotherapy (RT), and/or chemotherapy, a number of acute effects have been documented extensively. To give an example of these, De Smet et al. (2009) found hypersomnolentia, apathy, gaze paralysis, hemiparesis, left dysdiadochokinesia, emotional instability, incontinence, irritability, dysphagia, word-finding problems, diplopia, fatigue, etc. In what follows, this introduction will give an overview of a few of the most documented acute effects that can be linked to a specific type of treatment.

Radiotherapy

RT is one of the more common methods to treat a brain tumor. It turns out to be one of the most important factors that have improved survival rates of these patients (Muzumdar & Ventureyra, 2010). Over the past few years researchers unfortunately found that, apart from its great usage in fighting cancer, it also has serious physiological and psychological side effects, like neurocognitive impairments (including impaired attentional skills, deficiencies in processing speed, damaged memory

functions, etc.), motor impairment, hearing loss, endocrinal issues, and other. (De Smet et al., 2009; Dropcho, 2010; Muzumdar et al., 2010; Rueckriegel, Bruhn, Thomale, & Driever, 2015; Wefel, Kayl, & Meyers, 2004). These impairments are thought to be caused by neuroanatomical structural changes due to the neural injury which is a consequence of irradiation (Hoang et al., 2014). Since white and gray matter mature through myelination, a process that takes up until the second decade of the child's life to complete, damage during this process can have a great impact on the further cognitive development of the child. When the myelination is not complete, the brain is still vulnerable. As such, radiotherapy that is performed during this period can have a large impact on cognition (Palmer et al., 2012). In addition, frontocerebellar neuronal white matter loops and supratentorial structures (gray and white matter) are often damaged causing specific sequelae (Rueckriegel et al., 2015). Apart from the age at which radiation therapy is administered, other factors that seem to be determinative for the severity of the effects are the dosage of RT and the irradiated volume (Dropcho, 2010; Palmer et al., 2012). Often, children are treated with craniospinal radiation and sometimes they receive a boost to the posterior fossa or the tumor itself plus a certainty margin of a few centimeters. Today, physicians regularly opt for hyperfractioned radiation because this technique prevents toxicity to healthy cells as much as possible by administering the radiation with lower doses and higher frequencies (Muzumdar et al., 2010). Research showed that the reduction of the dose of craniospinal RT and that of the boost reduces the severity of long-term effects but cannot eliminate all side effects. The same pattern is seen when restricting the irradiation to a certain part of the brain, rather than whole brain RT (Dropcho, 2010).

Chemotherapy

Chemotherapy is more often seen as an adjuvant type of treatment in high-risk tumor patients (i.e. medulloblastoma). A variety of different chemotherapeutics are commonly used and sometimes even mixtures are administered (Muzumdar et al., 2010). A number of late effects have been documented, including acute and chronic encephalopathy, motor impairments, cerebellar syndrome, and different more peripheral neuropathies. 5-FU and methotrexate, specific chemotherapeutics, have been shown to cause diffuse injury to the brain, while other agents damage specific neurocognitive functions (e.g. CI-980 impairs memory) (Wefel et al., 2004). Hanzlik, Woodrome, Abdel-Baki, Geller, and Elbabaa (2015) found that chemotherapy causes deficits in perception skills, memory, and processing speed. In addition, a paper of Palmer et al. (2009) showed that chemotherapy on top of radiation caused poorer physical health, more general restrictions and an increased need for psychological therapy. The reason for these neurotoxic and other late effects probably lies, again, in the damage that the treatment causes to the brain. For example, Rueckriegel et al. (2015) demonstrated damage to the supratentorial structures (gray and white matter). Other studies also mention white matter changes after brain tumor treatment with chemotherapy (Moore, 2005). Finally, Elens et al. (2017) and Billiet et al. (2018) looked at the effects of chemotherapy in non-irradiated leukemia survivors. They respectively found

that after chemotherapy cerebrospinal fluid (CSF) phosphorylated Tau (p-Tau) is a significant predictor of long-term neurocognitive dysfunction and that the connectivity of the brain has changed.

Neurosurgery

When tumors are graded as low- to medium-risk, surgical resection alone is often assumed sufficient. Nevertheless, this type of treatment can also be combined with radiation therapy and sometimes adjuvant chemotherapy when patients are diagnosed with high-risk tumors. When resecting the tumor, physicians can perform a total resection, or they can opt to perform a subtotal resection and further treat it with RT. Either way, it is a possibility that this surgery damages specific neuronal pathways or cerebellar tissue. Steinlin et al. (2003) found that the problems that appeared post surgery were especially centered on the domains of attention, memory, processing speed, and visuoconstructive ability. Vaquero, Gomez, Quintero, Gonzalez-Rosa, and Marquez (2008) conducted a study on a group of astrocytoma patients who only had surgery as a treatment. They found that these patients show impairments in short-term memory, selective attention, and semantic verbal fluency. In addition, posterior fossa syndrome (PFS), which is known for its transient, post-operative sequelae (e.g. mutism, emotional instability, bulbar dysfunction, etc.), is diagnosed in 28.6% of patients who were treated with surgical resection in the study of Wolfe-Christensen, Mullins, Scott, and McNall-Knapp (2007). Patay (2015) found that PFS is caused by bilateral postoperative damage to the proximal efferent cerebellar pathways (pECPs). Another study (De Smet et al., 2009) demonstrated that children treated with posterior fossa tumor resection show hypoperfusion in supratentorial areas in the frontal and parieto-temporal areas (linked to language, executive function, and behavior) 2 years post-surgery. De Smet et al. (2009) report that: "these results add to the view that PFS might represent a cerebello-cerebral diaschisis (CCD) phenomenon, reflecting the metabolic impact of the cerebellar lesion on supratentorial cognitive and affective functions". Therefore, surgery should aim to avoid damage as much as possible. Further, Gadgil, Hansen, Barry, Change, and Lam (2016) discussed cerebellar mutism syndrome (CMS): a post-operational, mostly transient, complete absence of speech which is also observed as a consequence of infection, trauma or stroke. This syndrome occurs 1 to 2 days after surgical resection of the posterior fossa tumor and lasts, on average, for 8 weeks. Apart from mutism, other symptoms are hypotonia, signs of brain stem dysfunction, emotional inconsistency/mood instability, cognitive deficits, and ataxia.

LONG-TERM SEQUELAE IN POSTERIOR FOSSA TUMORS

Neurocognitive impairments are widely discussed in the field of chronic late effects after treatment in brain tumor patients. Cognitive domains like memory, attention, processing speed, executive function, intelligence, etc. have all been reported to be impaired. For example, Carroll et al. (2016) found that survivors of these tumors score, on average, less on verbal and performance IQ than their typically developing siblings. Also, Steinlin et al. (2003) already stressed the deficits these subjects display in

attention, memory, processing speed, and verbal fluency. Another study (Hodgson, Pitchford, Dineen, Schluppeck, & Walker, 2016), found that young adult posterior fossa tumor survivors perform significantly worse compared to matched healthy controls in the domains of linguistics, intellectual ability and motor skills. They show more widespread cortical activation during language processing, which suggests compensatory activity and less efficient language processing. Further, King et al. (2017) point out more than just cognitive problems. They evidenced that survivors have an increased risk of late-onset hearing loss, stroke, seizure, poor balance, coordination problems, tremor, tinnitus, and cataracts. Survivors were also less likely to have a college degree (25 vs. 55%), marry, or live independently. Additionally, they are less able to work and have a lower income. Further, they showed that survivors were 3 times as likely to report depression and 2 times as likely to have an impaired level of global functioning. As for continued motor problems, Oh et al. (2017) and Hartley, Kumar, Sneade, Williams, and Pizer (2016) discussed postsurgical ataxia to be related with a chronic motor problem. Also, Gadgil et al. (2016) reported on chronic dysarthria in terms of late effects of treatment. In the domain of psychosocial problems, Shippen et al. (2016) reported that survivors of posterior fossa tumors experience significantly more difficulties with theory of mind, affect recognition and social behavior (medium to large effect sizes). Results also suggest a relation between these outcomes and cognitive skills. Another frequently reported downside to the treatment of brain tumors are endocrinal problems. For example, a study of Massimino et al. (2012) reports a continued hormonal deficit, which is only known to be caused by irradiation. All these problems seem to be related to anatomical changes in the brain. Changes in the brain are often proposed as the cause of cognitive late effects like impaired full-scale IQ and attention deficits (Rueckriegel et al., 2015). Further, Miller and his colleagues (2010) wrote about damage to neuronal pathways like the pECPs and other structures.

As described in the section above, PFS is a very common cluster of symptoms after surgical resection. Therefore, it is worth mentioning that PFS in itself holds a certain risk to specific long-term sequelae. Schreiber et al. (2017) studied the difference in outcome between children who developed PFS after treatment for medulloblastoma and those who did not. They found that the PFS-group obtained significantly worse estimated scores on the examined subtests of the third edition of the Woodcock-Johnson Test of Cognitive Abilities (WJIII) than the non-PFS-group at 1, 3, and 5 years post diagnosis. The subtests concerned general intellectual ability (GIA), processing speed (PS), working memory (WM), broad attention (BA), and spatial relations (SR). Regarding GIA, PS, and BA, the estimated mean scores of the PFS-group were at least 1 SD below the mean for all 3 time points. In regard to WM similar results were found at 5 years post diagnosis only. Their study also yielded that over time both patient groups scored significantly lower on BA and lower but non-significant on WM. Furthermore, the PFS-group scored significantly higher over time on SR, but the rate of change did not differ from the one of the non-PFS-group. In addition, the researchers looked at caregiver report measured with the Behavior Rating Inventory of Executive Function (BRIEF) and found that these measures all remained within average range over time. However, they did find a significant difference

between both groups for the behavior regulation index (BRI) and the metacognition index (MI) at 1 year post diagnosis. The rate of change over time did not differ significantly between the PFS- and the non-PFS-group. For externalizing problems (EXT) and total problems (TP), there was a significant difference noted between both groups at 1 year post diagnosis. At 3 years post diagnosis, a significant difference in EXT and a big but not significant difference in TP was found.

PATIENT-RELATED RISK FACTORS

All the aforementioned effects seem to be influenced by other factors. A few patient-related risk factors were often reported as covariates in the analyses of several studies over the years. In what follows, some of the more researched variables will be listed.

Age at diagnosis and treatment

There is evidence that the age at diagnosis has an influence on the outcome of treatment. Robinson et al. (2013) wrote in their article that there is a difference between the treatment outcome for children with ages >7 years compared to those with ages <7 years old. The children in the younger group shows a progressive decline in IQ-scores over time, while the older children did not. In addition, they found evidence that age at diagnosis has also been proven important in other research. The younger group evidences a significantly larger decline in overall cognitive ability, and verbal and non-verbal intelligence. Yoo et al. (2016) reported significant differences in intelligence, memory, executive function, visuospatial integration, and simple motor function between children diagnosed before and after the age of 8 years old. Another article (Carroll et al., 2013) mentions a cut-off at age 5, noting that children younger than 5 years old have higher scores on measures of apathy. Palmer et al. (2012) showed that age at diagnosis is positively correlated with fractional anisotropy (a measure of anisotropy of the diffusion in the brain which is used to estimate for example the density of the fiber networks), processing speed, and visual matching. Furthermore, Palmer et al. (2009) wrote about the risk that the age of the patient at treatment holds on the development of verbal memory. According to Roncadin, Dennis, Greenberg, and Spiegler (2008) age at diagnosis also seems to be positively correlated to memory function, but also to overall intelligence, functional independence, and health-related quality of life (HRQoL). This shows that younger patients seem to be more vulnerable to neurotoxicity. As mentioned above (Palmer et al., 2012), myelination in white matter is still an ongoing process in young children and treatment with irradiation can therefore have a larger impact on cognition. Lemiere et al. (2014) for example, also showed that a younger age at diagnosis and treatment is a risk factor for worse outcome, because radiotherapy is especially toxic for the central nervous system of young children.

Socioeconomic status

Palmer et al. (2013) used parental education and marital status as a measure for socioeconomic status (SES). In their research on medulloblastoma patients, they found that these variables are significantly

correlated with baseline scores on working memory and broad attention. However, no correlation with change in scores over time was found. They did find that high-risk patients and patients with higher postsurgical baseline scores usually show a less favorable outcome. It is thought that patients with higher baseline scores are more vulnerable to show a prominent decline in their neurocognitive functioning. Further, Lassaletta, Bouffet, Mabbott, and Kulkarni (2015) found that HRQoL was worse for patients with a lower SES.

Gender

A study from 2010 by Porter, McCarthy, Freels, Kim, and Davis shows that in the United States females get diagnosed more often with a non-malignant primary brain tumor than males. Lemiere et al. (2014) showed that the gender of the patient can also be a risk factor for neuropsychological late effects. Namely, females have more chance of suffering from cognitive impairment. By contrast, another study (Tonning Olsson, Perrin, Lundgren, Hjorth, & Johanson, 2014) showed that male gender is associated with lower full-scale, verbal, and performance IQ. However, tumors in males are often larger in size, which eventually turned out to be a better predictor.

As these aforementioned studies describe, children treated for brain tumors, and especially posterior fossa tumors, are at risk for various impairments later in their lives. It is therefore important that long-term neuropsychological outcomes are investigated. Even more so, this study attempts to shed a light on the possible variables influencing this outcome. Its goal is to get a better understanding of possible treatment adaptations to minimize the risk of serious impairments. In order to gain this understanding, 3 questions are examined in the following systematic literature and follow-up study. The first question is which neurocognitive differences exist between patients treated for a posterior fossa tumor and their healthy counterparts. The second question examines what the specific risk factors for worse neurocognitive outcome are. Lastly, it is investigated whether treatment variables have an influence on the remaining cerebellar tissue in comparison to the cerebellum as a whole.

SYSTEMATIC LITERATURE STUDY

METHODS

To construct concrete hypotheses with regard to specific cognitive domains that might be affected, a systematic literature study was conducted. Only articles which concern behavior, emotion, and especially cognition as well as the diagnosis of a posterior fossa tumor and a pediatric population were included. The following search string based on MeSH terms was carried out in PubMed: *(cognition OR behavior OR emotion) AND posterior fossa (tumor OR neoplasm OR cancer) AND (child OR children OR survivors).*

In addition, it was made sure that the articles used in this study were all recent (≤10 years) studies, carried out in a human sample. The main focus of this study was to investigate posterior fossa tumor

survivors, within the age range of 16 to 35 years, who had finished treatment at least 1.5 years before the study. It was thus made sure that all articles implemented the same recruitment criteria as the current study. Nineteen articles were eventually selected (see Figure 1). The articles that did not get selected were excluded due to the lack of an available full text or the fact that they did not concern the right type or location of tumor, that the study did not discuss the general psychological outcome, that the time since treatment was less than 1.5 years, that the age range was not 16-35 years old, or that they only discussed cerebellar mutism. In what follows, the most frequently reported outcome variables and potential risk factors are discussed.

RESULTS

Outcome

In the past 10 years, a lot of research has focused on late effects of treatment of posterior fossa tumors. A wide variety of cognitive, behavioral, emotional, and physical domains seem to be significantly impaired, even up to years after treatment. A review by Robinson et al. (2013), which studied the neurocognitive outcome of posterior fossa tumor survivors, found that patients are impaired in 14 domains. These domains include overall cognitive ability, verbal and non-verbal intelligence, academic achievement in reading, math, and spelling, attention and processing speed, executive function, psychomotor skill, language, verbal and visual memory, and visuospatial skills.

Hoang et al. (2014) described that to get a better understanding of the role of the cerebellum and the link between a damaged cerebellum and cognition, Buckner, Krienen, Castellanos, Diaz, and Yeo (2011) studied the organization and functional connectivity of the human cerebellum. With resting-state fMRI, they found that functional connectivity appears between hemispheric lobules I-VI, vermal VIIb, IX, and the visual network; hemispheric lobules VI, VIIb, VIII and the auditory network; lobules I-VI, VIII and the sensorimotor network; hemispheric Crus I/II and the fronto-parietal network; and hemispheric lobules VIIb, VIII and the task-positive network. A study by Bernard et al. (2012), discussed in the article of Hoang et al. (2014), yielded that there are anatomical and functional associations between the anterior cerebellum and the cerebral motor network, and the posterior cerebellum and the prefrontal and parietal cortex, which play an important role in cognition. An overview of the late effects after treatment of a posterior fossa tumor can be found below (see Table 1).

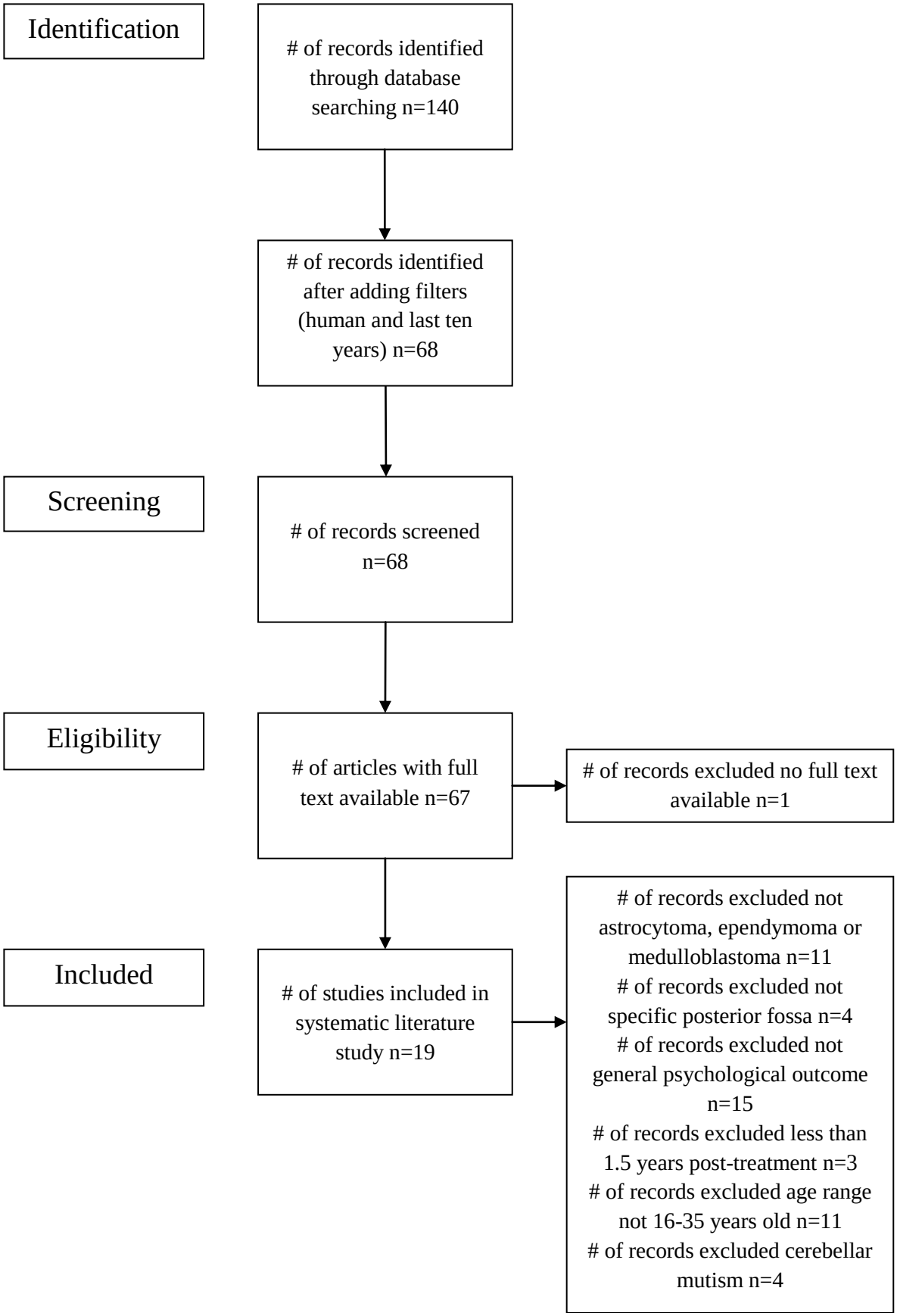

Figure 1. Flowchart

Table 1

Studies on late effects in children treated for posterior fossa tumors

Reference	Participants (N)	Late effects assessed	Risk factors	Main findings
Carroll et al., 2013	117	IQ, apathy	Female gender, age at diagnosis, surgical treatment, apathy	Lower IQ-scores. Higher apathy scores and lower chance of employment for female patients diagnosed before the age of 5 with partial tumor resection.
Charalambides et al., 2009	Literature study	IQ, memory, language, processing speed, attention, executive function, HRQoL	Age at diagnosis and treatment, radiotherapy, shunted hydrocephalus	Deficits in auditory, spatial and visual memory, language processing, attention, processing speed, verbal fluency and executive function. Progressive decline in IQ and HRQoL.
De Smet et al., 2012	8	IQ, language, processing speed, executive function, motor function, apathy, visual motor concentration	Treatment, structural changes	Hypoperfusion in areas important for language, executive function and behavior. Ataxia, speech defects, apathy, mental inflexibility and impaired performance IQ, executive function, working speed and visual motor concentration after mutism.
Hanzlik et al., 2015	Literature study	IQ, memory, attention, executive function	Age at treatment, type of treatment, chemotherapy, tumor type, structural changes	Worst performance in intelligence, attention, executive function and memory for MB survivors. Lower scores on IQ for EP survivors than AS survivors. Impaired attention and memory for AS survivors.
Hoang et al., 2014	Literature study	IQ, memory, attention, language, structural changes	Type of treatment, tumor type, medical events	Impaired attention, memory, executive function and IQ for MB survivors. Hypothesized impaired academic acquisition due to white matter damage.

Reference	Participants (N)	Late effects assessed	Risk factors	Main findings
Khajuria et al., 2015	34	IQ, memory, processing speed, attention, executive function, HRQoL, motor function	Surgical treatment, tumor location	Motor deficits, impaired selective attention, loss of executive function and behavioral problems. Lower scores on processing speed, fine motor function, selective attention, verbal memory and HRQoL for MB survivors than AS survivors. Association between atrophy and impaired IQ and attention.
Koustenis et al., 2016	42	Memory, accuracy, executive function, motor function	Type of treatment, tumor type	Impaired working memory, accuracy, inhibition, reaction speed and forward thinking for MB and AS survivors. Significant association between impairment and ataxia. Impaired planning in MB survivors which suggests a role of radio- and chemotherapy.
Lanier et al., 2017	Literature study	Language, motor function, endocrine problems	Age at diagnosis, surgical treatment, radiation medical events (PFS)	Remaining abnormal speech in PFS patients after recovery. Incomplete recovery after 1 year for 4 out of 5 patients. Several long-term impairments in PFS patients including neuropsychological impairment, neurologic deficits, and endocrine problems.
Lassaletta et al., 2015	Literature study	Executive function, language, motor function, short-duration perception, academic performance, living conditions	Age at treatment, type of treatment, tumor type and location, structural changes, medical events, SES	Less graduation, employment and independency, impaired short-duration perception, ataxic dysarthria, planning and cognitive set-shifting deficits and impaired balance and running speed in MB survivors. Dysfluent speech and deficits in balance and running speed in AS survivors.
Mabbott et al., 2008	74	IQ, memory, attention, processing speed	Craniospinal radiotherapy, medical events	Lower scores on a short-form IQ test and information processing for irradiated patients.

Reference	Participants (N)	Late effects assessed	Risk factors	Main findings
				Relatively intact working memory and sustained attention.
Mariën et al., 2010	Reaction to other study	Structural changes	/	Consistent pattern of damage to the pECP. Cerebello-cerebral diaschisis due to a decrease in blood flow within frontal regions. Damage to the cerebellum may influence the supratentorial regions via the dentatorubrothalamic tract.
Palmer et al., 2009	Literature study	IQ, memory, processing speed, attention, executive function, visuoconstructive ability, visual motor integration, HRQoL	Age at treatment, radiotherapy, structural changes	Correlation between intellectual decline and lower working memory capacity in combination with slower processing rate. Impairment in selective attention, short-term memory, semantic verbal fluency, processing speed and visuoconstructive ability after surgery. Declines in IQ-scores after radiotherapy. Declines in IQ-scores and visual motor integration and poorer physical and emotional health after adjuvant chemotherapy
Palmer et al., 2012	40	Processing speed, structural damage, visual matching, decision speed	Age at diagnosis	Worse processing speed and visual matching and lower fractional anisotropy in patients. Positive correlation between the rate of processing and the number of fiber tracts.
Robinson et al., 2013	Literature study	IQ, memory, processing speed and attention, executive function, language, motor function, visuospatial skill	Age at treatment	Impaired overall cognitive ability, verbal and non-verbal intelligence, attention, executive function, psychomotor skill, language, processing speed, verbal and visual memory, visuospatial skill and academic achievement in reading, math, and spelling in patients.

Reference	Participants (N)	Late effects assessed	Risk factors	Main findings
Roncadin et al., 2008	58	Neurobehavioral outcome, motor function, endocrinal function	Age at diagnosis, tumor type, medical events	Increase of motor events and treatment for hormonal dysfunctions after long-term survival (>5 years). Lower scores on all neurobehavioral outcomes for MB.
Rueckriegel et al., 2015	32	IQ, attention, executive function, motor function, structural changes	Structural changes	Full-scale IQ and ANT-scores correlated with skeletonized tract fractional anisotropy. Full-scale IQ and ICARS-scores (ataxia) correlated with frontocerebellar tract volume. This volume possibly correlates with deterioration of fine motor automation.
Schreiber et al., 2014	165	Reading skills and math ability (academic achievement)	Age at diagnosis, tumor type, medical events	Declines in reading skills and math ability in MB survivors. Significant decline in math ability over time in average- and high-risk patients.
Wolfe et al., 2012	Literature study	IQ, memory, attention and processing speed, executive function	Age at treatment, (craniospinal) radiotherapy, structural changes	Global deficits in attention. Hypothesis that impairment in one cognitive domain causes impairment in other interconnected cognitive domains. Decrease in capacity of working memory and rate of processing speed (linked to radiotherapy). Hypothesis that these impairments may influence intellectual ability. Deficits in executive function due to surgery.
Wolfe-Christensen et al., 2007	21	IQ, psychosocial life	Medical events (PFS)	More obsessive-compulsive types of behavior, a higher chance of showing withdrawal behavior and more social and internalizing problems in PFS patients.

Note. AS = astrocytoma; EP = ependymoma; MB = medulloblastoma; ATR = atypical teratoid rhabdoid

Intelligence and academic achievement

One affected domain that is discussed in the majority (n=12) of the articles, is intelligence and academic performance. The intellectual decline that is frequently observed after treatment could be a result of impairment in other cognitive domains, e.g. less capacity of the working memory and slower rates of information processing (Wolfe, Madan-Swain, & Kana, 2012). This decline has been observed post surgery, as well as after radio- and chemotherapy (Palmer et al., 2009). Wolfe-Christensen et al. (2007) did not find a difference between survivors who developed PFS and those who did not, so in their study PFS did not lead to a worse outcome. Rueckriegel et al. (2015) investigated the possibility of a significant correlation between the extent of functional loss and changes in white matter integrity estimates. They found that full-scale IQ, among other domains, is significantly correlated with functional loss and changes in these estimates. Secondly, full-scale IQ is also significantly correlated with frontocerebellar white matter tract volume. In a study in 2008 by Mabbott, Penkman, Witol, Strother, & Bouffet, a patient group that underwent surgery in combination with radiotherapy was compared to a group that only underwent surgery and a group that was treated for non-CNS solid tumors. A significant between-group difference was observed in the scores on a short-form IQ test, with survivors that underwent irradiation performing the worst. Carroll et al. (2013) also noted that survivors of a posterior fossa tumor who received radiotherapy, exhibit lower intelligence scores. Additionally, a study from Hanzlik et al. (2015) also described intellectual impairment. They did note that there is a difference in severity between medulloblastoma, ependymoma, and astrocytoma survivors. Medulloblastoma survivors consistently obtain the lowest scores on all dimensions and astrocytoma survivors perform still within normal range. It was also shown that medulloblastoma survivors perform significantly worse on full-scale IQ in comparison to astrocytoma survivors, who only score significantly lower on performance IQ (Khajuria et al., 2015). Moreover, one of the long-term symptoms in children who recovered from mutism, is that they show lower scores on performance IQ (De Smet et al., 2009). Furthermore, Charalambides, Dinopoulos, and Sgouros (2009) discussed the well documented evidence on the association between craniospinal radiation (dose and volume) and a progressive decline in IQ. In addition to this decline in IQ, other domains are impaired as well, leading to worse academic performance and outcome. Schreiber et al. (2014) conducted a research in a sample with average- and high-risk medulloblastoma patients and found that there are significant declines in reading skills and math ability, although the estimated scores 5 years post diagnosis remain in the normal range. They also noticed that in both average- as in high-risk patients, math ability decreases significantly over time. Hoang et al. (2014) hypothesized that the academic acquisition in medulloblastoma survivors may be impaired due to a deficit in reading, language (e.g. agrammatism, akinetic mutism, and dysarthria) and mathematics (e.g. working memory). These deficits most likely are a consequence of white matter damage in the cortico-ponto-cerebellar white

matter tract and the cerebello-thalamo-cortical white matter tract due to surgery and radio- and chemotherapy.

Attention and processing speed

As a second cognitive domain, attention and processing speed appear impaired long after treatment according to the majority (n=12) of the articles. For example, Palmer et al. (2009) reported that after surgery, selective attention and processing speed are significantly worse. Palmer et al. (2012) also found worse scores for processing speed and visual matching for low- and average-risk patients. Moreover, they found a significant positive correlation between the number of intact white matter fiber tracts and the rate of processing speed. After controlling for age at diagnosis, 3 bundles of fibers remained significantly related to processing speed. These bundles are the corpus callosum (body and splenium), the post thalamic radiation, and the external capsule. According to the literature study of Wolfe et al. (2012), global deficits in attention (computerized and motor-based sustained attention) are reported in many studies. Further, they found that colleagues proposed that the different cognitive domains are interrelated, causing children to perform worse in one domain if they are impaired in another. When looking for studies concerning processing speed, Wolfe et al. (2012) found that this function also suffers from craniospinal irradiation and decreases over time. In their own study, Mabbott et al. (2008) found that information processing impairment differs in severity depending on the type of treatment, with children treated with surgery in combination with irradiation performing the worst. Furthermore, the study from Steinlin et al. (2003), discussed in the review of Charalambides et al. (2009), also pointed to deficits in attention and processing speed after surgery only. De Smet et al. (2009), in addition, included deficits in visual motor concentration in the list of long-term symptoms after the recovery from mutism. In addition, Hanzlik et al. (2015) found a bigger impairment for attention in medulloblastoma survivors, but ependymoma and astrocytoma also show deficits on this domain. Also, Hoang et al. (2014) reported a deficit in attention for medulloblastoma survivors and finally, Khajuria et al. (2015) reported a clear impairment in processing speed for medulloblastoma but not for astrocytoma survivors. They also found that both groups score 1 SD below the mean for tonic alertness and selective attention.

Executive function

Executive functions are discussed in 8 studies on late effects of treatment of a posterior fossa tumor. Palmer et al. (2009), for example, reported problems in semantic verbal fluency after surgery. A literature study of Wolfe et al. (2012) also reported on the effects of surgery on executive function (e.g. planning, problem solving, fluency, cognitive flexibility, and cognitive set-shifting). They found that surgery alone can lead to major deficits in this domain, and that there is no significant difference between patients treated with surgery alone and those treated with a combination of surgery and radio- and chemotherapy. Rueckriegel et al. (2015) not only found a correlation between IQ and skeletonized changes in white matter integrity estimates, they also reported a significant connection between these

skeletonized changes and tasks of the Amsterdamse Neuropsychologische Taken (ANT), with the highest correlation for the subtest shifting attention. Further, Charalambides et al. (2009) discussed a study of Steinlin et al. (2003) reporting deficits in verbal fluency among others. They also noted the contribution of craniospinal irradiation to impairments in executive function and rate of skill acquisition. Furthermore, De Smet et al. (2009) discussed that, in children exhibiting mutism post surgery, SPECT neuroimaging shows hypoperfusion in supratentorial areas in the frontal and parieto-temporal areas that are important for language, executive function and behavior. Long-term symptoms – after mutism cleared up – also include diminished working speed and increased rigidity and mental inflexibility, which are impairments in executive functions. The study of Hoang et al. (2014) also tackled impaired executive function in medulloblastoma survivors. Koustenis, Driever, de Sonneville, and Rueckriegel (2015) reported impairments in accuracy, inhibition, reaction speed, and forward thinking (correlated with ataxia) in medulloblastoma and astrocytoma survivors. Results are worse for medulloblastoma survivors, who also show a deficit in planning. Finally, Lassaletta et al. (2015) described deficits in planning and cognitive set-shifting in medulloblastoma survivors.

Memory

Another well documented (n=9) impaired domain is memory. Palmer et al. (2009) reported postoperative problems in this domain, more specifically they mentioned a deficit in short-term memory. As for working memory, it was noted that the capacity decreases over time, with a more prominent decrease immediately after treatment (Wolfe et al., 2012). A review by Charalambides et al. (2009) discussed a study from Riva and Giorgi (2000) which showed impairments in auditory memory and language processing in children treated for right cerebellar tumors, and in spatial and visual memory in those with left cerebellar tumors. They also discussed the aforementioned study from Steinlin et al. (2003) which claimed that memory, among other domains, is impaired post-treatment. Also according to Charalambides et al. (2009), craniospinal irradiation highly affects visual memory impairment. Furthermore, Hanzlik et al. (2015) studied the post-treatment cognitive outcome regarding impairments in memory function in medulloblastoma, ependymoma, and astrocytoma survivors. The most prominent impairments were again noted in medulloblastoma survivors. Hoang et al. (2014) also mentioned memory impairment in medulloblastoma survivors. Finally, Khajuria et al. (2015) found that the medulloblastoma group has more false positives and interference in the verbal memory test.

Other cognitive functions

As for other cognitive functions, 4 studies mentioned specific late effects. Scores on decision speed are, according to Palmer et al. (2012), higher in the control group but still within normal range in the patient group. In addition, the results for decision speed correlate with the degree of activity in the corpus callosum (body and splenium) and post thalamic radiation. In the same research visual matching also seems to be related to the degree of activity in the corpus callosum (genu and body),

and the external capsule. Palmer et al. (2009) further reported impairments in visuoconstructive skill for children treated with surgery only and a deficit in visual motor integration after adjuvant chemotherapy. Finally, short-duration perception also seems to be impaired in medulloblastoma patients (Lassaletta et al., 2015).

Speech and language

Speech and/or language impairment is another frequently (n=6) reported outcome. CMS and PFS are the most prevalent examples, which typically occur in an acute phase. However, speech and other neuropsychological functions can stay impaired long after mutism has cleared up. Wolfe-Christensen et al. (2007) conducted a retrospective analysis of medical charts of posterior fossa tumor survivors and focused on the differences between children with and without PFS. Results show that there are no differences between the groups in terms of IQ-scores. They did find certain differences in psychosocial function which will be addressed further (see section on psychosocial life). Lanier and Abrams (2017) studied the different clinical presentations of PFS in children treated for posterior fossa tumors. They noted that during the phase in which children were recovering from PFS, when speech had already returned, speech remains abnormal. Also, 1 year after diagnosis only a small portion of the children (1 out of 5) has fully recovered. The remaining survivors still exhibit residual symptoms, like ataxia and dysarthria. They also reported several long-term cognitive sequelae in children with PFS, including neuropsychological impairment, neurological symptoms and endocrine problems. As previously mentioned (see section on executive function), De Smet et al. (2009) researched the outcome in children exhibiting mutism post surgery. Their SPECT imaging yielded that there is hypoperfusion in supratentorial areas in the frontal and parieto-temporal areas that are important for language, executive function and behavior. The authors hypothesized that these results are a consequence of CCD, which means that the loss of function could be caused by damage in a different but connected area in the brain. Amongst the long-term symptoms of posterior fossa tumors, bradylalia and dysarthric speech are also mentioned. The study from Hoang et al. (2014) that reported on impairment in medulloblastoma survivors, mentioned deficits in language, e.g. agrammatism, akinetic mutism, and dysarthria. They also discussed a study from Soelva et al. (2013), noting that survivors with CMS postoperatively show a significantly lower volume in fronto-cerebellar white matter tracts. Finally, Lassaletta et al. (2015) found more ataxic dysarthria in medulloblastoma survivors than in astrocytoma survivors. In astrocytoma survivors, speech production is comparable to that in healthy controls, but speech dysfluency is comparable to medulloblastoma survivors.

Motor problems

Motor dysfunction, and especially ataxia, is found in 7 articles. Rueckriegel et al. (2015) for example, discussed that ICARS-scores – that measure ataxia – are significantly correlated with frontocerebellar white matter tract volume. In addition, frontocerebellar white matter tract volume is significantly correlated with the deterioration of fine motor automation. Further, De Smet et al. (2009) also reported

ataxia as a long-term symptom observed after mutism. According to Khajuria et al. (2015), research has shown clear evidence for motor deficits, loss of executive functions, and behavioral problems in posterior fossa tumor survivors. Fine motor function was impaired in both medulloblastoma and astrocytoma survivors, with the worst impairment in medulloblastoma. Roncadin et al. (2008) also note more sensory and motor problems at long-term survival (>5 years post-treatment). Finally, Lassaletta et al. (2015) reported on deficits in balance and running speed, concluding that impairment is visible in medulloblastoma and astrocytoma survivors, but is more prominent in the medulloblastoma group.

Emotional and physical health

Emotional and physical well-being were mentioned in 5 studies. The paper from Palmer et al. (2009) addressed the outcome of adjuvant chemotherapy. Children who were treated with surgery, irradiation, and chemotherapy often report poorer physical and emotional health, based on scores for HRQoL, than children who did not receive chemotherapy. Further, Carroll et al. (2013) found that, in comparison to their healthy siblings, female childhood posterior fossa tumor survivors diagnosed before age 5 have a higher score on the apathy scale. Apathy was also mentioned by De Smet et al. (2009) as a long-term symptom after mutism. In addition, in the literature study of Charalambides et al., a study of Bhat et al. (2005) was discussed. They found that HRQoL (assessed by the Pediatric Quality of Life Inventory (PedsQL)) is worse in the survivor group than in the healthy control group. At long-term survival (>5 years post-treatment), intracranial pressure and cerebellar/bulbar events are reported more often according to Roncadin et al. (2008). Finally, lower scores for self-esteem as a measure of HRQoL also exist for the medulloblastoma group in the study of Khajuria et al. (2015).

Psychosocial life

Psychosocial aspects belong to another domain where deficits have been identified (n=2). In the study of Wolfe-Christensen et al. (2007), differences in psychosocial function between children with and without PFS were found. Significantly more PFS patients show signs of obsessive-compulsive types of behavior, social problems, and internalizing behavior. They also have a significantly higher chance of showing withdrawal behavior. Finally, a larger group of PFS patients scores significantly higher on overall internalizing problems. The review of Charalambides et al. (2009) discussed the fact that the subjects from the study of Steinlin et al. (2003) exhibit behavioral problems and psychiatric symptoms which are worse in patients with lesions in the vermis. Finally, Lassaletta et al. (2015) showed that medulloblastoma patients do not graduate as frequently as astrocytoma patients, and consequently are less often employed fulltime. Furthermore, only half of them were able to live independently.

Structural changes

Although structural changes did not belong to the scope of this systematic literature study, this subject was worth mentioning. Neuroanatomical changes or changes in the brain have been mentioned earlier

when discussing the other domains. In 4 articles, neural change or damage has been mentioned post-treatment (Palmer et al., 2012; Rueckriegel et al., 2015; Hoang et al., 2014). Mariën, De Smet, Paquier, and Verhoeven (2010) specifically focused on these changes by reporting on a study from Miller et al. (2010), which discussed a consistent pattern of damage to the pECP in pediatric posterior fossa tumor survivors who suffer from PFS. After this structural damage, a decrease in blood flow within the frontal regions was established, leading to CCD. Earlier research had already found an alteration in supratentorial perfusion in survivors who developed PFS. Their symptoms diminished as the perfusion re-increased. Damage to the cerebellum appears to influence the supratentorial brain regions via the dentatorubrothalamic tract and CCD. Furthermore, 6 articles mentioned that treatment can damage the brain and its networks, which can result in a negative neurocognitive outcome. For example, surgical damage to an area in the cerebellum called the vermis correlates with more severe impairment according to Palmer et al. (2009). Research also showed that damage to the vermis leads to deficits in body coordination (Lassaletta et al., 2015). In addition, the study of Rueckriegel et al. (2015) showed that damage to the cerebro-cerebellar connectivity is an important determinant of the severity of ataxia and fine motor impairment. Finally, decreased estimates for white matter integrity in the splenium (corpus callosum) are significantly related to more impaired processing speed.

Hormonal problems

Like structural changes, hormonal changes did not belong to the specific interest for this systematic literature study but are worth discussing. Endocrinological problems were reported in 1 study (Lanier & Abrams, 2017) and are also mentioned in the study of Roncadin et al. (2008) when discussing the most important medical events at 4 different points in time (diagnosis, perioperative phase, short-term survival and long-term survival). They found that the presence of treatment for hormonal dysfunctions is elevated in short-term (<5 years post-treatment) and long-term (>5 years post-treatment) survival.

Risk factors

Tumor

In the literature search, 9 studies mentioned that the tumor itself can lead to a specific outcome. For example, research (Schreiber et al., 2014) showed that the risk category of the tumor correlates with the outcome. The general intellectual ability and reading skills of high-risk medulloblastoma patients decreased significantly over time. They further found that average-risk patients are generally impaired on fewer domains or less severely. Moreover, Hoang et al. (2014) considered the type of tumor and the presence of metastasis as risk factors for cognitive late effects, with some treatments implicating more severe impact. Also, having a total resection of an astrocytoma compared to a complete resection of a medulloblastoma or partial resection of an astrocytoma results in better outcome (Carroll et al., 2013). As mentioned before, the location of the tumor in the fossa posterior region may influence neurocognitive, behavioral, and emotional outcome. However, according to Khajuria et al. (2015)

evidence is mixed. Lassaletta et al. (2015) did mention the location of the brain tumor again as a risk factor for specific deficits. They explained that vermian tumors specifically have a negative influence on language and affect, while other non-cerebellar tumors influence different cognitive functions. Furthermore, they also discussed the outcome of different types of tumors. Medulloblastoma survivors exhibit the worst outcome, deteriorating over time. Astrocytoma survivors show the most positive outcome, but are also impaired. Finally, according to Mabbott et al. (2008), a positive correlation exists between the size of the tumor and the development of PFS. It has become clear that the size as well as the risk category of the tumor are associated with the choice for a specific treatment. This is why the tumor and the treatment cannot be viewed separately.

Treatment

In the majority (n=12) of the articles it was shown that different treatments hold certain risks. Hoang et al. (2014) pointed this out by stating that the type of treatment influences cognitive outcome. As for surgery, it was found that opting for a partial tumor resection, instead of a resection of the entire tumor, can lead to higher post-treatment scores for apathy. Then again, research (Khajuria et al., 2015) showed deficits in speech and learning capacity in pilocytic astrocytoma survivors with larger postoperative lesion sizes. Lanier et al. (2017) found that surgery as well as radiotherapy has a significant influence on long-term neuropsychological deficits in children with PFS. Palmer et al. (2009) determined that when children were treated with radiation therapy, the dosage in combination with age at treatment determines the severity of late effects. A higher dose, in combination with a younger age, would then lead to a worse outcome. Not only the dose, but also the specific radiation therapy used seems to be important. Wolfe et al. (2012) suggested that craniospinal radiation therapy results in more attentional deficits in comparison to radiation therapy only directed to the tumor in the posterior fossa. Charalambides et al. (2009) already discussed the importance of the dose of irradiation and the volume that has been irradiated. As such, they classified both as risk factors for neurocognitive impairment. Further, they named craniospinal radiation as a risk factor for a progressive decline in IQ, which is worse in younger children. Finally, in their review they discussed the article of Bhat et al. (2005). According to this article, cranial radiation proves to be a risk factor for even lower scores on HRQoL. Research (Hanzlik et al., 2015) has also shown that the type of treatment (and the tumor histopathology) has an influence on cognitive late effects. In medulloblastoma and ependymoma patients, outcome is worse when whole brain irradiation with a higher dosage was used and when the children were younger at treatment. This may lead to more white matter damage, which in turn leads to lower scores on IQ tests. De Smet et al. (2009) believed that radiotherapy causes white matter density changes, which most likely lie at the root of the impairment seen. Finally, the study of Lassaletta et al. (2015) stated that the cerebello-thalamo-cerebral pathway, which is crucial for working memory, can be damaged by radiotherapy. Medulloblastoma patients often get treated with radiotherapy, which is an important cause of additional neurocognitive impairment and eventually

leads to an alteration in HRQoL. Craniospinal irradiation also had a detrimental effect on memory and IQ, and the severity of the impairment is significantly correlated with the dosage of irradiation. Nonetheless, reduced-dose radiotherapy (23.4 Gy) could also lead to white matter loss in addition to an elevated risk of relapse. Moreover, a tumor bed boost to the posterior fossa also leads to scattered radiation of the surrounding structures and therefore to worse cognitive outcome. They also found that radiation at a younger age may influence academic performance. Furthermore, the dosage of chemotherapy can be linked to worse outcome, namely more support needed, secondary health problems, and a worse outcome in HRQoL. Lastly, Hanzlik et al. (2015) found that chemotherapy leads to deficits in perception skills, memory, and processing speed.

Patient-related factors

Age at diagnosis has been consistently evidenced to be a risk factor, in such a way that younger children are more vulnerable for serious late effects. Age is discussed in 12 articles as a potential risk factor, with only 1 study (Mabbott et al., 2008) not being able to prove a significant relationship. Palmer et al. (2009) for example reported that the older the patient is at diagnosis, the lower the risk of intellectual decline is. Palmer et al. (2012) also found that age at diagnosis is positively correlated to results on processing speed and visual matching. Further, white matter integrity estimates are significantly correlated to age at diagnosis, meaning that a younger age at diagnosis predicts lower integrity estimates in patients. Robinson et al. (2013) noted that age at treatment (< 7 years vs. ≥ 7 years) is a significant predictor for decline in overall cognitive ability and verbal and non-verbal intelligence. Further, Roncadin et al. (2008) found that age at diagnosis is significantly correlated with intelligence in the medulloblastoma group and with intelligence, memory, and functional dependence in the astrocytoma group. Also, HRQoL seems to be negatively correlated with age at diagnosis. Schreiber et al. (2014) discussed age at diagnosis as a risk factor for cognitive outcome in medulloblastoma survivors, affecting the rate of decline in general intellectual ability, mathematics, and reading skills. When age was dichotomized at 7 years, it seems that patients' general intellectual ability and math skills mainly decrease significantly for the younger subjects. In the younger average-risk patients, only the declines in general intellectual ability and reading skills are significant, while in the younger high-risk patients all declines are. For the older patients the correlations are different. Again, all declines in the high-risk group are significant, but in the average-risk group the only significant decline was observed in math skill. Moreover, general intellectual ability seems to increase significantly in the older average-risk group. It is noteworthy that when the authors estimated what the mean scores at 5 years post diagnosis would be, all results remain within the average range. Other research (Wolfe et al., 2012) also reported that a younger age at treatment results in poorer sustained attention, deficits in planning and cognitive set-shifting, and a decreased amount of healthy white matter. The long-term symptoms in children with severe PFS reported by Lanier et al. (2017) are influenced by factors such as age at diagnosis and treatment. Additionally, Carroll et al. (2013)

discussed that children younger than 5 years at diagnosis are at increased risk for higher scores on apathy. Furthermore, Charalambides et al. (2009) found that cranial radiation at a younger age results in worse cognitive and behavioral outcome. Age at diagnosis and treatment, as well as time since treatment, were mentioned as risk factors for a more progressive neurocognitive decline. Also, in medulloblastoma and ependymoma patients, the outcome is worse when children were younger at the time of treatment (Hanzlik et al., 2015). Finally, Lassaletta et al. (2015) found that a younger age at the time of radiotherapy negatively influences academic performance, school problems, endocrinal symptoms, need for support (therapeutically and educationally) and cause secondary physical health problems (e.g. strokes, cavernomas, and secondary tumors).

Other patient-related risk factors were discussed in different articles selected for this literature study. SES has been mentioned before as a potential risk factor. In this literature search, SES was only mentioned in a study from Lassaletta et al. (2015). They found that HRQoL is negatively influenced by lower SES. Also, gender was only mentioned in 1 study (Carroll et al., 2013). They reported that the female gender is a risk factor for higher apathy scores, which in turn negatively influence chances for employment. Finally, as for other patient-related factors, left-handedness was put forward in a study from Mabbott et al. (2008). They found that PFS occurs significantly more often in left-handed children, which could be attributed to altered dominance of the 2 hemispheres in these cases.

Medical events

Lastly, medical events or post-treatment complications might worsen neurocognitive outcome even further (n=10). For example, Roncadin et al. (2008) found that intelligence is negatively correlated with the number of medical events during short-term survival. Memory and functional dependence are negatively correlated with the number of medical events during both the perioperative phase and short-term survival. According to Lassaletta et al. (2015) and Charalambides et al. (2009), (shunted) hydrocephalus, regardless of the tumor, is an important contributor to cognitive deficits and worse HRQoL. Further, Hoang et al. (2014) also named hydrocephalus as a risk factor for cognitive late effects. Schreiber et al. (2014) discussed that patients with serious post-treatment hearing loss, compared to those without, evidence a significant decline in general intellectual ability. It seems that this might also be a risk factor for intellectual outcome and reading skills. Also, they showed that subjects who have developed PFS show a significant decline in reading skills. Furthermore, Mabbott et al. (2008) discussed that in patients treated with craniospinal radiation, additional postsurgical complications result in worse performance on information processing. They also looked at the risk factors for developing PFS and found that having preoperative language deficits and behavioral disorders results in a higher risk for developing PFS. In addition, Lanier et al. (2017) suggested that children with severe PFS symptoms have a higher risk of having persistent residual symptoms 1 year later. Wolfe-Christensen et al. (2007) discussed that having PFS post-treatment predicts a higher risk for impairment in a number of psychosocial domains. Finally, not only PFS but even CMS alone could

lead to late effects. Lassaletta et al. (2015) concluded that patients who developed CMS, exhibit a worse outcome in the domain of HRQoL.

Conclusion

In conclusion, a number of late-term effects after the treatment of a posterior fossa tumor can arise. Declines in performance are especially observed in domains such as intelligence and academic achievement, attention and processing speed, executive function, and memory. Therefore, the follow-up cohort study will focus on these cognitive domains. Furthermore, the literature study has also found some interesting variables that may increase the risk for certain dysfunctions or declines in performance. Some of the most important ones are the type of tumor and its treatment, age at diagnosis and at treatment, and other patient-related factors such as SES. These risk factors will be given special considered during the conduction and analyses of the cohort study.

FOLLOW-UP COHORT STUDY

METHODS AND MATERIALS

Participants

This study concerns a follow-up of survivors of a pediatric brain tumor in the fossa posterior that were treated at the University hospital of Leuven in Belgium (UZ Leuven). 30 survivors, treated between 1990 and 2015, were considered eligible for this research. 21 patients agreed to participate in the study, of whom 15 were male (71,43%) and 6 were female (28,57%). The 9 remaining survivors declined the offer due to various reasons. The patient group consisted of people with an age range between 16 and 35 years old (M=25.202; SD=4.724). They were at least 1.5 years out of treatment and had Dutch as their native language. For the control group, healthy age- (M=24.931; SD=4.751) and gender-matched controls were searched with no neurological or psychiatric history. The average numbers of years of education were relatively equal between patients and controls (M=12.976, SD=1.764 and M=15.119, SD=2.345 respectively). After the testing, all participants received a financial compensation (voucher) and they could ask for their cognitive assessment result reports. The study had been approved in advance by the ethical commission of the hospital (UZ Leuven).

Measurements

Data acquistion consisted of a neuropsychological and a neuroimaging part. First a neuropsychological assessment (testings and questionnaires) was conducted by 1 of the 3 researchers and afterwards MRI images were made.

In order to assess neurocognitive function, a neuropsychological testing and self-reported questionnaires were administered. The neuropsychological testing itself lasted for approximately 2.5

hours and the questionnaires were filled in at home and brought to the hospital on the day of the appointment.

The Dutch version of the Wechsler Adult Intelligence Scale (WAIS-IV-NL) was administered to assess intelligence (Wechsler, 2012). COTAN rates the reliability of this test as good, the norms and construct validity as sufficient and the criterion validity as unsatisfactory due to a lack of research (Evers, Lucassen, Meijer, & Sijtsma, 2010). The subscore verbal comprehension was measured by the tests vocabulary and information. Perceptual reasoning was measured by the tests block design and matrix reasoning. Working memory was measured by the test digit span. The 4th subscore, processing speed, was measured by the tests symbol search and coding. To assess verbal memory, the Dutch version of the Auditory Verbal Learning Test (AVLT) was used (Kalverboer & Deelman, 1964). According to COTAN, the reliability as well as the construct validity are good, but the criterion validity is again unsatisfactory. Visual memory was assessed with the Rey Visual Design Learning Test (RVDLT) (Wilhelm, Swaab, Serlier-van den Bergh, & van der Heijden, 2010). COTAN assesses the reliability, the construct validity and the criterion validity as unsatisfactory because of too little or methodological unsatisfactory research. To assess attention, the Amsterdamse Neuropsychologische Taken (ANT) (de Sonneville, 2011) has been administered (test-retest reliability between .70 and -.94). The subtasks baseline speed, memory search letters, and shifting attentional set-visual were conducted to measure respectively reaction time and arousal, divided attention and memory, and inhibitory control and attentional flexibility. Word fluency was assessed by the Dutch version of the Controlled Oral Word Association Test (COWAT), which is a subtest of the MAE (Multilingual Aphasia Examination) (Benton, Hamsher, Rey, & Sivan, 1994). COTAN assesses the reliability and construct validity as sufficient. The criterion validity is judged unsatisfactory due to a lack of research. In addition to word fluency, vocabulary was measured using set 13 to 17 of the Peabody Picture Vocabulary Test (PPVT-III-NL) (Schlichting, 2005). According to COTAN, reliability is judged to be good, construct validity sufficient and criterion validity unsatisfactory due to lack of research.

The Dutch translation of the Behavior Rating Inventory of Executive Function (BRIEF) (Scholte & Noens, 2011) measures executive function, and is aimed for 18-65-year-olds (*test-retest reliability*=.75 and higher, *internal consistency*=.90 and higher). For this study, only the self-report version was used. Cognitive failure was measured using the Dutch version of the Cognitive Failure Questionnaire (CFQ) (Ponds, van Boxtel, & Jolles, 2006) (*internal consistency*=.88). To explore any self-reported symptoms of depression, the second (revised) Dutch version of the Beck Depression Inventory questionnaire (BDI-2-NL-R) was administered (van der Does, 2002) (*test-retest reliability*=.93, *internal consistency*=.91). The Dutch version of the Stait-Trait Axiety Inventory (STAI) (van der Ploeg, 2000) was used to measure anxiety (*test-retest reliability state anxiety*=.54, *test-retest reliability trait anxiety* =.86, *internal consistency*= .86-.95). This study also used the Pediatric Quality of Life Inventory (PedsQL) (Dutch translation) (Varni, Seid, & Rode, 1999), which sheds light on the subjective HRQoL. Originally it had been designed for pediatric patients who suffer from chronic

health issues, but it can also be used in healthy subjects. Due to the targeted age range of the questionnaire of 2-25 years old, this questionnaire would normally not be appropriate to use for the age range of this research. Since most of the participants (26 out of 42) are between the ages of 16 and 25 years old, it was decided that this was still the best option to measure HRQoL (reliability between .68 and .88 and construct validity lower than .001). Lastly, questions about education, living conditions, medical history (e.g. health problems and medication use), alcohol and drug use, smoking, and right/left handedness were asked on the day of testing itself, right before the start of the testing process.

In addition to these behavioral data, imaging data were gathered using magnetic resonance imaging for anatomical and functional whole-brain images. The entire MRI session lasted for 1 hour. MRI images were obtained using a 3T Philips Achieva ds scanner to assess brain anatomy. This manuscript specifically comprises anatomical information based on the T1-weigthed MRI images. These structural images were nonlinearly registered to MNI space to acquire spatially normalized images across subjects. These images enabled an estimation of the remaining proportion of cerebellar tissue (gray and white tissue) in comparison to the proportion of CSF within a cerebellar mask. (cfr. infra) This was done by applying a voxel-based morphometry (VBM) with Computational Anatomy Toolbox (CAT) to achieve a 3-tissue compartment segmentation (i.e. gray matter, white matter, CSF) (Zhang et al., 2008).

PROCEDURE

For each participant, written informed consent was obtained and an MRI safety checklist was evaluated before scanning. On the day of the appointment, participants came to the hospital for the assessment which started with neurocognitive testing. Firstly, a clinical interview about complaints was conducted. Then the neuropsychological assessment started with the AVLT learning phase and the subtasks block design, matrix reasoning, symbol search, and coding from the WAIS-IV-NL. Twenty minutes after the acquisition of the learning phase, the delayed reproduction and recognition of the AVLT were administered. This was followed by the learning phase of the RVDLT and the remaining WAIS-IV-NL subtasks (i.e. vocabulary, information, and digit span). The delayed reproduction and recognition of the RVDLT took place twenty minutes after the learning phase, as with the AVLT. The neuropsychological assessment was completed by administering the remaining subtasks if necessary, including the COWAT, the PPVT, and the subtasks of the ANT. Following the neuropsychological assessment, the MR scanning session was performed.

Statistical analysis

Statistical analyses were performed using SPSS v.24. Figure 2 shows the 3 main research questions that were examined and the 3 final multivariate models that were analyzed in order to answer these questions. *P* values <0.05 were considered significant.

The first question was whether there are significant outcome differences between posterior fossa tumor patients and healthy age- and gender-matched controls. Two models were generated to answer this question: one including both patient vs. control and SES[1] as predictors and one in which patient vs. control was the only predictor. Multivariate analyses were conducted to extract behavioral variables on which patients significantly differed from controls. Bonferroni correction was performed to reduce Type I error due to multiple analyses.

A similar GLM procedure for multivariate analyses was performed to answer the second research question, namely whether there are risk factors that could possibly explain these significant deviations of the patient group. Firstly, the relationship between several disease and treatment variables and the outcome variables selected based on the first research question were examined. Disease and treatment variables that showed a significant relationship with outcome were considered possible risk factors. Secondly, mutual associations between these possible risk factors were examined using the Pearson correlation coefficient (*r*) and crosstabs for linear and categorical variables respectively. As a result, independent risk factors were extracted and assigned to 3 different categories, namely radiotherapy, surgery, and timing. Different models were formed combining 3 independent risk factors (one from each category). From these possible models, the one with the highest explanatory value was extracted as final model for potential risk factors for worse behavioral outcome.

In addition to these 2 research questions, a third question was posed regarding the influence of treatment variables on current cerebellar tissue proportions. Long-term effects of treatment were examined using cerebellar tissue proportions, as measured by the relative total volume of CSF in comparison to that of the cerebellum as a whole (i.e. the total number of voxels containing CSF divided by the total voxel size of the cerebellum, indicating remaining cerebellar tissue). Figure 4 shows an MNI template on which the blue marking indicates the region in which the relative proportion of cerebellar tissue was calculated. The same procedure was followed as for the second research question, starting with an explorative analysis of the relationship between several treatment variables and remaining cerebellar tissue. Again, crosstabs were used first to check interdependency between treatment variables that were found to significantly relate to cerebellar tissue. Next, univariate analyses were performed to determine unassociated treatment variables that have significant explanatory value for the variance in relative voxel size of CSF.

[1] SES was measured using the Hollingshead Four Factor Index of Social Status. This index is based on the level of education and the prestige of occupation of both parents. Hollingshead, A. B. (1975). *Four factor index of social status*. New Haven, CT: Hollingshead.

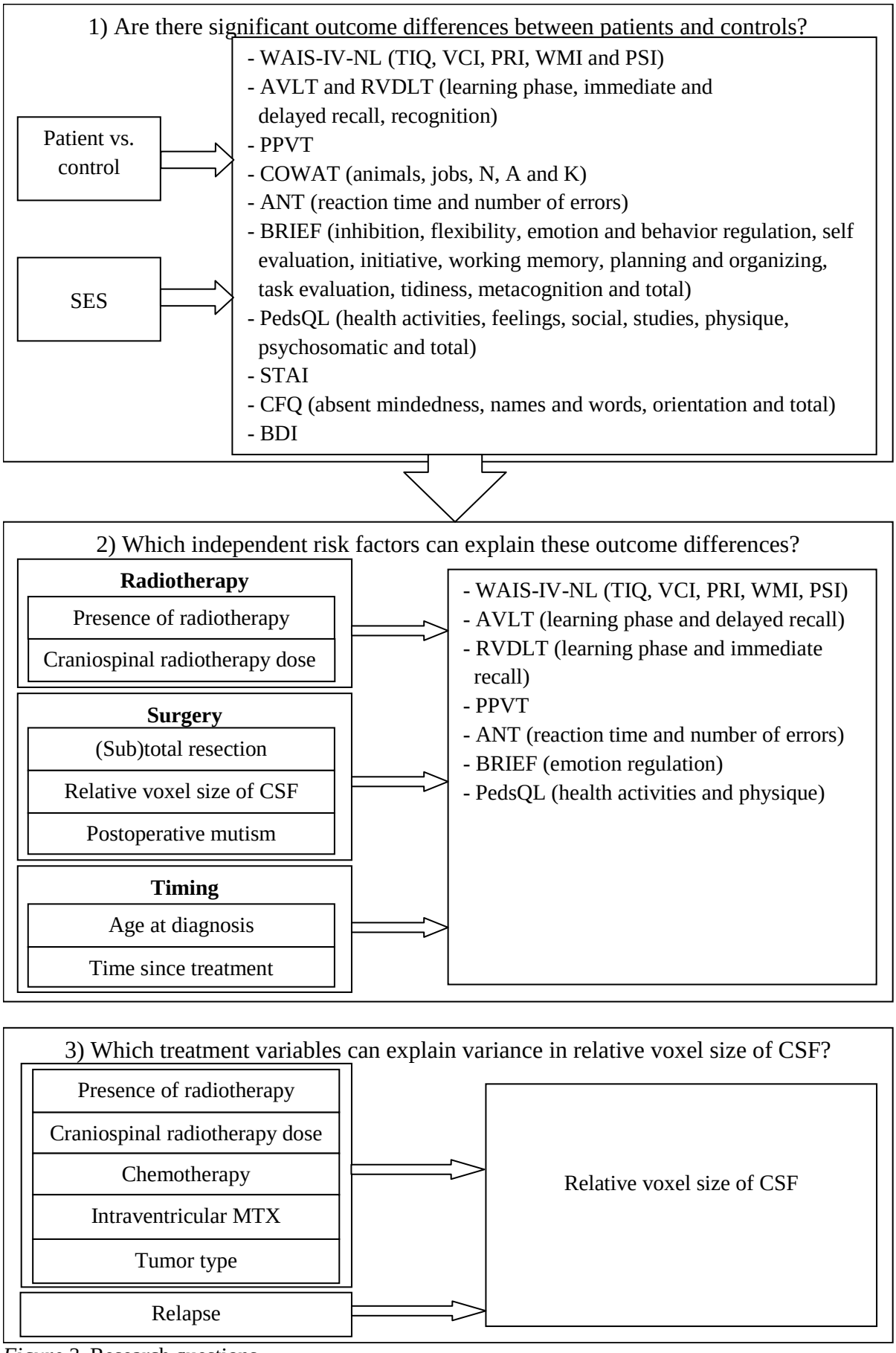

Figure 2. Research questions

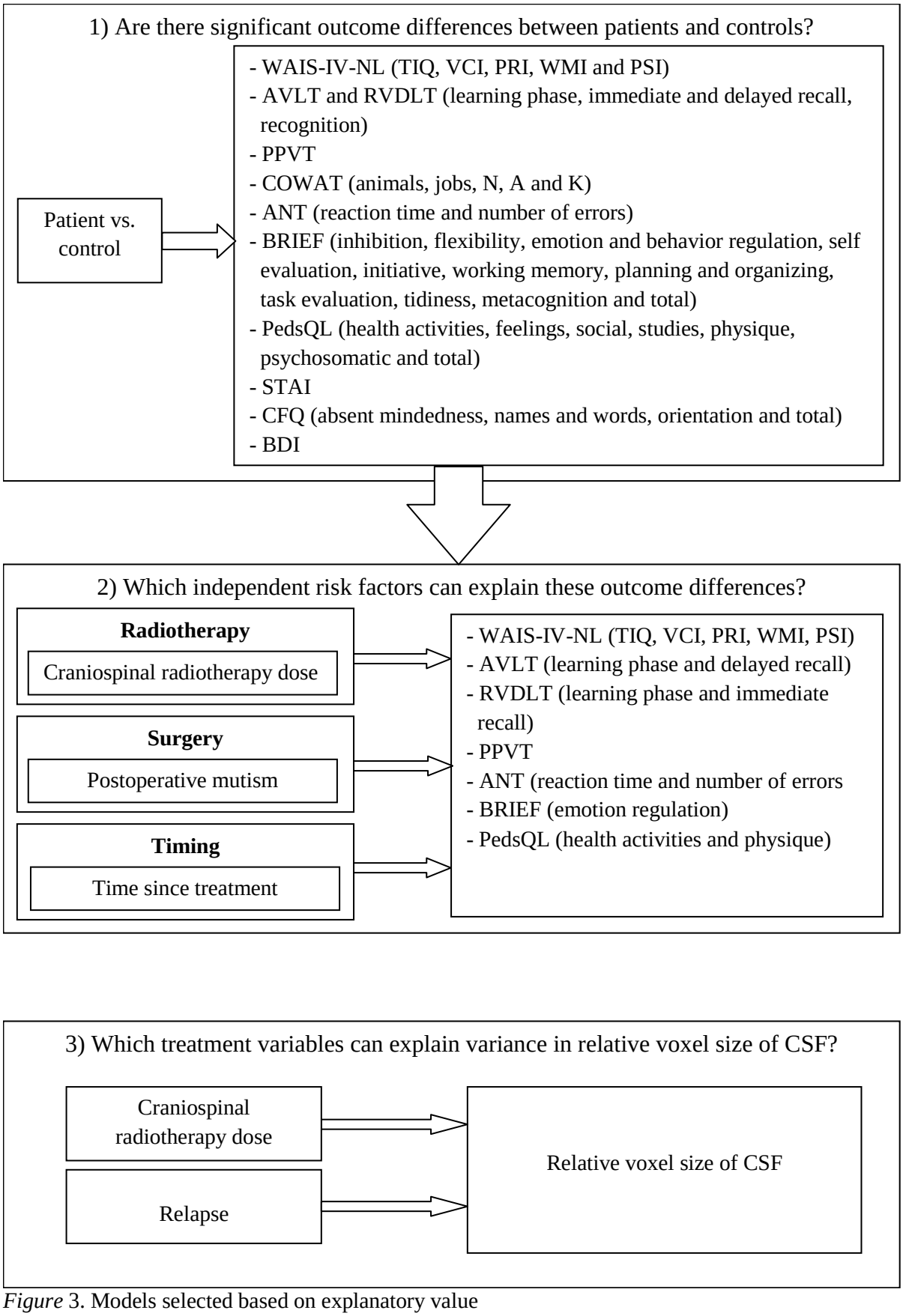

Figure 3. Models selected based on explanatory value

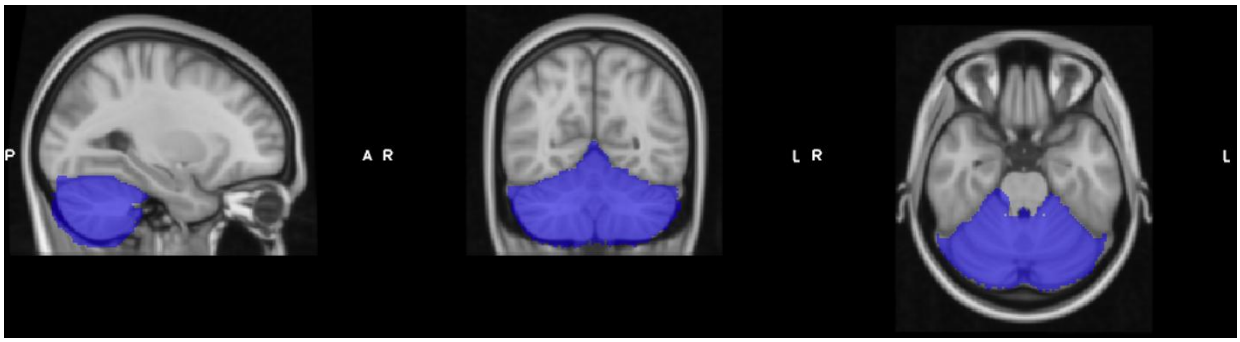

Figure 4. Mask for cerebellar tissue proportion

RESULTS

Descriptive results

The patient group included 21 pediatric posterior fossa tumor survivors (see Table 1). Eight patients (38.10%) were diagnosed with pilocytic astrocytoma, 1 patient (4.76%) with ependymoma, and 12 patients (57.14%) with medulloblastoma. Concerning treatment, 7 patients (33.33%) only had surgical tumor resection, while 5 patients (23.81%) received additional radiotherapy, and 9 patients (42.86%) also received chemotherapy. In 6 patients chemotherapy included intraventricular methotrexate (MTX), all of them were diagnosed with medulloblastoma. Most patients received craniospinal radiotherapy (n=12), with doses of 23.4 Gy, 35-36 Gy, or hyperfractionated 40 Gy. There are 2 patients who only received focal radiotherapy (doses 54 Gy and 55.8 Gy). Metastases occurred in 6 patients (28.57%). All of these 6 were diagnosed with medulloblastoma and received craniospinal radiotherapy doses of 35.2 Gy or more as well as focal radiotherapy of the posterior fossa. Five of them received additional radiation treatment of the metastases. Relapse occurred in 4 patients (19.05%), half of them were diagnosed with pilocytic astrocytoma and the other half with medulloblastoma. The control group consisted of 21 healthy age- and gender-matched participants. Patient-control differences in SES were non-significant. In sum, there were 30 males and 12 females and mean age was 24.8 years old (range 16.4-34.8).

The answers to the 3 research questions (cfr. supra) are briefly visualized in Figure 3. This figure contains the best models (i.e. the ones with the largest explanatory value) found after analyzing the models based on these 3 research questions.

Outcome differences

The first research question concerned the difference in behavioral outcome between posterior fossa tumor survivors and healthy controls. All collected behavioral data were compared between patients and controls. Table 2 gives an overview of the mean group scores for the outcome variables on which patients and controls significantly differ. These significant differences were found in intelligence, with large effects for total intelligence (TIQ), verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI), and processing speed (PSI). Regarding memory, patients showed significant

Table 2

Descriptive results

Patient	Age at dx (years)	Time since treatment (years)	Tumor type	Total resection	Radiotherapy	Craniospinal radiotherapy dose (Gy)	Hyperfractionated radiotherapy	Chemotherapy	Intraventricular MTX	Metastasis	Relapse
1	3.3	19.9	AS	+	-	0.0		-	-	-	-
2	11.1	15.0	MB	+	+	23.4	-	+	-	-	-
3	7.3	9.2	AS	+	-	0.0		-	-	-	-
4	4.6	22.7	MB	+	+	35.2	-	-	-	+	-
5	10.8	21.5	MB	+	+	35.2	-	-	-	-	-
6	2.9	19.5	MB	+	+	35.2	-	+	+	+	-
7	18.4	1.5	MB	+	+	23.4	-	+	-	-	-
8	10.2	20.0	AS	+	-	0.0		-	-	-	+
9	4.5	17.6	AS	+	-	0.0		-	-	-	-
10	7.8	17.0	AS	+	-	0.0		-	-	-	-
11	3.2	16.2	AS	+	-	0.0		-	-	-	-
12	13.3	17.2	MB	-	+	35.2	-	+	+	-	-

Patient	Age at dx (years)	Time since treatment (years)	Tumor type	Total resection	Radiotherapy	Craniospinal radiotherapy dose (Gy)	Hyperfractionated radiotherapy	Chemotherapy	Intraventricular MTX	Metastasis	Relapse
13	11.6	10.0	AS	+	-	0.0		-	-	-	-
14	8.8	15.6	AS	-	+	0.0	-	-	-	-	+
15	3.2	5.2	MB	+	+	36.0	-	+	+	+	+
16	7.1	21.9	MB	+	+	35.2	-	-	-	-	-
17	12.9	4.8	MB	-	+	36.0	-	+	-	-	-
18	7.2	16.8	MB	-	+	40.0	+	+	+	+	-
19	4.8	20.3	MB	-	+	35.2	-	+	+	+	+
20	8.0	26.0	EP	+	+	0.0	-	-	-	-	-
21	14.0	5.2	MB	+	+	40.0	+	+	+	+	-

Note. AS = pilocytic astrocytoma; EP = ependymoma; MB = medulloblastoma; dx = diagnosis

Table 2

Behavioral outcome for patients vs. controls

Outcome	Patients		Controls		Group comparisons		
	Mean	SD	Mean	SD	*F*-values	*p*-values	R^2_{Adj}-values
WAIS-IV-NL subscale							
TIQ	80.10	12.728	107.85	14.423	42.789	.000	.511
VCI	84.33	15.929	108.55	16.757	22.507	.000	.350
PRI	87.52	12.703	108.05	14.351	23.574	.000	.361
WMI	80.90	19.626	103.80	13.976	18.346	.000	.302
PSI	78.00	13.867	102.80	13.786	32.950	.000	.444
AVLT subscale							
Learning phase	-1.976	1.012	-.875	1.352	8.771	.005	.163
Delayed recall	-1.531	1.017	-.460	1.576	6.759	.013	.126
RVDLT subscale							
Learning phase	-1.434	1.473	.376	1.553	14.672	.000	.255
Immediate recall	-1.352	1.698	.257	1.608	9.682	.003	.178
PPVT	88.140	16.593	108.30	11.531	20.208	.000	.324
ANT subscale							
Reaction time	.641	1.771	-.486	1.168	5.727	.022	.106
Number of errors	.739	2.011	-.478	.907	6.125	.018	.114
BRIEF subscale emotion regulation*	54.29	12.438	45.70	5.686	7.941	.008	.148
PedsQL subscale							
Health activities	614.29	165.184	703.75	80.816	4.774	.035	.086
Physique	614.29	165.184	703.75	80.816	4.774	.035	.086

Note. SD = standard deviation; R^2_{Adj} = effect size

* higher scores reflect worse executive function

deficits in visual and verbal working memory and learning (RVDLT learning phase and AVLT learning phase respectively), visual short-term memory (RVDLT immediate recall), and verbal long-term memory (AVLT delayed recall). Concerning verbal function (PPVT), 32.4% of the variance in object naming was explained by the difference between patients and control participants. Significant differences were also found in several attentional functions, among which divided attention. Divided attention was measured by mean reaction time and the number of errors made in the presence of 2 distracters (ANT reaction time and ANT number of errors respectively). With regard to executive function, patients scored significantly lower than controls on emotion-regulation (BRIEF subscale emotion regulation). At last, as also shown in Table 2, HRQoL concerning health activities and physique (PedsQL subscale health activities and PedsQL subscale physique respectively) differ significantly between pediatric fossa posterior tumor survivors and healthy controls.

Table 3

MANOVA results of effects of craniospinal radiotherapy dose, postoperative mutism and time since treatment on behavioral outcome

Risk factor	Craniospinal radiotherapy dose *F*-values (*p*-values)	Postoperative mutism *F*-values (*p*-values)	Time since treatment *F*-values (*p*-values)	**Complete model**
WAIS-IV-NL subscale				
TIQ	3.768 (.034)*	3.359 (.087)	3.274 (.090)	**5.290 (.005)***
VBI	3.895 (.031)*	.185 (.673)	5.171 (.038)*	**5.341 (.005)***
PRI	1.207 (.341)	12.350 (.003)*	4.628 (.048)*	**3.191 (.037)***
WGI	3.075 (.060)	.678 (.423)	.033 (.858)	**3.064 (.042)***
VSI	4.561 (.018)*	1.475 (.243)	.032 (.861)	**4.409 (.011)***
AVLT subscale				
Learning phase	.966 (.434)	1.959 (.182)	4.513 (.051)	**1.447 (.265)**
Delayed recall	.714 (.559)	1.213 (.288)	2.226 (.156)	**.734 (.609)**
RVDLT subscale				
Learning phase	1.085 (.386)	1.549 (.232)	4.307 (.056)	**1.214 (.350)**
Immediate recall	1.310 (.308)	1.589 (.227)	5.211 (.037)*	**1.537 (.237)**
PPVT	1.959 (.164)	.349 (.563)	9.277 (.008)*	**3.336 (.032)***
ANT subscale				
Reaction time	5.792 (.008)*	1.518 (.237)	.007 (.933)	**4.292 (.013)***
Number of errors	8.784 (.001)*	.383 (.545)	.019 (.892)	**6.131 (.003)***
BRIEF subscale emotion regulation	2.682 (.084)	6.016 (.027)*	1.163 (.298)	**1.926 (.149)**
PedsQL subscale				
Health activities	1.408 (.279)	.643 (.435)	1.397 (.256)	**.957 (.474)**
Physique	1.408 (.279)	.643 (.435)	1.397 (.256)	**.959 (.474)**

* = significant results

Risk factors influencing outcome

The second research question included the search for independent risk factors that could explain the significant differences in outcome between patients and controls. Investigated variables included: age at diagnosis, time since treatment, tumor type, tumor location, (sub-)total tumor resection, radiotherapy, craniospinal radiotherapy dose (categorized into 4 groups, namely 0 Gy, 23.4 Gy, 35-36 Gy and 40 Gy), radiotherapy type (conventional vs. hyperfractionated), chemotherapy, intraventricular MTX, hydrocephalus, drainage, metastases, relapse, relative voxel size of CSF in comparison to the whole cerebellum, postoperative mutism, postoperative ataxia, postoperative hypotonia, postoperative irritability, postoperative paresis, SES, and gender. Radiotherapy type and postoperative hypotonia were excluded due to small category sizes. In addition, tumor location was judged unusable due to its shifted distribution, given that most tumors were located in the spinocerebellum. Bonferroni-corrected multivariate analyses of the remaining variables resulted in several risk factors that are significantly related to worse behavioral outcome.

To investigate interdependency of predictors, the Pearson correlation coefficient was calculated for each possible combination of continuous risk factors to examine their association. A significant negative correlation was found between age at diagnosis and time since treatment (r=-.506, p<.05). In addition, time since treatment is also negatively correlated to SES (r=-.534, p<.05), leading to the impossibility to include both variables as risk factors in the same model. All other correlations between continuous predictors were non-significant. Regarding categorical risk factors, crosstabs were applied in order to identify dependent variables. This resulted in a significant correlation between tumor type and craniospinal radiotherapy dose, chemotherapy, metastases, and intraventricular MTX (r=21.000, p=.002; r=11.813, p=.003; r=6.300, p=.043 and r=6.300, p=.043 respectively). In addition, presence of radiotherapy is significantly correlated with tumor type, chemotherapy, metastases, and intraventricular MTX (r=17.063, p=.000; r=7.875, p=.005; r=4.200, p=.040 and r=4.200, p=.040 respectively). Similar associations were found for craniospinal radiotherapy dose (r=21.000, p=.002; r=13.344, p=.004; r=11.200, p=.011 and r=11.200, p=.011 respectively). Metastases and intraventricular MTX were also interdependent (r=12.343, p=.000).

Since only unassociated risk factors can be included as predictors in the same model, the number of possible models was strongly decreased by these correlations. All evaluated possible models consisted of a combination of 3 predictors, one from each category (radiotherapy, surgery, and timing, cfr. supra and Figure 2). The GLM which included craniospinal radiotherapy dose, postoperative mutism, and time since treatment as independent predictors has shown the highest power and effect sizes to explain the variance in behavioral outcome in patients vs. controls. This model as a whole explained a significant amount of variance in total IQ, verbal comprehension, perceptual reasoning, working memory, processing speed, object naming, and divided attention as measured by reaction time and number of errors (F=5.290, p=.005, R^2_{Adj}=.517; F=5.341, p=.005, R^2_{Adj}=.520; F=3.191, p=.037,

R^2_{Adj}=.354; F=3.064, p=.042, R^2_{Adj}=.340; F=4.409, p=.011, R^2_{Adj}=.460; F=3.336, p=.032, R^2_{Adj}=.369; F=4.292, p=.013, R^2_{Adj}=.451; F=6.131, p=0.003, R^2_{Adj}=.562 respectively). Table 3 summarizes the influence of the different predictors on behavioral outcome. Larger craniospinal radiotherapy doses are significantly associated with worse scores on total IQ, verbal comprehension, processing speed, and divided attention. In addition, a significant amount of variance in perceptual reasoning and emotion-regulation is explained by postoperative mutism, with worse scores for those patients who showed symptoms of mutism. A longer time since treatment on the other hand is significantly related to worse performance on verbal comprehension, perceptual reasoning, visual short-term memory, and object naming.

Risk factors influencing cerebellar tissue

The third and last research question concerned the association between treatment variables and current cerebellar tissue proportion. These investigated treatment variables include: age at diagnosis, time since treatment, tumor type, (sub-)total tumor resection, radiotherapy, craniospinal radiotherapy dose (categorized into 4 groups, namely 0 Gy, 23.4 Gy, 35-36 Gy and 40 Gy), posterior fossa radiotherapy dose, chemotherapy, intraventricular MTX, hydrocephalus, drainage, metastases, relapse, and SES. As with the second research question, bonferroni-corrected multivariate analyses of these variables resulted in several risk factors that are significantly related to bigger relative voxel size of CSF in comparison to the cerebellum as a whole.

Since all of these predictors are categorical, only crosstabs were examined to identify interdependent treatment variables. These crosstabs showed significant correlations between craniospinal radiotherapy dose, chemotherapy, intraventricular MTX, and tumor type (cfr. supra). All of these 4 treatment variables were found to be independent from relapse, leading to the possibility to form 4 different models to explain the variance in relative voxel size of CSF, as shown in Figure 2.

The GLM which includes craniospinal radiotherapy dose and relapse as predictors for relative voxel size of CSF was shown to be the one with the largest explanatory value as objectified by its power (β) and effect size (F=6.555, p=.003, β=.959, R^2_{Adj}=.621). Both craniospinal radiotherapy dose and relapse were found to have a very large influence on relative voxel size of CSF (F=5.971, p=.006, β=.895 and F=6.792, p=.019, β=.687 respectively). These results are summarized in Table 4.

Table 4

ANOVA results of treatment variables on relative voxel size of CSF

Treatment variable	Craniospinal radiotherapy dose *F*-values (*p*-values)	Relapse *F*-values (*p*-values)	**Complete model**
Relative voxel size of CSF	5.971 (.006)	6.792 (.019)	**6.555 (.003)**

Note. CSF = cerebrospinal fluid

DISCUSSION

The goal of this systematic literature and follow-up study was to assess the long-term neuropsychological function of childhood posterior fossa tumors. In addition, we also aimed to get an overview of the different disease and treatment variables influencing long-term effects. A secondary goal was to gain insight into possible treatment adaptations that could result in better long-term outcome for posterior fossa tumor survivors. Based on literature findings, 3 research questions were posed. Firstly, we attempted to examine the difference in outcome between posterior fossa tumor patients and healthy controls, to get an overall view on patient deviation in neuropsychological function from their peers. Secondly, independent risk factors for worse outcome in patients were identified in order to get an idea of the relative contribution of disease and treatment variables on neuropsychological function. Thirdly, we aimed to assess whether specific treatment variables have an influence on cerebellar tissue loss.

OUTCOME DIFFERENCES

With regard to the first research question, we found very large (p<.001) differences between patients and controls in intelligence (i.e. all subscales of the WAIS-IV-NL), visual learning (i.e. learning phase of the RVDLT), and object naming (i.e. PPVT). Patients scored on average 20.53 points lower on PRI in comparison to controls, on VCI even 24.22 points. These results are even larger than the 13 and 18 points respectively found by Carroll et al. (2016). These smaller effects found by Carroll et al. (2016) could be attributable to the fact that they used siblings as controls. In addition, significant differences (.001<p<.05) were found for verbal learning and long-term memory (i.e. learning phase and delayed recall of the AVLT), short-term visual memory (i.e. immediate recall of the RVDLT), divided attention (i.e. reaction time and number of errors of the ANT), self-reported emotion regulation (i.e. BRIEF), and self-reported HRQoL concerning health activities and physique (i.e. PedsQL). These results are in line with studies by King et al. (2016) reporting learning or memory deficits in 60% of pediatric posterior fossa medulloblastoma survivors and Koustenis et al. (2015) reporting significant problems with attention as measured by the ANT. By contrast, no significant outcome differences were found between patients and controls concerning visual and verbal recognition (i.e. RVDLT and AVLT), word fluency (i.e. COWAT), most domains of self-reported executive function (i.e. inhibition, flexibility, behavior regulation, self-evaluation, initiative, working memory, planning, and organizing, task evaluation, tidiness, metacognition and total score of the BRIEF), several domains of self-reported HRQoL (i.e. feelings, social, studies, psychosomatic, and total score of the PedsQL), self-reported anxiety (i.e. STAI), self-reported cognitive mistakes (i.e. absent mindedness, names and words, orientation, and total score of the CFQ), and self-reported depressive symptoms (i.e. BDI). The lack of significant differences on most subscales of the PedsQL is contrary to the significantly lower patient scores on HRQoL found by Bhat et al. (2005). Their patient group consisted of younger

children (*M*=11.82, *SD*=5.39) with a shorter time since diagnosis (*M*=4.26, *SD*=4.41), of which 18.7% were still receiving treatment at the time of assessment. By contrast, Khajuria et al. (2015) also did not find an effect concerning HRQoL as measured by the KINDL-R, with exception of the subtest self-esteem. In closing, Lassaletta et al. (2015) only found a difference in HRQoL for medulloblastoma patients.

Given the remarkable differences in objective assessments, it is surprising that patients barely report subjective impairments. We hypothesized that time since diagnosis could be a possible confounding variable, with longer time since diagnosis resulting in more mental adaptation to impairment and as such less subjective complaints. In contrast to this hypothesis, there were no significant correlations found between time since diagnosis and self-reported impairments on questionnaires such as the BRIEF, PedsQL, CFQ, STAI, or BDI. We also hypothesized patients who were younger at diagnosis to perceive their limitations more as their baseline function due to their lack of other experiences and as such report less subjective impairment. To examine this, we assessed the correlation between age at diagnosis as a possible confounding factor and scores on the aforementioned questionnaires. However, no significant results were found, except for the correlation between age at diagnosis and the names and words subscale of the CFQ. The finding that patients who were older at diagnosis report more frequent problems remembering words and names could indicate that neuroplasticity plays an important role in minimizing verbal memory deficit in pediatric brain tumor survivors. Nevertheless, no correlation was found between age at diagnosis and AVLT and RVDLT scores. Further research is recommended to explore the exact nature of this relationship.

RISK FACTORS INFLUENCING OUTCOME

Regarding the second research question, independent predictors for worse outcome were categorized into radiotherapy-related factors (i.e. presence of radiotherapy and craniospinal radiotherapy dose), surgery-related factors (i.e. (sub)total resection, remaining cerebellar tissue and postoperative mutism) and timing (i.e. age at diagnosis and time since treatment). The statistical model combining these predictors with the largest explanatory value was found to include craniospinal radiotherapy dose, postoperative mutism, and time since treatment as predictors. This model yielded an explanation of a significant ($p<.05$) amount of outcome variance ($.340<R^2_{Adj}<.562$) in intelligence (all subscales of the WAIS-IV-NL), object naming (PPVT), and divided attention (ANT). No significant results were found for verbal or visual memory (AVLT and RVDLT), self-reported executive function (BRIEF), or self-reported HRQoL (PedsQL). These findings partly correspond to those of Tonning Olsson and colleagues (2014), who also found whole brain irradiation to be one of the most important risk factors for worse cognitive outcome. In addition to this predictor, their research also yielded age at diagnosis to be a profound risk factor. This is in contrast with our finding that the predictor time since treatment has a bigger explanatory value than the interrelated variable age at diagnosis. A younger age at diagnosis is however frequently reported in literature as a risk factor for worse outcome, especially

regarding intelligence (Dennis, Spiegler, Hetherington, & Greenberg, 1996; Edelstein et al., 2011; Mulhern et al., 2001; Palmer et al., 2001; Rønning, Sundet, Due-Tønnessen, Lundar, & Helseth, 2005).

Craniospinal radiotherapy dose appears to mainly affect processing speed (VSI) and divided attention (ANT). In addition, it was found to have a significant influence on total IQ (TIQ) and verbal comprehension (VBI). This correlation between dose of craniospinal irradiation and intelligence was also found by Grill et al. (1999) and Lassaletta et al. (2015). By contrast, presence of radiotherapy in general (i.e. focal and craniospinal) had no significant impact on divided attention in our study. We examined the possibility that this difference could be attributed to a lack of impact of focal radiotherapy (i.e. on posterior fossa only) on divided attention. This would implicate that attention problems could be avoided by applying more focal instead of craniospinal radiotherapy. There were however no significant differences found in ANT-scores between patients with craniospinal radiotherapy only and those with focal radiotherapy only. This leads us to conclude that the variance in divided attention is at least partly a consequence of the difference in craniospinal radiotherapy dose, with higher doses – even when hyperfractionated – leading to worse performance on the ANT. This could possibly also explain the association between metastases and lower ANT-scores, since patients with metastases received on average higher craniospinal radiotherapy doses. An important remark concerning this hypothesis is the fact that we are unable to distinguish between the consequences of treatment and the effect of the cancer itself. As such, the worse performance of patients with metastases on the ANT could also be attributable to neurotoxic effects of the metastases themselves, irrespective of their treatment. Furthermore, it needs to be mentioned that our study included just 2 patients with focal radiation only, which makes the aforementioned conclusion about the relationship between attention and craniospinal radiotherapy dose merely explorative. Postoperative mutism has a big impact on perceptual reasoning (PRI) and self-reported emotion-regulation (BRIEF). A study by De Smet et al. (2009) with children who exhibited mutism yielded similar results, with long-term impairment in performance intelligence scores for children who recovered from mutism. They also found long-term impairment in executive functions, such as mental flexibility. Surprisingly, no effects of mutism on verbal comprehension (VBI) were found. Finally, time since treatment mainly affects object naming (PPVT), with a longer time since treatment resulting in lower PPVT-scores. It was also found to influence verbal comprehension (VBI), perceptual reasoning (PRI), and short-term visual memory (immediate recall of the RVDLT). Research by Schreiber et al. (2014) resulted in the finding that math ability shows a decrease over time in medulloblastoma survivors. Gradual post-treatment increases in impairment of posterior fossa tumor survivors could be a result of a decelerated information acquisition in comparison to age-matched controls (Palmer et al., 2000). These effects are hypothesized to be attributable to anatomical and functional brain changes (Miller et al., 2010; Rueckriegel et al., 2015).

Surprisingly, no significant association was found between hydrocephalus and behavioral outcome. This is in contrast to multiple previous studies that have found hydrocephalus to be a risk factor for worse neurocognitive outcome (Charalambides et al., 2009; Hardy, Bonner, Willard, Watral, & Gururangan, 2008; Lassaletta et al., 2015) and more specifically intelligence, reducing it by 8 points (Lemiere, 2014). Papazoglou, King, Morris, & Krawiecki (2008) however also did not find a relationship between presence of hydrocephalus and worse adaptive function in children with cerebellar or third ventricle tumors. A possible explanation for this lack of significance in our study might be the fact that hydrocephalus was unequally distributed over tumor type, with 11 out of 16 patients with hydrocephalus (68.75%) having medulloblastoma, 4 out of 16 (25%) having astrocytoma, and 1 out of 16 (6.25%) having ependymoma. Hydrocephalus was absent in only 1 out 12 medulloblastoma patients (8.33%). Another finding that amazed us was the significant association between absence of postoperative ataxia and lower intelligence and object naming scores. It needs to be mentioned that the variable postoperative ataxia should be interpreted with caution since it was rated by different physicians and there was no gradual score of severity at our disposal. In order to attain a better understanding of this remarkable association, we checked the relationship between postoperative ataxia and possible confounding variables including tumor type, metastases, radiotherapy, chemotherapy, intraventricular MTX, (sub)total resection, and postoperative mutism, but no significant associations were found. Postoperative ataxia did however relate to time since treatment (p=.026), with ataxia occurring more often in patients with a shorter time since treatment. Intelligence and object naming scores are also found to be inversely proportional to time since treatment. As a result, time since treatment is a possible explanatory variable for the fact that we found an association between postoperative ataxia on the one hand and intelligence and object naming scores on the other. That is to say, a longer time since treatment is both associated with a smaller chance of postoperative ataxia and lower scores on the WAIS-IV-NL and the PPVT.

RISK FACTORS INFLUENCING CEREBELLAR TISSUE

The third research question led to the possible combination of either presence of radiotherapy, craniospinal radiotherapy dose, chemotherapy, intraventricular MTX, or tumor type with the predictor relapse to explain the variance in relative voxel size of CSF. The combination with the highest explanatory value was found to be the one with craniospinal radiotherapy dose and relapse. The influence of tumor type and craniospinal radiotherapy dose does not come as a surprise, since more severe tumor types, such as medulloblastoma, require higher doses of radiotherapy, which is associated with more extensive loss of brain tissue (Khajuria et al., 2015; Lassaletta et al., 2015).

LIMITATIONS

Our study includes several limitations that need to be discussed. Starting with the rather small sample size and heterogeneity of the sample in our study, which makes prudence necessary concerning

interpretations. Due to the small sample size, no separate analyses without any outlier data were possible to perform. Fortunately, an important strength of our study is the fact that there were no missing data and all participants successfully completed the whole test battery as well as the brain imaging session.

Other limitations concern the nature of our patient data. Our dataset is limited by the fact that clinical data during treatment consist of retrospective information assessed by the different physicians in attendance. Due to its absence in the available retrospective information, we are ignorant of the gradation and exact location of metastasis. This more detailed information about metastases, for example whether they were intracerebellar or not, is relevant for interpreting current behavioral outcome. Likewise, we did not have information available about the exact location of relapse. It would nonetheless be informative to identify patients with intracerebellar relapse, since they are likely to have a lower cerebellar tissue volume in comparison to patients with relapse elsewhere. In addition, there is a lack of baseline information about neuropsychological function before illness and a very limited amount of information about post-illness but pre-treatment function. This leads to an impossibility to detach the differential influence of disease and treatment variables, which complicates a comparison between different posterior fossa tumor types. Furthermore, there is an intrinsic correlation between tumor type and type of treatment, for example medulloblastoma tumors require more severe treatment than pilocytic astrocytoma tumors. Lassaletta et al. (2015) found radiotherapy to cause widespread brain damage, which leads us to suspect that radiotherapy has a bigger impact on outcome than the type of tumor as such. This corresponds to our finding that treatment variables explain a bigger amount of variance in outcome than tumor type, resulting in the decision to assess the effect of treatment instead of tumor type on long-term outcome. Since we opted for research questions about the effect of treatment, we cannot separately evaluate the influence of tumor type on neuropsychological function. Additional analyses based on tumor type predicted similar differences in behavioral outcome, which is a result of this association between tumor type and treatment.

Another limitation specific to our patient group is the inherent complexity of a clinical population that has received several different treatment interventions, with big differences in post-treatment stimulation as well. This leads to a complex variety of risk factors for worse outcome that are interrelated and as such cannot be clearly distinguished from one another. As a result, our findings are bound by the intrinsic statistical problem with clinical populations that the reduction in predictors might have excluded important, albeit interdependent, variables.

Limitations concerning our test battery include the fact that there was an incomplete assessment of the WAIS-IV-NL. The subtests similarities (VCI) and arithmetic (WMI) were not administered in order to limit the duration of the neuropsychological testing. Intelligence scores were assessed based on the remaining subtests. In addition, it is important to mention that we used the RVDLT to measure visual memory, but in fact this test also includes a major motor component which cannot be purely discerned from the visual memory component. Finally, there are lacunae in our test battery. For example, the

absence of heteroanamnesis is a weak point in our data collection. All subjective data is gathered via self-report questionnaires answered by the participants themselves. Additional information from family, partners, and/or employers could have provided a broader view on patient function, although this information needs to be interpreted critically due to its low reliability. On the positive side, the condensed administration of the intelligence testing allowed us to include a very extensive test battery, examining also other domains of cognitive function than just intelligence, such as attention and memory.

In addition, a few statistical limitations of our study need to be discussed. Firstly, there are 4 groups within the variable craniospinal radiotherapy dose, of which 2 consist of only 2 patients (9 patients received 0 Gy, 2 patients received 23.4 Gy, 8 patients received 35-36 Gy, and 2 patients received 40 Gy). This is attributable to our small sample size and an uneven distribution of craniospinal radiotherapy. Although these groups are statistically too small, we opted to use craniospinal radiotherapy dose instead of presence of radiotherapy for it is directly proportional to reaction time of the ANT. We opted for a division into 4 groups due to the fact that most patients with craniospinal radiotherapy (66.67%) received a dose of 35.2 or 36 Gy. Nevertheless, this limitation implies that conclusions about craniospinal radiotherapy dose need to be drawn with caution. Secondly, tumor location was too unevenly distributed across patients in order to use this predictor. This, in combination with the small size of our sample, made drawing conclusions about the influence of tumor location on outcome impossible. It could be interesting for future research to pay special attention to this variable, since research has suggested tumor location to have an important influence on broad long-term outcome (Lassaletta et al., 2015).

In conclusion, there are several interesting additional measurements that could be performed in future research. Commencing on the fact that our study focused on neurocognition, while outcome is much broader than just cognition. We do have self-reported data on the degree of anxiety and depressive symptoms perceived by patients and controls, but no significant results were found. It could for example be interesting to complement this study with more detailed research about the emotional long-term function (presence, regulation, etc.) of pediatric brain tumor survivors and its association with cognitive outcome. Carroll et al. (2013) have demonstrated an increase in apathy in childhood posterior fossa tumor survivors and found a link with lower VCI and TIQ scores. Furthermore, Shippen et al. (2016) suggest an important deficit in social cognitive function such as theory of mind in these patients. In addition, there is evidence that motor function is often impacted by posterior fossa tumors (Hartley et al., 2016; Lassaletta et al., 2015; Khajuria et al., 2015; King et al., 2016); Schmahmann & Caplan, 2006; Steinlin et al., 2007). Therefore, further research integrating neurocognitive, psychomotor, and psychosocial findings is highly recommended, since it could enhance a more complete understanding of long-term outcome in posterior fossa tumor survivors. Another interesting research question for future research is the role of white matter damage in the link

between certain treatment variables and long-term outcome. In our study, white matter damage was judged unusable since there are only 3 patients with a Fazekas rating of 2 or 3, and a Fazekas rating of 1 is ambiguous. This could possibly explain our lack of evidence found for an effect of radiotherapy or chemotherapy on white matter damage, contrary to multiple researchers who suggest an important relationship in which radiotherapy causes white matter damage, which on its turn impacts intelligence (Hoang et al., 2014; Mulhern et al., 2001). Furthermore, the link between cerebellar tissue loss and neurocognition could be further examined. Since we identified craniospinal radiotherapy dose as a risk factor for cerebellar tissue loss as well as worse long-term outcome, the possibility of a mediating role of this tissue loss could be interesting to investigate in future research.

Our research focused on giving a descriptive overview of long-term outcome in pediatric brain tumor survivors without assessing the influence of possible preventive or curative interventions. Given the neurocognitive weaknesses in childhood posterior fossa tumor survivors, it becomes highly important for future research to investigate possible interventions to improve the outcome deficiencies found in our and other research. For example, Lassaletta et al. (2015) have found promising results for a continued application of methylphenidate (Ritalin), donepezil, or cognitive remediation on several cognitive domains. By contrast, an explorative study of Massimino et al. (2011) did not provide much evidence for positive effects of pre-irradiation chemotherapy in order to reduce radiotherapy dose. Replication research on these possible interventions is necessary to enable an improvement of the treatment and follow-up of pediatric brain tumor survivors.

CONCLUSION

To conclude, our follow-up cohort study yielded several interesting findings. In regard to outcome differences between posterior fossa tumor patients and healthy controls, our findings mostly confirm previous research. Significant group differences were found for intelligence, visual and verbal memory, object naming, and divided attention. In contrast to these differences found in objective assessments, patients barely report subjective impairments. Several risk factors for worse outcome in patients were detected, with craniospinal radiotherapy dose, postoperative mutism, and time since treatment being the most important predictors for long-term neurocognitive function. We have additionally found craniospinal radiotherapy dose to be significantly associated with cerebellar tissue loss, which as such could play an important role in cognition. Despite consistent literature findings reporting hydrocephalus as a major risk factor, we found no significant association between hydrocephalus and outcome.

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