KU LEUVEN

FACULTY OF MEDICINE

Posterior fossa tumors in children and therapy-related long-term effects: a systematic review

Master Thesis proposed to achieve the degree of master in medicine by

Mathilde GHEYSEN

Unit: Faculty of Medicine

Department of Pediatrics

Promotor: Prof. dr. Anne UYTTEBROECK
Mentor: Charlotte SLEURS

Leuven, 2016-2017

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1. COVER LETTER

Dear members of the Editorial board,

We proudly present to you our paper entitled “Posterior fossa tumors in children and therapy-related long-term effects: a systematic review”.

Posterior fossa tumors constitute 60-70% of central nerve system tumors in children. The most frequent tumor types are medulloblastoma, astrocytoma and ependymoma. Treatment mainly depends on the tumor type and can consist of surgery, radiotherapy and chemotherapy. Major progress in treatment protocols during the last decades has led to significantly improved survival rates. However, as survival rates increased, long-term side-effects of therapy gained more and more attention. These effects comprise a broad spectrum of medical, neuropsychological and psychosocial sequelae.

Numerous studies have already depicted one or more of these effects. However, a complete overview of all long-term sequelae was missing to date. In this study, we systematically reviewed the bulk of existing research in order to give an extensive overview of all therapy-related consequences in the long term. Moreover, we specified for each treatment modality which long-term symptoms were related to it. To realize this, we screened the Pubmed/Medline database by using a comprehensive search algorithm. After systematically filtering the results, 67 qualitative articles were included for the analysis.

We found that the most frequent long-term sequelae were neurologic symptoms, endocrine deficits, speech problems and intellectual impairment. Recurring risk factors of greater treatment-related morbidity were medulloblastoma as tumor type, higher radiation dose and volume (e.g. when craniospinal radiotherapy is administered), younger age at diagnosis and perioperative complications like hydrocephalus.

This study is unique and contributes importantly to the existing research because of the following reasons:

- Our study is the first systematic review of all long-term treatment-related sequelae in posterior fossa tumor survivors.
- In our analysis, differences of long-term morbidity between the different tumor types (medulloblastoma, astrocytoma and ependymoma) were repeatedly described.
- Our study clearly indicates which treatment modality is responsible for which long-term effect.
- For the first time, a great deal of risk factors of worse long-term outcome in the different tumor types was described.

Considering these important statements, we believe that our study is an excellent candidate for publication in your journal. We would be very honoured if you could share our point of view.

Furthermore, we declare that our study is original, non-published work, that there was no funding for this research, nor any conflicts of interest.

Yours sincerely,

Mathilde Gheysen

2. ABSTRACT

Background: Posterior fossa tumors constitute 60-70% of central nerve system tumors in children. They are localized in the cerebellum and the brain stem. The most common tumor types are medulloblastoma, astrocytoma and ependymoma. Treatment for these life threatening neoplasms is established mainly according to the tumor type and can consist of surgery, radiotherapy and chemotherapy. Since survival rates have significantly increased during the last decades, long-term therapy-related effects have become more and more important. This study aims to give an extensive review of all treatment-related long-term sequelae in posterior fossa tumor survivors.

Methods: The Pubmed/Medline database was screened for articles published in 1990-2017 using the following search algorithm: ("Infratentorial Neoplasms"[Mesh] OR cerebellar tumor OR brain stem tumor) AND ("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh]) AND treatment AND (long term sequelae OR outcome). Studies including only adult patients or patients currently in treatment, studies not covering long-term effects and non-original research articles were excluded.

Results: The search algorithm returned 1367 articles. After screening, 67 studies were retained for the qualitative analysis. The most frequent long-term sequelae were neurologic symptoms, endocrine deficits, speech problems and intellectual impairment. Medulloblastoma patients suffered the greatest therapy-related morbidity. Other important risk factors for worse long-term outcome were radiation dose, radiation volume, preoperative hydrocephalus and younger age at diagnosis.

Conclusion: Therapy-related long-term effects are very frequent in all posterior fossa tumor survivors and comprise a broad spectrum of somatic, neuropsychological and psychosocial issues. Therefore, all caregivers involved should be aware of these sequelae, in order to maximally support vulnerable children who survived their cancer.

3. NEDERLANDSTALIGE SAMENVATTING

Achtergrond: Fossa posterior tumoren bestaan uit een groep tumoren gelokaliseerd in het cerebellum en de hersenstam. Bij kinderen maken ze 60-70% uit van alle tumoren in het centraal zenuwstelsel. De belangrijkste soorten zijn medulloblastomen, astrocytomen en ependymomen. De behandeling berust op drie pijlers: chirurgische resectie, radiotherapie en chemotherapie. De exacte combinatie van deze drie modaliteiten wordt voornamelijk bepaald door het tumor type. In de voorbije decennia werd enorme vooruitgang geboekt wat de overleving van deze tumoren betreft. Dit bracht op zijn beurt echter een nieuw probleem aan het licht, namelijk het op lange termijn ontstaan van symptomen veroorzaakt door de therapie. Het doel van deze studie bestaat erin een volledig overzicht te geven van al deze lange termijn effecten.

Methoden: De Pubmed/Medline database werd gescreend op artikels gepubliceerd tussen 1990 en 2017 aan de hand van de volgende zoekterm: ("Infratentorial Neoplasms"[Mesh] OR cerebellar tumor OR brain stem tumor) AND ("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh]) AND treatment AND (long term sequelae OR outcome). Er werden verschillende exclusiecriteria toegepast: alleen volwassen patiënten, het niet bestuderen van lange termijn effecten, case reports…

Resultaten: De zoekopdracht leverde 1367 artikels op. Na doorgedreven screening bleven er nog 67 relevante artikels over. De belangrijkste problemen op lange termijn bestonden uit neurologische symptomen, endocriene problemen, spraakstoornissen en cognitieve achterstand. Overlevers van medulloblastomas hadden hier het sterkst mee te kampen. Behalve het tumor type waren ook de bestralingsdosis, het bestralingsvolume, preoperatieve hydrocefalie en jonge leeftijd op het moment van diagnose belangrijke risicofactoren.

Besluit: Kinderen die hun fossa posterior tumor overleven, krijgen later zeer vaak te maken met gevolgen van de zware behandeling. Elke zorgverlener die betrokken is bij de zorg voor het kind moet hier steeds bedacht op zijn. Op die manier kunnen deze invaliderende symptomen vroegtijdig herkend en opvangen worden.

4. INTRODUCTION

Central nervous system (CNS) tumors are the most common type of solid neoplasms in children (1–3). These tumors also represent the second most common malignancy during childhood preceded by leukemia (1,4) and the most common cause of death from solid tumors (1). In Belgium, 621 cases of CNS tumors in children and adolescents (age 0-19 years) were reported in 2004-2009. Ependymoma was the most common CNS tumor in infants and astrocytoma was the dominant type in children and adolescents **(figure 1)** (5). 60-70% of CNS tumors in children occur in the posterior fossa (3). These posterior fossa tumors cover a heterogeneous group of tumor types, localized in the infratentorial compartment of the brain, more specifically the cerebellum and the brain stem (6). The most prevalent types of posterior fossa tumors found in children are medulloblastoma, cerebellar pilocytic astrocytoma, ependymoma, atypical teratoid rhabdoid tumor (ATRT) and brainstem glioma (1,3,7).

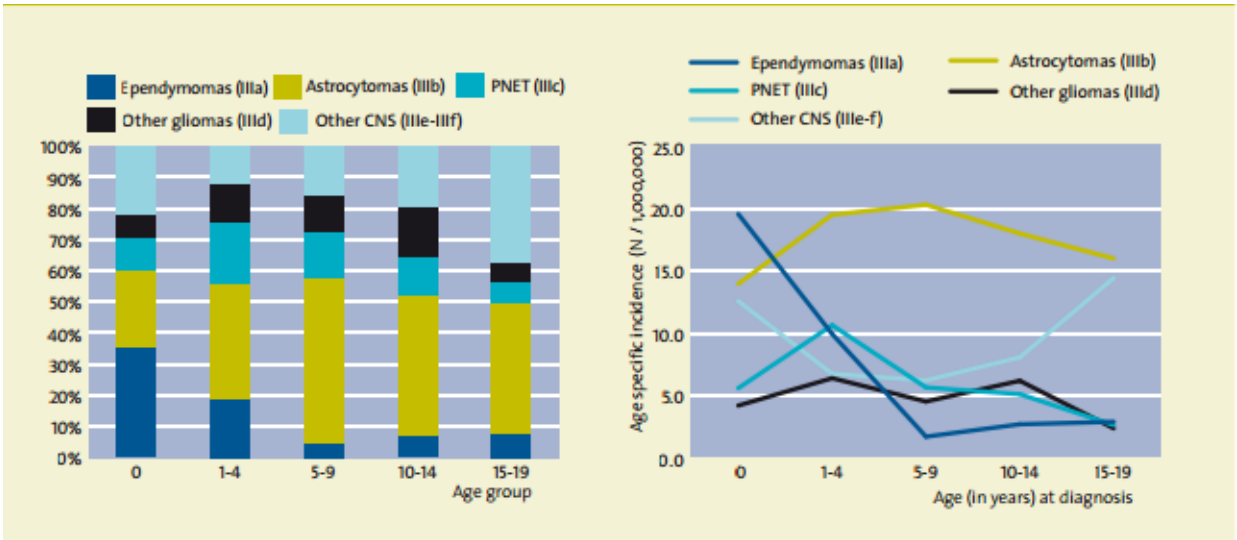

Figure 1: Central Nerve System tumors in Belgian children (2004-2009).
Note. In the left panel, distributions of diagnoses are depicted for each age group. In the right panel, incidence rates are presented per age. Derived from: http://www.kankerregister.org/media/docs/publications/CancerIncBel2010-ChildrenAdolescents.pdf (5)

Acute symptoms of posterior fossa tumors in children are mainly the result of increased intracranial pressure due to the mass effect of the tumor and obstructive hydrocephalus. Therefore, patients often present with headaches, nausea, emesis and cranial neuropathies causing extra-ocular muscle disorders. Signs of cerebellar derangement, such as ataxia and dysmetria are also frequent (1,8). Brain stem involvement, caused by brainstem gliomas or other posterior fossa tumors invading the brain stem, induces specific brainstem symptoms. These include pyramidal tract signs such as hemi-or quadriparesis, ataxia, dysmetria, swallowing problems and impairment of multiple cranial nerves such as the oculomotor, trochlear, abducens and the facial nerve(1,9).

When these alarming symptoms occur, imaging is the next step in order to define the diagnosis. Although CT-scans can be helpful in emergency situations to make a quick preoperative evaluation, MRI is the preferred imaging technique to determine the tumor extent, to provide arguments for the most suitable treatment plan and to evaluate treatment response later on (1). Furthermore, MRI-modalities such as diffusion weighted imaging, MR spectroscopy and MR perfusion have been shown valuable in discriminating between the histologic tumor types before pathological confirmation is accomplished (7,10). Craniospinal MRI is the golden standard to detect dissemination in the cerebrospinal fluid (1). Histological typing of the tumor is performed during pathological examination of the resection species.

A biopsy is only acquired if surgery is not possible (3). For instance, in diffuse intrinsic pontine glioma (DIPG), stereotactic biopsy taking is currently recommended in order to characterize the molecular features of the lesion. These findings provide a gateway to developing targeted therapies in this very agressive tumor type (11).

Once the diagnosis has been made, an individualized treatment plan should be established. Currently, three important treatment modalities are applied for posterior fossa tumors: surgery, radiotherapy and chemotherapy. A combination of these three modalities is administered according to the tumor type, localization and age at diagnosis. First, surgical resection is included in all treatments. However, precarious tumor localization (e.g. in the brain stem) can make a resection impossible (9). Other specific surgical treatments (an external ventricular drain, a ventriculoperitoneal shunt or a third ventriculostomy) are often urgently performed to reduce intracranial pressure in case of obstructive hydrocephalus (9,12,13). Second, radiotherapy is indispensable for some tumor types. Medulloblastoma patients receive craniospinal radiotherapy with posterior fossa boost (12,14), whereas in astrocytoma radiotherapy is exceptionally added in children with progressive and inaccessible tumors (13). Ependymoma patients receive postoperative 3D conformal radiation therapy to the tumor bed (15,16). Although radiotherapy is very effective, age at diagnosis is an important factor to consider here. Radiotherapy is usually avoided in patients younger than three years, due to the deleterious impact on the developing brain (3). Finally, another treatment option for fossa posterior tumors is adjuvant chemotherapy, for which administration mainly depends on the tumor histology. In medulloblastoma, postoperative chemotherapy is the standard of care (14), while in astrocytoma it is the first line therapy only if resection is not possible (13). In ependymoma, only patients younger than three years of age are postoperatively treated with chemotherapy. However the efficacy of this therapy appears disappointing in these patients (15).

Cancer treatment constituents can lead to both short and long-term symptoms. A well-known acute consequence of cerebellar surgery is the posterior fossa syndrome (PFS). This syndrome appears in 25% of children after tumor resection in the posterior fossa and comprises a spectrum of distressing symptoms (6), including postoperative cerebellar mutism (17), ataxia, hypotonia, emotional lability and behavioral symptoms. Recovery of PFS is slow and often incomplete. As a result, the syndrome is associated with potential long-term symptoms including reading deficits, lower intellectual ability, poor academic and cognitive outcomes, psychosocial complaints, neurologic deficits and lower quality of life (6).

Due to the nonuniformity of fossa posterior tumors and their treatment, prognosis is also very variable. The prognoses for medulloblastoma and ependymoma patients are moderate, with 5 year survival rates of approximately 70% and 60%, respectively. Astrocytoma patients have the best prognosis, with a 90% 5 year survival rate (3). This contrasts strongly with the dismal outlook of ATRT patients, with only 29.9% 5 year survival (18). Finally, DIPG patients suffer the worst prognosis: the mean overall survival is 11 months and the 5 year overall survival is 2% (9,19–21).

Since survival rates for medulloblastoma, ependymoma and astrocytoma have significantly increased during the last decades (3), long-term therapy-related sequelae receive more and more attention. These sequelae could include somatic (e.g. endocrine problems (2,12,22), second neoplasms (12,22), kyphosis and vertebral demineralization (12)), neuropsychological (e.g. motor speech deficits (23), intellectual impairment, attention deficits, memory difficulties and executive dysfunction (3,4,12)) and psychosocial issues (e.g. unemployment, incapacity to drive and lower quality of life (22)).

A bulk of research exists for the different domains of long-term deficits of posterior fossa tumor survivors. However, a systematic review of problems that these children can experience throughout the rest of their lives is missing. Therefore, this study aims to give an integrated overview of all long-term sequelae (including somatic, neurocognitive and psychosocial outcomes) related to posterior fossa tumor therapy in children.

5. METHODS

We explored the long-term effects of the different treatment modalities for posterior fossa tumors with respect to three domains of symptoms: somatic, neuropsychological and psychosocial symptoms. The aim was to link the various treatment types to specific long-term sequelae. The PubMed/Medline database was screened using the following search algorithm: ("Infratentorial Neoplasms"[Mesh] OR cerebellar tumor OR brain stem tumor) AND ("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh]) AND treatment AND (long term sequelae OR outcome). Two additional filters were applied including: date of publication in 1990-2017 and English as publication language. Studies were excluded in case of in vitro or animal studies, also studies with patients > 18 years who did not receive treatment during childhood, studies including current patients (i.e. if >50% of study population was followed <2 years after cancer diagnosis), studies covering other diagnoses (i.e. non-cancer or other types of cancer), non-original-research articles (case reports, expert opinions, conference summaries) and articles not reporting long-term effects. Duplicates were removed from the dataset. Studies were divided into three categories (medical, neuropsychological and psychosocial effects) and related to the treatment modality (surgery, chemotherapy and radiotherapy).

6. RESULTS

The literature search returned 1369 articles, which were screened in a systematic way. Stepwise amounts of included/excluded articles are shown in the flowchart below **(Figure 2)**. After removal of duplicates (n=2), the first selection was based on screening of the titles. 857 titles were eliminated implementing the specified exclusion criteria. Next, the remaining articles were screened for eligibility based on the abstracts. 433 records were removed, which resulted in 75 remaining studies for full-text screening. 7 studies were excluded, since full text was not available. Subsequently, each included record was classified into one of the categories mentioned above. 16 of the included articles described somatic symptoms, 39 articles reported on neuropsychological long-term effects, 3 articles covered psychosocial issues and 9 studies reported on all these effects. One article was excluded after analysis of the full text, since it only indicated the Karnofsky Performance Scale (KPS), without specifying the deficits. Characteristics of the included studies are represented in **table 1**, as well the number of articles describing long-term effects of each treatment modality.

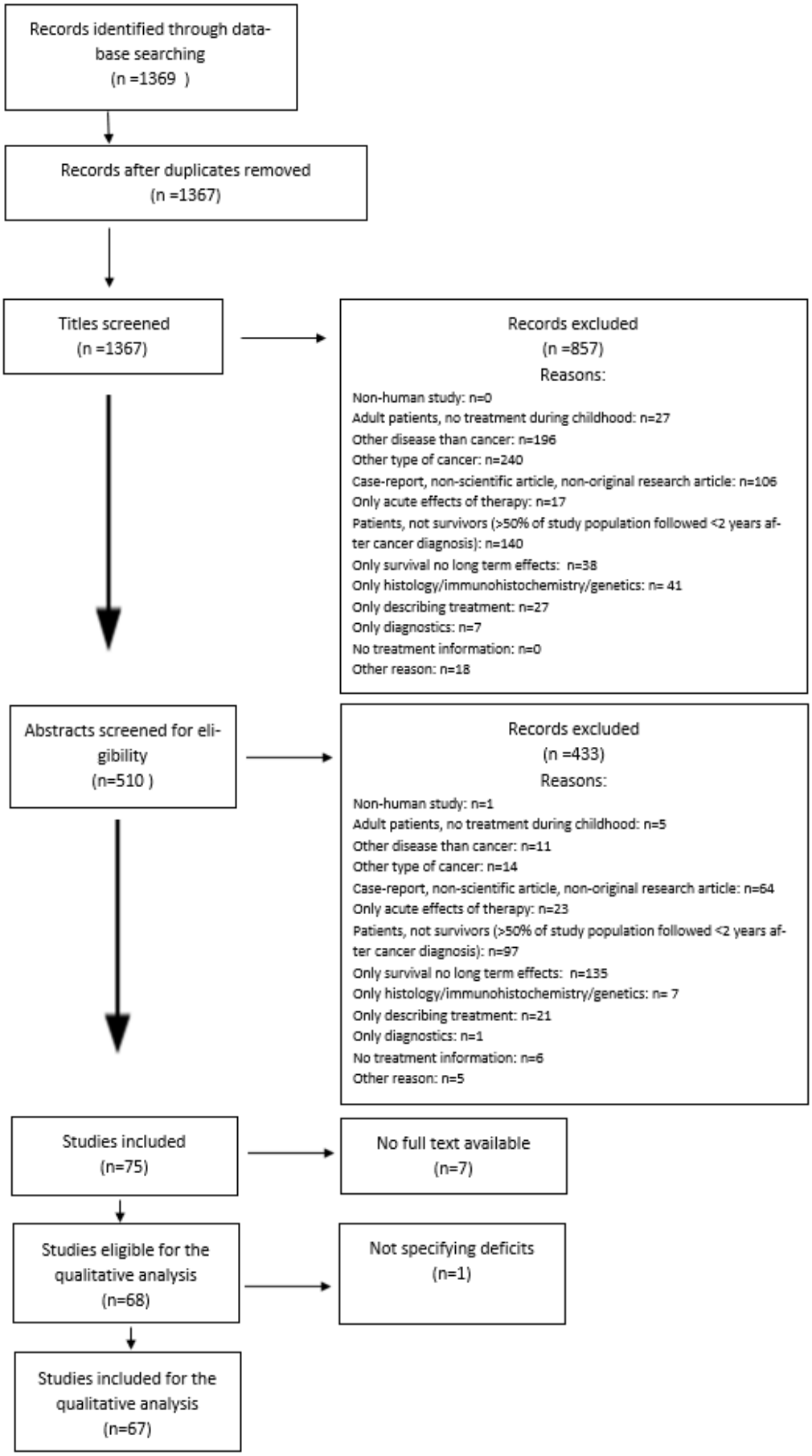

Figure 2: Flow chart of results

Table 1: Included articles

Treatment	#Articles	#Patients Included (ranges)	Somatic	Neuro-psycho-logical	Psychoso-cial	All	Medullo-blastoma	Ependy-moma	Astrocy-toma	Multiple
Surgery	18	4-203	4	12	1	1	1	1	9	7
RT	33	7-151	11	17	1	4	27	0	0	6
Chemo	1	21-35	1	0	0	0	1	0	0	0
Surgery+RT	2	15-23	0	2	0	0	0	2	0	1
Surgery +RT+Chemo	13	16-137	0	8	1	4	7	0	0	5
Total	**67**	**4-203**	**16**	**39**	**3**	**9**	**36**	**3**	**9**	**19**

Note. Articles were classified into the different treatment modalities, categories of long-term sequelae and tumor types. Abbreviations: RT=radiotherapy, Chemo=chemotherapy

6.1 Long-term effects related to surgery

Long-term effects related merely to surgery, have only recently gained interest. An excellent patient population to study these long-term effects are cerebellar pilocytic astrocytoma patients, because their treatment often consists of surgery only. Zuzak et al. (2008) reviewed multiple long-term effects in 21 cerebellar astrocytoma survivors. Neurological deficits (limb ataxia, truncal ataxia, dysarthria, and ocular movement disorders) occurred frequently (41%, n=9). 33% of these patients (n=7), had behavioral problems and 19% (n=4) required special education due to cognitive deficits. However, most of them were still capable to perform normal daily life activities and their health-related quality of life was rated similar to or even higher than controls. Apparently, these objective deficits had only minor influence on the subjective quality of life (24). The remaining studies included in this review discussed one domain of long-term effects more in specific.

6.1.1 Long-term somatic effects

Nagib et al. (1996) reported permanent lower cranial nerve dysfunction in 2 of the 4 included patients after surgery for posterior fossa lateral ependymoma, a rare type of ependymoma (25). The effects of surgery on brainstem functions for ependymoma patients in general were studied by Merchant et al. (2010). They conducted a long-term neurological follow-up in 64 ependymoma patients treated with surgery and conformal radiotherapy (54–59.4 Gy). 23 patients experienced incomplete brain stem recovery after 5 years, defined as impaired function of cranial nerves V-VII and IX-XII, motor weakness and dysmetria. These neurological outcomes depended more on surgical variables than radiotherapy. CSF shunting, the number of interventions (resection and shunting), the extent of resection, tumor volume and male gender were significantly related to incomplete brainstem recovery (26). Another study of Schoch et al. (2006) depicted the balance function in 22 patients treated for benign and malign posterior fossa tumors in childhood. More specifically, this study compared patients with and without affected cerebellar nuclei and patients with and without adjuvant therapy (chemotherapy and/or radiotherapy). The authors concluded that surgical damage of the deep cerebellar nuclei, especially the fastigial nucleus was responsible for balance impairment in these patients, rather than radiation or chemotherapy (27). Villarejo et al. (2008) retrospectively reviewed more general neurologic deficits in 203 astrocytoma survivors. Most of these patients exhibited no neurological deficits (55%). Some of them (27%) had mild neurological deficits without psychosocial implications (strabismus, nystagmus

or ataxia), while a few survivors (4%) were severely disabled and incapable of leading a normal life (28). These results are consistent with the findings of Zuzak et al. (2008) (24).

6.1.2 Long-term neuropsychological effects

Five records covered the neuropsychological consequences of pilocytic astrocytoma surgery in childhood. 249 adolescents and adults were included. Although most of these patients obtained a normal intelligence quotient and close to normal academic achievements, milder neuropsychological deficits were reported in 57-100% of them. These deficits included: dysarthria (see below), difficulties in sustained attention, visuospatial capacities, executive functioning, memory, processing speed, behavioral problems, psychiatric symptoms (29–33). Special education was needed in 11-24% of patients (29,30). Beebe et al. (2005) (n= 103) found little effect of tumor localization on these deficits (31), whereas Steinlin et al. (2003) claimed that vermis involvement was associated with more neuropsychological problems (n=24) (32). Additionally, Levisohn et al. (2000) evaluated astrocytoma patients (n=7), as well as medulloblastoma and ependymoma patients in whom radiotherapy was not yet administered (n=41). They found impairments of executive function, visuospatial capacities, verbal memory and affect modulation, the latter being in particular associated with vermal lesions. Age at diagnosis also influenced these neurocognitive outcomes: the youngest children (<7 years) treated with surgery only, had better cognitive and affective long-term outcomes than older children, although the authors pointed at a possible lack of sensitivity of the testing in this group (34). In another study of Grill et al. (2004), perioperative risk factors of intellectual impairment were reviewed in 76 patients treated for malignant posterior fossa tumors. Average verbal intelligence quotient (VIQ) appeared normal (86.9 +/- 18.9), whereas performance intelligence quotient (PIQ) was subnormal (75.8 +/-17.5). Preoperative hydrocephalus, vermis incision and the amount of postoperative cerebellar damage were significantly related to lower IQ scores (35). Puget et al. (2009) also highlighted the effect of surgical cerebellar nuclei damage in 61 children treated for malignant posterior fossa tumors. Damage of the dentate nuclei and the inferior vermis was related to lower intellectual outcome than patients without this damage, after correction for other risk factors (radiation, hydrocephalus, surgical complications…) (36).

Not only cognitive and affective symptoms define the spectrum of long-term neuropsychological outcome. Also speech can be affected. Four studies explored long-term speech deficits in 56 patients (astrocytoma n=25, medulloblastoma n=29, ependymoma n=2) following surgery. Most patients who experienced postoperative cerebellar mutism also encounter cerebellar dysarthria, slower speech and dysfluency in the long-term (37,38), but results are somewhat inconclusive for patients without postoperative mutism. Huber et al. (2006) found no difference in speech capacities between patients without postoperative mutism and healthy controls (37). On the contrary, De Smet et al. (2012) and Morgan et al. (2011) both found higher percentages of long-term speech deficits (e.g. distorted vowels, slow rate, voice tremor) even in patients without postoperative cerebellar mutism (39,40).

6.1.3 Long-term psychosocial effects

Psychosocial effects associated with surgery were investigated by Pompili et al. (2002), who described quality of life (Qol) in 20 adults treated for cerebellar astrocytoma in childhood compared to 20 matched controls. They used two Qol questionnaires: the KPS and a detailed QoL questionnaire. These adult survivors had normal global functioning (as indicated by the KPS) and were capable of leading a normal life. However, using the more profound Qol questionnaire, they had significant lower satisfaction than the control group when it came to social contacts, cognition, memory, well-being and adolescence (41).

6.2 Long-term effects related to radiotherapy

6.2.1 Long-term somatic effects

All articles describing long-term somatic effects related to radiotherapy, considered medulloblastoma survivors only. Seven of these studies explored long-term endocrine sequelae in 188 patients treated with postoperative craniospinal radiotherapy (doses ranging from 18 to 39 Gy craniospinal and 18-53 Gy posterior fossa boost). The most frequent endocrine long-term effects found in these studies included growth hormone (GH) deficiency and both primary and secondary thyroid dysfunction. GH deficiency resulted together with spinal radiation in diminished adult height and sitting height (42–48). Less frequent endocrine sequelae were adrenal insufficiency, hypogonadism and precocious puberty (48). These long-term effects could manifest up to 15 years post-treatment and were more prevalent in patients treated with chemotherapy (cisplatin, vincristine and lomustine) (47). Symptoms also appeared to be dose-dependent (48). Regarding GH deficiency, starting GH hormone administration at younger age resulted in better growth outcomes (46).

Another important long-term somatic effect related to radiotherapy is the development of secondary neoplasms in and around the radiated area. This was illustrated in several studies with a total of 167 included patients, who were all treated with craniospinal radiotherapy for medulloblastoma. Malign secondary neoplasms included breast cancer, thyroid cancer, lung cancer, stomach cancer, basal cell carcinoma and glioblastoma multiforme. Benign neoplasms described were meningiomas and cavernomas (49–52). Intensity modulated proton therapy (IMPT), one of the newer radiotherapy techniques, was associated with a lower risk of secondary neoplasms compared to 3D conformal radiotherapy (CRT) (49). One study made a risk estimation of developing secondary malignancies after conventional craniospinal radiotherapy, IMPT and another technique called inversely-optimized arc therapy (RA). They made hypothetical treatment plans for the three techniques in 10 medulloblastoma survivors who already received craniospinal radiotherapy. Next, they estimated the risk of secondary neoplasm by means of organ-equivalent dose concepts combined with childhood cancer survivor data. The life time risk of a solid secondary neoplasm was estimated the highest in RA, the lowest in IMPT and increased with higher radiation dose. However, these estimations were merely based on calculations. Exact data was missing in this study (52).

6.2.2 Long-term neuropsychological effects

Neurocognitive dysfunction is the most extensively investigated long-term effect in posterior fossa tumor survivors. Most patients participating in these studies are medulloblastoma survivors treated with craniospinal radiotherapy. Nevertheless, ependymoma and astrocytoma patients were also occasionally included. Both high (range 30.6-41.4 Gy) and reduced (range 18-25.2 Gy) doses of craniospinal radiotherapy were applied. Posterior fossa boost was between 12.6 and 60 Gy, tumor bed boost between 16 and 86 Gy. The most frequently assessed outcome was intelligence, objectified by the Wechsler scale of intelligence (population mean= 100, SD= 15).

George et al. (2003) studied long-term general cognitive sequelae for medulloblastoma and astrocytoma survivors (n=15). The mean FSIQ, VIQ, and PIQ were all significantly lower than the normal population, as were verbal, visual and general memory. There was no significant difference between VIQ and PIQ. Verbal and visual memory were also equally affected. Younger age at diagnosis (<6 years) resulted in lower long-term IQ scores than older age (53). A study of Mabbott et al. (2008) specifically compared patients treated with surgery and cranial radiation and patients who received surgery only.

Both cranial radiation and postsurgical complications were related to lower IQ and information processing speed. Age at diagnosis was not significant here (54). According to Abd El-aal et al. (2005), the addition of postoperative chemotherapy (vincristine, etoposide and cisplatin) had no effect on cognitive outcome (55).

The evolution and determinants of this intellectual decline were investigated in three studies, including 191 medulloblastoma and 9 ependymoma survivors treated with 23.4 or 35-40 Gy craniospinal radiation (56–58). IQ declined year after year (1.70-2.05 points per year) (56,58), as well as academic achievement (58). Higher baseline intelligence was associated with steeper intellectual decline (56–58). Younger age at diagnosis also resulted in steeper decline in two of the three records (57,58). This effect of age at diagnosis was confirmed by Rutkowski et al. (2008). These researchers observed 29 children with medulloblastoma diagnosed younger than three years old. 12 of them relapsed during chemotherapy and were administered 24 Gy craniospinal radiotherapy with a boost on the metastases. These patients had very low intellectual outcome 6.1 years after diagnosis (IQ 77.7 +/- 7.2) (59).

The mechanism of radiation-induced intellectual deterioration could be found in both volume reduction and microscopic injury of white matter. Three studies investigated brain damage after craniospinal and posterior fossa boost radiotherapy with diffusion tensor MRI imaging (DTI). In a record of Riggs et al. (2014) irradiated astrocytoma and medulloblastoma survivors (n=20) exhibited reduced white matter volume compared to healthy controls (n=13). The fasciculus uncinatus and the right hippocampus were the most affected areas. Volume reductions resulted in lower memory scores (60). Additionally, Mabbott et al. (2006, n=8) and Law et al. (2011, n=29) focused on apparent diffusion coefficient (ADC) and fractional anisotropy (FA). Craniospinal radiotherapy was associated with increased ADC and decreased FA of white matter. If the cerebello-thalamo-cerebral connections were affected by these changes, this was associated with poor intellectual outcome and working memory (61,62). Similarly, a study of Wilburn confirmed reduced white matter in pediatric brain tumor survivors to be associated with lower IQ and academic achievements (63).

Extensively analyzed characteristics of intellectual decline are the influence of radiation volume and dose-dependency. This was illustrated in four studies comparing posterior fossa or tumor boost radiotherapy (45-55.4 Gy) without craniospinal radiotherapy, with reduced dose (15-25 Gy) and with standard dose craniospinal radiotherapy (30.6-39 Gy) in 184 patients. All of these studies concluded that local radiotherapy only resulted in smaller decrease in FSIQ than combined with craniospinal radiotherapy. Furthermore, higher craniospinal doses were associated with greater decrease in FSIQ (57,64–66). study of Moxon-Emre et al. (2014). also added that higher boost volumes (posterior fossa boost vs. tumor bed boost), hydrocephalus and postoperative mutism resulted in poorer intellectual outcome (65).

Beside radiation dose, genetics could also influence the risk of radiation induced brain injury, as postulated by Bracket et al. (2012). The childhood cancer survivor study neurocognitive questionnaire and the Brief Symptom Inventory of 109 medulloblastoma patients were compared to 143 healthy siblings. Polymorphisms in multiple antioxidant enzymes (SOD2, GPX1, GSTP1, GSTM1, GSTT1) were determined in both groups. Medulloblastoma survivors scored significantly worse on memory and task efficiency, the latter even more impaired in children <7 years at diagnosis. Globally these findings were independent of the investigated polymorphisms. However, a subgroup of survivors with homozygous GTMS 1 experienced significantly more anxiety, depression and global distress (67).

Finally, modern radiotherapy methods have received attention only more recently, but results about cognitive outcomes are already reassuring. Jain et al. (2008) showed that there was no difference in cognitive decline between IMRT and conventional radiotherapy in 25 medulloblastoma patients (68). Similarly, FSIQ in standard risk medulloblastoma patients treated with HFRT (n=71) did not significantly differ from patients treated with conventional radiotherapy (n=66) (69).

6.2.3 Long-term psychosocial effects

Radiotherapy for posterior fossa tumors can lead to serious psychosocial problems. This was described in a study of Mabbott et al. (2005). This record included 53 posterior fossa tumor survivors (46 medulloblastoma patients and 7 ependymoma patients). 48 patients were treated by craniospinal radiation (23.4-41.6 Gy) with a posterior fossa boost (45.0-55.8 Gy). They were evaluated with standardized achievement tests as well as parent and teacher questionnaires. Three years post-diagnosis, school skills and academic achievement were about one standard deviation below the population average. Hydrocephalus and younger age at diagnosis were associated with poorer academic outcome, whereas radiation dose, extent of resection and use of chemotherapy were not. Behavioral problems were only mild. A longitudinal analysis (median follow-up after diagnosis 4.84 years for academic achievement and 4.17 years for behavioral function) revealed that academic skills continued to decline over time. Behavior remained more or less stable according to parent questionnaires, however some social withdrawal and attention problems became evident after a few years (70).

6.2.4 Long-term somatic, neuropsychological and psychosocial effects

Several studies did not focus on only one category of long-term effects. These more general articles confirmed the findings mentioned above. Helseth et al. (1999) studied the long-term outcome of 34 medulloblastoma survivors, treated with 35 Gy craniospinal radiation and 20 Gy posterior fossa boost. They found psychosocial impairments in 61% of the participants (learning abilities, sociability, hobbies, relations), diminished height in most patients, the need of hormonal therapy in 50% and second neoplasms in 14% of patients (71). Christopherson et al. (2014) followed up 53 medulloblastoma patients treated with a median craniospinal dose of 28.8 Gy and a posterior fossa or tumor bed boost of 25 Gy. The authors added to the findings of Helseth et al. that the most important long-term effect of craniospinal radiotherapy was growth suppression (61.5% of patients). Nevertheless, cognitive impairment (18%) appeared a major problem as well. They also sporadically observed hearing loss, due to radiation-induced serous otitis media and sensorineural damage, skull radionecrosis, and cerebral ischemia or aneurysm development (72). Again, consistent with the findings of Rutkowski, children treated with craniospinal radiotherapy under three years of age experienced similar problems, albeit to a higher degree than older patients. Furthermore, 75% of these younger patients suffered from severe neurologic late effects as ataxia, epilepsy, cranial nerve deficits and blindness (73). When it comes to hyperfractionated radiotherapy, Kennedy et al. (2014) demonstrated worse growth, but improved executive functioning in patients treated with HFRT (n=74) compared to conventional radiotherapy. However this was not related to behavior nor quality of life (n=75) (74) .

6.3 Long-term effects related to chemotherapy

6.3.1 Long-term somatic effects

This review only returned one article describing a well-known consequence of chemotherapy in medulloblastoma surivors: hearing loss. Lafay-Cousin et al. (2013) acquired audiograms in 35 children during and after cisplatin treatment for average risk (AR) and high risk (HR) medulloblastoma patients. AR patients received higher doses of cisplatin (412.5 mg/m^2 vs 270 mg/m2 in HR), whereas HR patients were administered higher doses of craniospinal radiotherapy (36-39 Gy. vs 23.4 Gy in AR). Both AR and HR patients often required hearing support five years after treatment. However, the AR group more frequently required dose reduction of cisplatin during treatment due to hearing loss. This finding suggests that the effect of higher cumulative dose of cisplatin exceeds the damage of a higher radiation dose in the short term. However, this early difference between AR and HR patients disappears over time. (75).

6.4 Long-term effects related to the combination of surgery and radiotherapy

6.4.1 Neurocognitive long-term effects

Von Hoff et al. (2008) and Chapman et al. (1995) investigated the influence of both radiotherapy and surgery on neurocognitive outcome at the same time (76,77). Von Hoff et al. evaluated intellectual functions in 23 ependymoma survivors treated with surgery and posterior fossa boost radiotherapy (mean 54 Gy). PIQ was significantly lower than normal, whereas FSIQ, VIQ were only moderately impaired. All patients experienced reading difficulties. However, no decline in IQ scores was notified in a longitudinal analysis. Factors associated with lower IQ included the persistence of the posterior fossa syndrome, preoperative hydrocephalus and larger radiation volume. Again younger age at irradiation resulted in lower neurocognitive outcome (76). In the record of Chapman et al. 13 medulloblastoma and 2 ependymoma patients treated between 1970-1984 were included. The radiotherapy protocols consisted of high radiation doses and volumes, also in children under three years of age. Younger age at diagnosis was once more associated with worse neurological and neurocognitive outcome, but also with a higher incidence of obtundation at diagnosis and perioperative issues (preoperative hydrocephalus, resection of cerebellar tissue outside the vermis). The authors therefore suggested that worse intellectual and neurological outcome in younger children is not only related to radiation-induced damage, but also to perioperative complications (77).

6.5 Long-term effects related to the combination of surgery, radiotherapy and chemotherapy

6.5.1 Neuropsychological long-term effects

Several authors studied and compared multiple treatment modalities with respect to their neuropsychological effects. Huber et al. (2007) studied long-term speech deficits in both astrocytoma survivors (treated with surgery only) and medulloblastoma survivors. All experienced dysfluent speech, but atactic dysarthria and slow speech were only frequent in medulloblastoma survivors (23). In a record of Szathmari et al. (2010), speech deficits in medulloblastoma survivors could be predicted by tonsillar herniation and a higher ratio of tumor volume to posterior fossa volume on preoperative MRI (78). Other neuropsychological differences between medulloblastoma and astrocytoma survivors were described by Roncadin et al. (2008) and Ronning et al. (2005). As expected, medulloblastoma survivors clearly scored worse on several outcome scales (memory, intelligence, attention) than astrocytoma survivors. (79,80). The important contribution of craniospinal radiotherapy on cognitive decline was

once more confirmed in a prospective study of 35 posterior fossa tumor survivors by Stargatt et al. (2007). The previously described detrimental effect of hydrocephalus was replicated by Roncadin et al. and two other studies (79,81,82). Regarding age at diagnosis, both Roncadin et al. and Ronning et al. stated that younger age at diagnosis predicted lower cognitive functioning in medulloblastoma survivors. This was less clear in astrocytoma survivors (79,80). Finally, Schreiber et al. (2014) added the presence of the posterior fossa syndrome, hearing loss, and high risk status as significant risk factors for intellectual and academic decline in 165 medulloblastoma survivors, next to younger age at diagnosis (83).

6.5.2 Long-term psychosocial effects

Kulkarni et al. (2013) investigated long-term Qol in 62 survivors of different types of posterior fossa tumors (medulloblastoma, astrocytoma and ependymoma). Consistent with previous findings, quality of life in those survivors was not significantly lower than the general population. No differences in outcome were found between the different tumor types. Risk factors for lower scores included hydrocephalus and socioeconomic issues (family problems and household income) (84).

6.5.3 Long-term somatic, neuropsychological and psychosocial effects

Multiple included studies (n=142 patients in total, mostly medulloblastoma patients) depicted different types of long-term effects of different treatment regiments (surgery+craniospinal radiotherapy with or without chemotherapy). All of them could confirm the abovementioned results. Neuropsychological issues, endocrine deficits, neurologic sequelae, hearing loss and academic difficulties were very frequent in all of these studies (22,85–88). Younger age at diagnosis again resulted in lower IQ (85,87). Regarding Qol, Ribi et al. (2005) specified that social functioning was the lowest rated item in 18 medulloblastoma survivors, lower than school functioning. Notably, parents rated Qol for their children was lower than the rating of the patients themselves (88).

7. DISCUSSION

7.1 Summary of long-term effects and risk factors

Treatment for posterior fossa tumors has known an important evolution over the last decades. This had led to improved survival rates for children diagnosed with medulloblastoma, astrocytoma and ependymoma. However, this positive trend also involves the apparition of higher treatment-related morbidity, reflected by a broad spectrum of both somatic, neuropsychological and psychosocial long-term effects. This was extensively illustrated by the 67 articles included in this review.

Surgery is responsible for neurologic symptoms (ataxia, impaired balance and cranial nerve deficits) and mild cognitive and psychosocial issues. Radiotherapy on the other hand (especially craniospinal radiotherapy) is related to a much wider range of long-term sequelae. These include endocrine deficits, secondary neoplasms, some neurologic sequelae like hearing loss, important intellectual decline and severe psychosocial problems (lower academic achievement and social functioning). The third important treatment modality, chemotherapy, is only associated with one specific long-term effect: hearing loss. As different treatment modalities result in different long-term sequelae, it is evident that the long-term effects a posterior fossa tumor survivor can experience depend on the treatment that was administered. This in turn is determined by the tumor type. Astrocytoma survivors treated with surgery only can experience severe neurologic sequelae due to the surgery, but cognitive and psychosocial impairment seem rather mild in this group. On the contrary, medulloblastoma survivors suffer the greatest treatment-related morbidity due to the burdensome combination of surgery, craniospinal radiotherapy and chemotherapy. Logically, the results of ependymoma survivors are situated somewhere in between these two extremities. We will now discuss the different types of long term sequelae and their risk factors more in detail.

When it comes to somatic long-term sequelae, an evident consequence of surgery-induced brain damage are neurological symptoms. Indeed, these sequelae are highly frequent in posterior fossa tumor survivors. The most important neurological symptoms include ataxia, impaired balance and several cranial nerve deficits. The latter can cause ocular movement disorders (n. III, IV, VI) (24,25,27,28). Radiotherapy can also give rise to neurological symptoms such as hearing loss (n.VIII) and even blindness (n.II) in severe cases. Hearing loss can be induced both by this radiation-induced serous otitis media or sensorineural damage and by platinum based chemotherapy (72,75). Damage to the cerebellar nuclei is associated with worse neurological outcome, particularly balance dysfunction (27). Another very relevant problem in these children is endocrine impairment. This is caused by radiation to the hypothalamic–pituitary axis and the thyroid gland. The most common clinical manifestations are GH deficiency, hypothyroidism (both primary and secondary), adrenal insufficiency, hypogonadism and precocious puberty (42–47,89). On top of that, posterior fossa tumor survivors are smaller than their peers, because of GH deficiency and spinal radiation. These deficits are clearly dose-dependent (45). While endocrine defects are very frequent (up to 50%) but not life-threatening (due to hormonal substitution), the development of second neoplasms is rarer (14%) but can be fatal (71). Second neoplasms can occur within the radiated area (meningiomas, cavernomas, glioblastomas, thyroid cancer, basal cell carcinoma) or even in areas not strictly localized in the radiation field (breast cancer, lung cancer). These remote neoplasms were mostly seen in older radiotherapy regiments with higher doses and larger radiation fields (49–52) . Mortality is due either to the inherent malignant character of the neoplasm, either to local complications of the lesion (for instance bleeding of a cavernoma) (49,50).

Although these somatic sequelae are very important, the greatest problem of long-term survivors in daily life might be neuropsychological impairment. This is present in all types of posterior fossa tumors, but obviously more prominent in the medulloblastoma group. These children exhibit clearly worse FSIQ, PIQ, VIQ, memory, nonverbal intellectual functioning, processing speed and academic skills than the normal population (53,67). Furthermore, IQ continues to decline year after year (56,90). Astrocytoma and ependymoma survivors also encounter more subtle problems like reading difficulties and slower processing speed. However, IQ and academic achievement are normal or only moderately impaired (29–33,76). Younger age at diagnosis and treatment results in lower neuropsychological outcome in medulloblastoma and ependymoma survivors (76,77). In astrocytoma patients treated by surgery only this finding could not be replicated. Younger patients even had better neurocognitive outcome than older patients. This could be explained either by great neuronal plasticity in a young brain unexposed to radiotherapy, either by a lack of sensitivity of the testing in younger children (34). Preoperative hydrocephalus also holds a risk of greater intellectual disabilities and poorer academic outcome in all posterior fossa tumors, as did the presence of postoperative mutism, the posterior fossa syndrome and other surgical complications (e.g. damage of the dentate nuclei or vermis) (36,65,79,83). Important causes of neuropsychological sequelae are underlying neuroanatomical changes, especially radiation-induced volume reduction and microscopic damage of cerebral white matter (60–62). This could explain why risk factors described above result in greater intellectual decline, since they either directly induce more white matter injury (higher radiation volume and dose, hydrocephalus) or increase the susceptibility to radiation-induced white matter damage (younger age at diagnosis).

Another disabling long-term problem that stems from both somatic (ataxia, cranial nerve deficits) and neuropsychological origin, is speech impairment. Medulloblastoma as well as astrocytoma survivors experience dysfluency. However other pathologic speech characteristics such as atactic dysarthria and slow speech are only evident in children treated for medulloblastoma. This indicates that posterior fossa tumor therapy (surgery and even more radiotherapy) has detrimental effects not only on cognitive abilities but also on the important cerebellar role of motor coordination (23,37–40).

It is not surprising that all these sequelae have a major impact on the future lives of these patients. They all have to deal with multiple psychosocial issues, especially medulloblastoma survivors. These patients frequently need special education, have lower school skills (reading, mathematics, spelling), are unemployed and have lower academic achievements. Similar to intellectual decline, academic skills also continue to decline year after year in medulloblastoma patients. Hydrocephalus and younger age at diagnosis result in poorer academic outcome. Again, in astrocytoma patients, psychosocial issues are clearly less pronounced than in medulloblastoma patients and they can even obtain close to normal academic achievement. Considering Qol, one subitem of the Qol questionnaires recurrently had low scorings: social functioning. However despite these difficulties in establishing and sustaining relationships, global Qol of medulloblastoma, astrocytoma and ependymoma survivors is not lower than normal. This might signify that patients eventually learn to cope with their disabilities and that some children also have another way of looking at life after surviving cancer (24,41,70,71,84).

7.2 Limitations

This study has several limitations. First of all, there was great heterogeneity in the included studies. These studies all included different patient populations of different ages. Furthermore, they all depicted multiple risk factors and did often not differentiate between tumor subtypes (e.g. low risk vs. high risk). Secondly, the exact radiotherapy doses of the cranial and the spinal component of craniospinal radiation were usually not specified. This made it impossible to determine if the long-term effect was due primarily to the cranial or the spinal radiation dose. Thirdly, the included articles were rather old. Only 19 of the 77 articles were published in 2015-2017. This might be due to the fact that recent research focusses more on new therapy possibilities of which therapy related long-term effects cannot be judged yet. Finally, the search algorithm did not return many articles about chemotherapy-induced sequelae. The reason for this could be that chemotherapy was added only quite recently and therefore it might still be too early to evaluate its long-term effects. Furthermore, chemotherapy was always applied in combination with craniospinal radiotherapy. As a result, it was difficult to disentangle to which of both the long-term sequelae could be attributed.

7.3 Future directions

The diagnostic approach for brain tumors, including those in the posterior fossa is dramatically changing. While the former WHO classification of CNS tumors (2007) primarily categorized the neoplasms according to histology, the most recent classification (2016) is based on the combination of both histological and genetics findings. As a result, formerly recognized histological entities are subdivided into different genetic subtypes. For instance, medulloblastomas can be assigned to one of five genetic subgroups (WNT activated, SHH activated TP53 mutated, SHH activated TP53 Wild Type, group 3 and group 4) next to the pre-existing histological classification. These strictly defined subgroups will most likely contain greater prognostic value and will certainly be a guide line for personalized CNS tumor therapy in the future (91,92). When it comes to preoperative inquiries, advanced MRI technique (dynamic contrast enhanced, susceptibility weighted imaging, diffusion tensor imaging and functional MRI) will more and more be implemented for maximal preoperative tumor characterization. Additionally, 11C-methionine PET is recently been shown useful in discriminating between high grade and low grade tumors. On the other hand, intraoperative MRI (iMRI) is a promising modality for evaluating the extent of resection during surgery (8). These new technologies will hopefully also contribute to a more tailored treatment plan.

As the diagnostic field of posterior fossa tumors is dramatically evolving, treatment regiments are changing as well. Advances in radiation therapy, such as intensity modulated radiation therapy (IMRT), intensity modulated photon therapy (IMPT) and hyperfractionated radiation therapy (HFRT), have recently been introduced in posterior fossa tumor therapy. In HFRT, overall survival is similar to standard craniospinal radiotherapy (93). For IMPT and IMRT survival reports are not yet available. However, first results about therapy-related sequelae were promising. HFRT was associated with better long-term executive functioning compared to conventional radiotherapy (74). IMRT resulted in less hearing loss (94) and IMPT in lower risk of second neoplasms (95). Additionally, there was no difference in cognitive decline between IMRT and HFRT compared to conventional radiotherapy in medulloblastoma patients (68,69). A different development in treatment protocols is the use of myeloablative chemotherapy with autologous stem cell transplantation in high risk or recurrent medulloblastoma, especially in children younger than three years (96,97). This therapeutic strategy may reduce the need of craniospinal

radiation in this high risk group and may in that way decrease the risk of intellectual decline (96). However, it is too early to evaluate long-term effects related to this more recent treatment protocol. Another interesting topic is the age limit for craniospinal therapy. Because intellectual decline is clearly more pronounced in patients with younger age at diagnosis (53,56,57,76,79,83,85,87) and chemotherapy regiments are indeed evolving in this group, delaying craniospinal radiotherapy until the age of six might be feasible. Again, further large international clinical studies are necessary to demonstrate the efficacy, safety and impact on long-term effects of this approach.

8. CONCLUSION

Posterior fossa tumors in children constitute a heterogeneous group of neoplasms, with medulloblastoma, astrocytoma and ependymoma as the predominant tumor types. Advances in treatment over the last decades have led towards better survival, but also gave rise to the development of treatment-related long-term sequelae. This study gave an overview of different somatic, neuropsychological and psychosocial effects linked to the different treatment regiments. Medulloblastoma, astrocytoma and ependymoma survivors all suffered deficits in those domains, although to different extents. Medulloblastoma suffered the highest treatment-related morbidity. Besides tumor type, other important risk factors for long-term sequelae were craniospinal radiotherapy, younger age at diagnosis and perioperative hydrocephalus. As a conclusion, long-term treatment-related sequelae should receive sufficient attention of all specialists involved (neurosurgeons, radiotherapists and oncologists), as all constituents of treatment can have tremendous effects on patient's long-term functioning.

9. CONFLICTS OF INTEREST

None

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