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SPECIAL ANNUAL ISSUE

Functional and neuropsychological late outcomes in posterior fossa tumors in children

Alvaro Lassaletta[1] · **Eric Bouffet**[1] · **Donald Mabbott**[2] · **Abhaya V. Kulkarni**[3]

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Abstract Tumors of the posterior fossa (PF) account for up to 60 % of all childhood intracranial tumors. Over the last decades, the mortality rate of children with posterior fossa tumors has gradually decreased. While survival has been the primary objective in most reports, quality of survival increasingly appears to be an important indicator of a successful outcome. Children with a PF tumor can sustain damage to the cerebellum and other brain structures from the tumor itself, concomitant hydrocephalus, the consequences of treatment (surgery, chemotherapy, radiotherapy), or a combination of these factors. Together, these contribute to long-term sequelae in physical functioning, neuropsychological late outcomes (including academic outcome, working memory, perception and estimation of time, and selective attention, long-term neuromotor speech deficits, and executive functioning). Long-term quality of life can also be affected by endocrinological complication or the occurrence of secondary tumors. A significant proportion of survivors of PF tumors require long-term special education services and have reduced rates of high school graduation and employment. Interventions to improve neuropsychological functioning in childhood PF tumor survivors include (1) pharmacological interventions (such as methylphenidate, modafinil, or donepezil), (2) cognitive remediation, and (3) home-based computerized cognitive training. In order to achieve the best possible outcome for survivors, and ultimately minimize long-term complications, new interventions must be developed to prevent and ameliorate the neuro-toxic effects experienced by these children.

Keywords Posterior fossa · Children · Neurocognitive outcome · Neuropsychological · Craniospinal radiation · Chemotherapy

Introduction

Tumors of the posterior fossa (PF) account for up to 60 % of all childhood intracranial tumors [1]. With the exception of diffuse intrinsic pontine gliomas, which will not be included in this review, initial treatment of PF tumors generally includes surgery aimed at maximal resection of the tumor with minimal morbidity. Postoperative management depends on the histological type and may include radiation and/or chemotherapy. Over the last decades, the mortality rate of children with posterior fossa tumors has gradually decreased. Survival rates are essentially related to the underlying histology and are close to 100 % for children with low-grade glioma [2]. Five-year survival rates above 90 % have been reported in children with non-metastatic medulloblastoma [3], whereas results in ependymoma are still lagging behind in the range of 30–70 %, depending on the extent of resection and the use of postoperative radiation [4, 5]. While survival has been the main focus of most recent reports on these different entities, quality of survival increasingly appears to be an important indicator of a successful outcome. Very few studies have reported both survival rates, and data on functional outcome and information on the latter remains limited. A number of factors can affect functional outcome. Children with a posterior fossa

✉ Abhaya V. Kulkarni
abhaya.kulkarni@sickkids.ca

[1] Division of Pediatric Neuro-oncology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[2] Division of Psychology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[3] Division of Neurosurgery, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8

tumor can sustain damage to the cerebellum from the tumor itself, surgical resection, chemotherapy [6], radiotherapy [7], or a combination of any of these factors. In addition, other parts of the brain can be affected by factors such as hydrocephalus [8] or radiotherapy, also impairing functional outcome. These complications contribute to long-term physical, endocrine, and neuropsychological impairments in survivors, and such that a significant proportion of survivors of posterior fossa tumors require long-term special education services and have reduced rates of high school graduation and employment [9].

As a result of the improved survival in these tumors, there is now an increased awareness of the long-term outcomes in this patient population. The objective of this manuscript is to review current knowledge pertaining to the functional and neuropsychological outcomes of patients treated for a posterior fossa tumor.

Factors that contribute to impaired late outcomes

A number of factors contribute to impaired functional and neuropsychological late outcomes in posterior fossa tumors in children. Complications at the time of presentation such as raised intracranial pressure and hydrocephalus, complications of surgery, peri-operative events, and later episodes of tumor recurrence have all been postulated as risk factors for cognitive morbidity.

Children with PF tumors often present with hydrocephalus, because the tumor impedes CSF flow within the ventricular system [8, 10, 11]. CSF accumulation increases intracranial pressure and produces mechanical stress that decreases cerebral blood flow, reduces the availability of neurotransmitters, and damages axons and myelin. A proportion of these patients go on to require permanent CSF diversion. Hydrocephalus, even when not tumor related, has been found to have a significant cognitive impact in children. The cognitive effects of hydrocephalus include a wide range of deficits including attention and information processing as well as memory, language, and executive deficits [12–14].

Perhaps most importantly, cranial irradiation is associated with adverse neuropsychological sequelae in all children treated for cancer, with impairments in short-term memory, attention, and cognitive processing [7, 12, 14–20].

White matter injury can also occur with chemotherapy. Leukoencephalopathy induced by methotrexate, mainly studied in acute lymphoblastic leukemia, usually resolves over time on imaging, but the cognitive consequences, secondary to the white matter compromise, may still emerge as a late effect of treatment [6].

Importance of the cerebellum and hippocampus

Cerebellum

Most PF tumors involve the cerebellum and the long-term outcome is often, in part, related to cerebellar dysfunction. The role of the cerebellum in motor function has been well recognized, but it is now clear that the cerebellum has an important role in cognitive functions. Anatomical studies have identified the neural circuitry through which the cerebellum is able to modulate cognitive functions [21–23]. Neuroimaging studies have demonstrated the cerebellum's involvement in cognitive functions during tasks that do not need motor functions [24], with cognitive tasks activating the posterior portion of the cerebellum and motor tasks the anterior portion [25]. Additionally, clinical studies have shown that damage to the cerebellum can result in decreased intellectual functions and cognitive impairments that resemble impairments seen in patients with injuries of supratentorial brain areas. These cognitive impairments have been grouped into four distinct categories: disturbances of executive functions (i.e., planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency), impaired spatial cognition (i.e., visuospatial disorganization and impaired visuospatial memory), personality change (i.e., flattening or blunting of affect and disinhibited or inappropriate behavior), and linguistic difficulties (i.e., dysprosodia, agrammatism, and mild anomia) [26, 27]. Collectively, these have been termed the cerebellar cognitive affective syndrome (CCAS).

The type of cerebellar impairment seen may be related to the location of the tumor within the cerebellum. In a study by Riva et al., the authors presented data on the intellectual, language, and executive functions of 26 children who underwent surgery for cerebellar hemispheric or vermian tumors [28]. They showed that the children with right cerebellar tumors developed disturbances of auditory sequential memory and language processing, whereas those with left cerebellar tumors showed deficits on tests of spatial and visual sequential memory. Vermian lesions led to two profiles: (1) post-surgical mutism, which evolved into speech disorders or language disturbances similar to agrammatism, and (2) behavioral disturbances ranging from irritability to behaviors reminiscent of autism. In general, tumors located in the vermis are associated with impairments of language and affect; tumors of the right cerebellar hemisphere are associated with declines in verbal intelligence, complex language tasks, and verbal sequential memory; and tumors of the left hemisphere cause diminished capacity to process non-verbal tasks, impaired prosodic intonation, and deficits in visual sequential memory [28].

Hippocampus

Structures outside the PF may be damaged as a result of adjuvant treatments. The hippocampus is particularly at risk, and this structure is particularly important in memory. Declarative memory (sometimes referred to as explicit memory) is one of two types of long-term human memory. Declarative memory refers to memories that can be consciously recalled, such as facts and knowledge. In children and adults, declarative memory relies predominantly on specific regions of the brain such as the prefrontal cortex and medial temporal lobe. In support of this, our group found that the structure of the uncinate fasciculus, the major white matter tract connecting the anterior temporal lobe with the medial and lateral orbitofrontal cortex, was predictive of audio-verbal memory performance in healthy children [29]. The hippocampus is a critical structure for declarative memory, and in humans, its volume continues to increase throughout adolescence. Despite the importance of the hippocampus for declarative memory and its vulnerability to craniospinal radiation, there are only two studies in children that directly examined its critical role, [30, 31]. In the first one, Nagel et al., through a longitudinal study, assessed hippocampal volume of children treated for medulloblastoma and showed a progressive decline in volume for approximately 2 years after diagnosis before returning to a positive growth pattern. However, as the researchers focused on changes in raw hippocampal size, it is not possible to ascertain whether these changes reflected overall declines in brain size or a specific vulnerability of the hippocampus to treatment [30]. In the second study, Riggs et al. used volumetric MRI and diffusion tensor imaging in 19 pediatric survivors of medulloblastoma and one survivor of astrocytoma treated with cranial or craniospinal radiation and in 13 healthy controls [29]. Compared to controls, the survival group showed reduced white matter volume, damage to the uncinate fasciculus, and a smaller right hippocampus (Figs. 1 and 2). It is important to note that reduced hippocampal volume was not related to differences in overall brain volume, indicating that this injury was limited to the hippocampus. In this study, hippocampal and uncinate fasciculus volume loss correlated with poorer scores in the Children's Memory Scale [31].

Neuropsychological late outcomes

Effects of radiation on neuropsychological outcome

Several studies have investigated the effects of radiation on neurocognitive outcome in patients with posterior fossa tumors. In 1979, Hirsch et al. published a series of 57 children with medulloblastoma treated with surgery, radiotherapy, and chemotherapy (including intrathecal methotrexate in some patients). This study was one of the first to show that the quality of life of survivors was altered by mental, behavioral, or language disturbances. Notable declines in IQ were evident in over half of the patients. When they compared the neurocognitive outcome of medulloblastoma patients with a cohort of 26 patients with posterior fossa astrocytoma treated exclusively with surgery, the latter group showed less impairment. This study suggested that radiotherapy could be at least partially responsible for long-term mental and behavioral disturbances [19]. In a prospective study involving 35 children (age 4–16 years) with posterior fossa tumors attending the Royal Children's Hospital in Melbourne, factors that contributed to adverse neuropsychological outcome included hydrocephalus, white matter injury, and radiation therapy. These factors impacted intelligence, attention, and information processing skills to varying degrees [32]. Ellenberg et al. showed that patients with PF tumors treated with craniospinal radiation showed persistent neurocognitive dysfunction, including memory impairment and IQ decline [33]. These findings were not seen in patients with PF tumors who received focal radiation only. Similar observations have been confirmed in several subsequent studies [12, 14, 16].

Craniospinal radiation dose

A number of patients with PF tumors require craniospinal radiation as part of their postoperative management. The neurocognitive deficits observed in this population have been attributed mainly to the late effects of radiotherapy. Some deficits might not be easily noticeable, even by trained professionals, and in order to be properly assessed, they require a battery of age-adjusted tests. These deficits are largely related to the radiation damage to supratentorial brain structures or to a decrease in cerebral white matter.

Grill et al. retrospectively reviewed 31 children who had received radiotherapy for PF tumors. Patients were divided into three subgroups according to the craniospinal irradiation (CSI) doses: (1) 0 Gy (only PF radiation), (2) 25 Gy, and (3) 35 Gy. There was a significant correlation between the full-scale IQ score and the CSI dose, with mean scores at 84.5 for the 0-Gy group, 76.9 for the 25-Gy group, and 63.7 for the 35-Gy group [34]. In 2005, the same group reported the intellectual outcome of 31 children with medulloblastoma and 9 with ependymoma, treated with (1) PF radiation alone (50 Gy), (2) reduced CSI (25 Gy) plus PF boost, (3) standard CSI (35 Gy) plus PF boost, and (4) high-dose chemotherapy (HDCT) with stem cell support followed by PF radiation (50 Gy). Results showed that intellectual outcome continued to decline more than 4 years after the diagnosis, but the magnitude of this decline was most pronounced in the 35-Gy CSI and the HDCT + RT groups [35].

Many attempts have been made to reduce radiation damage by decreasing the radiation dose to the neuraxis and/or the irradiated posterior fossa volume. For this purpose,

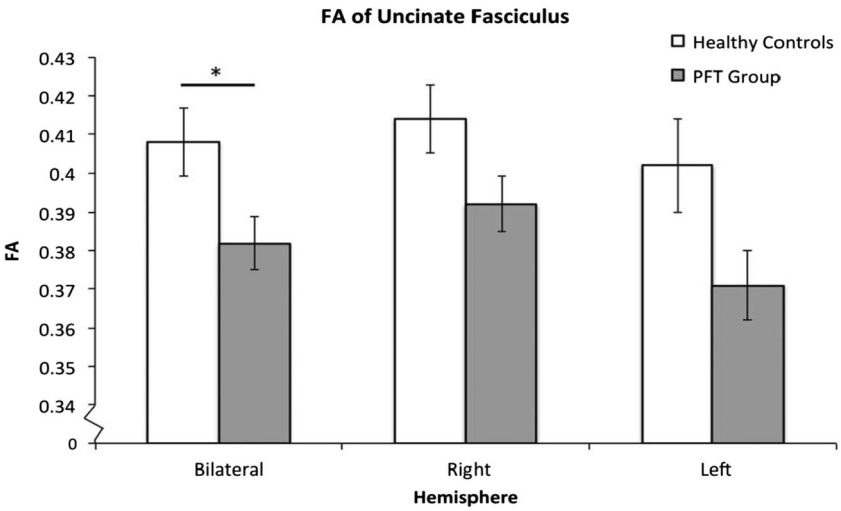

Fig. 1 Survivors of PF tumors exhibited significantly lower fractional anisotropy of the bilateral uncinate fasciculus. There was no significant main or interaction effect by hemisphere. From Riggs L et al. J Int Neuropsychol Soc. 2014 Feb;20(2):168–80. "Reprinted with permission. © 2014 International Neuropsychology Society. All rights reserved"

techniques, such as reduced-dose craniospinal radiotherapy, hyperfractionated radiotherapy, and conformal radiotherapy, to treat tumors of the posterior fossa have been studied. Thomas et al. prospectively evaluated the effects of reduced-dose (23.4 Gy in 13 fractions) compared with standard-dose (36 Gy in 20 fractions) neuraxis radiation in 126 patients 3 to 21 years of age with average-risk medulloblastoma. This study had to close early because patients randomized to the reduced neuraxis treatment had increased frequency of relapse [36]. Years later, Mulhern et al. analyzed the cognitive outcome of survivors of this study. Within their sample of long-term survivors, the most prominent impairment in the health-related quality of life scale was their cognitive functioning, with 12 of 22 patients requiring special educational assistance. Higher cognitive functioning was found among those patients who were treated with 23.4-Gy compared to 36-Gy cranial radiation with regard to performance IQ, full-scale IQ, attention index, and reading and arithmetic achievement. However, patients treated with 23.4 Gy still showed cognitive impairment. Older children experienced less toxicity than children who were younger at the time of irradiation [37].

Because of these concerns, reduced-dose craniospinal radiotherapy has become the standard treatment for most patients with average-risk malignant embryonal tumors of the posterior fossa in children. When reduced-dose radiotherapy is coupled with adjuvant chemotherapy, 5-year event-free survival in patients with medulloblastoma has been shown to reach a rate comparable to that of patients treated with standard-dose radiotherapy [38].

However, as Cantelmi et al. state in their review [25], the inability of the reduced-dose protocols to completely eliminate the cognitive decline implies that either cognitive decline in patients with tumors of the PF does not depend only on radiation damage or that radiation doses over a certain threshold are responsible for cognitive decline. Steen et al. showed that 20 Gy is the minimum radiation dose to cause a decrease in the volume of normal white matter [39]. It is therefore not surprising to observe white matter changes even with the use

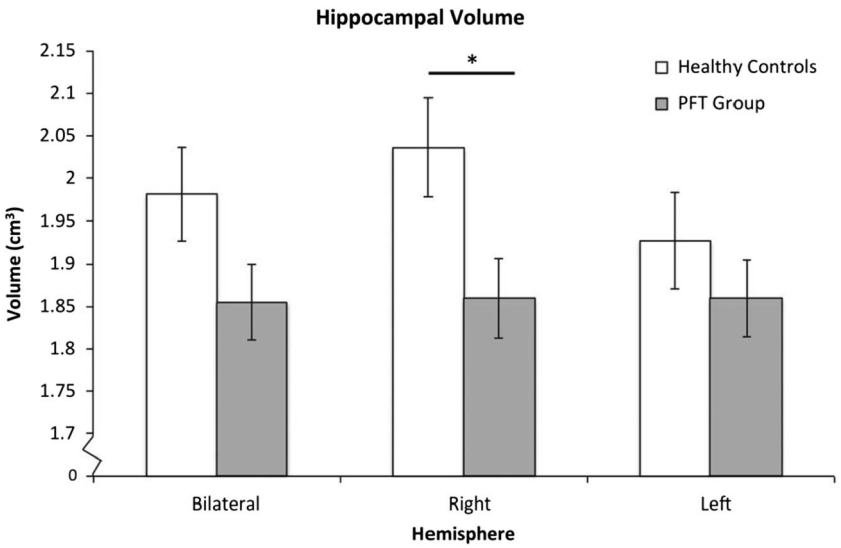

Fig. 2 Survivors of PF tumors had significantly smaller right hippocampus as compared to healthy controls; there were no effects of hemisphere for either group. From Riggs L et al. J Int Neuropsychol Soc. 2014 Feb;20(2):168–80. © 2014 International Neuropsychology Society. All rights reserved"

of reduced-dose (23.4 Gy) craniospinal radiation and associated neurocognitive declines of long-term survivors. A Children's Oncology Group (COG) study (ACNS0331) is attempting to reduce the craniospinal radiation dose to 18 Gy in young children (age 3–8 years old) with newly diagnosed standard-risk medulloblastoma. The results of this randomized trial are pending. However, a previous pilot study conducted two decades ago showed promising neurocognitive outcome in a small cohort of children treated with this approach [40].

Posterior fossa radiation field

PF radiation boost volume may also be important in determining the neurocognitive outcome of medulloblastoma patients. A PF boost delivers substantially more scattered radiation to structures located outside the targeted area, including the cochlea, temporal lobes, and parotid glands, than a boost limited to the tumor bed. The first study to suggest that intelligence after treatment with reduced-dose CSI and sequential focal conformal boosts to the PF and tumor bed was preserved was reported by Mulhern et al. [18]. Moxon-Emre et al. analyzed the respective impact of craniospinal dose, boost volume, and neurologic complications on intellectual outcome in a series of 113 patients with medulloblastoma treated at the Hospital for Sick Children [9]. They found that patients treated with reduced-dose CSI plus tumor bed boost showed stable intellectual trajectories, whereas patients treated with higher doses and larger boost volumes experienced significant intellectual declines. Merchant et al. prospectively treated 86 patients with newly diagnosed average-risk medulloblastoma with 23.4 Gy CSI, PF irradiation to 36 Gy, and primary site irradiation to 55.8 Gy using conformal techniques. The primary site irradiation included all gross residual tumor and/or the tumor bed at the primary site with an added margin of 2 cm. The 5-year EFS was 83.0 ± 5.3 % demonstrating that irradiation of less than the entire PF after 23.4 Gy CSI for average-risk medulloblastoma results in disease control comparable to that after treatment of the entire PF [41]. However, tumor bed boost is not yet a part of standard of care in most institutions around the world, with most ongoing medulloblastoma protocols still deferring to PF boost. We believe that this practice should be reconsidered.

Specific types of neuropsychological outcome

Academic outcome

Survivors of pediatric brain tumors have lower rates of high school graduation and employment relative to the overall population [42, 43]. Although the progressive decline in intellectual functioning associated with craniospinal radiation is now well documented [9, 32], changes in academic and behavioral functioning after radiation have received considerably less attention. Intelligence is certainly related to academics and, to a lesser degree, to behavioral functioning. Examining whether neurobehavioral changes are observed in real-world settings, such as at school and at home, is increasingly important. Cranial radiation during childhood has been associated with school problems and poor academic performance 2 to 5 years after diagnosis based on standardized achievement tests, parents' reports, or utilization of special education services [25].

Behavioral outcome is also related to family factors, such as family stress, and parental coping. Mabbott et al. examined the patterns of academic and behavioral functioning in a series of 53 patients treated for malignant PF tumors (46 medulloblastomas and 7 ependymomas) at the Hospital for Sick Children in Toronto. Poor academic scores on standardized tests and on parent and teacher ratings of school performance were found in these patients. Academic outcome was poorer for children who required CSF diversion for the control of hydrocephalus. Notably, no differences in academic outcome were observed between children treated with standard-dose versus reduced-dose radiation. Younger age at diagnosis was also associated with poorer parent and teacher ratings of overall academic functioning and reading achievement. This study also found that children fall progressively further behind their peers in reading, spelling, and mathematics achievement [44].

Working memory

Working memory is a system that involves the transient storage and processing of information, an important process for reasoning, comprehension, learning, and memory updating. Notably, the cerebellum interacts with the frontal cortex to support working memory function. In 67 children with PF tumors treated with surgery alone or surgery and radiation, our group [45] described bilateral tracts connecting the cerebellum and the dorsolateral prefrontal cortex, replicating the cerebello-thalamo-cerebral pathway documented in animal and adult models. Cranial radiation was associated with white matter damage within the cerebellar region of this pathway, especially in young children and those with a longer time since diagnosis, and was associated with poorer working memory. Specifically, reduced anisotropy and higher radial diffusivity within the entire cerebello-thalamo-cerebral pathway itself predicted lower working memory. This study concluded that the integrity of the cerebello-thalamo-cerebral pathway is critical for an effective working memory in children. Such information is crucial in the ongoing modification of treatment protocols to reduce damage to healthy tissue and preserve neurocognitive function [45].

Perception and estimation of time

The lateral cerebellum and the vermis have been both implicated in the perception of durations in the hundreds of milliseconds range and in cognitive timing [46]. Perception of duration classically refers to tasks such as the ability to discriminate intervals as more or less simultaneous or to judge events that take place in the psychological present with an upper limit of 5 to 8 s. Beyond this point, the event that marks the beginning of the interval must be stored in short-term memory, and the temporal judgment is more properly considered to involve estimation. Hetherington et al. examined short-duration perception (400 ms), long duration estimation (30 and 60 min), and spatiotemporal estimation in long-term survivors of childhood cerebellar tumors with a mean time since diagnosis of 14.2 years. The study included 20 patients with medulloblastomas, 20 with astrocytomas, and 40 healthy controls. Childhood lesions of the cerebellum produced enduring deficits in short-duration perception, but spared the ability to functionally estimate long durations, regardless of the pathology or treatment of the tumor. The utilization of sensory and somatomotor information to refine real-world spatiotemporal estimates was compromised in the medulloblastoma group only [46].

Selective attention

Selective attention refers to the process whereby one is able to focus on a particular object for a period of time, while simultaneously ignoring irrelevant information that is also occurring. Mabbott et al. assessed selective attention with covert-orienting, filtering, and visual search tasks in 54 patients with either (1) PF tumors treated with cranial radiation and surgery ($n = 22$), (2) PF tumors treated with surgery alone ($n = 17$), or (3) non-CNS tumors ($n = 15$), who served as a patient control group. To account for normal development, patient performance was also compared with that of healthy age-matched controls ($n = 10$). This study found that selective attention was impaired in PF tumor patients, regardless of treatment, compared to either non-CNS tumor patients or healthy controls. However, patients treated with cranial radiation showed the most significant impairment [47].

Neuromotor speech outcome

The cerebellum is part of a neural system that coordinates fluent speech production, by modulating movements, based on continuous auditory and proprioceptive feedback. Specific speech deficits are associated with cerebellar lesions. Ataxic dysarthria includes motor slowing, altered prosody of speech, imprecise articulation, and insufficient phonation resulting in monotonous vocal pitch, monoloudness, and harsh voice quality. The temporal regulation of speech production is also disrupted by cerebellar lesions, resulting in a dysfluent speech characterized by repeated syllables and phonemes and aberrant prolongation of intervals between syllables and words. Huber et al. assessed 54 survivors of PF tumors (29 cerebellar astrocytomas and 25 medulloblastomas) as well as 40 healthy controls. Medulloblastoma survivors had significantly more ataxic dysarthric features than either survivors of astrocytomas or controls, who did not differ from each other. Survivors of medulloblastoma and astrocytomas were more dysfluent than controls, but did not differ from each other. Speech rate varied with age and tumor type, being slower in medulloblastoma adult survivors [48]. In conclusion, posterior fossa tumors of childhood cause long-term neuromotor speech deficits, with survivors of medulloblastoma exhibiting a poorer outcome. Early involvement of a speech pathologist may be helpful in the management of these patients.

Executive functioning

The term "executive functioning" is used to describe several related cognitive functions such as selective and sustained attention, working memory, cognitive fluency, cognitive flexibility, and planning and organization [49, 50]. A study of a large group of pediatric cancer survivors ($n = 7147$) revealed that adolescent and young adult survivors with executive function limitations were less likely to graduate from school, be employed, have household incomes greater than 20,000 US dollars, or be married [43]. Focusing on PF tumors, a study with 20 adult survivors of medulloblastoma, on average 29 years of age and 18 years from diagnoses, showed that the mean full-scale intelligence quotient was nearly 1 SD below the normative mean (86.3 vs. 100, $p = 0.04$). Seventy-five percent of survivors were impaired on at least one measure of executive function. Sixty percent of survivors were employed less than full time, and 50 % were living dependently [51]. Maddrey et al. investigated executive functioning in 10-year survivors of pediatric medulloblastoma, who all had received CSI. Seventy-nine to eighty-five percent of the patients showed deficits on tests of planning and cognitive set-shifting, most pronounced in those with younger age at diagnosis [52]. Another study [53] compared a cohort of young adults treated for childhood astrocytoma with surgery only and young adult survivors of medulloblastoma treated with surgery, chemotherapy, and CSI. Both groups performed below the mean on a measure of executive functions. The interesting point was that both groups' scores did not significantly differ. This suggests that cerebellar damage from the tumor or the surgery can be associated with deleterious outcomes in executive functioning in children with PF tumors, independently of post-operative management [21, 53].

Physical functioning late outcomes

The physical consequences of childhood brain tumor have not been as extensively evaluated as other long-term complications. One study at our institution [42] assessed 30 patients with PF tumors with a median age of 11.4 years and mean time from diagnosis of 6.1 years. Cerebellar astrocytoma (43.3 %) and medulloblastoma (40 %) were the most common diagnoses. As a group, significantly decreased functioning, compared with norms, was observed in balance and running speed/agility. Specifically in balance, 21 (70 %) participants performed below or well below average. Participants with a non-astrocytoma tumor performed significantly worse than norms in all areas, independent of age at diagnosis, whereas the cerebellar astrocytoma subgroup was not statistically significantly different from normative data. Survivors with tumors infiltrating the vermis demonstrated significantly lower body coordination than norms. Unfortunately, despite these deficits, ongoing rehabilitation programs and long-term resources for these survivors to engage in physical activities are broadly unavailable.

Cerebellar mutism syndrome

Cerebellar mutism syndrome (CMS) typically manifests 1–2 days after a posterior fossa surgery and is characterized by reduced or entirely absent speech, dysarthria, emotional lability, personality/behavioral changes, and linguistic difficulties. It occurs in up to 25–30 % of children following resection of pediatric medulloblastoma. The incidence of CMS is classically lower in other tumor types such as ependymoma and low-grade glioma. Despite multiple hypotheses, the exact pathophysiology of CMS remains unclear. Although symptoms tend to improve with time, and in some cases resolve completely, a significant percentage of patients, especially those with severe CMS, continue to have persistent symptoms. The timing of this improvement is highly variable, with some patients improving within weeks of symptom onset, whereas up to two thirds might have speech and language dysfunction 1 year after severe CMS diagnosis. Children with CMS can have persistent sequela that may be any combination of neurological, speech, cognitive, behavioral, and psychosocial aspects. CMS can have a devastating impact on the individual and those around them.

Palmer et al. prospectively assessed early neurocognitive outcome of children following surgical resection of a PF embryonal tumor and compared patients who developed CMS with carefully matched control patients. While the matched control patients exhibited performance in the average range, patients who developed CMS were found to have significantly lower performance in processing speed, attention, working memory, executive processes, cognitive efficiency, reading, spelling, and math. Patients treated for medulloblastoma who experience postoperative CMS show an increased risk for neurocognitive impairment, evident as early as 12 months following diagnosis [54]. A recent study by Walsh et al. showed in a matched sample of medulloblastoma survivors that CMS is associated with greater impairments across a range of neurocognitive functions (performance IQ, verbal IQ, working memory, flexibility, memory, processing speed, and visual motor integration) in the years following treatment [55]. These studies highlight the need for careful follow-up with neuropsychological evaluation and for obtaining critical support for patients and their families. Unfortunately, there is no specific treatment for CMS, which continues to represent a significant challenge for neurorehabilitation teams.

Long-term quality of life

The concept of quality of life (QOL) broadly encompasses how an individual measures the "goodness" of multiple aspects of their life. These evaluations include one's emotional reactions to life occurrences, disposition, sense of life fulfillment and satisfaction, and satisfaction with work and personal relationships [56].

The QOL issues for survivors of pediatric PF tumors are unique and relate to many potentially important factors, including physical, intellectual, and psychological concerns. Following treatment for a PF tumor, a child may be left with numerous physical deficits, including difficulty walking and running, balance and coordination problems, weakness, difficulty swallowing food, visual and speech problems, and long-term cognitive outcome. The impact of any of these deficits on QOL can be significant. In a study performed at our institution [57], we assessed the QOL of 62 children with PF tumors (pilocytic astrocytoma 45.2 %, medulloblastoma 30.6 %, ependymoma 11.3 %, and brainstem astrocytoma 11.3 %) after a median of 5.2 years since the last active treatment (range, 2.4–10.1 years). QOL was measured using the *PedsQL Generic Core Scales* and the Health Utilities Index mark 3 (*HUI3*) questionnaires at least 6 months after the end of their therapy. In this study, the overall QOL of children was actually relatively good with a mean PedsQL total score of 77.2 (parent reported) and 81.7 (child reported). However, 25 % of the cohort had PedsQL total scores ≤64.1 and HUI3 utility scores ≤0.71. Worse QOL was seen in those who experienced hydrocephalus and those with a lower socioeconomic status (family functioning and family income). Bull et al. [58] compared the quality of survival after CSI alone with CSI plus chemotherapy (CT) in 147 long-term survivors of medulloblastoma treated in the UK as per the SIOP-PNET 3 randomized trial. Health status was significantly poorer in the group treated in the CSI and CT arm of the trial than in the CSI alone arm, and there were also trends to poorer outcomes for behavior and QOL scores. The CSI plus CT group was also significantly

more restricted physically and needed more therapeutic and educational support. Although improved survival rates in medulloblastoma have been attributed to the addition of CT to CSI, this suggests that CT can aggravate the adverse effects of the CSI and affect the neurocognitive outcome and QOL of the survivors. Reimers et al. [59] assessed QOL in 126 consecutive Danish childhood brain tumor patients treated between 1970 and 1997 and being 7.9–40.4 years at follow-up. Treatment with RT was the most important risk factor for reduced health-related QOL, with lower scores for physical functioning and energy, social functioning, cognitive functioning, body image, outlook of life, and intimate relations. Tumor location in the PF was also associated with lower scores for physical functioning and energy. Younger age at diagnosis was associated with lower scores for social functioning and intimate relations, and younger age at follow-up was associated with more physical symptoms. In contrast, neither gender nor presence of hydrocephalus predicted significantly reduced QOL in the multivariate analyses. Benesh et al. [60] assessed 23 patients with medulloblastoma ($n = 18$) or ependymoma ($n = 5$) with extensive neurocognitive and QOL testing at a median of 56 months (range, 1–174) after the end of treatment. They found that younger patients with more severe late effects reported a worse QOL.

While the current literature provides some insight into the predictors of poor QOL outcome, further work is needed to better delineate these so that we can more definitively identity patients at higher risk.

Endocrinology outcomes

Endocrine deficits are frequently seen as a direct effect of the radiation treatment used in the management of some PF tumors in children [61]. These deficits are observed with both focal and craniospinal radiation fields, although the development of conformal radiation techniques and, more recently, the increasing use of proton therapy have dramatically reduced the risk of endocrinopathy after focal radiation treatments. These deficits include growth hormone deficiency (GHD), peripheral or central hypothyroidism, adrenocorticotropic hormone (ACTH), and sex steroid deficiencies. The occurrence of endocrine sequelae depends of the total dose and other specific clinical factors, in particular the age of the patient. Laughton et al. prospectively followed 88 patients with embryonal tumors treated with the SJMB96 protocol with endocrine follow-up. Seventy-eight patients had a tumor located in the PF. Patients were treated with craniospinal radiation (23.4 Gy for standard risk and 36–39.6 Gy for high-risk patients + tumor bed boost for a total of 55.8 Gy) followed by four cycles of high-dose chemotherapy (vincristine, cisplatin, and cyclophosphamide). The cumulative incidence of GHD, thyroid-stimulating hormone (TSH) deficiency, adrenocorticotropic hormone deficiency, and primary hypothyroidism at 4 years from diagnosis was 93 ± 4 %, 23 ± 8 %, 38 ± 6 %, and 65 ± 7 %, respectively. Radiation dosimetry to the HP axis was associated only with the development of TSH deficiency; the 4-year cumulative incidence was 44 ± 19 % versus 11 ± 8 % ($P = 0.014$) for those receiving more or less than the median dose to the hypothalamus (>42 vs <42 Gy), respectively [62] (Fig. 3). GHD and primary hypothyroidism are diagnosed in a majority of subjects relatively soon after the completion of therapy. Recent series with protons [63] and tumor bed boost suggests decreased pituitary damage. Merchant et al. estimated the dose characteristics to targeted tumor and normal tissue contours, to determine whether proton radiotherapy has clinical advantages over photon radiotherapy, in 10 patients with medulloblastoma and 10 with PF ependymoma. They showed that for patients with PF ependymoma, proton radiotherapy can avoid growth hormone deficiency and, thus, any endocrinopathy based on the location and size of the primary tumor. For patients with medulloblastoma, sparing the pituitary gland from high-dose radiation may be achieved to a higher degree with protons than with photons, which may impact central hypothyroidism, gonadotropin insufficiency, and adrenal insufficiency [64]. Endocrine deficits can significantly impact QOL and require management by a multidisciplinary team that should include a pediatric endocrinologist.

Vascular complications and secondary tumors

Beyond the endocrinogical side effects, radiation has been associated with late complications, including strokes and the

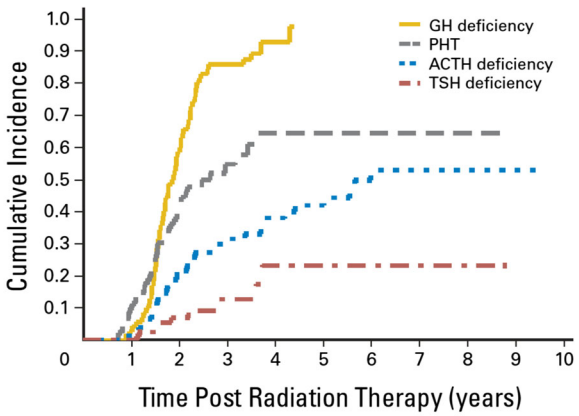

Fig. 3 Cumulative incidence of specific endocrine deficits in 88 patients with embryonal tumors treated with the SJMB96 protocol following radiation therapy. *GH* growth hormone, *PHT* primary hypothyroidism, *ACTH* adrenocorticotropic hormone, *TSH* thyroid-stimulating hormone. From Laughton SJ et al. J Clin Oncol. 2008 Mar1;26(7):1112–858. "Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved"

development of cavernomas [65]. However, one of the most concerning long-term complication is the occurrence of secondary tumors. Both radiotherapy and chemotherapy are associated with increased relative risk for the development of secondary malignancies (Fig. 4). Armstrong et al. collected information on treatment, mortality, chronic medical conditions, and neurocognitive functioning of children who survived at least 5 years after a CNS malignancy diagnosed between 1970 and 1986 within the Childhood Cancer Survivor Study. Among all eligible 5-year survivors ($n = 2821$), patients who received cranial RT of 50 Gy or more ($n = 813$) had a cumulative incidence of a subsequent neoplasm within the CNS of 7.1 % (95 % CI = 4.5 to 9.6 %) at 25 years from diagnosis compared with 1.0 % (95 % CI = 0 to 2.3 %) for patients who had no RT [43]. Peterson et al. conducted an analysis of the Surveillance, Epidemiology, and End Results (SEER) Program in the USA and found that 39 patients out of 2506 survivors of childhood primary brain tumor developed a secondary malignant tumor. The median time to secondary malignant tumor diagnosis was 14.1 years [66]. Packer et al. described 15 patients experiencing secondary tumors in 379 patients with localized medulloblastoma treated with 23.4 Gy of craniospinal and 55.8 Gy of posterior fossa irradiation and chemotherapy, with a median follow-up of 9.7 years. The median time to secondary tumor was 5.8 years, with four occurring within 5 years. The estimated cumulative incidence rate of secondary tumors at 5 and 10 years for the entire cohort was 1.1 % (95 % CI 0.0 %–2.3 %) and 4.2 % (95 % CI 1.9 %–6.5 %), respectively. Tumors included six high-grade gliomas, two myelodysplastic syndromes, two thyroid papillary adenocarcinoma, one acute lymphoblastic leukemia, one osteosarcoma, one basal cell carcinoma (Gorlin syndrome), one spindle cell carcinoma of the nasal region, and one low-grade glioma [38]. In summary, all patients with PF tumors treated with radiation have an increased relative risk for the development of secondary malignancies, which varies between approximately 1 to 8 %. The most common malignancies reported are high-grade gliomas and meningiomas. Secondary high-grade gliomas tend to occur early, during the first decade following treatment, whereas meningiomas are observed at a later stage, typically 15 to 25 years after radiation.

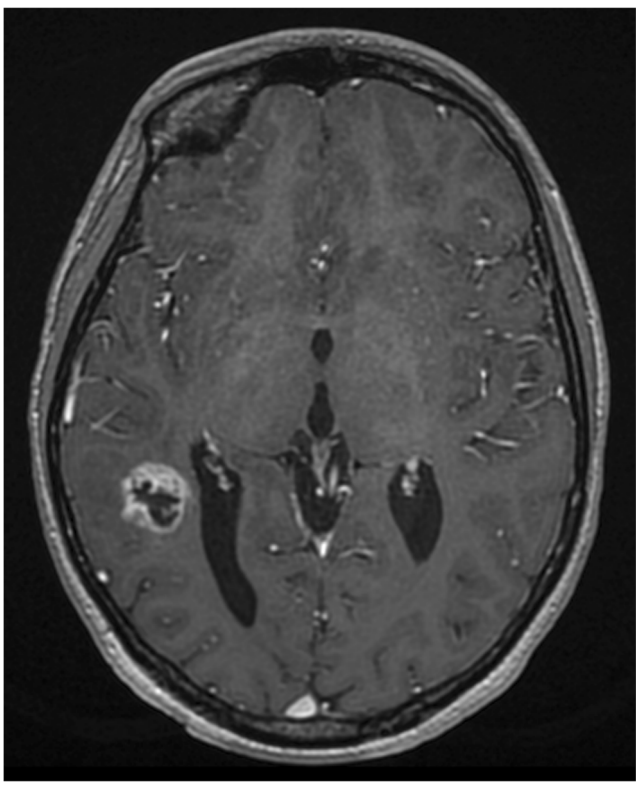

Fig. 4 MRI showing a secondary glioblastoma multiforme in the right posterior temporal lobe in a 17-year-old male 12 years after a diagnosis of an average-risk medulloblastoma

Interventions to improve neuropsychological outcome

Efforts to improve neuropsychological function in survivors of brain tumors have increased substantially. Neuropsychologists, oncologists, clinical psychologists, and physiatrists are devoting increased attention to not only applying traditional brain injury rehabilitation but also developing innovative modes of treatment that are likely to be equally relevant for pediatric and even adult patients who suffer more common CNS insults such as traumatic brain injuries and epilepsy [67]. A number of treatment approaches have been evaluated in recent years, including medication, clinic-based cognitive remediation, and home-based computerized cognitive training.

Pharmacological interventions

Delong et al. reported in 1992 one of the first attempts to pharmacologically stimulate neurocognitive functioning in pediatric survivors of a CNS-related malignancy [68]. In a pilot study of 12 children previously radiated who had survived treatment for a brain tumor or acute lymphoblastic leukemia (ALL), 75 % of the children who received methylphenidate (Ritalin) exhibited a "good response." Despite some methodological weaknesses, this study was the very first attempt at improving neurocognitive functioning in irradiated children. A subsequent study by Meyers et al. in 1998 suggested that methylphenidate was also effective in improving neurocognitive functioning within the adult brain tumor population, with benefits observed in information processing speed, memory, mental flexibility, mood, activities of daily living, and improved affect [69]. In 2001, Thompson et al. reported the results of a double-blinded, placebo-controlled randomized clinical trial of methylphenidate administered to 32 survivors of brain tumors (the majority) and ALL. Findings

indicated significantly improved functioning associated with methylphenidate in terms of both sustained attention and caregiver report of attentional functioning [70]. Three years later, Mulhern et al. reported the results of a similar randomized double-blind crossover study in 83 long-term survivors of ALL and brain tumors. Patients who received methylphenidate achieved significant improvements in attention/concentration, parent and teacher reports of attentional deficits, social functioning, and academic competence, although there were nine patients who had to discontinue the medication due to side effects [71]. In 2012, Gehring et al. conducted a randomized trial in 24 adults with brain tumors receiving methylphenidate or modafinil for 4 weeks. This study showed a positive effect associated with the use of stimulants on test performance in speed of processing and executive function requiring divided attention. Inconsistent, differential effects were found on a measure of attention in favor of methylphenidate and on a measure of processing speed in favor of modafinil. There was also evidence of a general beneficial effect on patient-reported measures of fatigue, mood, and quality of life, however, with no statistically significant differences between treatment arms in these measures over time [72]. As Butler et al. describe in their review, stimulant medication may improve attentional functioning in long-term survivors of a CNS-related malignancy, although with some limitations. The first one is that stimulant medications are short acting and effective while prescribed, but they do not result in sustained improvement in academic achievement/neurocognitive functioning once they are discontinued. They also have side effects, which can affect the QOL of these patients [67].

Recently, Rapp et al. randomly evaluated the benefit of donepezil, a neurotransmitter modulator, in improving cognitive function in 198 adult brain tumor survivors who had received partial- or whole-brain irradiation. After 24 weeks of treatment, the composite scores did not differ significantly between groups; however, significant differences favoring donepezil were observed for memory (recognition, $P = 0.027$; discrimination, $P = 0.007$) and motor speed and dexterity ($P = 0.016$). Significant interactions between pretreatment cognitive function and treatment were found for cognitive composite ($P = 0.01$), immediate recall ($P = 0.05$), delayed recall ($P = 0.004$), attention ($P = 0.01$), visuomotor skills ($P = 0.02$), and motor speed and dexterity ($P < 0.001$), with the benefits of donepezil greater for those who were more cognitively impaired before initiation of the study treatment [73].

Clinic-based cognitive remediation

Cognitive remediation is another intervention that has been offered in survivors of brain tumors who experience neurocognitive deficits. These programs typically focus on the repetition of tasks thought to develop core cognitive skills, as well as the acquisition and practice of strategies to compensate for deficits in these areas (e.g., organizational skills, self-monitoring). Most studies to date have focused on clinic-based programs involving primarily face-to-face work with one or more providers. A multi-center randomized trial of a hospital-based cognitive remediation program was completed with 161 survivors of pediatric cancer. While treatment efficacy was demonstrated through increases in attention and academic achievement, effect sizes were small for a number of functional outcomes. Conclusions regarding the effectiveness of this program were also mitigated by a sizable percentage of participants who failed to complete the 6-month program [74]. A similar intervention that focused on problem-solving training was piloted with a small group of survivors. Again, preliminary efficacy was demonstrated through improvements on each outcome measure; however, this study was also characterized by a low participation rate and suboptimal adherence. The authors noted that the most frequent reason given for lower adherence was perceived inconvenience of coming to the clinic [75]. Collectively, these results suggest that intensive, therapist-directed, in-person interventions may not be practical or desirable for some subgroups of survivors.

Home-based computerized cognitive training

Home-based, computerized cognitive training has recently emerged as a cognitive remediation paradigm with the potential to address core neuropsychological deficits in survivors. This approach is associated with a low risk of side effects (compared to pharmacological treatment) and may carry a reduced treatment burden (compared to clinic-based interventions) because it can be completed at home, at any time during the day. Computerized cognitive training employs game-like exercises to target core cognitive skills such as working memory and attention. Such programs have demonstrated efficacy across a wide variety of individuals with cognitive difficulties: children with ADHD, TBI and stroke, schizophrenia, extremely low birth weight, cochlear implants, and borderline intellectual disabilities [76, 77].

Hardy et al. examined the feasibility and preliminary efficacy of a home-based, computerized working memory training program, CogmedRM, with survivors of childhood cancer. Twenty survivors of ALL and brain tumors with identified deficits in attention and/or working memory were randomized to either the success-adapted computer intervention or a non-adaptive, active control condition. Specifically, children in the adaptive condition completed exercises that became increasingly challenging with each correct trial, whereas those in the non-adaptive version trained with exercises that never increased in difficulty. All participants were asked to complete 25 training sessions at home, with weekly, phone-based coaching support. Brief assessments were completed pre- and post-intervention; outcome measures included both

performance-based and parent-report measures of working memory and attention. In this study, 85 % of survivors were compliant with the intervention, with no adverse events reported. After controlling for baseline intellectual functioning, survivors who completed the intervention program evidenced significant post-training improvements in their visual working memory and in parent-rated learning problems compared with those in the active control group. However, no differences in verbal working memory functioning were observed between groups [76].

Future directions

In order to achieve the best possible outcome for survivors, and ultimately minimize the long-term consequences of the disease and its treatment, new interventions must be developed to ameliorate the neuro-toxic effects experienced by children. Various new agents and intervention programs with potential to stimulate neuro-recovery are now available, and there are a number of ongoing clinical trials in this area, including the following:

1) A placebo-controlled double-blind crossover trial of metformin for brain repair in children with cranial of cranial-spinal radiation for brain tumors (NCT02040376) will examine whether metformin can enhance cognition or promote brain repair following radiation-induced brain injury.
2) "The neuro-protective effects of exercise in children with brain tumors" (NCT01944761) is a study to evaluate the feasibility of conducting a structured exercise program in children treated with cranial radiation for brain tumors and to test whether exercise results in improved thinking skills and emotional function. It will also examine potential mechanisms of improved outcome, particularly recovery of the white matter and gray matter.
3) "A Phase II Placebo-Controlled Trial of Modafinil to Improve Neurocognitive Deficits in Children Treated for a Primary Brain Tumor" (NCT01381718) will determine whether a 6-week drug trial of modafinil, compared to placebo, is associated with improvement in neurocognitive function as defined by parent report of inattention or working memory deficits or by direct assessment of attention, working memory, or processing speed in children with cognitive impairment after treatment for a primary brain tumor.

Conclusions

In recent years, our knowledge of the determinants of long-term functional and neurocognitive deficits has dramatically increased. Most of the focus has been on survivors of ependymoma and medulloblastoma, and extensive studies on long-term outcome of adult survivors of cerebellar astrocytomas operated on as children are lacking. This is likely due to the fact that a large number of patients in the latter group have excellent functional outcome and an uneventful recovery. Although patients with malignant PF tumors appear to represent the high-risk population, there is a large spectrum of deficits in PF tumor survivors and ideally all patients, not only those with medulloblastomas and ependymomas, should be assessed and followed on a long-term basis. Follow-up of all patients ideally should include comprehensive neuropsychological testing at regular intervals, ideally every other year. This may be of benefit for school and later career/employment planning. Children at risk for severe neuropsychological deficits could benefit from early and individualized rehabilitation programs, once they have been identified.

Radiotherapy is probably the most deleterious factor affecting long-term outcome. Newer treatment regimens are being designed to reduce the impact of cranial radiotherapy by implementing protocols with reduced dose and by more sophisticated delivery systems to reduce the amount of tissue exposed to radiation.

– With better therapies, survival outcomes of PF brain tumors have improved. It is now recognized that the goals of treatment should include not just survival but quality of life as well. Ongoing and future trials should systematically assess QoL in long-term survivors.

Conflict of interest Authors disclose no conflict of interests.

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