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Risk factors for domain-specific neurocognitive outcome in pediatric survivors of a brain tumor in the posterior fossa—Results of the HIT 2000 trial

Martin Mynarek[†], Anne Rossius[†], Anika Guiard, Holger Ottensmeier, Katja von Hoff, Denise Obrecht-Sturm, Lisa Bußenius, Carsten Friedrich, Andre O. von Bueren, Nicolas U. Gerber, Thomas Traunwieser, Rolf-Dieter Kortmann, Monika Warmuth-Metz, Brigitte Bison, Ulrich-W. Thomale, Juergen Krauss, Torsten Pietsch, Steven C. Clifford, Stefan M. Pfister, Dominik Sturm, Felix Sahm, Tanja Tischler[†],[1], and Stefan Rutkowski[†]

All author affiliations are listed at the end of the article

[1]Current address: Psychotherapeutenkammer Hamburg, Hamburg, Germany

[†]These author are equally contributed.

Corresponding Author: Stefan Rutkowski, Dr. med., Department for Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, Hamburg 20246, Germany (s.rutkowski@uke.de).

Abstract

Background. Neurocognition can be severely affected in pediatric brain tumor survivors. We analyzed the association of cognitive functioning with radiotherapy dose, postoperative cerebellar mutism syndrome (pCMS), hydrocephalus, intraventricular methotrexate (MTX) application, tumor localization, and biology in pediatric survivors of a posterior fossa tumor.

Methods. Subdomain-specific neurocognitive outcome data from 279 relapse-free survivors of the HIT-2000 trial (241 medulloblastoma and 38 infratentorial ependymoma) using the Neuropsychological Basic Diagnostic tool based on Cattell–Horn–Carroll's model for intelligence were analyzed.

Results. Cognitive performance 5.14 years (mean; range = 1.52–13.02) after diagnosis was significantly below normal for all subtests. Processing speed and psychomotor abilities were most affected. Influencing factors were domain-specific: CSI-dose had a strong impact on most subtests. pCMS was associated with psychomotor abilities ($\beta = -0.25$ to -0.16) and processing speed ($\beta = -0.32$). Postoperative hydrocephalus correlated with crystallized intelligence ($\beta = -0.20$) and short-term memory ($\beta = -0.15$), age with crystallized intelligence ($\beta = 0.15$) and psychomotor abilities ($\beta = -0.16$ and $\beta = -0.17$). Scores for fluid intelligence ($\beta = -0.23$), short-term memory ($\beta = -0.17$) and visual processing ($\beta = -0.25$) declined, and scores for selective attention improved ($\beta = 0.29$) with time after diagnosis.

Conclusions. The dose of CSI was strongly associated with neurocognitive outcomes. Low psychomotor abilities and processing speed both in patients treated with and without CSI suggest a strong contribution of the tumor and its surgery on these functions. Future research therefore should analyze strategies to both reduce CSI dose and toxicity caused by other treatment modalities.

Key Points

- CSI-dose has an influence on the neurocognitive outcomes of brain tumor survivors.
- Psychomotor abilities and processing speed are particularly affected, even in patients who received no CSI.
- Future research should aim at improving low processing speed.

Importance of the Study

Neurocognitive impairment is a major concern in survivors of pediatric brain tumors and craniospinal radiotherapy (CSI) is considered one of the key contributing factors. We compared domain-specific neurocognitive outcomes of survivors of medulloblastoma treated with either standard-dose or high-dose CSI or ependymoma, who did not receive CSI. We identified domains that are specifically affected in survivors who received CSI and others, especially fine motor skills and reaction time, which were severely affected independent of whether the patient received CSI or not. Specifically, low scores in these domains were also associated with the postoperative cerebellar mutism syndrome, indicating that these impairments at least in part might be induced by the surgery. Hereby, this study provides strong evidence that future studies, besides efforts to reduce the dose of CSI, should address the question of the optimal neurosurgical approach to posterior fossa tumors.

Central nervous system (CNS) tumors are the most common solid tumor in childhood.[1,2] Treatment usually starts with maximal safe surgical resection, followed by radiotherapy, chemotherapy, or a combination of both according to the histological diagnosis. Radiotherapy is associated with significant neurotoxicity, especially if large target volumes or higher doses are required. In medulloblastoma, irradiation of the entire CNS is usually required ("craniospinal irradiation," CSI), and has been associated with impaired long-term neuropsychological outcomes.[3–5] In contrast, CSI is usually not required to treat ependymoma and radiotherapy is delivered to the tumor region only.[6] With the advanced understanding of treatment-related toxicities and the increasing number of survivors, long-term quality of life, and especially neurocognition are of increasing relevance for the patients and their therapists.[6–10]

Not all neuropsychological domains are affected in the same way in brain tumor survivors. However, core cognitive functions like working memory, psychomotor skills, processing speed, attention, and visual processing,[11] as well as problem-solving and language-related abilities[12,13] are often impacted. Declines in scores for executive functioning, selective attention, processing speed, and simple reaction time are related to radiotherapy.[14–17] Therefore, omission of CSI has been investigated in very young children who are known to be highly affected by CSI. This is associated with a relevant increase in the risk of relapse especially in non-WNT/non-SHH medulloblastoma.[18–20] Others investigated the omission of CSI in patients with low-risk, WNT-activated medulloblastoma,[21,22] resulting in a high incidence of relapse. Therefore, the omission of CSI is currently not considered acceptable in older children. The ACNS0331 trial investigated the reduction of CSI dose below 23.4 Gy in nonmetastatic medulloblastoma patients under the age of 7 irrespective of the biological subgroup and also found an increased risk of relapse in patients treated with 18 Gy.[5] Current trials aim to reduce the CSI dose in patients with a low-risk biological profile only (eg SIOP-PNET5-MB [NCT02066220], SJMB12 [NCT01878617], or ACNS1422 [NCT02724579]).[23]

Additional factors are also associated with the neurocognitive outcome of brain tumor survivors, among them postoperative cerebellar mutism syndrome (pCMS, "posterior fossa syndrome"), hydrocephalus, and the tumor itself, its molecular subtype[24,25] and its surgery.[26]

The clinical trials HIT 2000 and SIOP PNET4 were designed to improve outcomes of children and young adults with medulloblastoma, CNS-PNET and ependymoma from birth to age 21. Patients older than 4 at diagnosis with medulloblastoma were treated by risk-adapted approaches using either moderate-dose or high-dose CSI with risk-stratified chemotherapy.[27,28] Patients with ependymoma received focal radiotherapy to the tumor bed with or without chemotherapy depending on clinical risk factors.[29] We describe domain-specific neurocognitive outcomes of survivors of medulloblastoma or ependymoma of the posterior fossa and assess their relationship to therapy-related risk factors, especially CSI dose.

Methods

HIT 2000/SIOP-PNET4

Patients diagnosed younger than 21 years of age with medulloblastoma, ependymoma, or CNS primitive neuroectodermal tumor between January 1, 2001 and December 31, 2011 were eligible for the HIT 2000 trial (NCT00303810). The study concept included interventional arms for eligible patients and an observational program for patients not included in the interventional strata. One of these arms (HIT 2000-AB4) formed the national cohort of the European SIOP-PNET4 trial.[27]

Eligibility Criteria

Children and adolescents with medulloblastoma or infratentorial ependymoma who participated in the HIT 2000 trial were eligible for this cross-sectional neurocognitive outcome study if they were older than 4 years at the diagnosis and remained free of relapse or progression at the time of neuropsychological assessment. Participation was voluntary. Patients and/or their legal representatives gave their written informed consent before inclusion. The neuropsychological follow-up study was approved by the Ethics Committee. Data from 76 assessments has been previously published.[30]

Treatment

Details on the therapy for medulloblastoma were described previously.[27,28,31] Supplementary Figure 1 summarizes the therapy principles for patients included in this analysis. Briefly, patients with medulloblastoma received a combination of chemotherapy and CSI. Patients with ependymoma received postoperative radiotherapy to the tumor bed (but no CSI) with chemotherapy for anaplastic ependymoma (WHO III) and/or postoperative residual tumor.[32]

For correlation with neuropsychological outcome, CSI-dose was categorized into 3 groups according to given dose: no CSI/focal RT (only focal radiotherapy for ependymoma), moderate CSI-dose (ie <30 Gy CSI), and high CSI-dose (>30 Gy CSI). All but 1 patient received photon radiotherapy (1 proton and 22 not documented).

Neuropsychological Assessment

Neuropsychological follow-up assessments were carried out using the neuropsychological basic diagnostic (NBD) tool. The test selection for the NBD tool was based on the Cattell–Horn–Carroll (CHC) model for intelligence[33,34] and the concept of cross-battery assessment (XBA).[34] Within the concept of the CHC model, intelligence is represented by the general g-factor and can be tested considering several subdomains. Relevant domains used in the NBD are the following: fluid intelligence, crystallized intelligence, visual processing, verbal short-term memory, psychomotor abilities (separate for dominant hand (DH), nondominant hand (NDH), and both hands (BH)), processing speed and selective attention. The NBD is a modified version of the “Wuerzburger psychologische Kurzdiagnostik (WUEP-KD).”[35] The WUEP-KD was cross-validated in order to determine an appropriate combination of cognitive tests to measure cognitive abilities. Supplementary Table 1 summarizes the tests used in NBD.

Further Risk Factors for Neuropsychological Outcome

Data on factors influencing neuropsychological outcomes were collected from the HIT 2000/SIOP-PNET4 database. Tumor localization and preoperative hydrocephalus were determined by a central review of preoperative magnetic resonance imaging (MRI).[36] Postoperative hydrocephalus was defined by the presence of a VP-shunt. Postoperative cerebellar mutism syndrome (pCMS) was assessed retrospectively from patient records and was defined as postoperative mutism with or without ataxia and/or hypotonia. Histological type of medulloblastoma was diagnosed according to the WHO classification of tumors of the CNS. Medulloblastoma molecular/biological entity was assessed by DNA methylation-based classification.[37–39]

Statistical Approach

Data analysis was performed using IBM SPSS version 29 (IBM Corp.). Neuropsychological test measurements were transformed into z-scores (mean [M] =0, standard deviation [SD]=1 in the healthy standardized sample). The results of patients’ assessments were compared to the standardized sample using independent sample t-tests. Results of the t-test were reported with t-statistic and degrees of freedom t(df). Cohen's d was used to quantify effect sizes.[40,41] Univariate ANOVAs with fixed effects were performed to determine and quantify differences between groups receiving different CSI doses. Post hoc comparisons were calculated and Bonferroni-corrected when ANOVAs were significant. t-Tests were carried out for the independent variables of preoperative hydrocephalus, postoperative hydrocephalus, postoperative cerebellar mutism, and sex. Relationships with age at diagnosis and time since diagnosis were assessed with Pearson correlations. Factors were chosen based on published literature and the availability of data. Multiple linear regression analyses were conducted to investigate confounding factors, using stepwise backward selection. Predictors included CSI as 2 dummy variables (no vs. moderate CSI dose, no = 0, moderate = 1, and no vs. high CSI dose, no = 0, high = 1), as well as preoperative hydrocephalus, postoperative hydrocephalus and postoperative cerebellar mutism syndrome (no = 0, yes = 1), as well as sex (female = 0, male = 1), age at diagnosis and time since diagnosis (in years). Assumptions for the validity of the model were checked. All analyses were done exploratory and all P-values were adjusted according to the Benjamini–Hochberg procedure[42] to control for the familywise error rate at $\alpha = 0.05$. Unavailable data were coded as missing data.

Results

Patient Characteristics

Two hundred and seventy-nine eligible patients underwent neuropsychological testing at $M = 5.1$ years ($SD = 2.8$; range = 1.5–13.0) after diagnosis. Two hundred and forty (86.0%) patients had medulloblastoma and 39 (14.0%) had infratentorial ependymoma. Age at diagnosis was $M = 9.3$ (SD = 3.6; range = 4.0–19.0). See Table 1 for detailed patients’ characteristics and Figure 1 for a consort diagram.

Mean values (z-scores) of all subtests were significantly below 0 (mean of standardized sample) in the cohort (fluid intelligence: $M = -0.67 \pm 1.29$, $t(278) = -8.61$; visuomotor integration: $M = -0.90 \pm 1.07$, $t(268) = -13.77$; short-term memory: $M = -0.54 \pm 0.87$, $t(271) = -10.16$; crystallized intelligence: $M = -0.29 \pm 1.16$, $t(229) = -3.77$; psychomotor abilities: $M_{DH} = -1.85 \pm 1.72$, $t(254) = -17.16$; $M_{NDH} = -2.55 \pm 2.07$, $t(254) = -19.67$; $M_{BH} = -2.54 \pm 2.05$, $t(253) = -19.75$; selective attention: $M = -0.27 \pm 1.00$, $t(159) = -3.41$; processing speed: $M = -2.42 \pm 2.21$, $t(160) = 13.88$; all Benjamini–Hochberg corrected $P' < .001$). The results of psychomotor abilities and processing speed were especially poor with about 50% (range 40.4–55.3%) of survivors scoring lower $z = -2$.

Effects of CSI Dose on Neurocognitive Outcomes

Neurocognitive results differed between groups receiving focal RT without CSI ($n = 38$), moderate ($n = 110$) or high ($n = 131$) CSI doses for most subtests, especially for fluid

Table 1. Patient Characteristics

Characteristic	Total (*N* = 279) No. (%)	Focal Radiation of Tumor Area (*n* = 38) No. (%)	Moderate CSI Dose (*n* = 110) No. (%)	High CSI Dose (*n* = 131) No. (%)	Fisher's Exact Test
Diagnosis					
Medulloblastoma (M0)	161 (57.7%)	–	110 (100%)	50 (38.2%)	$P < .001$
Medulloblastoma (M+)	80 (28.7%)	–	–	80 (61.1%)	
Ependymoma, infratentorial	38 (13.6%)	38 (100%)	–	1 (0.7%)[a]	
Sex					
Female	103 (36.9%)	17 (44.7%)	42 (38.2%)	44 (33.6%)	$P = .436$
Male	176 (63.1%)	21 (55.3%)	68 (61.8%)	87 (66.4%)	
Postoperative Hydrocephalus (Shunt)					
No shunt postoperatively	236 (84.6%)	34 (89.5%)	93 (83.2%)	109 (85.8%)	$P = .523$
Required shunt postoperatively	39 (14.0%)	4 (10.5%)	13 (2.3%)	22 (16.8%)	
Missing data	4 (1.4%)	–	4 (4.5%)	–	
Hydrocephalus on Preoperative MRI					
No hydrocephalus	53 (19.0%)	7 (18.4%)	19 (17.3%)	27 (19.0%)	$P = .876$
Mild	45 (16.1%)	8 (21.1%)	16 (14.5%)	21 (16.0%)	
Moderate	102 (36.6%)	13 (34.2%)	44 (40.0%)	45 (34.4%)	
Severe	52 (18.6%)	8 (21.1%)	17 (15.5%)	27 (20.6%)	
Requiring EVD	7 (2.5%)	–	2 (1.8%)	5 (5.4%)	
Missing data	20 (7.2%)	2 (5.3%)	12 (10.9%)	6 (4.6%)	
Postoperative Cerebellar Mutism Syndrome					
Yes	47 (16.8%)	4 (10.5%)	16 (14.5%)	27 (20.6%)	$P = .310$
No	223 (79.9%)	34 (89.5%)	87 (79.1%)	102 (77.9%)	
Missing Data	9 (3.2%)	–	7 (6.4%)	2 (1.5%)	
Age at Diagnosis (Years)					**ANOVA**
Mean	9.3	7.9	10.1	8.9	$P < .001$
SD	3.6	3.4	3.7	3.3	
Range	4.0–19.0	4.0–15.1	4.1–19.0	4.0–17.0	
Time From Diagnosis to Assessment (Years)					
Mean	5.1	4.7	4.5	5.8	$P < .001$
SD	2.8	2.3	2.6	2.9	
Range	1.5–13.0	2.0–10.7	1.5–11.5	1.5–13.0	

Abbreviations: CSI: craniospinal irradiation; EVD: extraventricular drainage; MRI: magnetic resonance imaging; SD: standard deviation.

[a] One patient was diagnosed with medulloblastoma and after therapy reclassified as an ependymoma.

intelligence, short-term memory, visuomotor integration and psychomotor abilities (see Figure 2 for further details and post hoc CSI comparisons in horizontal brackets). Results for fluid intelligence, crystallized intelligence, short-term memory, and selective attention were within normal for patients treated with focal RT without CSI (all $P' > .05$). No significant differences between CSI dose groups were found in crystallized intelligence, selective attention, and processing speed.

Effects of Further Risk Factors

Survivors with hydrocephalus on preoperative MRI ($n = 161$) did not show a significantly worse performance (Figure 3A). However, survivors with postoperative hydrocephalus requiring shunts ($n = 39$) had significantly worse outcomes in fluid intelligence ($t(273) = -2.37$, $P' = .034$, $d = 0.41$,), short-term memory ($t(266) = -2.78$, $P' = .013$, $d = 0.50$), crystallized intelligence ($t(224) = -3.17$, $P' = .008$, $d = 0.61$), and psychomotor abilities ($t_{NDH}(249) = -2.86$, $P' = .014$, $d = 0.53$; $t_{BH}(248) = -3.32$, $P' = .009$, $d = 0.61$). No significant differences were found for visuomotor integration, 1 subtest of psychomotor abilities (for the dominant hand), selective attention and processing speed (all $P' > .05$) (Figure 3B).

The group with pCMS ($n = 47$) had a worse outcome in almost all cognitive domains: fluid intelligence ($t(268) = -3.39$, $P' = .002$, $d = 0.54$), visuomotor integration ($t(258)$

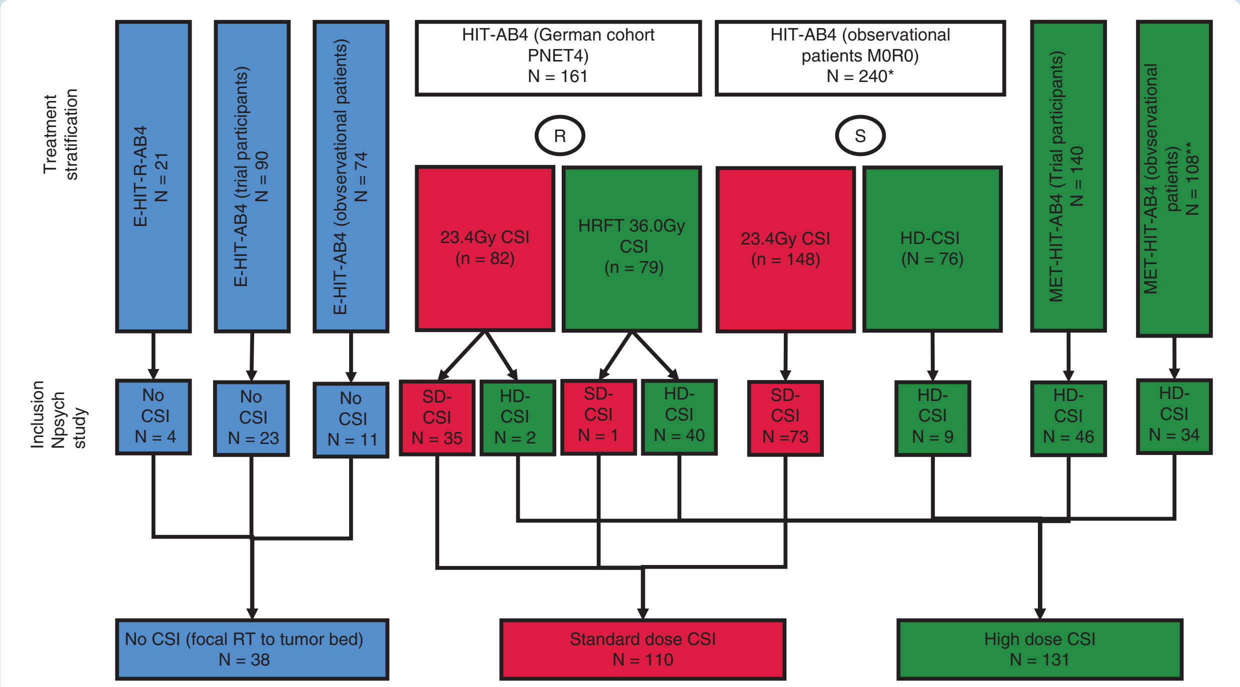

Figure 1. Consort Diagram for Recruitment into the Neuropsychology Follow-up Study from the HIT2000 Clinical Trial Strata for Children Older Than 4 Years at Diagnosis. (R): Randomized Allocation, (S): Stratified Allocation. *For 16 HIT-AB4 Observational Patients, CSI-Dose Was Not Reported; None of These Were Included Into the Neuropsychology Follow-up Study

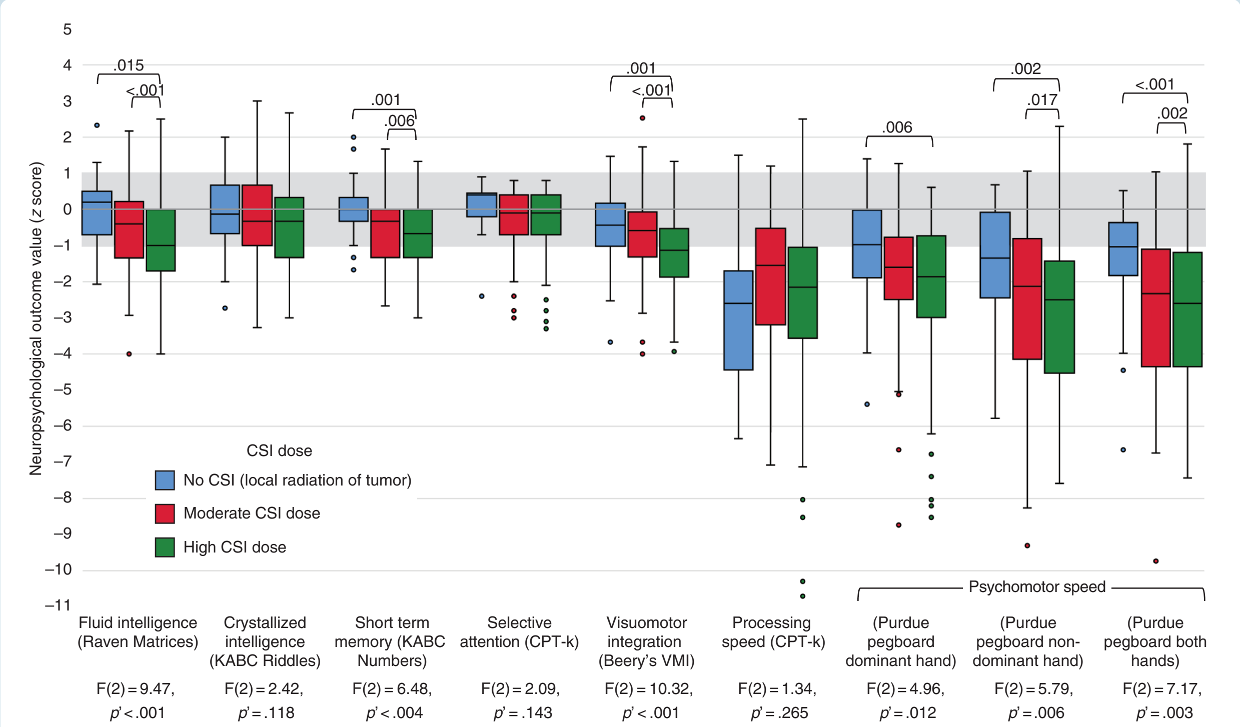

Figure 2. Distribution of the Cognitive Outcome of the Patient Cohort for Each Subtest According to CSI-Dose (No CSI [Focal RT to Tumor Bed] vs. Moderate-Dose CSI [<30 Gy] vs. high-dose CSI [≥30 Gy]). *Z*-Values Were Used as a Unit of Standardization with a Mean of 0 and a Norm Range of 2 SD. Outliers Are Marked as Points Outside the Boxes. ANOVA Results (*P*-values Bonferroni-Corrected) Are Described Below the Variable Names and Post Hoc Significant Differences (*P*-Values Bonferroni-Corrected) Are Marked by a Horizontal Bracket. Please Note That the Subtests CPT-k (Selective Attention and Processing Speed) and Purdue Pegboard (Psychomotor Abilities) Had to be Completed Within a Time Limit.

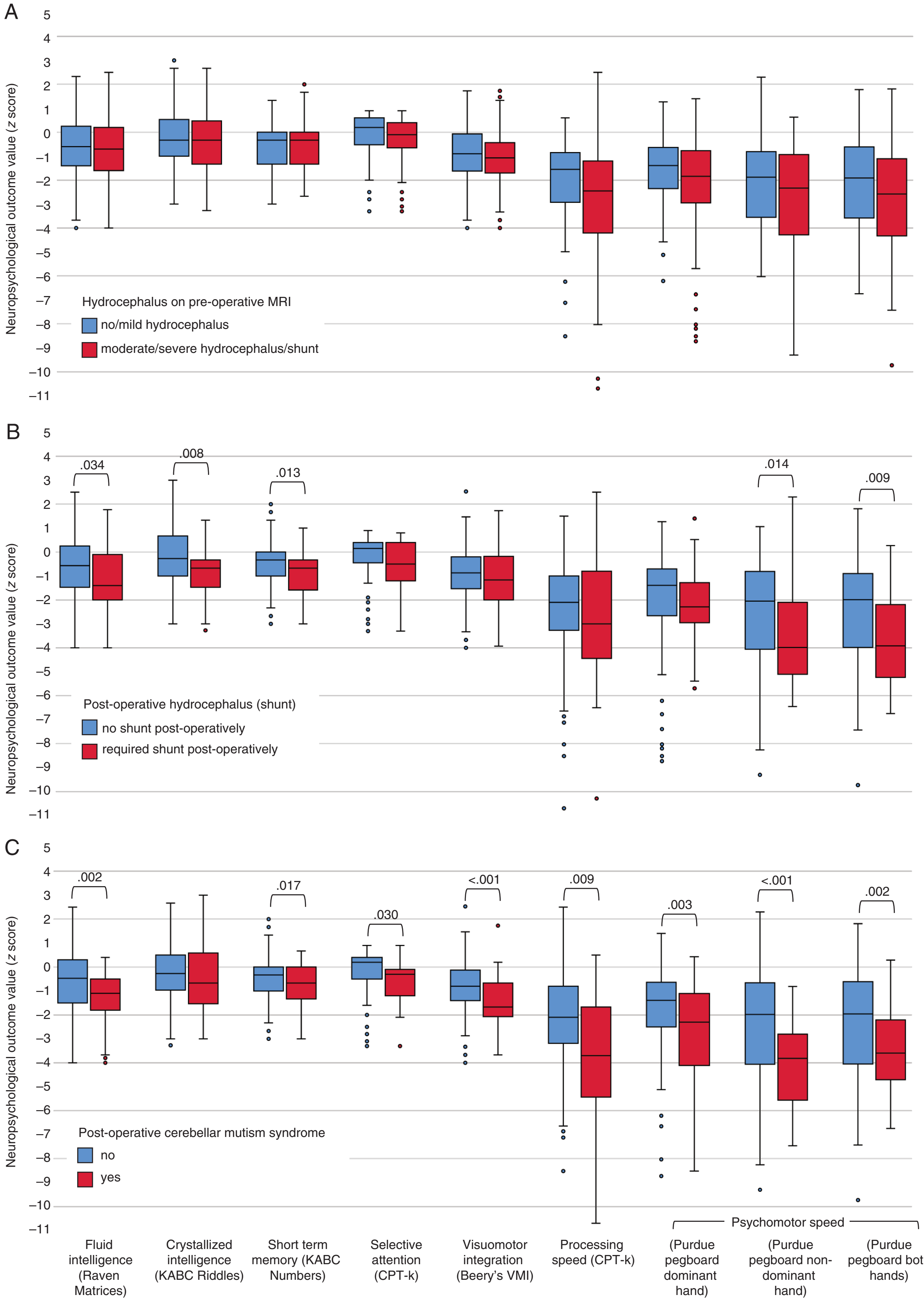

Figure 3. Distribution of the Cognitive Outcome for Each Subtest According to: (A) Preoperative Hydrocephalus According to MRI; (B) Postoperative Hydrocephalus; (C) Postoperative Cerebellar Mutism Syndrome (pCMS); *z*-Values Were Used as a Unit of Standardization With a Mean of 0 and a Norm Range of 2 SD. Outliers Are Marked as Points Outside the Boxes. Significant Differences (*t*-Tests, *P*-Values Bonferroni-Corrected) Are Marked by a Horizontal Bracket.

$= –4.32$, $P' < .001$, $d = 0.70$), short-term memory ($t(262) = –2.50$, $P' = .017$, $d = 0.41$), psychomotor abilities ($t_{\mathrm{DH}}(49.61) = -3.34$, $P' = .003$; $t_{\mathrm{NDH}}(245) = –4.19$, $P' < .001$, $d = 0.84$; $t_{\mathrm{BH}}(244) = –3.31$, $P' = .002$, $d = .56$), selective attention ($t(154) = –2.24$, $P' = .030$, $d = 0.51$) and processing speed ($t(25.55) = -3.01$, $P' = 0.009$, $d = 0.89$; Figure 3C). After the Benjamini–Hochberg correction, we found no significant differences according to sex.

Age at diagnosis had significant results only in crystallized intelligence ($r = 0.19$, $P = .004$) and in 1 subtest of psychomotor abilities ($r_{BH} = –0.16$, $P = .013$) (Supplementary Figure 2A–I). Fluid intelligence ($r = –0.28$, $P < .001$), crystallized intelligence ($r = –0.17$, $P = .010$), short-term memory ($r = –0.20$, $P < .001$), and visuomotor integration ($r = –0.32$, $P < .001$) significantly decreased with time since diagnosis, while performance in selective attention ($r = 0.28$, $P < .001$) increased (Supplementary Figure 3A–I).

Multivariate Regression

To further assess the effect of the individual factors on neuropsychological criteria, we performed a stepwise backward multivariate regression analysis (Figure 4, for detailed results please see Supplementary Table 2). High-dose CSI in contrast to focal RT without CSI retained its association with poor neurocognitive outcomes in all domains but processing speed, for which pCMS was the only risk factor included in the final model. Moderate dose CSI as compared to focal RT without CSI remained an important predictor for fluid intelligence ($\beta = –0.63$), short-term memory ($\beta = –0.59$), and 2 subtests for psychomotor abilities ($\beta_{NDH} = –1.05$; $\beta_{BH} = –1.01$).

Preoperative hydrocephalus was a significant predictor of all psychomotor abilities ($\beta_{DH} = –0.16$; $\beta_{NDH} = –0.13$;$\beta_{BH} = –0.13$) and postoperative hydrocephalus of crystallized intelligence ($\beta = –0.20$) and short-term memory ($\beta = –0.15$). pCMS significantly predicted almost all tests: fluid intelligence ($\beta = –0.139$), visual processing ($\beta = –0.22$), all psychomotor abilities ($\beta_{DH} = –0.24$;$\beta_{NDH} = –0.25$; $\beta_{BH} = –0.16$) and processing speed ($\beta = –0.32$).

Discussion

This study analyses domain-specific neurocognitive functions to better understand the patterns of neurocognitive impairment in children treated for posterior fossa ependymoma or medulloblastoma. By comparing 2 entities with similar locations but different treatment strategies, our data help to understand the pattern of neuropsychological deficits associated with different modalities of posterior fossa brain tumor treatment. Besides the known strong influence of CSI,[2] we observed 2 overarching patterns of impairment: cognitive functions closely related to motor functions were equally impaired in all patients while functions unrelated to motor function differed depending on the dose of craniospinal radiotherapy.

In this sense, both patients treated with focal radiotherapy and those who received CSI performed worse than healthy children in subtests closely related to motor function, especially psychomotor abilities and processing speed (mean z-scores between –2.55 and –1.85). While results in psychomotor abilities additionally were associated with CSI-dose, this was not the case for processing speed. Notably, pCMS and preoperative hydrocephalus had a strong influence specifically on these tests, and scores did not further decline. This indicates that “mechanical” damage by the tumor or by the surgery may play a role in these tests and is in line with the important role of the cerebellum in motor function. The sustained low scores for psychomotor abilities in survivors with pCMS long time after diagnosis suggest the long-term impact of pCMS on fine motor skills, even if the clinically obvious ataxia in patients with pCMS is in part reversible in many patients.[43]

Functions less dependent on motor function, like fluid intelligence, crystallized intelligence, short-term memory, and visual processing were less severely reduced. Unlike motor-dependent functions, these scores declined with time since diagnosis (FI, STM, and VP), correlated with the presence of postoperative hydrocephalus (CI and STM) and were strongly influenced by the CSI-dose (all tests). The strong dependence on CSI-dose is well described in patients with medulloblastoma, especially in young children who were treated with the aim of avoiding CSI.[44] Moreover, this finding is in line with recent neurocognitive outcome data from the SJYC07 trial, where patients treated with focal radiation did not have a significant decline in neurocognitive performance after focal radiotherapy compared to chemotherapy alone.[45]

Although significantly lower than in the healthy population, crystallized intelligence, and selective attention were within the average range for most survivors and the impact of variables evaluated here was not very strong and selective attention even increased with time. This is in contrast to recent series of brain tumor survivors, where parent-reported attention problems either increased or remained stable over time.[46,47]

One reason for the discrepancy in the present results could be a difference in the construction of the tests used to measure selective attention. The test used in this analysis assesses response time and selective attention outcome in combination and therefore, the patients potentially can compensate for the rate of false positive reactions (press the button although the stimulus was not given with accuracy of the reaction interpreted as selective attention) by a longer interval from stimulus to reaction (interpreted as processing speed). However, close-to-normal results in selective attention and scores severely below normal for processing speed argue against a strong impact of this effect.

For crystallized intelligence, the duration of follow-up might also have contributed to scores being within the average range. Assuming that learning is slower in children after radiotherapy, but survivors do not forget what they already have learnt, the time for crystallized intelligence to be affected by radiotherapy might be much longer than for other factors. This was supported in our data because the age at diagnosis was associated with scores in crystallized intelligence. Longer follow-up studies and longitudinal assessments will be needed to strengthen this assumption.

The poor performance in processing speed requires special attention because tests for fluid intelligence, visual processing, short-term memory, and psychomotor abilities

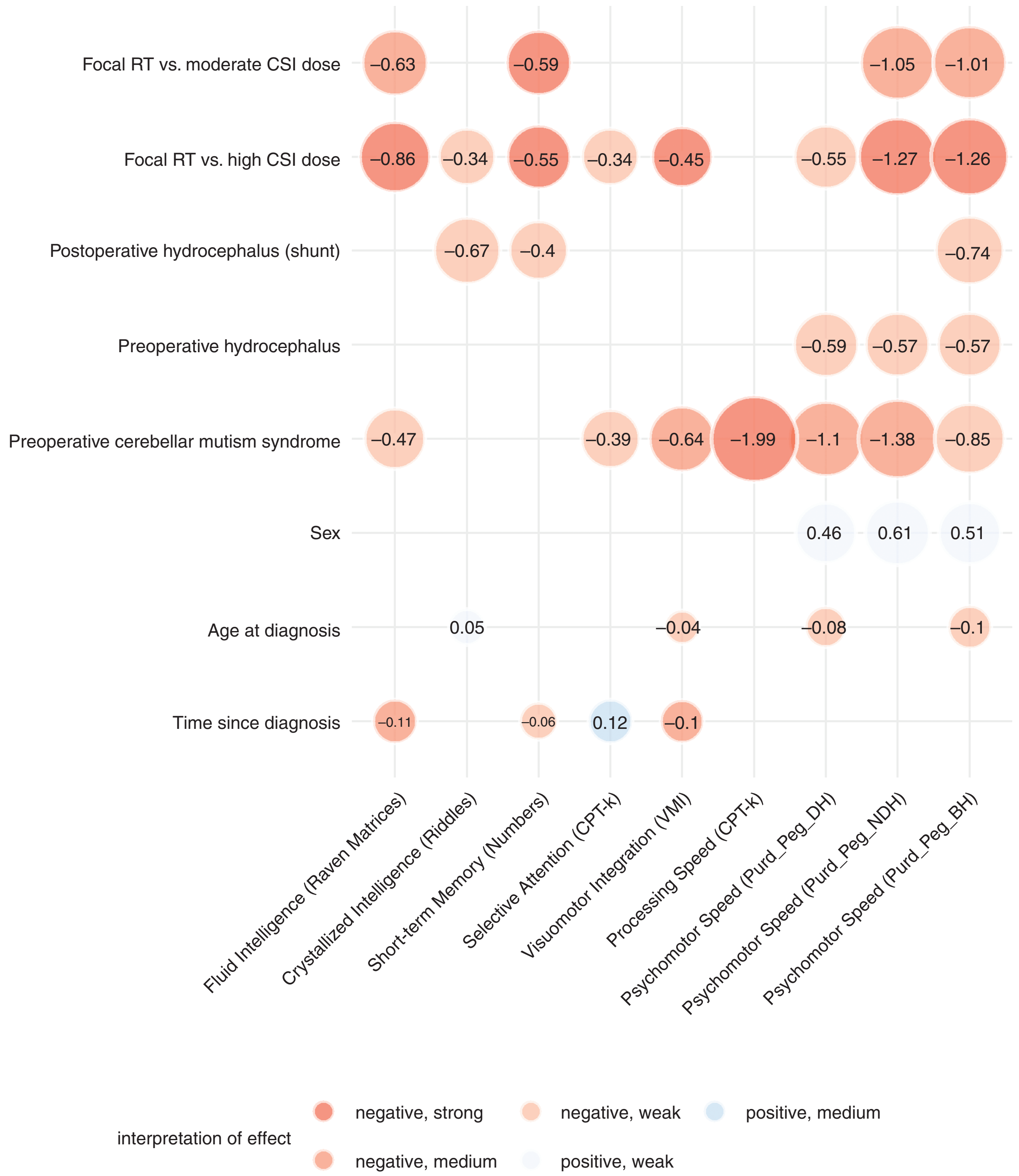

Figure 4. Results of Multivariate Linear Regression Analysis. Multivariate Regression Analysis of Potentially Influencing Factors (*Y*-Axis) With Backward Selection Was Computed For Each of the Subtests (*X*-Axis). Factors Selected During Variable Selection Are Displayed as Circles, with the Size and Color of the Dot Representing the Standardized Coefficient β. Within the Circles, the Regression Coefficient (β) Is Specified.

are performed without an upper time limit, ie the patient may take as much time as he or she needs to solve the problem. This together with the poor performance in motor-dependent tests, for which time is restricted, allows the hypothesis that survivors in “every day” situations might not be able to complete a task because of limitations of time. This might be another explanation for the discrepancy between attention problems reported by patients and the observed outcome in the direct testing: the delay in response to a given task can be interpreted as a lack of attention, while in fact, it is a result of slow processing. Mechanistically, the interruption of connections between the cerebellum and the cerebrum may be an explanation for the lower processing speed, as also seen in other diseases affecting the cerebellum.[48] Because this can result in restrictions in social participation,[49] it is of high importance for the patients and their families.

CSI-dose significantly impacted neuropsychological outcomes in all subdomains but processing speed. High CSI dose was associated with a 0.34–1.27 z-score (corresponding to 5–19 IQ-points) mean decline in multivariate regression analysis when compared to focal radiotherapy alone. This was independent of potentially confounding variables like age at diagnosis, time after diagnosis, hydrocephalus and pCMS, for which we also observed significant associations with cognitive functioning.

This study is limited by its cross-sectional design. The main reason for this is that the systematic collection of neurocognitive data was initiated only late during the course of the HIT 2000 trial. Moreover, differences in radiotherapy were not randomly distributed but depended on clinical risk. Higher CSI doses were more likely to be given to patients with clinical high-risk features, which might also contribute to worse neurocognitive outcomes. Survivors of ependymoma received focal radiotherapy to the tumor bed, while for survivors of medulloblastoma, the boost was delivered to the entire posterior fossa. However, these effects are more likely to lead to an overestimation of the effect of CSI than to mask a larger effect.

Neurocognitive assessments must cover various domains of cognition and, at the same time, remain feasible within the setting of a clinical investigation. The NBD used for this study is a broad but short assessment of cognitive functions that is largely in line with current recommendations of the European Society for Pediatric Oncology (SIOP-E) Brain Tumor Group.[6,8,10] However, motor disabilities might influence tests that are not designed to assess motor skills (eg processing speed and selective attention) and patients might develop compensation strategies, which are not directly measured. Although this cannot be completely prevented, further development of the test battery is necessary to reduce these effects. Finally, the assessment of preoperative hydrocephalus in this analysis was based on a semi-quantitative assessment of MRI alterations. Alternative methods exist,[50] and the optimal technique to assess the severity of hydrocephalus is not clear.

The differentiation of preoperative from postoperative hydrocephalus is 1 of the strengths of this study. The definition of hydrocephalus is very variable between studies. Preoperative, usually acute and severe, hydrocephalus in posterior fossa tumors might have a different impact on long-term outcomes than postoperative, usually chronic, hydrocephalus, which is treated with VP-shunting.

Even with our domain-specific cognitive testing, regression models explained <19% of the observed variability, implying that major influencing factors are not yet identified. Further potential confounding factors include hearing loss,[51] socio-economic status of the parents, familial, and economic factors,[52] radiotherapy dose to intracerebral substructures[53,54] or differences in neurosurgical management. However, it also gives hope in the sense that the fate of a patient diagnosed with a high-grade brain tumor that requires high-dose CSI is not determined by the therapy alone[55] and that other modulating factors might be addressable.[9] Among these, the use of proton beam radiotherapy,[56] modifications of the boost volume for the tumor bed[5] and surgery by an experienced neurosurgeon[43] are getting more and more into the focus of clinicians taking care of brain tumor patients. Training and rehabilitation interventions as well as pharmacological interventions might therefore be valuable in these patients and deserve further analysis.[45]

Conclusions

Our data validate the important negative impact of radiotherapy for infratentorial brain tumors on neuropsychological outcomes and support efforts to reduce CSI-dose in selected indications. Moreover, the tumor itself, its surgical resection and associated complications strongly and domain-specifically contribute to neurocognitive sequelae. The study provides evidence on how to specifically investigate the effects of different interventions within the multimodal therapy concept to reduce neurotoxicity and indicates that besides CSI-dose and radiotherapy techniques, also surgery might be an important factor to improve neurocognitive outcomes. Given the impact of motor speed on human response behavior, processing speed is a key factor and should become an important focus of future research, aiming at preservation, rehabilitation, or interventions to improve outcomes in this domain.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

ependymoma | infant | medulloblastoma | neuropsychological late effects | quality of survival

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Conflict of interest statement

S.R. received consulting fees for membership in advisory boards (Bayer, Novartis, BMS, and Roche), data safety monitoring boards (Celgene) and consulting (German Childhood Cancer

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Authorship statement

Design of research: M.M. (Design of research, Acquisition of data, Analysis of data, Interpretation of data, and Manuscript writing), A.R. (Design of research, Acquisition of data, Analysis of data, Interpretation of data, and Manuscript writing), A.G. (Design of research, Acquisition of data, Analysis of data, and Interpretation of data), H.O. (Design of research), T.T. (Design of research, Acquisition of data, Analysis of data, Interpretation of data, and Manuscript writing), S.R. (Design of research, Acquisition of data, Interpretation of data, and Manuscript writing), L.B. (Design of research, Analysis of data, Interpretation of data, and Manuscript writing), K.v.H. (Acquisition of data), D.O.S. (Acquisition of data), C.F. (Acquisition of data), A.O.v.B. (Acquisition of data), N.G. (Acquisition of data), R.D.K. (Acquisition of data), M.W.M. (Acquisition of data), B.B. (Acquisition of data), U.W.T. (Acquisition of data), J.K. (Acquisition of data), T.P. (Acquisition of data), S.C.C. (Acquisition of data), S.M.P. (Acquisition of data), D.S. (Acquisition of data), F.S. (Acquisition of data), and all authors (Manuscript review).

Data availability

Raw data of neurocognitive test results is available from the corresponding author (S.R.) on reasonable request for noncommercial use.

Previous presentation

This work has been presented in part at the annual meeting of the International Society for Pediatric Neurooncology (ISPNO) 2020 in Japan.

Affiliations

Department of Pediatric Hematology and Oncology, University Medical Center Hamburg Eppendorf, Hamburg, Germany (M.M., A.R., K.v.H., D.O-.S., L.B., T.T., S.R.); Mildred Scheel Cancer Career Center HaTriCS4, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (M.M.); Department of Pediatrics, University Hospital Rostock, Rostock, Germany (A.G.); Department of Pediatric Hematology and Oncology, University Children's Hospital Wuerzburg, Wuerzburg, Germany (H.O.); Department of Pediatric Hematology and Oncology, Charité—University Medicine, Berlin, Germany (K.v.H.); Department for General Pediatrics and Pediatric Hematology and Oncology, University Children's Hospital Oldenburg, Oldenburg, Germany (C.F.); Division of Pediatric Oncology and Hematology, Department of Pediatrics, Gynecology and Obstetrics, University Hospital of Geneva, Geneva, Switzerland (A.O.v.B.); CANSEARCH Research Platform in Pediatric Oncology and Hematology, Department of Pediatrics, Gynecology and Obstetrics, University of Geneva, Geneva, Switzerland (A.O.v.B.); Department of Oncology, University Children's Hospital, Zurich, Switzerland (N.U.G.); Paediatrics and Adolescent Medicine, University of Augsburg, Augsburg, Germany (T.T.); Department of Radiation Oncology, University of Leipzig, Leipzig, Germany (R-.D.K.); Institute of Diagnostic and Interventional Neuroradiology, University Hospital Wuerzburg, Wuerzburg, Germany (M.W-.M.); Department of Neuroradiology, University Hospital Augsburg, Augsburg, Germany (B.B.); Department of Neurosurgery, Charité-Universitätsmedizin Berlin, Berlin, Germany (U-.W.T.); Department for Neurosurgery, University Hospital Wuerzburg, Wuerzburg, Germany (J.K.); Institute of Neuropathology, Brain Tumor Reference Center of the German Society for Neuropathology and Neuroanatomy (DGNN), University of Bonn, DZNE German Center for Neurodegenerative Diseases, Bonn, Germany (T.P.); Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle University, Newcastle Upon Tyne, UK (S.C.C.); Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany (S.M.P., D.S., F.S.); Division of Pediatric Neurooncology (B062), German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany (S.M.P., D.S.); Department of Pediatric Hematology and Oncology, Heidelberg University Hospital, Heidelberg, Germany (S.M.P., D.S.); Clinical Cooperation Unit Neuropathology (B300), German Cancer Research Center (DKFZ), Heidelberg, Germany (F.S.); Department of Neuropathology, Heidelberg University Hospital, Heidelberg, Germany (F.S.).

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