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RESEARCH ARTICLE

Survivors of infant atypical teratoid/rhabdoid tumors present with severely impaired cognitive functions especially for fluid intelligence and visual processing: data from the German brain tumor studies

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Abbreviations: ATRT, atypical teratoid rhabdoid tumor; ChT, chemotherapy; CNS, central nervous system; CSI, craniospinal irradiation; eMRT, extracranial malignant rhabdoid tumor; Gy, gray; IQ, intelligence quotient; LGG, low-grade glioma; MTX, methotrexate; NBD, Neuropsychological Basic Diagnostic Tool; LGG, low-grade glioma; QoL, quality of life; QoS, quality of survival; RT, radiotherapy; RTK, rhabdoid tumor of the kidney; SD, standard deviation; SIOP, International Society for Pediatric Oncology (Societé Internationale d'Oncologie Pédiatrique); SIOPE, European branch of the International Society for Pediatric Oncology.

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Abstract

Background: The contribution of tumor type, multimodal treatment, and other patient-related factors upon long-term cognitive sequelae in infant brain tumor survivors remains undefined. We add our retrospective analysis of neuropsychological and quality of survival (QoS) outcome data of survivors of atypical teratoid/rhabdoid tumors (ATRT) and extracranial malignant rhabdoid tumors of the soft tissues (eMRT) and kidneys (RTK) treated within the same framework. Neuropsychological data from children with ATRT were compared to data from children with non-irradiated low-grade glioma (LGG).

Patients and methods: Following surgery, patients (0–36 months at diagnosis) had received radio-chemotherapy (up to 54 Gy; ATRT: $n = 13$; eMRT/RTK: $n = 7$), chemotherapy only (LGG: $n = 4$; eMRT/RTK: $n = 1$) or had been observed (LGG: $n = 11$). Neuropsychological evaluation employing comparable tests was performed at median 6.8 years (ATRT), 6.6 years (eMRT/RTK), and 5.2 years (LGG) post diagnosis.

Results: We detected sequelae in various domains for all tumor types. Group comparison showed impairments, specifically in fluid intelligence ($p = .041$; $d = 1.11$) and visual processing ($p = .001$; $d = 2.09$) in ATRT patients when compared to LGG patients. Results for psychomotor speed and attention abilities were significantly below the norm for both groups ($p < .001$–$.019$; $d = 0.79$–1.90). Diagnosis predicted impairments of cognitive outcome, while sex- and age-related variables did not. QoS outcome for all rhabdoid patients displayed impairments mainly in social ($p = .008$; $d = 0.74$) and school functioning ($p = .048$; $d = 0.67$), as well as lower overall scores in psychosocial functioning ($p = .023$; $d = 0.78$) and quality of life ($p = .006$; $d = 0.79$) compared to healthy controls.

Conclusion: Survivors of infant ATRT experience various late effects in cognition and QoS following multimodal treatment, while infant LGG patients without radiotherapy demonstrated comparable impairments in psychomotor and attention abilities. Early onset and multimodal treatment of rhabdoid tumors require close monitoring of neuropsychological and QoS sequelae.

KEYWORDS
infant, low-grade glioma, neuropsychological late-effects, quality of survival, rhabdoid brain tumor

1 | INTRODUCTION

Atypical teratoid/rhabdoid tumors (ATRT) and their extracranial counterparts are rare and aggressive tumors of early childhood. The implementation of combined surgical, chemo-, and radiotherapeutic approaches has helped to improve survival rates. Still, many patients die due to progression or early relapse,[1–5] but up to 70% of patients with a favorable constellation of risk factors survive into later childhood.[6] For these patients, questions of neuropsychological late effects and quality of life (QoL) gain importance, that is, for (re-)integration into everyday life. Reports on cognitive sequelae in this patient group are rare, but indicate distinct cognitive sequelae for

ATRT in performance or full-scale intelligence quotient (IQ) scores[7–9] and the need for special educational services after treatment.[9] QoL has been assessed solely after proton therapy with no significant abnormalities shortly after treatment.[10] A recent study by Ali et al.[11] investigated cognitive performance, as well as executive, behavioral, and adaptive functioning in infants with various central nervous system (CNS) tumors, including ATRT. The authors demonstrated inferior outcome in IQ results, working memory, attention, adaptive behavior, and executive functions, which were predominantly explained by tumor location, as well as demographic and surgical factors. Patients with ATRT were included along with other tumor types to validate neurocognitive outcome of specific treatment regimens, but results were not compared among brain tumor types.

As focal radiotherapy (RT), applied in patients younger than 3 years, is an effective element in the ATRT treatment strategy, subsequent cognitive decline could be an important risk factor for long-term outcome.[12] Yet, in a single comprehensive study investigating ATRT alone, Lafay-Cousin et al.[13] emphasized that ATRT survivors experienced significant cognitive impairments, even if they had not received RT as part of their treatment regimen. The authors concluded that ATRT patients may be at an increased risk for neurocognitive impairment compared to other infants with CNS tumors undergoing comparable therapies. The universal validity and the cognitive elements affected by this predisposition remain to be investigated. Thus, while neurocognitive deficits were predominantly explained in terms of tumor location independently of tumor types by some authors,[11] an underlying inherent risk for ATRT patients was suspected.[13]

"Quality of survival" (QoS) is recognized to be strongly influenced by neurocognitive deficits, and encompasses the dimensions of survival, cognitive, and medical late effects and their impact upon patients' daily functioning and subjective QoL.[14–16]

Extracranial ATRT include malignant rhabdoid tumors of soft tissues (eMRT) and the kidneys (RTK); within the EU-RHAB framework, their treatment follows the same principles as ATRT.[5] Reports on late effects[17] to date have not included details on neurocognitive development, and so knowledge about survivors' QoS is lacking.

In order to contribute to understanding of long-term consequences for survivors of rhabdoid tumors of different anatomical origins, we gathered data on cognitive and QoS outcomes of German patients cared for in the framework of the EU-RHAB registry. ATRT, eMRT, and RTK patients underwent comparable age-appropriate neuropsychological test batteries during routine long-term medical and psychosocial care.

We compared results of neuropsychological tests of ATRT patients to those of low-grade glioma (LGG) survivors with tumors at comparable neuro-anatomical sites from the SIOP-LGG 2004 study and LGG-registry who received different drug therapies.[18] It was recognized that survivors of LGG when diagnosed in the first years of life do experience neuropsychological deficits,[19] including deficits in memory, fine motor function, attention, and executive function.[20] In the German LGG study cohort, impairments in cognitive functions, specifically in visual processing, fine motor skills, and processing speed, were detected even if patients received surgical treatment only or no treatment at all.[18] Comparison of neurocognitive data to a historical German series of infant medulloblastoma patients is also included in the Supporting Material.[21,22]

The aim of this retrospective cohort comparison study was to investigate the differences of cognitive functioning and QoS parameters determined by the different anatomical locations, tumor types and their surgical, drug, and radiation treatments.

2 | METHODS

2.1 | Treatment strategies

Patients with rhabdoid tumors of all anatomical sites (ATRT, eMRT, RTK) were treated according to a multimodal consensus therapy regimen,[3,5,23] consisting of initial resection, nine courses of anthracycline-based chemotherapy (ChT) (doxorubicin; ICE: ifosfamide, carboplatin, etoposide; VCA: vincristine, cyclophosphamide, actinomycin D), and RT. In ATRT, simultaneous RT was recommended in patients older than 18 months applying focal RT (M0) or craniospinal irradiation (CSI) plus local boost (M+) depending on tumor localization and/or metastases (M0 or M+). Intraventricular methotrexate (MTX) was added pre-RT to each course of ChT. Patients with RTK and eMRT received irradiation depending on local or distant dissemination not including CNS sites.

The treatment strategies of the SIOP-LGG 2004 study and LGG-registry are detailed in Kandels et al.[24] and Gnekow et al.[25]

Informed consent was obtained from patients, parents, and/or legal guardians. All studies adhered to the Declaration of Helsinki in its revised version (Edinburgh, Scotland, 2000), the World Health Organization (WHO) and European Community rules of "Good Clinical Practice" (effective January 17, 1997), and had been approved by local and central ethic boards. EU-RHAB has received repetitive ethics approval by the ethics committee "Westfalen-Lippe" of the Westfaelische Wilhelm's University of Muenster, Germany (No.2009-532-f-S, last amendment: September 16, 2021). The SIOP-LGG 2004 study and LGG-registry protocols were approved by the ethics committee of the Ludwig Maximilian's University of Munich, Germany (No.179-08 and 136-12).

2.2 | Measures and eligibility

2.2.1 | Choice of neuropsychological test tools

European guidelines to fully assess neurocognitive and QoS late effects in pediatric brain tumor trials have been established by the SIOPE (European branch of the International Society for Pediatric Oncology) Brain Tumor Group,[15,16] as the full-scale or estimated IQ does not reflect all necessary outcome variables comprehensively.[26,27] The ATRT-Neuropsychology Tool (for details see Table S1) for EU-RHAB patients is based on these current recommendations, and was

	FI	CI	verSTM	PS	VSP	PMS	VR	visSTM	SA
Cognitive abilities	Fluid intelligence/ Fluid reasoning	Crystallized intelligence/ Verbal comprehension	Verbal short-term memory/ Working memory	Processing speed	Visual processing	Psychomotor speed	Visual reasoning	Visual short-term memory	Sustained attention/ Alertness
ATRT Neuropsychology	Raven matrices (CPM/SPM)	Vocabulary (WISC-IV/V)/ Picture naming (WPPSI-IV)/ Riddles (K-ABC)	Number recall (K-ABC II) Digit span (WISC-V)	Coding/ Symbol search Test (WISC-V)	The Beery-Buktenica Test of Visual-Motor Integration (VMI)	Purdue Pegboard	Block design (WPPSI-IV/ WISC-V)	Picture memory (WPPSI-IV)/ Picture span (WISC-V)	Test of attentional performance (TAP)*
LGG Neuropsychological Basic Diagnostic	Raven matrices (CPM/SPM)		Number recall (K-ABC II)						Short continuous performance task (CPT-k)

FIGURE 1 Core tests of atypical rhabdoid teratoid tumor (ATRT)-Neuropsychology and corresponding tests from the Neuropsychological Basic Diagnostic (NBD) Tool for low-grade glioma (LGG) patients.

developed in close cooperation with the SIOPE QoS group. It represents the most recent consensus and covers important variables, which are known to be impaired in pediatric brain tumor patients. The German version of the ATRT-Neuropsychology Tool was used to investigate the German EU-RHAB cohort generating data for comparison with the current SIOPE ATRT01 trial. Patients were tested locally by trained research staff or psychologists of the participating centers.

The German Neuropsychological Basic Diagnostic Tool (NBD) for SIOP-LGG 2004 and LGG-registry patients was described in Traunwieser et al.[18] The NBD is based on the Wuerzburg intelligence diagnostics by Ottensmeier et al.[21] It provides a valid battery assessment for the evaluation of cognitive deficits in pediatric brain tumor patients.

Subtests of the ATRT-Neuropsychology Tool conform with components of the Cattel–Horn–Carol model of intelligence, and allow for group comparisons with results of the NBD as detailed in Figure 1.

2.2.2 | Eligibility for neuropsychological testing

Investigations were part of regular long-term follow-up, but analysis of data for this report was performed retrospectively. Surviving German patients were tested, if they: (i) had the diagnosis of ATRT, eMRT, RTK, or LGG (excluding neurofibromatosis type 1) at an age less than 36 months; (ii) had received cranial RT at an age less than 36 months (ATRT patients) or no prior cranial RT (LGG patients); (iii) had adequate visual and auditory acuity to operate the test material; (iv) had no concurrent oncological therapy; (v) had appropriate age for the test material; and (vi) had no neurologic symptoms at the time of assessment or long-term complications of cancer therapy rendering impossible the execution of the tests. ATRT patients had not had relapse and/or second-line treatments. LGG patients were matched for age and tumor location with ATRT patients.

2.2.3 | Timing of neuropsychological testing

Data from ATRT, eMRT, and RTK patients were collected approximately 6–7 years following diagnosis (screening period: 3.0–14.5 years). To expand the number of patients and account for the different age range in the randomized SIOPE ATRT01 trial, $n = 3$ patients younger than 18 months suffering from ATRT were included from the EU-RHAB registry. These patients had received focal RT and ChT, with a median age at the start of RT of 16 months. Patient data from the German SIOP-LGG 2004 study and LGG-registry were collected approximately 5 years after diagnosis (screening period: 3.7–6.6 years). Cognitive function was assessed at one single time point, and multiple assessments were not done.

2.2.4 | Review for neuropathology and neuroradiology

Central review for neuropathology and neuroradiology was recommended for all patients. The extent of neurosurgical resection was classified based on both surgical and radiological judgments.[28] Hydrocephalus was graded as detailed in Traunwieser et al.[18]

2.3 | Statistics

Descriptive statistical analyses included the calculation of location (mean, median) and scale (standard deviation [SD], quartiles, range) statistics, Cohen's *d*, and box-and-whisker plots. Individual patient data above/below 1 SD from the normative values were rated "impaired" according to the recommendations for neuropsychological tests and QoS questionnaires (Table S1). In inferential statistical analyses, Wilcoxon signed-rank tests were applied for group and normative comparisons, paying tribute to the small number of patients, as

well as skewness and kurtosis statistics that indicated non-normally distributed data. If necessary, group comparisons of (metric) neuropsychological data were adjusted for the factors sex, location, age at diagnosis, degree of hydrocephalus, and time between diagnosis and testing using multivariable linear models. Following the retrospective approach of our study without predefined hypotheses, results are considered exploratory, not confirmatory. Individual *p*-values are not adjusted for multiple testing. Results are regarded noticeable in case of $p \leq .05$, and are labelled "statistically significant" despite the lack of an overall controlled significance level. Sample size calculations showed that in two-sample tests with $n \geq 10$ per subgroup large effect sizes with Cohen's *d* higher than 1.3 can be detected with greater than 80% power.

3 | RESULTS

3.1 | Patient cohorts

Our cohort included 36 survivors of infant rhabdoid tumors (ATRT $n = 13$, eMRT/RTK $n = 8$) and pediatric low-grade glioma (LGG) ($n = 15$) (Table 1). Patients were recruited from 19 centers participating in the cooperative brain tumor studies of the German Society of Pediatric Oncology and Hematology. Neurocognitive testing was performed from 2019 to 2021 for the rhabdoid tumor group and from 2010 to 2016 for LGG patients. The subgroups were comparable for age at diagnosis, sex, and localization, but differed with respect to median age at testing (ATRT 9.5 years; eMRT/RTK 7.8 years; LGG 7.2 years) and median time to testing since diagnosis (ATRT 6.8 years; eMRT/RTK 6.6 years; LGG 5.2 years), with ATRT patients being older. The majority of CNS tumors was located in the posterior fossa (ATRT: 8/28; LGG: 10/28). One LGG was located in the optic pathway. Extracranial rhabdoid tumors were located in the soft tissues ($n = 5$; head and neck $n = 3$, trunk $n = 2$) or the kidneys ($n = 3$). Within this cohort, local RT fields did not involve CNS structures. CSI was not performed in any of the patients. Methylation subgroup was specified for 10 recently diagnosed ATRT patients (SHH $n = 3$, TYR $n = 6$, MYC $n = 1$), while tissue for molecular-genetic analyses was missing in three patients. Most LGGs were pilocytic astrocytoma (11/15).

Total/subtotal resection was achieved in the majority of CNS tumors (21/28), followed by partial resection (6/28), one tumor was biopsied only. Postsurgical treatment consisted of RT and ChT for all ATRT patients (median age at start of RT: 22.0 months, range: 15.0–37.0). ChT was conventional ChT with intraventricular MTX ($n = 12$), and/or high-dose carboplatin/thiotepa ($n = 2$). Following incomplete tumor resection, four LGG patients received vincristine/carboplatin.

Hydrocephalus was graded as moderate in seven of 13 ATRT patients, minor in one of 13, while five of 13 had no hydrocephalus. Most LGG patients had no or minor hydrocephalus (9/15), but two of 15 had moderate or severe hydrocephalus (no information four of 15). Data on cerebellar mutism syndrome or leukoencephalopathy had not been systematically captured in the patient subgroups.

3.2 | Comparison of neuropsychological data between histological groups

Neuropsychological data of ATRT patients were used for group comparisons, while datasets for patients with extracranial rhabdoid tumors (eMRT/RTK) were limited. Group comparisons were conducted according to affiliation of the subtests of ATRT-Neuropsychology and NBD to the Cattel–Horn–Carol model (Figure 1).[29]

QoS data were gathered for all rhabdoid tumor patients, while they were not available for LGG patients.

3.2.1 | ATRT versus LGG

Compared to the LGG cohort, the ATRT cohort demonstrated statistically significant impairments with respect to visual processing ($p = .001$; $d = 2.21$) and fluid intelligence ($p = .015$; $d = 1.12$) (Figure 2, Table 2). When controlling for sex, location, age at diagnosis, degree of hydrocephalus, and time between diagnosis and testing, histological diagnosis of ATRT was the only significant predictor for differences in visual-spatial processing ($p = .002$; $d = 2.34$), whereas fluid intelligence was predicted significantly by histological diagnosis of ATRT ($p = .030$; $d = 1.40$) and location ($p = .024$; $d = 1.31$). Both patient cohorts scored below the expected population score for attentional performance and psychomotor speed (Tables S12–S14 and S17).

3.3 | Results of neuropsychological testing for patient subgroups

3.3.1 | Rhabdoid tumors (ATRT/eMRT/RTK)

All ATRT patients demonstrated statistically significant impairments with respect to fluid intelligence ($\bar{x} = 89.9$; SD = 9.2), verbal short-term memory ($\bar{x} = 90.5$; SD = 7.6), visual processing ($\bar{x} = 78.8$; SD = 10.1), processing speed ($\bar{x} = 87.1$–90.0; SD = 11.8–14.4), psychomotor speed of the dominant hand ($\bar{x} = 70.2$; SD = 16.0), the non-dominant hand ($\bar{x} = 63.3$; SD = 22.5), coordination of both hands ($\bar{x} = 69.8$; SD = 18.3), as well as attentional performance scores for alertness ($\bar{x} = 83.0$; SD = 13.2–14.5) and inhibition ($\bar{x} = 77.2$–86.6; SD = 10.5–11.4), if compared to the expected population norm ($p < .001$–$.035$; $d = 0.70$–2.16) (Figure 3; Tables S5–S27). Small sample sizes precluded statistical comparison of patients receiving photon versus proton RT, but consistent differences were not obvious (Table S28).

The collective rhabdoid tumor subgroup (ATRT, eMRT, and RTK patients) demonstrated a slightly better overall performance, though still significantly impaired, compared to the expected population norm (Figure S2; Tables S5–S27). Small sample size impeded group comparisons of ATRT with extracranial rhabdoid tumor patients, and of eMRT/RTK patients to the expected population score. However, median test results were mostly inferior for ATRT patients in seven of 11 cognitive domains compared to RTK and eMRT patients with two

TABLE 1 Epidemiologic data.

	All ($n = 36$)	Rhabdoid tumors ($n = 21$)		LGG ($n = 15$)
		ATRT ($n = 13$)	eMRT and RTK ($n = 8$)	
Median age at diagnosis (years, range)	1.7 0.2–3.0	1.6 0.5–3.0	1.3 0.3–2.3	1.9 0.2–2.9
Median age at testing (years, range)	7.7 4.4–15.8	9.5 5.5–14.5	7.8 4.9–15.8	7.2 4.4–8.5
Sex				
Male	24	9	6	9
Female	12	4	2	6
Median time to testing since diagnosis (years, range)	5.8 3.0–14.5	6.8 4.2–13.6	6.6 3.0–14.5	5.2 4.0–6.0
Median age at cranial radiotherapy (months, range)	22.0 10.0–37.0	22.0 15.0–37.0	n.a.	n.a.
Tumor localization				
- Supratentorial	10			
Cerebral hemispheres (right/left/both)	7	4	–	3
Supratentorial midline	3	1	–	2
- Infratentorial	18			
Cerebellar hemispheres (right/left)	7	1	–	6
Cerebellar vermis/4th ventricle	5	3	–	2
Brainstem/spinal	5	3	–	2
Not specified	1	1	–	–
- Extracranial	8[a]		8[a]	
Extent of resection				
Complete resection	18	9	7	2
Subtotal resection	10	4	–	6
Partial resection	6	–	–	6
Biopsy	2	–	1	1
Histology				
-ATRT/eMRT/RTK (molecular subgroups)	21			
Not specified		3	8	
SHH		3		
TYR		6		
MYC		1		
-Low-grade glioma	15			
Pilocytic astrocytoma WHO grade 1				11
Diffuse astrocytoma WHO grade 2				1
Low-grade astrocytoma nos				1
Glioneuronal tumors (DIG, GG)				2
Hydrocephalus at diagnosis				
None	11	5	–	6
Minor	4	1	–	3
Moderate	8	7	–	1
Severe	1	–	–	1
No information	12	–	8	4

(Continues)

TABLE 1 (Continued)

	All ($n = 36$)	Rhabdoid tumors ($n = 21$)		LGG ($n = 15$)
		ATRT ($n = 13$)	eMRT and RTK ($n = 8$)	
Treatment				
Surgery only	11	–	–	11
Surgery and chemotherapy	5	–	1	4
Surgery and radio-chemotherapy	20	13	7	–
Type of chemotherapy				
Intravenous (conventional)	23	11[b]	8[b]	4[c]
High-dose chemotherapy with autologous bone marrow rescue	2	2[d]	–	–
Intraventricular methotrexate	11	11	–	–
Cranial radiotherapy (doses, Gy)				
Tumor bed		54[e]	n.a.	n.a.

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; DIG, desmoplastic infantile ganglioglioma; eMRT, extracranial malignant rhabdoid tumor; GG, ganglioglioma; LGG, low-grade glioma; nos, not otherwise specified; n.a., not applicable; RTK, rhabdoid tumor of the kidneys. Chemotherapy regimens: [b–d].

[a]Localization of extracranial rhabdoid tumors: $n = 3$ kidney, $n = 2$ cervical, $n = 1$ parotid gland, $n = 1$ chest wall, $n = 1$ abdominal.

[b]Doxorubicin, ifosfamide, carboplatin, etoposide, vincristine, cyclophosphamide, actinomycin D.

[c]Carboplatin, vincristine.

[d]Carboplatin, thiotepa.

[e]Type of radiotherapy: proton beam therapy $n = 6$, photon beam therapy $n = 7$. Just 1 ATRT patient received craniospinal irradiation, with 24 Gy to brain and spine and 49.2 Gy to the tumor bed.

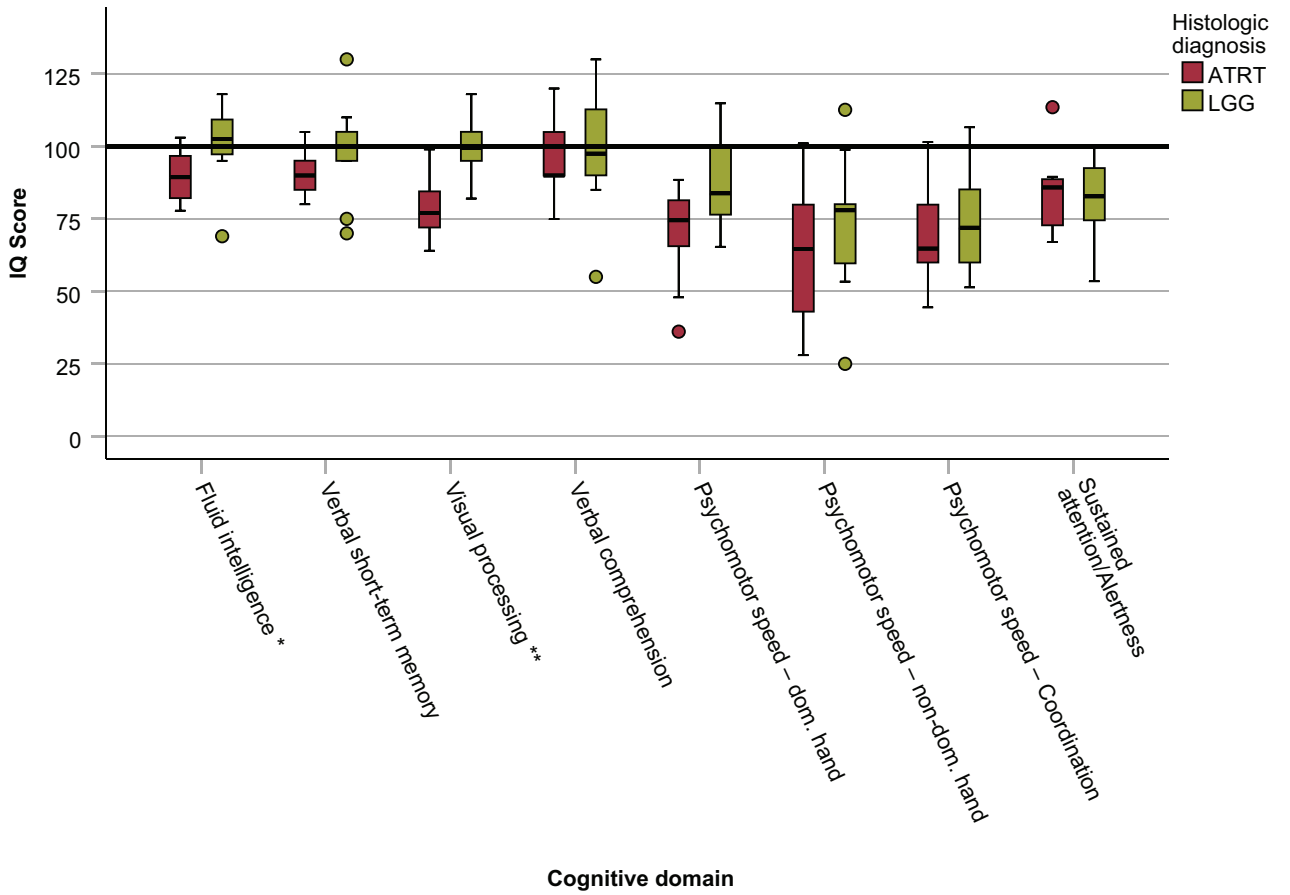

FIGURE 2 Comparison of IQ scores of cognitive domains for atypical rhabdoid teratoid tumor (ATRT) versus low-grade glioma (LGG) cohorts (*$p < .05$, **$p < .01$, ***$p < .001$).

TABLE 2 Results of Wilcoxon two-sample test of ATRT-Neuropsychology and NBD results for ATRT vs. LGG.

	p	*d*
Fluid intelligence/fluid reasoning	.015*	1.12
Verbal short-term memory	.096	0.68
Visual processing	.001**	2.21
Crystallized intelligence/verbal comprehension	.350	0.18
Psychomotor speed (dominant hand)	.061	1.05
Psychomotor speed (non-dominant hand)	.483	0.43
Psychomotor speed (coordination)	.576	0.27
Alertness—intrinsic	.959	0.19

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; *d*, Cohen's *d*; LGG, low-grade glioma; NBD, Neuropsychological Basic Diagnostic Tool.
*$p < .05$
**$p < .01$.

of 11 inferior domains for extracranial rhabdoid patients and two of 11 equivalent results (Tables S5–S27).

Evaluation of QoS parameters (Tables S29–S32) disclosed significant impairments below the average mean for the parental rating of the entire rhabdoid cohort in social and school functioning, psychosocial summary score, and total quality of life score ($p = .006–.048$; $d = 0.67–0.79$). Small sample sizes precluded group comparisons of QoS parameters between ATRT and extracranial rhabdoid tumor patients. Upon comparison of mean scores between intra- and extracranial rhabdoid subgroups, ATRT patients showed significant impairments in executive functions at teachers' rating. Parental rating indicated significant scores for problems with peers and of physical and social functioning. ATRT patients themselves stated significant impairments in physical, social, and school functioning. Parental scores of executive functions were lower for patients with extracranial rhabdoid tumors, and revealed significant emotional problems and impairments in emotional functioning, when compared to ATRT patients.

Patient-specific data (Table 3) revealed cognitive impairments in at least three and up to seven domains for the majority of ATRT patients (9/13), whereas fewer (up to three) somatic late effects, such as growth disorder or ototoxicity, were present in less than half of the patients (6/13). Most patients with somatic impairments also experienced six or more cognitive difficulties (4/6). Tumors of ATRT patients with most somatic and/or cognitive late effects were located both supratentorially (Patients 3 and 8, including the only patient who received CSI: Patient 10) and infratentorially (Patients 1 and 9), three of five had had subtotal resection. Five of 13 ATRT patients also disclosed impairments in QoS domains, mostly associated with three or more cognitive late effects (4/5). Two patients with fewest impairments in cognitive and QoS dimensions had completely resected tumors and had been 21 months or older at the start of RT (Patients 2 and 12).

3.3.2 | LGG

Analysis disclosed statistically significant impairments for all 15 LGG patients compared to the expected population score with respect

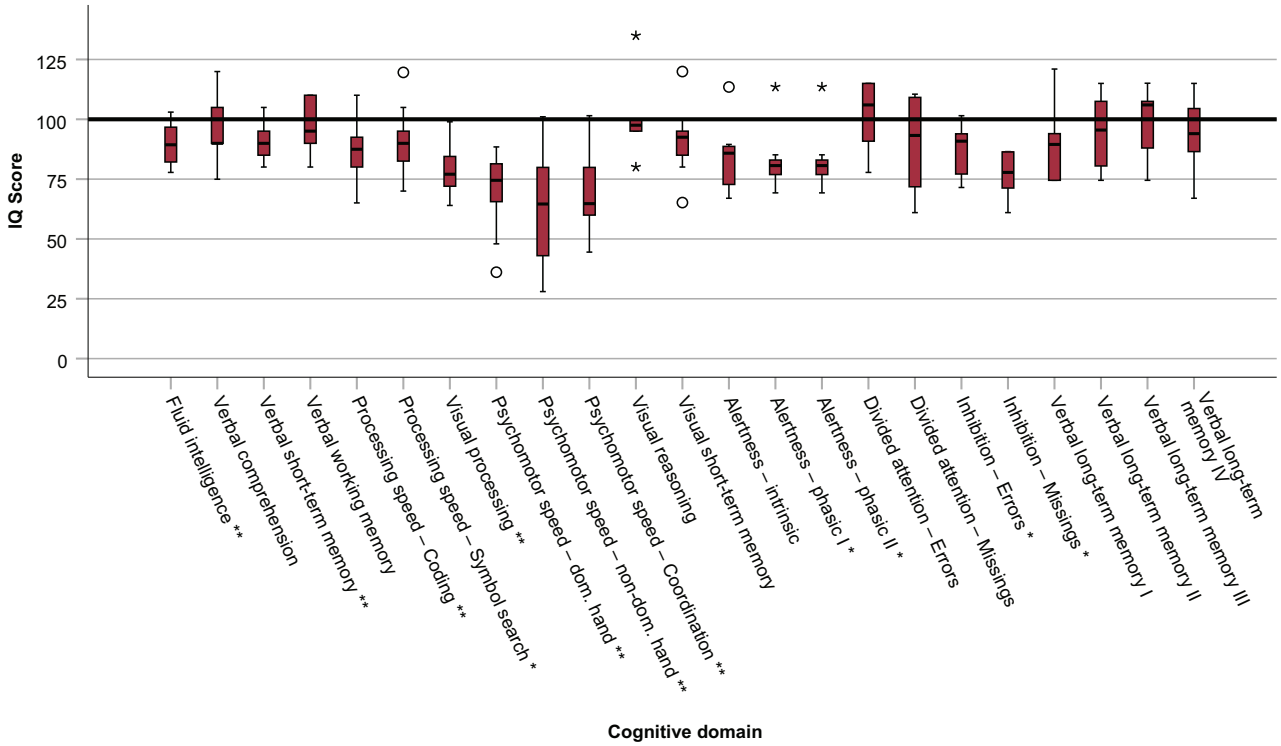

FIGURE 3 Results of atypical rhabdoid teratoid tumor (ATRT)-Neuropsychology for the ATRT cohort ($n = 13$) compared to the expected population score (*$p < .05$, **$p < .01$).

TABLE 3 Results for the rhabdoid cohort.

Pat	Diagnosis	Sex	Age at diagnosis (years)	Age at RT (months)	Focal RT (Gy)	Age at testing (years)	Extent of resection	Localization[a]	Grade of hydrocephalus[b]	Impaired somatic domains[c]	Impaired cognitive domains[d]	Impaired QoS domains[e]
1	AT/RT	M	1.2	21	54	12.4	TR	infra	2	OS;NL	PM	–
2	AT/RT	F	1.9	24	54	12.2	TR	supra	2	–	PS;PM	–
3	AT/RT	M	2.4	32	54	6.7	TR	supra	2	NL	CI	–
4	AT/RT	M	1.5	20	54	7.4	TR	infra	2	–	VP;PM;AT;VL	QL;EF;PF
5	AT/RT	F	0.5	16	54	10.1	Subtotal	supra	2	OC	FI;PS;VP;PM;VM;AT;VL	QL
6	AT/RT	M	1.9	26	54	8.2	Subtotal	infra	0	–	CI;VS;VP;PM;VM;VL	EF;PF
7	AT/RT	M	2.3	34	54	8.4	TR	supra	0	NL;OC;EN	CI;VS;VW;PS; VP; PM;AT	QL;EF;PF
8	AT/RT	M	0.9	19	54	14.5	Subtotal	infra	2	OT;GP;NL	PS;VP;PM;VR;AT;VL	*none*
9	AT/RT	F	0.6	15	54	10.2	TR	infra	1	–	FI;VS;VP;PM;AT	QL;EF
10	AT/RT	F	1.7	28	24/49.2[f]	8.4	TR	supra	0	EN	FI;PS;VP;VM;AT;VL	*none*
11	AT/RT	M	1.0	17	54	5.5	Subtotal	infra	2	–	PS;PM;VM;	QL
12	AT/RT	M	3.0	27	54	9.9	TR	supra	0	–	FI;VP;PM;AT;VL	EF
13	AT/RT	F	1.6	22	54	9.5	TR	infra	0	–	VP	QL;EF;PF
14	eMRT	F	0.3	22	36	9.9	TR	extra	–	EN;GD	FI;CI;VP;VR;AT	EF;PF
15	eMRT	F	1.2	17	36	4.9	TR	extra	–	EN	–	*none*
16	eMRT	F	1.5	14	52.8	7.3	TR	extra	–	–	VS;AT	EF
17	eMRT	M	2.0	27	45	8.7	TR	extra	–	–	PM;AT	QL;EF;PF
18	eMRT	F	2.3	34	45	5.3	Biopsy	extra	–	–	PM	QL;PF
19	RTK	F	0.5	13	19.8	8.2	TR	extra	–	–	VS;PM;VL	EF
20	RTK	F	1.0	17	30.4	15.8	TR	extra	–	NL;EN	CI;VS;VW;PS;VP;PM;VR;\	EF
21	RTK	M	1.8	22	19.8	6	TR	extra	–	–	CI;VS;PM;VL	QL;EF;PF

Note: Individual patient data above/below 1 standard deviation (SD) from the normative values were rated "impaired" according to the recommendations for neuropsychological tests and QoS questionnaires (Table S1).

Abbreviations: eMRT, extracranial malignant rhabdoid tumor; F, female; M, male; RT, radiotherapy; RTK, rhabdoid tumor of the kidney; TR, total resection.

[a]Localization: infra = infratentorial; supra = supratentorial; extra = extracranial.

[b]Grade of hydrocephalus: 0 = none; 1 = minor; 2 = moderate.

[c]Impaired somatic domains: OS = osteopathies; NL: neurological late effects; OC = oculopathies; EN = endocrinopathies; OT = ototoxicity; GD: growth disorders.

[d]Impaired cognitive domains: PM = psychomotor speed; PS = processing speed; CI = crystallized intelligence; VP = visual processing; AT = attention; VL = verbal long-term memory; VM = visual short-term memory; VR = visual reasoning; FI = fluid intelligence; VS = verbal short-term memory; VW = verbal working memory.

[e]Impaired QoS domains: QL = health-related quality of life; EF = executive functioning; PF = psychosocial functioning. Self and proxy reports were included, except for Patient 7 (proxy rating only).

[f]24 Gy to brain and spine and 49.2 Gy to the tumor bed.

to attentional performance, as well as psychomotor speed of the dominant hand, the non-dominant hand, and the coordination of both hands ($p < .001–.016$; $d = 0.80–1.50$) (Tables S5–S7, S11–S14 and S17).

4 | DISCUSSION

Survivors of pediatric brain tumors are at increased risk of cognitive decline following diagnosis and treatment, suggesting young age at diagnosis and cranial RT as important contributing factors.[7,8,11,12,18,19,22,30] Despite efforts to evaluate these sequelae in patients with ATRT and other infant brain tumors, reports on neurocognitive late effects in the frame of European treatment strategies are scarce.[7–11,13] Some reports just provide descriptive neuropsychological results if neurocognitive data are implemented at all.[10] We present results of a European recommendation-based screening tool for patients with ATRT below 5 years at diagnosis. Comparing these data to a group of infants with LGG to better understand contributing factors, our results point toward a strong role for the detrimental effects of early cranial irradiation.

Cranial RT has long been perceived as a causal factor for impaired cognitive development in a group of highly vulnerable young children, as RT may impair brain development and induce white matter loss.[31] Other reasons and risk factors encompass a variety of patient-specific, biological, treatment, and environmental factors, such as sex, histology, extent of resection, and family-related factors.[12,32]

4.1 | Comparison of ATRT and LGG subgroups for neurocognitive deficits

Group comparison indicates that the ATRT cohort experienced significantly more neurocognitive late effects in all domains than the LGG cohort treated without intensive ChT and/or intraventricular MTX and/or RT. Intensive treatment was associated with relevant impairments in fluid intelligence and visual processing, the latter previously described as visual-spatial performance problems by Lafay-Cousin et al.[13] In a recent study of infant survivors of various pediatric brain tumors, estimated IQ and attentional functions were found below the expected population score,[11] but were rather related to tumor location and just surgery than subsequent treatment. As full-scale or estimated IQ is highly dependent on processing speed and visuomotor coordination, our findings suggest that simply evaluating the IQ score does not reflect all possible impairments associated with multimodal treatment.[26] Major deficits in visual processing, as represented in our cohort, are known to increase problems in acquiring reading skills, as well as difficulties in visual-motor coordination and social interaction.[33] In our patient group, location of the tumor contributed to results in fluid intelligence, possibly adding to location-specific impairments for scores like the estimated IQ.[27] Lafay-Cousin et al. found corresponding deficits in reasoning tests in the ATRT cohort,[13] although just few patients had been irradiated, underlining a possible location-dependent contribution. Although fluid intelligence appeared as a mild cognitive deficit in our ATRT cohort, even slightly reduced neuropsychological functions may have an impact in the context of social difficulties associated with pediatric brain tumors and functions associated with fluid intelligence such as working memory and attention.[12,34]

As the extent of resection was comparably high, with just a few additional partial resections in the LGG subgroup, our findings point toward the histological diagnosis with its growth characteristics and subsequent tumor-specific treatment as prominent predictors of cognitive impairments. The corresponding consequences are more deficits in higher malignant tumors receiving more intensive multimodal therapy. Other variables such as sex, age at diagnosis, degree of hydrocephalus, and time from diagnosis to testing did not contribute. Thus, we corroborate reports on different outcomes for patients with specific tumor types associated with different treatments.[35–37]

Both groups, ATRT and LGG patients, displayed sequelae in attentional performance and psychomotor speed. Although neurocognitive outcome was better in LGG patients, they still experienced significant impairments when compared to the population norm. Their sequelae included attentional performance and psychomotor speed as described before for this histologic group, even if patients just received surgical resection.[18,20,37] Such deficits are probably associated with tumor location,[11,18] white matter volume reduction,[38] and impaired cerebello-thalamo-cerebral pathways[39] in both ATRT and LGG patients. Impaired attention performance is especially associated with academic underachievement in pediatric brain tumor patients.[30] Children with difficulties in motor functions require additional support to participate in social activities and experience further loneliness when compared to their peers.[40]

4.2 | Pattern of neurocognitive deficits in rhabdoid tumor patients

Sequelae for ATRT patients concerned fluid intelligence, verbal short-term memory, visual processing, processing speed, psychomotor speed, and attention in terms of alertness and inhibition ability. Most ATRT patients experienced variably combined impairments additionally affecting QoS. In particular, patients with subtotally resected supratentorial and infratentorial masses suffered from most combined impairments. Supratentorial tumor site is considered as special risk factor for cognitive sequelae.[41] While Lafay-Cousin et al.[13] reported that most patients experienced various comparable impairments, our study—summarizing the most comprehensive assessment of ATRT patients to-date—indicates a significant spread and multiple combinations of deficits. Still, further long-term evaluation of this patient group needs to investigate causes for the specific impairments and high vulnerability of cognitive functions in ATRT. Late effects in the field of visual processing seem in part comparable to those of historical cohorts of medulloblastoma patients having received either dose-intense CSI or intraventricular MTX, while our ATRT cohort demonstrated fewer impairments for verbal short-term memory. A tentative comparison of the groups was added to the Supporting Material of this manuscript. Novel therapeutic strategies, for example,

targeting specific molecular pathways, are needed for these very young and vulnerable patients[42] to reduce the burden of therapy and to help avoiding RT. Multimodal treatment, early onset of disease, and the associated adverse experience of a life-threatening disease are also hypothesized to enhance neurodevelopmental deficits,[43] not compensated for by neuronal plasticity,[44] while sex, time to testing since diagnosis, and hydrocephalus do not seem to contribute to the observed late effects. Further research needs to be conducted with a bigger cohort to reveal details of the underlying mechanisms and generate recommendations for clinical practice.

Our cohort consisted mostly of ATRT patients with the biological denomination of ATRT-TYR. These patients appear to have a survival advantage compared to the SHH and MYC groups.[3,45] The small size of the methylation subgroups precluded comparisons of neuropsychological results.

For the first time, we report data on cognitive impairments in extracranial rhabdoid tumors. Due to small sample sizes, no detailed analysis could be conducted, but median results indicated that even these patients affected by extracranial and renal tumor locations experienced difficulties in memory and divided attention functions. Emerging results suggest variable impairments following various pediatric cancer treatment regimens,[46] but further investigation is needed.

4.3 | Quality of survival analysis for rhabdoid tumor patients

The assessment for health-related QoL displayed significant impairments for infant rhabdoid tumor patients in social and school functioning, as well as psychosocial aspects and overall QoL, indicating that established psychosocial problems for pediatric cancer survivors were also present in our cohort.[47] The remainder of QoS questionnaires showed no further significant late effects, but results varied considerably among patients with high deviation in various subscores. Comparison of mean scores for ATRT and eMRT/RTK patients disclosed problems in psychosocial behavior and with hyperactivity more frequently for ATRT patients. Deficits in school functioning were accompanied by noticeably lower teacher ratings in executive functioning, especially in terms of behavior regulation. In addition, ATRT patients reported lower levels of health-related QoL. These findings are in line with Murphy et al., who stated that behavioral difficulties, due to executive dysfunction, impact upon the patients' health-related QoL.[48] In consequence, it is critical to identify such executive dysfunction early on in order to initiate appropriate interventions that may improve as well executive functioning as QoL.

On the other hand, patients with eMRT/RTK tumors displayed lower mean scores in emotional functioning, and parents reported lower executive functioning compared to parents of ATRT patients. There have been reports on promising outcomes regarding psychosocial problems and overall QoS for pediatric cancer survivors, but patients diagnosed at a young age, with tumors of the CNS, and having received RT remain at risk for major impairments.[49] Following their cognitive late effects, ATRT patients are prone to increased problems in school reintegration and psychosocial participation.[50] Chronic health deficits following treatment may serve as an explanation for impaired emotional outcome in eMRT and RTK patients.[51] There has been evidence that endocrinopathies, as frequently found in the extracranial patient subgroup, could be associated with higher prevalence of emotional distress.[52]

To improve investigation of cognitive and psychosocial outcomes for patients with rhabdoid tumors, inclusion of cognitive assessment should be compulsory in future rhabdoid tumor trials, for example, to directly compare the effects of high-dose ChT- and RT-based treatment regimens. The ATRT-Neuropsychology Tool has been implemented in the randomized trial SIOPE ATRT01 (EudraCT 2018-003335-29). Analyses should also comprise molecular subgrouping,[53] biomarkers,[54] socioeconomic status,[55] family functioning,[32] neurocognitive profiles,[56] and participation in everyday-life after treatment.[57]

5 | LIMITATIONS

Our retrospective analyses of neurocognitive outcome in patients affected by ATRT were exploratory rather than confirmatory in nature. We had to rely on historic data for comparison and, therefore, could not systematically evaluate data on hydrocephalus, leukoencephalopathy, and cerebellar mutism syndrome for all patient subgroups. Furthermore, ATRT and LGG patients differed slightly in the median time following diagnosis. Longitudinal data were unfortunately not available. Due to the small sample sizes in a very rare tumor type, analysis of specific aspects was limited, for example, regarding the role of specific tumor location and extent of resection. For the Purdue Pegboard test, few current normative data exist resulting in a possible bias for the results of psychomotor speed domains.

6 | CONCLUSION

Infants surviving rhabdoid tumors of all sites experience various serious cognitive sequelae and late effects in QoS. Sequelae in infant ATRT patients treated on multimodal therapy regimens (surgery, multiagent ChT, focal RT, and/or CSI) comprise deficits in fluid intelligence, short-term memory, visual processing, processing speed, psychomotor speed, and attention, while infant LGG patients treated with surgery with or without ChT, yet without RT, demonstrated fewer though still relevant late effects. These late effects in ATRT patients appear to be comparable to historical data for infants treated with CSI. Overall QoS impairments were revealed, with particular sequelae in social, school, and psychosocial functioning indicating successive problems in participation for all rhabdoid patients after treatment. Efforts should be made to avoid RT in ATRT treatment by introducing other effective strategies. Early onset and multimodal treatment of rhabdoid tumors require standardized close monitoring of neuropsychological and QoS parameters, as has been implemented in the SIOPE ATRT01 trial.

AUTHOR CONTRIBUTIONS

Conception and design: Thomas Traunwieser, Elena Loos, Holger Ottensmeier, Astrid K. Gnekow, and Michael C. Frühwald. Acquisition of data: Thomas Traunwieser, Elena Loos, Holger Ottensmeier, Karolina Nemes, and Martin Mynarek. Statistics: Joachim Gerss, Thomas Traunwieser, and Elena Loos. Analysis and interpretation: Thomas Traunwieser, Elena Loos, Holger Ottensmeier, Katharina Gastberger, Karolina Nemes, Martin Mynarek, Stefan Rutkowski, Astrid K. Gnekow, and Michael C. Frühwald. Drafting article and critically revising: all authors.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets for the current study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Woehrer A, Slavc I, Waldhoer T, et al. Incidence of atypical teratoid/rhabdoid tumors in children: a population-based study by the Austrian Brain Tumor Registry, 1996–2006. *Cancer*. 2010;116(24):5725-5732.
2. Ostrom QT, Chen Y, M de Blank P, et al. The descriptive epidemiology of atypical teratoid/rhabdoid tumors in the United States, 2001–2010. *Neuro Oncol*. 201416(10):1392-1399.
3. Nemes K, Johann PD, Steinbügl M, et al. Infants and newborns with atypical teratoid rhabdoid tumors (ATRT) and extracranial malignant rhabdoid tumors (eMRT) in the EU-RHAB Registry: a unique and challenging population. *Cancers (Basel)*. 2022;14(9):2185.
4. Bartelheim K, Nemes K, Seeringer A, et al. Improved 6-year overall survival in AT/RT—results of the registry study Rhabdoid 2007. *Cancer Med*. 2016;5(8):1765-1775.
5. Nemes K, Johann PD, Tüchert S, et al. Current and emerging therapeutic approaches for extracranial malignant rhabdoid tumors. *Cancer Manag Res*. 2022;14:479-498.
6. Frühwald MC, Hasselblatt M, Nemes K, et al. Age and DNA methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors. *Neuro Oncol*. 2020;22(7):1006-1017.
7. An KJ, Joung YS, Sung KW, Kim JH. Health-related quality of life and cognitive functioning at on- and off-treatment periods in children aged between 6–13 years old with brain tumors: a prospective longitudinal study. *Yonsei Med J*. 2013;54(2):306-314.
8. Odagiri K, Omura M, Hata M, et al. Treatment outcomes and late toxicities in patients with embryonal central nervous system tumors. *Radiat Oncol*. 2014;9:201.
9. Slavc I, Chocholous M, Leiss U, et al. Atypical teratoid rhabdoid tumor: improved long-term survival with an intensive multimodal therapy and delayed radiotherapy. The Medical University of Vienna experience 1992–2012. *Cancer Med*. 2014;3(1):91-100.
10. Weber DC, Ares C, Malyapa R, et al. Tumor control and QoL outcomes of very young children with atypical teratoid/rhabdoid tumor treated with focal only chemo-radiation therapy using pencil beam scanning proton therapy. *J Neurooncol*. 2015121(2):389-397.
11. Ali JS, Ashford JM, Swain MA, et al. Predictors of cognitive performance among infants treated for brain tumors: findings from a multisite, prospective, longitudinal trial. *J Clin Oncol*. 2021;39(21):2350-2358.
12. Oyefiade A, Paltin I, De Luca CR, et al. Cognitive risk in survivors of pediatric brain tumors. *J Clin Oncol*. 2021;39(16):1718-1726.
13. Lafay-Cousin L, Fay-McClymont T, Johnston D, et al. Neurocognitive evaluation of long term survivors of atypical teratoid rhabdoid tumors (ATRT): the Canadian registry experience. *Pediatr Blood Cancer*. 2015;62(7):1265-1269.
14. Fallowfield L, Nadler E, Gilloteau I, et al. Quality of survival: a new concept framework to assess the quality of prolonged life in cancer. *Expert Rev Qual Life Cancer Care*. 2017;2(4):225-232.
15. Limond JA, Bull KS, Calaminus G, et al. Quality of survival assessment in European childhood brain tumour trials, for children aged 5 years and over. *Eur J Paediatr Neurol*. 2015;19(2):202-210.
16. Limond J, Thomas S, Bull KS, et al. Quality of survival assessment in European childhood brain tumour trials, for children below the age of 5 years. *Eur J Paediatr Neurol*. 2020;25:59-67.
17. Nemes K, Frühwald MC. Potential late effects of rhabdoid tumor therapy in childhood and adolescents. In: Beck JD, Bokemeyer C, Langer T, eds. *Late Treatment Effects and Cancer Survivor Care in the Young: From Childhood to Early Adulthood*. Springer International Publishing; 2021;331-342.
18. Traunwieser T, Kandels D, Pauls F, et al. Long-term cognitive deficits in pediatric low-grade glioma (LGG) survivors reflect pretreatment conditions-report from the German LGG studies. *Neurooncol Adv*. 2020;2(1):vdaa094.
19. Ris MD, Leisenring WM, Goodman P, et al. Neuropsychological and socioeconomic outcomes in adult survivors of pediatric low-grade glioma. *Cancer*. 2019;125(17):3050-3058.
20. Heitzer AM, Ashford JM, Hastings C, et al. Neuropsychological outcomes of patients with low-grade glioma diagnosed during the first year of life. *J Neurooncol*. 2019;141(2):413-420.
21. Ottensmeier H, Zimolong B, Wolff JE, et al. Neuropsychological short assessment of disease- and treatment-related intelligence deficits in children with brain tumours. *Eur J Paediatr Neurol*. 2015;19(3):298-307.
22. Ottensmeier H, Schlegel PG, Eyrich M, et al. Treatment of children under 4 years of age with medulloblastoma and ependymoma in the HIT2000/HIT-REZ 2005 trials: neuropsychological outcome 5 years after treatment. *PLoS One*. 2020;15(1):e0227693.

23. Nemes K, Bens S, Kachanov D, et al. Clinical and genetic risk factors define two risk groups of extracranial malignant rhabdoid tumours (eMRT/RTK). *Eur J Cancer*. 2021;142:112-122.
24. Kandels D, Pietsch T, Bison B, et al. Loss of efficacy of subsequent non-surgical therapy after primary treatment failure in pediatric low-grade glioma patients—report from the German SIOP-LGG 2004 cohort. *Int J Cancer*. 2020;147(12):3471-3489.
25. Gnekow AK, Kandels D, Pietsch T, et al. Doubling recruitment of pediatric low-grade glioma within two decades does not change outcome—report from the German LGG studies. *Klin Padiatr*. 2021;233(3):107-122.
26. Wegenschimmel B, Leiss U, Veigl M, et al. Do we still need IQ-scores? Misleading interpretations of neurocognitive outcome in pediatric patients with medulloblastoma: a retrospective study. *J Neurooncol*. 2017;135(2):361-369.
27. Burgess L, Pulsifer MB, Grieco JA, et al. Estimated IQ systematically underestimates neurocognitive sequelae in irradiated pediatric brain tumor survivors. *Int J Radiat Oncol Biol Phys*. 2018;101(3):541-549.
28. Gnekow AK. Recommendations of the Brain Tumor Subcommittee for the reporting of trials. SIOP Brain Tumor Subcommittee. International Society of Pediatric Oncology. *Med Pediatr Oncol*. 1995;24(2):104-108.
29. Schneider WJ, McGrew KS. The Cattell–Horn–Carroll theory of cognitive abilities. In: *Contemporary Intellectual Assessment: Theories, Tests, and Issues*. 4th ed. Guilford Press; 2018;73-163.
30. Chevignard M, Câmara-Costa H, Doz F, Dellatolas G. Core deficits and quality of survival after childhood medulloblastoma: a review. *Neurooncol Pract*. 2017;4(2):82-97.
31. Reddick WE, Taghipour DJ, Glass JO, et al. Prognostic factors that increase the risk for reduced white matter volumes and deficits in attention and learning for survivors of childhood cancers. *Pediatr Blood Cancer*. 2014;61(6):1074-1079.
32. Schepers SA, Schulte FSM, Patel SK, Vannatta K. Cognitive impairment and family functioning of survivors of pediatric cancer: a systematic review. *J Clin Oncol*. 2021;39(16):1795-1812.
33. Chokron S, Kovarski K, Dutton GN. Cortical visual impairments and learning disabilities. *Front Hum Neurosci*. 2021;15:713316.
34. Cochrane A, Simmering V, Green CS. Fluid intelligence is related to capacity in memory as well as attention: Evidence from middle childhood and adulthood. *PLoS One*. 2019;14(8):e0221353.
35. Rey-Casserly C, Diver T. Late effects of pediatric brain tumors. *Curr Opin Pediatr*. 2019;31(6):789-796.
36. Fraley CE, Thigpen JC, Pearson MM, et al. Predictors of cognitive function in pediatric brain tumor patients: pre-surgery through 24-month follow-up. *Appl Neuropsychol Child*. 2021;10(4):340-347.
37. Levitch CF, Holland AA, Bledsoe J, et al. Comparison of neuropsychological functioning in pediatric posterior fossa tumor survivors: medulloblastoma, low-grade astrocytoma, and healthy controls. *Pediatr Blood Cancer*. 2022;69(2):e29491.
38. Rueckriegel SM, Bruhn H, Thomale UW, Hernáiz Driever UP. Cerebral white matter fractional anisotropy and tract volume as measured by MR imaging are associated with impaired cognitive and motor function in pediatric posterior fossa tumor survivors. *Pediatr Blood Cancer*. 2015;62(7):1252-1258.
39. Oh ME, Driever PH, Khajuria RK, et al. DTI fiber tractography of cerebro-cerebellar pathways and clinical evaluation of ataxia in childhood posterior fossa tumor survivors. *J Neurooncol*. 2017;131(2):267-276.
40. Mimouni-Bloch A, Tsadok-Cohen M, Bart O. Motor difficulties and their effect on participation in school-aged children. *J Child Neurol*. 2016;31(11):1290-1295.
41. Duffner PK. Risk factors for cognitive decline in children treated for brain tumors. *Eur J Paediatr Neurol*. 2010;14(2):106-115.
42. Fruehwald MC, Biegel JA, Bourdeaut F, Roberts CW, Chi SN. Atypical teratoid/rhabdoid tumors-current concepts, advances in biology, and potential future therapies. *Neuro Oncol*. 2016;18(6):764-778.
43. Marusak HA, Iadipaolo AS, Harper FW, et al. Neurodevelopmental consequences of pediatric cancer and its treatment: applying an early adversity framework to understanding cognitive, behavioral, and emotional outcomes. *Neuropsychol Rev*. 2018;28(2):123-175.
44. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*. 2011;134(8):2197-2221.
45. Upadhyaya SA, Robinson GW, Onar-Thomas A, et al. Relevance of molecular groups in children with newly diagnosed atypical teratoid rhabdoid tumor: results from prospective St. Jude multi-institutional trials. *Clin Cancer Res*. 2021;27(10):2879-2889.
46. Foster R, Zheng DJ, Netson-Amore KL, Kadan-Lottick NS. Cognitive impairment in survivors of pediatric extracranial solid tumors and lymphomas. *J Clin Oncol*. 2021;39(16):1727-1740.
47. Brinkman TM, Recklitis CJ, Michel G, Grootenhuis MA, Klosky JL. Psychological symptoms, social outcomes, socioeconomic attainment, and health behaviors among survivors of childhood cancer: current state of the literature. *J Clin Oncol*. 2018;36(21):2190-2197.
48. Murphy C, Upshaw NC, Thomas AS, et al. Impact of executive functioning on health-related quality of life of pediatric brain tumor survivors. *Pediatr Blood Cancer*. 2021;68(8):e29130.
49. Bitsko MJ, Cohen D, Dillon R, Harvey J, Krull K, Klosky JL. Psychosocial late effects in pediatric cancer survivors: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2016;63(2):337-343.
50. de Ruiter MA, Schouten-van Meeteren AYN, van Vuurden DG, et al. Psychosocial profile of pediatric brain tumor survivors with neurocognitive complaints. *Qual Life Res*. 2016;25(2):435-446.
51. Mader L, Sláma T, Schindera C, et al. Social, emotional, and behavioral functioning in young childhood cancer survivors with chronic health conditions. *Pediatr Blood Cancer*. 2022;69(9):e29756.
52. Vuotto SC, Krull KR, Li C, et al. Impact of chronic disease on emotional distress in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2017;123(3):521-528.
53. Johann PD, Erkek S, Zapatka M, et al. Atypical teratoid/rhabdoid tumors are comprised of three epigenetic subgroups with distinct enhancer landscapes. *Cancer Cell*. 2016;29(3):379-393.
54. Williams AM, Cole PD. Biomarkers of cognitive impairment in pediatric cancer survivors. *J Clin Oncol*. 2021;39(16):1766-1774.
55. Torres VA, Ashford JM, Wright E, et al. The impact of socioeconomic status (SES) on cognitive outcomes following radiotherapy for pediatric brain tumors: a prospective, longitudinal trial. *Neuro Oncol*. 2021;23(7):1173-1182.
56. Sharkey CM, Mullins LL, Clawson AH, et al. Assessing neuropsychological phenotypes of pediatric brain tumor survivors. *Psychooncology*. 2021;30(8):1366-1374.
57. Pletschko T, Felnhofer A, Schwarzinger A, Weiler L, Slavc I, Leiss U. Applying the international classification of functioning - children and youth version to pediatric neuro-oncology. *J Child Neurol*. 2017;32(1):23-28.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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