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Long-term neuropsychological outcomes of survivors of young childhood brain tumors treated on the Head Start II protocol

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Abstract

Background. The Head Start treatment protocols have focused on curing young children with brain tumors while avoiding or delaying radiotherapy through using a combination of high-dose, marrow-ablative chemotherapy and autologous hematopoietic cell transplantation (AuHCT). Late effects data from treatment on the Head Start II (HS II) protocol have previously been published for short-term follow-up (STF) at a mean of 39.7 months post-diagnosis. The current study examines long-term follow-up (LTF) outcomes from the same cohort.

Methods. Eighteen HS II patients diagnosed with malignant brain tumors <10 years of age at diagnosis completed a neurocognitive battery and parents completed psychological questionnaires at a mean of 104.7 months' post-diagnosis.

Results. There was no significant change in Full Scale IQ at LTF compared to baseline or STF. Similarly, most domains had no significant change from STF, including verbal IQ, performance IQ, academics, receptive language, learning/memory, visual-motor integration, and externalizing behaviors. Internalizing behaviors increased slightly at LTF. Clinically, most domains were within the average range, except for low average mathematics and receptive language. Additionally, performance did not significantly differ by age at diagnosis or time since diagnosis. Of note, children treated with high-dose methotrexate for disseminated disease or atypical teratoid/rhabdoid tumor displayed worse neurocognitive outcomes.

Conclusions. These results extend prior findings of relative stability in intellectual functioning for a LTF period. Ultimately, this study supports that treatment strategies for avoiding or delaying radiotherapy using high-dose, marrow-ablative chemotherapy and AuHCT may decrease the risk of neurocognitive and social-emotional declines in young pediatric brain tumor survivors.

Keywords

intellectual functioning | late effects | neurocognitive | pediatric brain tumors | survivorship

Key Points

- At LTF, intellectual functioning did not significantly change from baseline or STF.
- HS II survivors were functioning within normal limits across domains, albeit individual variability in outcomes.
- Children who received HD-MTX were at higher risk for poorer neurocognitive functioning.

Importance of the Study

The current study provides long-term follow-up (LTF) of the neuropsychological and psychological functioning of pediatric brain tumor patients treated on the Head Start II (HS II) protocol, which aimed to avoid or delay use of cranial radiation. Intellectual functioning remained generally stable across baseline, short-term follow-up, and LTF. Furthermore, the HS II survivors experienced fewer and more subtle neurocognitive, academic, and psychological late effects than typically seen in young children treated with radiotherapy. Although the group as a whole appears to be fairly resilient over time, it is important to acknowledge that there is variability in performance for most neurocognitive domains. Furthermore, children with more extensive and/or resistant diseases who received HD-MTX were at higher risk for poorer neurocognitive functioning at LTF. These findings highlight the importance of collecting prospective, serial outcome data to monitor the trajectory of survivors' neurocognitive and psychological functioning over development. Ultimately, this study expands survivorship knowledge of a novel pediatric brain tumor treatment that was designed to minimize neurotoxicity.

Advances in treatment approaches for pediatric cancers have resulted in improvements in survival rates for children diagnosed with malignant CNS tumors over the last 3 decades.[1] For medulloblastoma, it is estimated that children diagnosed with the disease have a 75% likelihood of reaching adulthood, with variability depending upon various factors such as age at diagnosis, dissemination of the disease, and molecular subtyping.[2]

The increasing percentage of pediatric brain tumor survivors has attracted a greater understanding of the late effects of treatment on individuals' overall quality of life and functioning.[3–6] Specifically, many pediatric brain tumor survivors experience declines in neuropsychological and psychological functioning, with focal vulnerabilities in psycho-motor processing speed, executive functioning, attention, and memory.[7,8] Risk factors associated with these long-term consequences include younger age at diagnosis, higher volume and dosage of irradiation, and time since treatment.[9–12] Consequently, it is of great importance that pediatric brain tumor survivors undergo serial assessment of their neuropsychological functioning.

Pediatric neurooncologists have developed irradiation-sparing or -delaying strategies to prevent the negative effects of irradiation and to reduce the abovementioned late effects in this population.[13–18] Since 1991, the Head Start trials have been at the forefront of this initiative and have focused on avoiding radiotherapy in young children with malignant CNS tumors through the use of high-dose, marrow-ablative chemotherapy and autologous hematopoietic cell transplantation (AuHCT).[19–24] Head Start II (HS II) was the second of these trials.

Although research on late effects in survivors of pediatric brain tumors has been informative, there is a paucity of studies that have serially tracked the neuropsychological functioning of patients in a prospective manner.[25,26] Specifically, many prior studies evaluated patients' functioning posttreatment without obtaining baseline assessments,[15,27–29] which, therefore, is not able to assess change in neuropsychological functioning both before and after the course of medical treatment. Although obtaining a baseline level of neurocognitive functioning is often difficult,[8,26,30,31] it is necessary for providing best practice care as well as informing late effects research, combined with serial follow-up asessments.[25]

In response to this need, the HS II study included baseline neuropsychological testing after resection of the primary tumor and induction chemotherapy but prior to patients undergoing consolidation chemotherapy and AuHCT, along with bi-annual follow-up evaluations. As reported previously,[19] assessments conducted on average 3 years after baseline testing revealed that HS II patients' mean performance was within the low average range for intelligence, academic achievement, receptive language, and visual-motor integration, and within the average range for learning/memory and social-emotional domains. Additionally, there were no statistically significant changes in intelligence scores from baseline to the short-term follow-up (STF) assessment.

These findings provide encouraging data suggesting that avoiding or delaying craniospinal irradiation in pediatric brain tumor patients may prevent or at least minimize declines in neurocognitive functioning over time, which is consistent with previous research.[15,17,32–34] However, as

reported in the HS II STF study, patients further from diagnosis demonstrated lower intelligence, reading skills, and delayed verbal memory than those more recently diagnosed.[19] This preliminary finding is consistent with previous studies that report children with CNS tumors do not learn at the same rate as their healthy peers.[35] Consequently, there is a need for long-term follow-up (LTF) of this HS II population to assess the possibility of a plateau or continued decline in intelligence and other neurocognitive domains over time.

The current study, therefore, aims to address these gaps in the literature by providing LTF data on the neurocognitive and psychological functioning of pediatric brain tumor patients who have avoided or have had delayed craniospinal irradiation. Based on previous findings from this cohort,[19] it was hypothesized that these patients will display no or minimal decline in intellectual functioning from baseline or STF and that most aspects of neurocognitive and psychological functioning will remain within the average to low average ranges.

Methods

Patients

The patient population for this study met eligibility criteria for HS II between 1997 and 2003,[19] which included patients with newly diagnosed malignant CNS tumors including medulloblastoma, primitive neuroectodermal tumor, ependymoma, glioblastoma multiforme, choroid plexus carcinoma, atypical teratoid/rhabdoid tumor (AT/RT), pineoblastoma, or anaplastic glioma who were under 10 years of age at diagnosis. Institutional Review Board approval was obtained by each participating center and neuropsychological assessment requirements were integrated into the treatment protocol.

Procedures

Treatment consisted of maximum safe resection of the primary tumor, multiple (4 or 5) cycles of induction chemotherapy, followed by a single cycle of marrow-ablative chemotherapy with AuHCT for children without progressive disease.[21] Induction therapy for patients with non-glial tumors without neuraxis dissemination consisted of 5 cycles of chemotherapy with vincristine, cisplatin, etoposide, and cyclophosphamide (Regimen A). Patients with neuraxis dissemination or those diagnosed with AT/RT received additional intensification with high-dose methotrexate (HD-MTX) at 400 mg/kg or 12 g/m^2 (Regimen A2). Patients with high-grade glial neoplasms and diffuse intrinsic pontine tumors received 4 cycles of vincristine, carboplatin, and temozolomide (Regimen C). Consolidation chemotherapy consisted of high-dose carboplatin, thiotepa, and etoposide for patients with non-glial tumors and carboplatin and thiotepa alone for patients with glial tumors. Patients received reduced-dose radiotherapy following recovery from AuHCT if they were 6 years or older at the time of diagnosis or had unresectable persistent residual disease at the end of induction.

Patients underwent baseline neuropsychological assessment following completion of induction chemotherapy, prior to AuHCT, and were scheduled to be re-evaluated every 2 years thereafter, although there was variability in the timing of follow-up assessments. Evaluations were performed by licensed psychologists in an outpatient setting.

Measures

Participants completed a validated battery of neurocognitive measures. A full description of the measures, along with references, is provided in Supplementary Table 1. In brief, intelligence was assessed using the Bayley Scale of Intellectual Development (BSID-II) and the Wechsler Intelligence Scales (WPPSI-R, WISC-R, and WISC-III). These measures are well correlated (BSID-II-WPPSI-R, $r = 0.73$; WPPSI-R-WISC-R, $r = 0.82$). Perceptual-motor functioning was assessed with the Beery Test of Visual-Motor Integration (VMI-4), receptive language was assessed with the Peabody Picture Vocabulary Test (PPVT-III), academic achievement was assessed using the Wechsler Individual Achievement Test (WIAT and WIAT II), and learning and memory was assessed using the Children's Memory Scale (CMS). Lastly, psychological functioning was assessed using the Behavior Assessment System for Children-Parent (BASC).

Statistical Analysis

Individual intelligence and neurocognitive subtest scores were converted to standard scores using standardized age norms. A repeated-measures ANOVA and exploratory reliable change statistics were conducted to assess for differences in intellectual functioning between baseline, STF, and LTF. Two-tailed, paired-samples *t* tests were conducted to assess for differences between STF score and LTF score. Group-average analyses were performed for survivors who received neuropsychological testing at STF and LTF. Scores on each measure at LTF were also categorized, indicating the percentage of participants who scored within normal limits (±1 SD from the normative mean), below normal limits (<1 SD below the normative mean), or above normal limits (>1 SD above the normative mean). Relationships between age at diagnosis, time since diagnosis, and neuropsychological outcomes at LTF were assessed using bivariate correlations. Because of the small sample size and exploratory nature of this study, Bonferroni corrections were not used, and *P* values and effect sizes are reported. Exploratory post hoc analyses of chemotherapy intensification (no HD-MTX vs HD-MTX) were performed for descriptive purposes only.

Results

Forty-nine of 51 (96%) HS II survivors received baseline neuropsychological testing, whereas 26 of 31 (84%) survivors received STF testing. Seventeen of 25 (68%) survivors underwent LTF assessment. Eight patients (32%) were lost to medical follow-up. One patient did not have

baseline or STF testing but underwent LTF and was included in the analyses (n = 18).

Table 1 provides a summary of the patient demographics at the time of baseline, STF, and LTF. Twelve participants (66.7%) had 1 LTF evaluation, 5 participants (27.8%) had 2 LTF evaluations, and 1 participant (5.6%) had 3 LTF evaluations. It is important to note that for the 6 patients with several LTF evaluations, the most recent LTF may not have included all measures, in which case the most recent score available on a given measure was utilized.

In the current sample that underwent LTF assessment, the mean age at diagnosis was 35.7 months old (SD = 22.6), the mean age at baseline testing was 45.7 months old (SD = 22.5), and the mean age at LTF was 122.8 months old (SD = 45.0; 10.2 years). Categorically, 61.1% of survivors had been diagnosed at <3 years of age (n = 11), 27.8% had been diagnosed between 3 and 5 years of age (n = 5), and 11.1% had been diagnosed between 6 and 10 years of age (n = 2). The sample was 61.1% male (n = 11). Eight survivors (44.4%) received intensive chemotherapy with HD-MTX. Six survivors (33.3%) received radiotherapy, which was administered at a mean age of 75.0 months (SD = 30.9). Two survivors received radiotherapy due to being six or older at diagnosis and 4 survivors due to unresectable residual disease at end of induction. Unfortunately, 3 of these survivors were not administered many of the neurocognitive measures at LTF. As such, this very small sample size precluded making statistical comparisons by group (ie, radiation therapy vs no radiation therapy). To present the data in the most meaningful way, each individual child's outcomes are reported in Supplementary Table 2. Five survivors (27.8%) received both intensive chemotherapy with HD-MTX and radiotherapy, while 9 survivors (50%) received neither treatment.

Table 1. Demographics and Medical Variables of Children Who Received Neuropsychological Testing at Baseline, Short-Term, and Long-Term Follow-Up

	Baseline (n = 51)		STF (n = 26)		LTF[a] (n = 18)	
	n	%	n	%	n	%
Male/female	31/20		18/8		11/7	
Months at diagnosis—mean (SD)	35.9 (25.0)		36.0 (24.1)		35.7 (22.6)	
Months at baseline—mean (SD)			42.74 (27.7)		45.7 (22.5)	
Months at assessment—mean (SD)	–		84.2 (29.4)		122.8 (45.0)	
Age group (diagnosis)						
<3 years	28	54.9	14	53.8	11	61.1
3 to <6 years	17	33.3	9	34.6	5	27.8
6-10 years	6	11.8	3	11.5	2	11.1
Months from diagnosis—mean (SD)	6.41 (5.2)		41.5 (17.3)		104.7 (33.1)	
Months at radiation—mean (SD)	–		67.2 (28.5)		75.0 (30.88)	
Diagnosis						
Medulloblastoma/PNET	22	43.1	12	46.2	11	61.1
Other	29	56.9	14	53.8	7	38.9
Ependymoma					3	16.7
Glioblastoma multiforme					1	5.6
AT/RT					1	5.6
Choroid plexus carcinoma					1	5.6
Not available					1	5.6
Extent of resection						
Complete	33	64.7	15	57.7	10	55.6
Subtotal	18	35.3	11	42.3	8	44.4
Tumor location						
Supratentorial	21	41.2	9	34.6	6	33.3
Infratentorial	30	58.8	17	65.4	12	66.7
Chemotherapy treatment						
Regimen A	24	47.1	11	42.3	8	44.4
Regimen A2	22	43.1	12	46.2	8	44.4
Regimen C	5	9.8	3	11.5	2	11.1
Radiotherapy						
Yes	16	31.4	7	29.2	6	33.3
No	33	64.7	16	66.7	12	66.7
Refusal or violation	2	3.9				
Survival status						
Alive	31	60.8	25		18	
Deceased	20	39.2	1			

Abbreviations: AT/RT, atypical teratoid/rhabdoid tumor; LTF, long-term follow-up; STF, short-term follow-up.
[a]These survivors had additional testing after STF and the demographics are based on the most recent follow-up assessment, regardless of which assessments were administered at that time.

Serial Analysis of Intellectual Functioning Between Baseline, STF, and LTF

As presented in Figure 1, for the 13 survivors with IQ data at all time points, mean overall intelligence scores did not significantly differ between baseline, STF, or LTF ($F(2, 24) = 0.17$, $P = .844$, $\eta^2 = 0.014$). From baseline to LTF, mean overall intelligence score increased by 1.92 points ($P = .70$), and from STF to LTF, mean overall IQ decreased by 0.23 points ($P = .94$). The mean interval between baseline and LTF intelligence testing was 100.70 months (SD = 38.74), and the mean interval between STF and LTF intelligence testing was 67.22 months (SD = 36.55). In addition, based on Jacobson and Traux's reliable change index calculator,[36] there was no significant change in overall intelligence score between baseline, STF, or LTF (Baseline-STF, $z = 0.72$; Baseline-LTF, $z = 0.64$; STF-LTF, $z = –0.07$).

Serial Analysis of Neuropsychological Functioning Between STF and LTF

As presented in Table 2, comparison change scores were not statistically significant for most variables (Ps > .05) and the effect sizes were very small to small in magnitude (Cohen's $d < 0.50$). For example, the mean performance IQ score decreased by 2.54 points at LTF ($P = .50$,

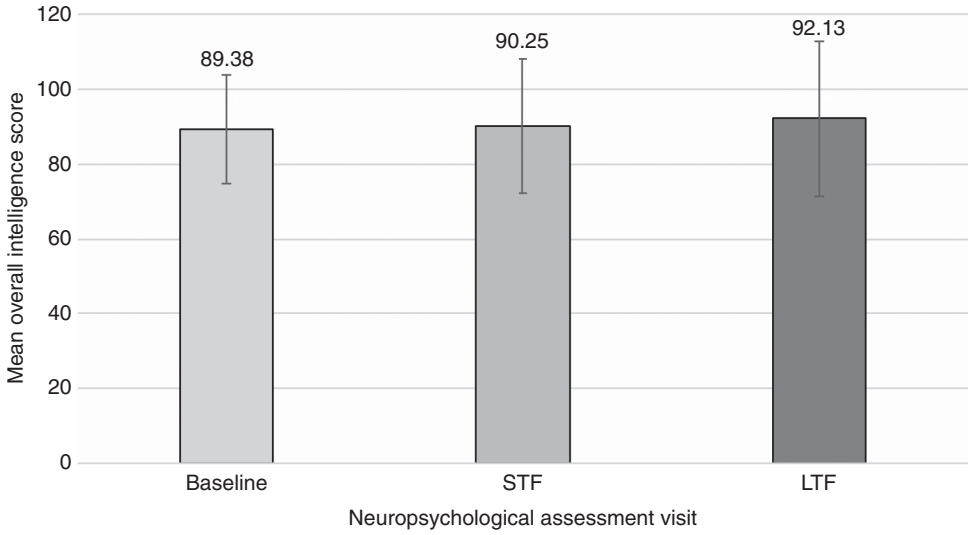

Figure 1. Mean intellectual functioning at baseline, short-term follow-up, and long-term follow-up (n = 13).

d = 0.22) and the mean verbal IQ score increased by 3.15 points at LTF (*P* = .27, *d* = 0.32). The remaining analyses were limited by small sample size (n < 10). That said, there was a significant change in internalizing behaviors (*P* = .04, *d* = 0.70), with greater internalizing symptoms reported by parents at LTF (*M* = 53.30, SD = 12.33) than at STF (*M* = 49.11, SD = 13.85), although both are well within the normal range.

Analysis of Neuropsychological Functioning at LTF

As presented in Table 2, at LTF, after an average of 104.7 months' post-diagnosis, the mean overall IQ for survivors was within the lower limits of the average range (*M* = 92.13; SD = 20.80). The mean functioning was also within the average range for: verbal IQ, performance IQ, reading, spelling, visual-motor integration, learning/memory, internalizing behaviors, and externalizing behaviors. Survivors were functioning within the low average range for mathematics and receptive language. Of note, there was considerable individual variability in the outcome variables.

To aid in the interpretation of the functional level of these survivors relative to normative expectations, the percentage of survivors falling within, below, or above normal limits was calculated using a normal distribution of standardized scores (see Table 3). At LTF, approximately two-thirds of the HS II survivors were performing within or above normal limits on most neurocognitive, academic, and psychological domains assessed. Clinically, this indicates that they were performing at a commensurate level as their same-aged peers in the general population. However, it is important to note that approximately one-third of the participants performed below normal limits for overall IQ, while roughly half of the participants performed below normal limits for performance IQ and mathematics.

Bivariate correlations for age at diagnosis, time since diagnosis, and neurocognitive/psychological outcomes at LTF are presented in Table 4. Neither age at diagnosis nor time since diagnosis was significantly related to any neuropsychological or psychological variables at LTF (*P*s > .05).

Exploratory Analysis of HD-MTX

Patients with either disseminated disease in the CNS or a diagnosis of AT/RT received additional intensification with HD-MTX. As presented in Table 5, there were medium to large effect sizes for several neurocognitive domains at LTF (Cohen's *d* ≥0.5 and ≥0.8, respectively), whereby survivors who received HD-MTX performed worse than those who did not receive HD-MTX. These domains were reading, learning/memory, and receptive language.

Discussion

The current study addresses gaps in the literature by providing LTF data for the neurocognitive and psychological functioning of young survivors of pediatric brain tumors who were treated on the HS II protocol. As hypothesized, overall intelligence did not significantly change from previously reported functioning at baseline or STF to LTF. Other comparisons for change over time were not significant and were very small to small in magnitude, except for a slight increase in internalizing symptoms. Furthermore, neurocognitive and psychological functioning generally remained with the average to low average ranges, with significant individual variability in functioning. Participants who received HD-MTX were at higher risk for poorer

Table 2. Neuropsychological Outcome Measures at Long-Term Follow-Up and Change from Short-Term Follow-Up Presented as Mean (SD)

Neurocognitive	STF Group (n = 26)			LTF Group (n = 18)			Change from STF—Most Recent LTF				
	N	Mean (SD)	Desc.	N	Mean (SD)	Desc.	N	Follow-up time in months	Mean change (95% CI)	*P*	*d*
Intelligence[a]											
FSIQ/MDI	24	87.92 (17.1)	Low Average	15	92.13 (20.80)	Average	14	67.22 (36.55)	0.23 (–6.44, 6.90)	.94	0.01
Verbal IQ	19	89.00 (16.8)	Low Average	15	93.27 (19.12)	Average	13	69.47 (39.21)	–3.15 (–9.08, 2.77)	.27	0.32
Performance IQ	20	89.25 (17.9)	Low Average	15	93.20 (21.13)	Average	13	70.98 (36.86)	2.54 (–4.53, 9.61)	.50	0.22
Academic achievement[a]											
Reading	13	88.77 (16.2)	Low Average	15	96.33 (19.37)	Average	9	74.01 (36.47)	–1.00 (–9.29, 11.29)	.83	–0.05
Math	10	86.20 (18.6)	Low Average	14	88.07 (15.55)	Low Average	6	74.30 (29.52)	–2.83 (–6.56, 12.23)	.47	–0.18
Spelling	11	86.45 (16.3)	Low Average	14	96.21 (17.14)	Average	9	74.06 (36.47)	–3.11 (–9.83, 16.05)	.59	–0.18
Learning and memory[a]											
General memory index	8	93.00 (22.5)	Average	11	98.55 (23.87)	Average	3	41.04 (23.98)	–6.33 (–89.53, 102.2)	.80	–0.27
Visual immediate index	10	90.80 (19.3)	Average	13	97.00 (16.81)	Average	6	49.56 (22.13)	–0.17 (–28.25, 25.97)	.92	–0.01
Visual delayed index	8	98.63 (14.1)	Average	11	102.55 (18.35)	Average	5	60.26 (32.66)	–1.80 (–38.18, 41.78)	.91	–0.10
Verbal immediate index	8	99.13 (12.6)	Average	10	99.30 (18.99)	Average	5	60.26 (32.66)	–6.00 (–5.78, 17.78)	.23	–0.32
Verbal delayed index	9	93.11 (24.7)	Average	10	102.40 (20.60)	Average	5	60.26 (32.66)	–6.20 (–20.19, 32.59)	.55	–0.30
Learning index	7	91.57 (21.9)	Average	10	96.30 (18.93)	Average	4	49.75 (26.21)	–2.25 (–46.92, 51.42)	.89	–0.12
Delayed recognition index	7	97.29 (14.2)	Average	11	96.55 (19.27)	Average	4	49.75 (26.21)	–9.50 (–25.62, 44.62)	.45	–0.49
Receptive language[a]											
PPVT	16	88.38 (14.1)	Low Average	7	85.86 (15.32)	Low Average	6	57.33 (30.93)	–7.17 (–8.32, 22.65)	.29	–0.47
Visual-motor integration[a]											
VMI	13	88.23 (14.0)	Low Average	13	95.92 (18.36)	Average	7	53.68 (28.91)	–6.43 (–2.29, 15.15)	.12	–0.35
Psychological[b]											
Internalizing problems	10	47.60 (13.6)	Average	10	53.30 (12.33)	Average	6	62.31 (28.75)	8.67 (–16.76, –0.57)	.04	0.70
Externalizing problems	10	49.50 (7.3)	Average	10	50.90 (6.10)	Average	6	62.31 (28.75)	1.33 (–7.79, 5.12)	.62	0.22

Abbreviations: FSIQ, Full Scale Intelligence Quotient; MDI, Mental Development Index; PPVT, Peabody Picture Vocabulary Test; VMI, visual-motor integration.
[a]Scores are standard scores (mean = 100; SD = 15). [b]Scores are *T* scores (mean = 50; SD = 10).

neurocognitive functioning at LTF. Overall, these LTF data are consistent with our previous findings, which indicated fewer neurotoxic effects for patients who have avoided or delayed craniospinal irradiation.

Findings from the present study are encouraging when compared to the literature demonstrating significant and progressive declines in intellectual functioning following completion of chemotherapy and radiotherapy in young children treated for cancer.[4,5,37,38] In this sample, overall intelligence was largely preserved over an average period of 5.6 years from STF evaluation and 8.7 years from baseline evaluation, and the effect size for this comparison was in the very small range. In addition, reliable change indexes revealed that there was no significant change in intellectual functioning across time points in exploratory analyses. This finding is consistent with our initial, STF study from this cohort,[19] as well as other studies that aimed to minimize late effects through delaying or avoiding use of radiotherapy.[15,21,34,39,40]

For other neurocognitive and psychological domains, there were also no significant changes at LTF, except for an increase in reported internalizing behaviors, albeit still

Table 3. Classification of Neuropsychological Outcome Scores Based on Standard Deviation Units at Most Recent Long-Term Follow-Up[a]

Domain	Below Normal Limits (<1 SD)		Within Normal Limits (±1 SD)		Exceeding Normal Limits (>1 SD)	
	n	%	n	%	n	%
Intelligence						
FSIQ/MDI	5	33.3	9	60.0	1	6.7
Verbal IQ	4	26.7	10	66.7	1	6.7
Performance IQ	7	46.7	6	40.0	2	13.3
Academic achievement						
Reading	4	26.7	9	60.0	2	13.3
Spelling	4	28.6	9	64.3	1	7.1
Math	7	50.0	6	42.9	1	7.1
Receptive language						
PPVT	2	28.6	5	71.4	0	0.0
Visual-motor integration						
VMI	4	30.8	6	46.2	3	23.1
Learning and memory						
General memory index	3	27.3	4	36.4	4	36.4
Verbal immediate index	2	20.0	6	60.0	2	20.0
Verbal delayed index	2	20.0	5	50.0	3	30.0
Visual immediate index	3	23.1	9	69.2	1	7.7
Visual delayed index	2	18.2	6	54.5	3	27.3
Delayed recognition index	2	18.2	7	63.6	2	18.2
Learning index	2	20.0	6	60.0	2	20.0
Psychological functioning						
Internalizing problems	0	0.0	9	90.0	1	10.0
Externalizing problems	0	0.0	10	100.0	0	0.0

Abbreviations: FSIQ, Full Scale Intelligence Quotient; MDI, Mental Development Index; PPVT, Peabody Picture Vocabulary Test; VMI, visual-motor integration.
[a]Total n varies by measure.

Table 4. Correlations Between Age at Diagnosis, Time Since Diagnosis, and Neuropsychological and Psychological Outcomes at Long-Term Follow-Up

Domain	Age at Diagnosis		Time since Diagnosis	
	r	*P*	*r*	*P*
Intelligence				
FSIQ/MDI	−0.18	.53	0.04	.88
Verbal IQ	0.20	.66	0.20	.48
Performance IQ	−0.51	.25	−0.07	.80
Academic achievement				
Reading	−0.09	.76	−0.15	.60
Spelling	−0.07	.82	−0.25	.39
Math	0.17	.57	−0.22	.45
Receptive language				
PPVT	−0.19	.68	0.15	.75
Visual-motor integration				
VMI	−0.28	.36	0.01	.97
Learning and memory				
General memory index	0.09	.79	−0.24	.48
Verbal immediate index	0.04	.91	−0.13	.71
Verbal delayed index	−0.06	.87	−0.27	.46
Visual immediate index	−0.04	.89	−0.14	.65
Visual delayed index	−0.30	.38	−0.14	.68
Delayed recognition index	−0.06	.87	0.07	.83
Learning index	0.23	.52	−0.26	.46
Psychological functioning				
Internalizing problems	0.55	.10	0.13	.72
Externalizing problems	−0.26	.47	−0.55	.10

Abbreviations: FSIQ, Full Scale Intelligence Quotient; MDI, Mental Development Index; PPVT, Peabody Picture Vocabulary Test; VMI, visual-motor integration

within normal limits. However, the sample sizes for these comparisons were small due to limited measures being administered at STF given the predominantly young age at diagnosis, psychologist time/availability, and patient availability. Examination of effect sizes indicates that the findings (besides internalizing behaviors) were in the very small to small range in magnitude. Therefore, as the study was not sufficiently powered to detect a small effect, it is possible that true effects were not detected (type II error). As such, these null findings should be interpreted with some caution, and it is possible that the HS II survivors experienced slight declines in aspects of neurocognitive functioning that were not detected given the small sample size. For example, the approximately 7-point decline in receptive language may have been statistically significant in a larger sample.

Nevertheless, it is important to keep in mind the larger clinical significance of the findings. Consistent with our hypothesis, at both STF and LTF, the HS II survivors were generally functioning within the average to low average ranges across all neurocognitive and psychological domains assessed, with individual variability in the scores. While mathematics and receptive language were within the low average range, these domains were also in the low average range at STF. Furthermore, approximately two-thirds of the HS II survivors were performing within or above normal limits on most neurocognitive and academic domains at LTF. Although this is lower than expected

Table 5. Comparison of High-Dose Methotrexate and No High-Dose Methotrexate Group Means for Neuropsychological and Psychological Outcomes

	No High-Dose MTX			High-Dose MTX				
Domain	n	Mean (SD)	Range	n	Mean (SD)	Range	*P*	*d*
Intelligence[a]								
FSIQ/MDI Most Recent	9	93.56 (23.60)	Average	6	90.90 (17.64)	Average	.72	0.12
Verbal IQ	8	93.00 (22.95)	Average	7	93.57 (22.95)	Average	.96	0.03
Performance IQ	8	96.88 (24.30)	Average	7	89.00 (17.73)	Low Average	.49	0.38
Academic achievement[a]								
Reading	9	101.44 (20.19)	Average	6	88.67 (16.78)	Low Average	.69	0.69*
Math	8	86.13 (12.71)	Low Average	6	90.67 (19.70)	Average	.10	0.27
Spelling	8	96.63 (19.45)	Average	6	95.67 (15.29)	Average	.48	0.05
Learning and memory[a]								
General memory index	6	107.33 (19.05)	Average	5	88.00 (26.76)	Low Average	.28	0.83**
Visual immediate index	8	100.00 (10.76)	Average	5	92.20 (24.46)	Average	.03+	0.41
Visual delayed index	7	110.29 (4.19)	High Average	4	89.00 (26.52)	Low Average	.001+	1.12**
Verbal immediate index	6	105.17 (15.36)	Average	4	90.50 (22.72)	Average	.22	0.76*
Verbal delayed index	6	110.67 (21.52)	High Average	4	90.00 (12.65)	Average	.31	1.17**
Learning index	6	101.00 (9.98)	Average	4	89.25 (28.27)	Low Average	.04+	0.55*
Delayed recognition index	6	100.83 (14.39)	Average	5	91.40 (24.68)	Average	.45	0.47
Receptive language[a]								
PPVT	5	90.40 (7.20)	Average	2	74.50 (28.99)	Borderline	.00+	0.75*
Visual-motor integration[a]								
VMI	7	97.71 (19.49)	Average	6	93.83 (18.52)	Average	.78	0.20
Psychological functioning[b]								
Internalizing problems	5	51.60 (6.07)	Average	5	55.00 (17.26)	Average	.21	0.26
Externalizing problems	5	51.40 (6.03)	Average	5	50.40 (6.84)	Average	.59	0.16

Abbreviations: FSIQ, Full Scale Intelligence Quotient; MDI, Mental Development Index; MTX = methotrexate; PPVT, Peabody Picture Vocabulary Test; VMI, visual-motor integration.
[a]Scores are standard scores (mean = 100; SD = 15). [b]Scores are *T* scores (mean = 50; SD = 10).
+ Represents $P < .05$.
* Represents a medium effect size (0.5).
** Represents a large effect size (>0.8).

based on the normal distribution curve, it is higher than typical neuropsychological outcomes for young children treated for brain tumors, wherein pronounced deficits are commonly seen.[5,37] These findings support that while HS II survivors' neurocognitive functioning may not be completely spared, they experience fewer and more subtle cognitive difficulties than expected. Exceptions are for visual-spatial reasoning (performance IQ) and mathematics, in which approximately half of the current sample performed below normal limits. Both visual-spatial skills and mathematics are areas known to be negatively impacted by cancer and its associated treatments due to their reliance on the widespread integrity of white-matter networks, as well as the impact of school absences on cumulative skill acquisition for the latter.[5,41,42] Of note, there was no significant decline in these abilities over time but rather they remained areas of relative weakness across time points.

Additionally, the parents of all the HS II survivors reported their child's psychological functioning to be within or above normal limits at LTF. Although there was an increase in internalizing behaviors over time, the overall mean was still well within normal limits. Nevertheless, it is important to continue to monitor the survivors' emotional functioning across development, especially as they enter adolescence. Adolescence is a developmental phase characterized by physical, cognitive, and psychosocial transitions as well as increased expectations on independence, and is a time period associated with increased rates of internalizing symptoms for survivors of childhood cancer.[7,43]

In prior research of survivors of childhood cancer, age at diagnosis and time since diagnosis typically emerge as strong predictor variables of neurocognitive and academic outcomes.[35,44] In contrast, there was no significant relationship between age at diagnosis and time since diagnosis with the outcome variables in this sample, which was consistent with findings from a subsequent Head Start III study.[39] The lack of an association in this sample suggests the potential benefit of avoiding or delaying use of radiotherapy in very

young children. However, given the small size and the constricted age range of our sample, further research is clearly warranted.

Although overall neurocognitive functioning appears relatively intact from a group perspective, it is important to note that survivors who received HD-MTX displayed lower reading, learning/memory, and receptive language skills at LTF. However, this treatment was not randomized and was given only for those diagnosed with either disseminated disease or an AT/RT tumor, representing more difficult to treat disease. As a result, it is not clear the extent to which the lower cognitive functioning at LTF is due to the CNS disease or the additional treatment with HD-MTX. That said, pediatric leukemia studies have reported neuropsychological deficits following chemotherapy-only treatment regimens including high-dose intrathecal methotrexate.[45] Furthermore, in children with medulloblastoma, treatment with HD-MTX is associated with worse cognitive functioning.[46–48]

This study has several strengths, including that participants underwent baseline assessment and had at least 2 longitudinal assessments. However, there are important limitations to acknowledge. As is quite common in studies of survivors of pediatric brain tumors, the sample size of the study can be small. Additionally, given the young age at diagnosis, numerous domains could not be assessed at baseline and STF, which further limits the sample size of longitudinal comparisons, and different measures were given depending on age at time points (ie, BSID, WPPSI, or WISC). Due to limited patient and psychologist availability, allowance was made for administering follow-up tests at any feasible time point to maximize the number of evaluations rendering it not possible to compare intraindividual performances across all domains. Overall, given the small sample size for most longitudinal comparisons, the lack of statistically significant findings should be interpreted with some caution, as it is possible that differences would emerge with larger sample sizes that may have more statistical power. However, for change in overall intelligence from baseline and STF to LTF, the effect sizes were very small in magnitude, there was no significant change on reliable change indexes, and the findings were consistent with both our a priori hypotheses and the existing literature, thereby lending more confidence to the null effect.

Another limitation was the administration of the baseline assessment after surgery and induction chemotherapy. Although this approach has been used in previous research, establishing a baseline after diagnosis, surgery, and induction chemotherapy may lead to inaccurate conclusions about the long-term effects of the subsequent treatment, due to internal or environmental factors that may affect test performance.[49] However, given the logistical complications of testing before initiation of any treatment on consortium studies and the importance of obtaining a baseline from which to compare potential change over time, this was the most feasible option. That said, future studies should aim to collect baseline testing prior to initiation of treatment,[50] in addition to collecting medical variables such as tumor subtype (ie, medulloblastoma vs other tumors), as well as the incidence of posterior fossa syndrome and hearing loss, both of which are risk factors for poorer neurocognitive and academic outcomes.[15,51] Further, 6 survivors did ultimately receive radiation therapy; their functioning at LTF was highly variable and was unable to be analyzed at the group level due to small sample size. With a larger sample, the impact of radiation therapy and other treatment variables (ie, dose, volume, and type of radiotherapy) can be better elucidated. However, it is salient to note that two-thirds of this sample did not receive radiation therapy, which has typically been a mainstay of brain tumor treatment. Lastly, information regarding race/ethnicity and proxies for socioeconomic status (ie, parental education level, insurance status) was not collected, which are emerging as important risk factors for neurocognitive late effects.[52]

In conclusion, for young survivors of pediatric brain tumors treated on the HS II protocol, intellectual functioning remained generally stable at LTF and within the average range. Furthermore, the HS II survivors experienced fewer and more subtle neurocognitive, academic, and psychological late effects with sparing or delaying use of radiotherapy. Although the group as a whole appears to be fairly resilient over time, it is important to acknowledge that approximately 20%-33% of children were functioning below normal limits across most neurocognitive domains, with the greatest percentage (40-50) for visual-spatial functioning and mathematics. Furthermore, children with more extensive and/or resistant disease who received HD-MTX were at higher risk for poorer neurocognitive functioning at LTF. These findings highlight the importance of collecting prospective, serial outcome data to monitor the trajectory of survivors' neurocognitive and psychological functioning over development, as well as the need for future research with larger samples to better understand risk factors for poorer LTF outcomes. Ultimately, this study expands survivorship knowledge of a novel pediatric brain tumor treatment that was designed to minimize neurotoxicity and provides important clinical information for future researchers, clinicians, patients, and families.

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