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Neuropsychological outcomes on Head Start III: a prospective, multi-institutional clinical trial for young children diagnosed with malignant brain tumors

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Abstract

Background. Current pediatric brain tumor treatment focuses on titrating toxicity based on risk factors while simultaneously improving survivorship. The Head Start (HS) protocols I to IV (1991-present) use high-dose chemotherapy (HDCTx) with an aim of reducing or eliminating cranial irradiation in very young children, the most vulnerable to its effects.

Methods. We examined estimated Full Scale IQ, overall Adaptive Functioning, Working Memory, Processing Speed, and Verbal and Nonverbal Memory outcome data for 43 HS III patients diagnosed between ages 2 months and 7 years from 15 institutions in the United States and Canada.

Results. At a mean of 5.12 years postdiagnosis, the HS III patients performed within the average to low-average ranges across these variables; however, individual variability was noted with scores ranging from superior to impaired, and the sample as a whole performed lower than age expectations. Performance did not significantly differ by sex or ethnicity, diagnosis, or for those treated with an intravenous methotrexate dose of 400 mg/kg vs 270 mg/kg. Additionally, performance did not significantly differ by age at diagnosis or length of follow-up.

Conclusions. The results, indicating overall average to low-average neurocognitive functioning, are encouraging, though significant individual variability was noted. Those who were younger at diagnosis, received more intensive methotrexate, and were further out from treatment were not at significantly increased risk of cognitive decline within our sample, suggesting a strategy of using HDCTx and autologous hematopoietic progenitor cell rescue to reduce or eliminate irradiation may allow for continued CNS development in young children treated for a brain tumor.

Keywords

cognition | late effects | neurocognitive | pediatric brain tumors | survivorship

Brain and CNS tumors are the most common cause of cancer death in infants and children ages 0 to 14 years in the United States.[1] Improved characterization of tumor histology and molecular genetic features as well as advances in treatment approaches have resulted in overall survival rates for this age group increasing from approximately 57.2% in 1977 to 75.8% in 2015,[2] prompting heightened awareness of the importance of examining the long-term impact of various treatment modalities. Current strategies involve multimodal therapy, typically including surgical resection, chemotherapy with or without stem-cell rescue, and radiation therapy (RT). RT in particular has contributed greatly to improved survival rates in certain types of intracranial tumors over the past decades; however, consequent adverse neurological side effects, including changes in brain structure[3] and vasculature[4] have been documented in the literature, with greatest risk associated with younger age at treatment.[5,6] In addition to potential cortical and hippocampal gray-matter alterations,[7] studies have reported RT may lead to reductions in white-matter integrity and volume and to disruptions in circuitry,[8,9] with normal-appearing white-matter development over time particularly vulnerable in children who received RT at age 6 years in comparison to healthy controls and to patients who received RT at age 12 years.[9] Decreases in white-matter volume or development following RT may be primarily responsible for the declines seen in at least some neurocognitive functions.[5] Although several factors have been implicated in white-matter volume and integrity and subsequent neurocognitive sequelae, including hydrocephalus and chemotherapeutic agents, RT may pose the greatest risk for intellectual and learning declines. For this reason, several clinical trials have explored ways to reduce or eliminate cranial irradiation to minimize neurotoxicity during early childhood, a period of rapid myelination and brain development.

The premise of the Head Start (HS) I and II treatment protocols (1991-1997 and 1997-2003, respectively) was to use highly intensive chemotherapy over a relatively short time period following diagnosis to either avoid or reduce the dose of cranial irradiation using age- and response-based criteria for infants and young children with malignant brain tumors. Prior published results of neuropsychological outcomes from the HS II protocol have been promising, with stable overall intellectual functioning at a 7-year follow-up, as well as preserved memory, visual-motor skills, and academic achievement; however, additional prospective studies were deemed necessary to further explore treatment-related factors and the impact on specific domains of neuropsychological functioning.[10] HS III, a prospective, nonrandomized, multi-institutional clinical trial, was open for enrollment between 2003 and 2009. In this report, we present the neuropsychological outcomes for patients on HS III.

Materials and Methods

Patients with histopathologically confirmed medulloblastoma, primitive neuroectodermal tumor, ependymoma, atypical teratoid/rhabdoid tumor, glioblastoma multiforme, or choroid plexus carcinoma who were younger than 10 years at the time of diagnosis were eligible for HS III, which was open for enrollment between 2003 and 2009. A total of 220 patients were enrolled at 36 institutions in the United States, Canada, New Zealand, and Switzerland. Of these, 26 institutions had surviving participants (N = 107). Fifteen institutions (58%) provided the neurocognitive test data used in this study. The remaining institutions (42%) did not provide data per the protocol or reported the lack of a psychologist or funding as barriers to participation.

The treatment protocol consisted of surgical resection, 5 cycles of induction chemotherapy, and second-look surgery when indicated for residual tumor, followed by consolidation with myeloablative chemotherapy and autologous hematopoietic progenitor cell rescue. RT was given following recovery from consolidation based on patient age, disease extent at diagnosis, and treatment response to induction. All participants, except those with malignant gliomas, were treated with either regimen D or D2. Regimen D was suspended temporarily in January 2007 because of toxicities. The study reopened in October 2007 with regimen D2, with the following chemotherapy dose reductions for all patients: high-dose methotrexate in induction cycles 1, 3, and 5 was reduced from 400 mg/kg (regimen D) to 270 mg/kg (regimen D2), and cyclophosphamide in each induction cycle was reduced from 65 mg/kg (regimen D) to 55 mg/kg (regimen D2) per dose on each of 2 days.[11]

Forty-six patients underwent neuropsychological assessment during follow-up. Of these, 3 patients were treated on a separate regimen (C) for high-grade glioma, did not receive any high-dose methotrexate, and were too few in number to compare with the larger sample treated on regimen D or D2. The remaining 43 patients comprised the final sample (Tables 1 and 2). Table 3 provides the age at initiation of RT and the volume and dose for the 12 (27.9%) patients who received RT.

These 43 patients had neuropsychological evaluations performed at least 9 months postdiagnosis (range, 9 months-10.75 years; mean, 61.40 months/5.11 years) and were evaluated at one of the following institutions: Children's Hospital Los Angeles (N = 13), New York University Medical Center (N = 7), New York-Presbyterian Hospital (N = 5), Riley Hospital for Children (N = 3), DeVos Children's Hospital (N = 3), UCSF Benioff Children's Hospital (N = 3), British Columbia Children's Hospital, (N = 2), Penn State Children's Hospital (N = 2), Miller Children's & Women's Hospital (N = 2), Phoenix Children's Hospital, (N = 1), Columbus Children's Hospital (N = 1), and Rainbow Babies & Children's Hospital (N = 1).

Neuropsychological evaluations were conducted in outpatient settings by licensed psychologists or doctoral trainees under their supervision using well-validated psychometric measures.

Measures

From a comprehensive research battery assessing multiple cognitive domains, we selected 7 psychometric outcome variables for the primary analyses: estimated intelligence (Full-Scale Intelligence Quotient [FSIQ-4]), working memory (Digit Span [DS]), processing speed (Processing Speed Index [PSI]), overall adaptive functioning (Adaptive Behavior Assessment System–Second Edition [ABAS-2] General Ability Composite [GAC]), verbal memory (Children's Memory Scale [CMS] Stories and California Verbal Learning Test–Children's Version

Table 1 Sample Characteristics for Categorical Variables

Variable	No.	Percentage
Sex		
Male	23	53.5%
Female	20	46.5%
Ethnicity		
Non-Hispanic Caucasian	26	60.5%
Hispanic	14	32.6%
African American	1	2.3%
Other	2	4.7%
Collapsed (binary) ethnicity		
Non-Hispanic Caucasian	26	60.5%
Other	17	9.5%
Diagnoses		
Medulloblastoma	24	55.8%
PNET	12	27.9%
Ependymoma	5	11.6%
CPC	2	4.7%
Collapsed (binary) diagnoses		
Medulloblastoma	24	55.8%
Other	19	44.2%
Regimen		
D	23	53.5%
D2	20	46.5%
Tumor location		
Infratentorial	30	69.8%
Supratentorial	13	30.2%
RT		
Yes	12	27.9%
No	31	72.2%

Abbreviations: CPC, choroid plexus carcinoma; PNET, primitive neuroectodermal tumor; RT, radiation therapy.
Ethnicity and Diagnoses were collapsed into binary options for certain analyses (as described in the Methods and Results sections).

[CVLT-C]), and nonverbal memory (CMS Dot Locations). FSIQ-4 was obtained using 4 primary subtests from the age-appropriate Wechsler scale[12]: Vocabulary, Similarities, Block Design, and Matrix Reasoning. The ABAS-2[13] provided parent report of overall adaptive functioning/daily living skills. Processing speed was obtained from the Coding and Symbol Search (PSI) subtests and working memory from the Digit Span subtest of the age-appropriate Wechsler scale.[14] Memory was obtained from the CVLT-C[15] and the Stories and Dot Locations subtests of the CMS.[16]

Statistical Analyses

Analyses were conducted using IBM SPSS Statistics, version 25.0.[17] An alpha level of 0.05 was used to indicate statistical significance for all preliminary analyses and hypotheses. Corrected probability cutoffs and false discovery rates were applied to multiple comparisons. Demographic (ie, sex and ethnicity), diagnostic (ie, tumor type/location and age at and time since diagnosis), and treatment-related factors (ie, treatment regimen, RT use) for the sample were analyzed using means ($\bar{x}$), SD, and minimum to maximum values for continuous variables (Table 2), as well as frequencies and proportions for categorical variables (Table 1). These factors were compared between the 2 treatment groups (D vs D2) using either independent samples t tests for continuous variables or chi-square calculations for categorical variables to determine potential group differences in baseline characteristics, with the intention of identifying covariates to include in hypothesis testing. Chi-square analyses were also conducted to identify differences in diagnostic and treatment factors based on sex and ethnicity.

Because there were few patients who identified as either African American or "Other" (n = 3), an additional binary ethnicity variable was also computed (ie, Caucasian, n = 26, vs non-Caucasian, n = 17) to more broadly assess potential differences based on majority/minority ethnicity. Similarly, diagnosis levels were also collapsed so the variables could be treated as binary for certain analyses because of small sample size (see Table 1 for binary levels).

Because the timing and frequency of neuropsychological evaluations varied across patients, only the most recent evaluations were examined to increase the likelihood of capturing potential late effects. Standardized scores were reported based on normative data calculation for each measure using measure-specific scales: either standard scores (SS mean = 100; SD = 15), scaled scores (ss mean = 10; SD = 3), or z scores (mean = 0.0; SD = 1.0). Univariate descriptive analyses were conducted for the 7 primary outcome variables (FSIQ-4, PSI, ABAS, DS, CMS: Stories, CMS: Dot Locations, and CVLT-C), including $\bar{x}$, SD, and range based on regimen and binary diagnosis (Table 4). One-sample t tests were used to analyze whether outcome variables differed significantly from age expectations, with one-sample Wilcoxon signed rank test used as a nonparametric alternative in the case of violated normality assumptions. Given variability related to which sites administered certain measures (ultimately creating variability among patients), none of the measures were administered to the entire sample (sample sizes for each measure ranged from 25 to 31, and only 4 patients received all measures). Therefore, multivariable analyses of variance were not feasible and individual analyses of variance (ANOVAs) were used instead. Welch's ANOVA was computed in the case of violated homogeneity of variance assumption. Group comparisons were not made in the case of multiple violated assumptions. Outliers calculated using a 2.2 multiplier were removed for associated analyses. Multiple regression and analyses of covariance were used to test for outcome variables and potential interaction effects by age at diagnosis and length of follow-up.

Results

As a group, HS III patients performed within the average to low-average range across all 7 variables; however, individual scores varied between the superior to severely

Table 2 Sample Characteristics for Continuous Variables: Total, by Regimen, and by Diagnosis

Group	Minimum	Maximum	Mean	SD
Age at diagnosis, y				
Total sample	0.17	7.08	2.85	1.97
By regimen				
Regimen D	0.50	7.08	3.21	2.06
Regimen D2	0.17	6.00	2.43	1.84
By diagnosis				
Medulloblastoma	0.17	5.92	2.35	1.48
PNET	0.33	7.00	3.74	2.30
Ependymoma	1.25	7.08	3.72	2.75
CPC	1.17	1.25	1.21	0.06
Time since diagnosis at neuropsychological assessment, y				
Total sample	0.75	10.75	5.12	2.60
By regimen				
Regimen D	0.75	9.83	5.36	2.92
Regimen D2	0.75	10.75	4.84	2.22
By diagnosis				
Medulloblastoma	0.92	10.75	4.93	2.29
PNET	0.75	9.33	5.21	3.45
Ependymoma	0.75	7.58	5.35	2.69
CPC	5.92	6.42	6.17	0.35
Age at evaluation, y				
Total sample	2.50	15.00	7.96	3.21
By regimen				
Regimen D	2.50	15.00	8.56	3.59
Regimen D2	3.33	14.50	7.27	2.62
By diagnosis				
Medulloblastoma	2.50	14.50	7.29	3.05
PNET	2.75	15.00	8.94	4.02
Ependymoma	7.75	11.67	9.07	1.59
CPC	7.08	7.67	7.38	0.41

Abbreviations: CPC, choroid plexus carcinoma; PNET, primitive neuroectodermal tumor.

impaired ranges. One-sample t tests indicate a significant downward trend for the whole sample in terms of intellectual functioning (FSIQ-4 $t(30) = -2.65$, $P = .007$), processing speed (PSI $t(26) = -2.96$, $P = .003$), and adaptive functioning (ABAS $t(24) = -5.24$, $P = .00001$, $P < .001$). Although a downward trend was also noted for working memory (DS one-sample Wilcoxon signed rank test, $P = .044$), this trend was not significant once corrected probability cutoffs were applied. No significant differences between the sample and normative expectations were noted for memory (CVLT-C one-sample Wilcoxon signed rank test, $P = .64$; CMS Stories $t(23) = -0.35$, $P = .73$; CMS Dot Locations $t(21) = 1.04$, $P = .31$). Table 4 presents results for the overall sample as well as results by regimen and binary diagnosis.

Performance by Treatment Regimen, Diagnosis, and Irradiation

Psychometric test scores (where available) did not significantly differ between treatment regimen (D vs D2), between diagnoses (Table 5) (medulloblastoma vs primitive neuroectodermal tumor, ependymoma, choroid plexus carcinoma), or between those who received irradiation and those who did not (Table 5). Welch's ANOVA was used for comparison of PSI between diagnosis groups and for CVLT-C between regimen groups given violation of homogeneity of variance assumption. Group comparisons were not available for analyses with multiple violations of assumptions. All other analyses were conducted using classic ANOVA. Given significant overlap between diagnosis and

Table 3 Radiation Therapy (RT)

Variable	No.	Percentage
Received RT		
Yes	12	27.9%
No	31	72.2%
Local field	4	33.3%
CSI + boost	8	66.6%
Age at initiation of RT	RT volume/dose in cGy	
1 y, 10 mo	LF: 5940	
3 y, 5 mo	LF: 5940	
5 y, 6 mo	LF: 5400	
6 y, 10 mo	LF: 5940	
3 y, 8 mo	CSI: 2340/TD: 5400	
4 y, 4 mo	CSI: 2340/TD: 5400	
4 y, 9 mo	CSI: 2700/TD: 5400	
6 y, 8 mo	CSI: 1800/TD: 5400	
7 y, 3 mo	CSI: 1800/TD: 5580	
7 y, 8 mo	CSI: 3960/TD: 5580	
7 y, 9 mo	CSI: 2340/TD: 5400	
8 y, 4 mo	CSI: 3600/TD: 5940	

Abbreviations: CSI, craniospinal; LF, local field; TD, total dose.

tumor location (supratentorial vs infratentorial; χ^2 (3) = 27.04, P = .000), additional analyses based on tumor location were thought to be repetitive and were therefore not completed.

Performance by Sex and Ethnicity

ANOVAs and chi-square analyses revealed no significant differences in neuropsychological test performance based on sex or ethnicity.

Performance by Age at Diagnosis and Length of Follow-up

No significant differences in neuropsychological test performance were indicated based on age at diagnosis or time since diagnosis for the sample as a whole or when incorporating diagnosis as a potential covariate.

Discussion

Our overall results, indicating average to low-average neurocognitive functioning for the group as a whole suggest a treatment strategy of using high-dose chemotherapy followed by autologous hematopoietic progenitor cell rescue with an intention of either eliminating or reducing the dose of RT, may allow for continued CNS development in young children, the most vulnerable to the effects of cranial irradiation.

The 43 patients in our analysis were diagnosed at a mean age of 34.14 months (range, 2 months-7.08 years). Within this early age range, our findings did not indicate that age at diagnosis was a factor in the overall neurocognitive outcomes with this treatment strategy, in contrast to prior research,[5,6,18] suggesting the potential benefit of avoiding irradiation or reducing dose of cranial irradiation in very young children. In contrast to prior research findings,[19] we also found no significant differences based on length of time since diagnosis, suggesting neurocognitive functioning for these patients might be relatively stable over time, although given limitations within our sample, further research is warranted.

All participants in this study received intravenous methotrexate as an integral component of their medical treatment. Pediatric leukemia studies have reported neuropsychological deficits, primarily in IQ, information processing speed, working memory, and fine motor functioning following chemotherapy-only treatment regimens including intrathecal methotrexate.[20] Although our sample size was too small to explore potential differences between those who did or did not receive irradiation in combination with either regimen D or D2, we were able to examine general outcomes for cumulative methotrexate dose received between regimen D vs D2. We hypothesized that regimen D would affect cognition more than regimen D2; however, no differences were indicated, which is noteworthy although possibly due to the sample size being insufficient to determine subtle effects.

Comparison of HS III neurocognitive outcomes with those from other irradiation-sparing pediatric brain tumor protocols is difficult, given different neurocognitive tests also used at different time points, as well as different treatment protocols (eg, variation in chemotherapies such as the use of intraventricular methotrexate). However, European[21,22] and North American[23] studies both have reported similar outcomes, with average to low-average performance on psychometric measures for children treated with irradiation-sparing strategies. Nevertheless, as with HS III, these studies are limited by small sample size and individual variability in psychometric test performance, making conclusions based on mean performance limited. For example, Grill et al (2005) reported IQ findings at the low end of the average range at a mean of 23 months postdiagnosis for children diagnosed at younger than 5 years with medulloblastoma and treated with chemotherapy alone (which did not include methotrexate) compared with IQ in the well below-average range at a mean of 62 months postdiagnosis for children who received irradiation after relapse.[21] Additionally, Rutkowski and colleagues (2005) indicated overall patient IQ within the low-average range on a comprehensive measure and in the average range on a single fluid reasoning task, with outcomes on both measures lower for patients than for controls, in 14 medulloblastoma patients 4.8 years postdiagnosis.[22] Rutkowski et al further reported a nonsignificant trend toward higher scores for children who received only systemic chemotherapy in comparison to those treated both with systemic and intraventricular chemotherapy.[22] In a North American study, Fay-McClymont and colleagues (2017) reported neurocognitive outcomes at a mean of

Table 4 Outcome Variables: by Regimen, Binary Diagnosis, and Radiation Therapy (RT) Exposure

Outcome Variable by Group	Minimum	Maximum	Mean	SD
FSIQ-4 (n = 31) (SS)	67	127	94.10[a]	12.39
By regimen				
Regimen D (n = 18)	74	111	95.17	10.73
Regimen D2 (n = 13)	67	127	92.62	14.72
By binary diagnosis				
Medulloblastoma (n = 15)	77	127	95.40	12.97
Other (n = 16)	67	111	92.88	12.11
By RT exposure				
Yes (n = 10)	74	111	94.00	12.55
No (n = 21)	67	127	94.14	12.62
PSI (n = 27) (SS)	65	126	91.26[a]	15.33
By regimen				
Regimen D (n = 14)	65	118	92.86	16.62
Regimen D2 (n = 13)	70	126	89.54	14.27
By binary diagnosis				
Medulloblastoma (n = 16)	70	110	89.19	9.61
Other (n = 11)	65	126	94.27	21.35
By RT exposure				
Yes (n = 7)	68	109	88.71	12.66
No (n = 20)	65	126	92.15	16.36
ABAS: GAC (n = 25) (SS)	67	111	87.28[a]	12.13
By regimen				
Regimen D (n = 13)	67	111	91.31	12.26
Regimen D2 (n = 12)	68	98	82.92	10.825
By binary diagnosis				
Medulloblastoma (n = 14)	67	111	85.93	13.27
Other (n = 11)	69	111	89.00	10.89
By RT exposure				
Yes (n = 9)	80	111	89.56	9.54
No (n = 16)	67	111	86.00	13.50
DS (n = 22) (ss)	5	15	8.86	2.92
By regimen				
Regimen D (n = 11)	5	13	8.45	2.91
Regimen D2 (n = 11)	5	15	9.27	3.01
By binary diagnosis				
Medulloblastoma (n = 13)	5	15	8.92	2.72
Other (n = 9)	5	13	8.78	3.35
By RT exposure				
Yes (n = 7)	6	13	8.71	2.75
No (n = 15)	5	15	8.93	3.08
CMS: stories (n = 24) (ss)	4	16	9.79	2.90
By regimen				
Regimen D (n = 15)	4	16	9.13	3.04
Regimen D2 (n = 9)	6	14	10.89	2.42
By binary diagnosis				
Medulloblastoma (n = 14)	5	16	10.21	3.26
Other (n = 10)	4	13	9.20	2.35

Table 4 Continued

By RT exposure				
Yes (n = 9)	4	14	9.00	2.83
No (n = 15)	5	16	10.27	2.94
CMS: dot locations (n = 22) (ss)	5	15	10.59	2.67
By regimen				
Regimen D (n = 13)	5	15	10.23	2.71
Regimen D2 (n = 9)	5	14	11.11	2.67
By binary diagnosis				
Medulloblastoma (n = 15)	5	15	10.40	3.09
Other (n = 7)	10	14	11.00	1.53
By RT exposure				
Yes (n = 8)	9	14	10.75	1.58
No (n = 14)	5	15	10.50	3.18
CVLT-C (n = 28) (z score)	–3.5	1.5	–0.16	1.36
By regimen				
Regimen D (n = 17)	–3.5	1.5	–0.44	1.56
Regimen D2 (n = 11)	–1.5	1.5	0.27	0.88
By binary diagnosis				
Medulloblastoma (n = 14)	–2.5	1.0	–0.36	1.18
Other (n = 14)	–3.5	1.5	0.04	1.54
By RT exposure				
Yes (n = 10)	–3.5	1.0	–0.55	1.50
No (n = 18)	–2.5	1.5	1.27	

Abbreviations: ABAS, Adaptive Behavior Assessment System; CMS, Children's Memory Scale; CVLT-C, California Verbal Learning Test–Children's Version; DS, Wechsler Digit Span; FSIQ-4, Full-Scale IQ–Four Subscale; GAC, General Ability Composite; PSI, Processing Speed Index; SS, standard score (mean = 100; SD = 15); ss, scaled score (mean = 10; SD = 3); z score (mean = 0.0; SD = 1.0).
[a]Significant difference of the entire sample from expected mean ($P < .05$).

Table 5 Analyses of Variance for Regimen, Binary Diagnosis, and Radiation Therapy (RT) Exposure

Variable	Regimen (D/D2)	Diagnosis[a]	RT Exposure (Y/N)
FSIQ-4	F = 0.313, $P = .58$	F = 0.314, $P = .58$	F = 0.001, $P = .98$
PSI	F = 0.308, $P = .58$	Welch = 0.548, $P = .47$	F = 0.253, $P = .62$
ABAS: GAC	F = 3.266, $P = .08$	F = 0.385, $P = .54$	F = 0.484, $P = .49$
DS	F = 0.421, $P = .52$	[c]	F = 0.026, $P = .87$
CMS stories	F = 4.602, $P = .04$[b]	F = 0.702, $P = .41$	F = 1.074, $P = .31$
CMS: dot locations	F = 0.568, $P = .46$	[c]	F = 0.043, $P = .84$
CVLT-C	Welch = 2.393, $P = .13$	[c]	[c]

Abbreviations: ABAS, Adaptive Behavior Assessment System; CMS, Children's Memory Scale; CVLT-C, California Verbal Learning Test–Children's Version; DS, Wechsler Digit Span; FSIQ-4, Full-Scale IQ–Four Subscale; GAC, General Ability Composite; N, no; PSI, Processing Speed Index; Y, yes.
[a]Binary diagnosis: medulloblastoma vs primitive neuroectodermal tumor, ependymoma, choroid plexus carcinoma.
[b]Outlier removed from D group.
[c]Not interpretable because of multiple violations of assumptions.
No significant group differences ($P < .05$) using corrected probability cutoffs for multiple comparisons.

3.5 years postdiagnosis for 24 medulloblastoma patients diagnosed at younger than age 6 years treated with a high-dose chemotherapy strategy as per Children's Cancer Group 99703.[23] IQ and working memory were reported as within the average range for the group, with processing speed within the low-average range.[23] The recent development of brief paper-and-pencil and computerized test batteries and parent questionnaires available in multiple languages provides an opportunity to use serial assessments on various pediatric brain tumor studies both nationally and internationally, thereby increasing the potential to clearly identify effective medical strategies as well as the quality of survivorship.[24,25]

A limitation of this study is the small sample size, which is unfortunately common in follow-up of single-treatment studies for pediatric brain tumor patients. Further research is needed to examine outcomes in specific neuropsychological domains (eg, attention) for chemotherapy agents vs irradiation. Our study was also limited by missing data from sites that did not collect follow-up data, as well as by participating sites performing evaluations at different time points. Because we have moved from focusing solely on survival to focusing on quality of survival, the importance of neuropsychological follow-up has been well established as a clinical standard of care. In reviewing pediatric hospitals, the US News and World Report includes neuropsychological evaluations in its ratings. These evaluations are critical to assess late effects, determine cognitive strengths and weaknesses, and assist in educational planning to help children reach their full potential. Neuropsychological follow-up is also critical in advancing brain tumor research, and formal guidelines have been published that establish the scientific and clinical need for serial assessments.[26] Furthermore, the Children's Oncology Group (COG) has made this a priority. The COG ALTE07C1 study has clearly demonstrated that neuropsychological evaluations can be performed efficiently and inexpensively given the highly successful participation in gathering these important data at 9-, 30-, and 60-months postdiagnosis from more than 900 pediatric oncology patients across more than 100 consortium sites in North America (COG communications). Neuropsychological functioning remains a key aspect of evaluating future treatment protocols, including molecular- and genetically targeted therapies, for pediatric brain tumors. As such, future outcome studies are encouraged to make this follow-up an essential priority.

In summary, our results suggest chemotherapeutic treatment strategies aimed at either avoiding or allowing reduced-dose irradiation may be helpful in reducing CNS damage and allow for continued neurocognitive development in young children. Additional follow-up is necessary to determine whether these positive neuropsychological outcomes persist over time.

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