

Cognitive Outcomes Following Contemporary Treatment Without Cranial Irradiation for Childhood Acute Lymphoblastic Leukemia

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Background Treatment of acute lymphoblastic leukemia (ALL) has included the use of prophylactic cranial irradiation in up to 20% of children with high-risk disease despite known cognitive risks of this treatment modality.

Methods Patients enrolled on the St Jude ALL Total Therapy Study XV, which omitted prophylactic cranial irradiation in all patients, were assessed 120 weeks after completion of consolidation therapy (n = 243) using a comprehensive cognitive battery. χ^2 analysis was used to compare the percentage of below-average performers among the entire ALL patient group to the expected rate based on the normative sample. Univariate logistic regression was used to estimate the effect of intensity of chemotherapy (treatment arm), age at diagnosis, and sex on the probability of below-average performance. All statistical tests were two-sided.

Results Overall, the ALL group had a statistically significantly higher risk for below-average performance on a measure of sustained attention (67.31% more than 1 SD below the normative mean for omission errors, $P < .001$) but not on measures of intellectual functioning, academic skills, or memory. Patients given higher intensity chemotherapy were at greater risk for below-average performance compared with those given lower intensity therapy on measures of processing speed (27.14% vs 6.25%, $P = .009$) and academic abilities (Math Reasoning: 18.60% vs 3.90%, $P = .008$; Word Reading: 20.00% vs 2.60%, $P = .007$; Spelling: 27.91% vs 3.90%, $P = .001$) and had higher parent-reported hyperactivity (23.00% vs 9.84%, $P = .018$) and learning problems (35.00% vs 16.39%, $P = .005$). Neither age at diagnosis nor sex was associated with risk for below-average cognitive performance.

Conclusions Omitting cranial irradiation may help preserve global cognitive abilities, but treatment with chemotherapy alone is not without risks. Caregiver education and development of interventions should address both early attention deficits and cognitive late effects.

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The prognosis for children diagnosed with acute lymphoblastic leukemia (ALL) has improved dramatically, with 5-year event-free survival rates as high as 79% to 82% among patients treated in the 1990s (1–3). Higher survival rates have resulted in heightened focus on improving quality of life of survivors by reducing treatment-related late effects, including cognitive deficits.

Historically, treatment of childhood ALL with cranial irradiation has been associated with substantial cognitive morbidity (4,5); however, these findings are based on doses generally exceeding those used in modern therapy. When directly compared, treatment with lower dose cranial irradiation (eg, ≤ 18 Grey [Gy]) used in contemporary clinical trials typically (6–9), but not always (10), results in worse cognitive outcomes than chemotherapy alone on measures of intellectual function as well as more specific cognitive abilities. There is also some evidence (11) to suggest that different chemotherapy regimens carry greater cognitive risk than others based on drugs used (eg, triple intrathecal methotrexate, hydrocortisone and cytarabine [ITMHA] vs intrathecal methotrexate alone;

dexamethasone vs prednisone) as well as drug dosage and mode of administration (eg, lower dose oral methotrexate vs high-dose intravenous methotrexate [HDMTX]). Partly because of inconsistent reports of cognitive difference between treatment with lower dose cranial irradiation and intensive chemotherapy, and partly because of concern about increased central nervous system relapse, most pediatric collaborative study groups continue to use prophylactic cranial irradiation in their clinical trials in up to 20% of ALL patients (12).

The St Jude Total Therapy XV study evaluated whether intensification of systemic drugs that affect control of ALL in the central nervous system, together with optimal intrathecal treatment, would allow for complete omission of prophylactic cranial irradiation without compromising overall survival. The clinical trial resulted in 5-year event-free survival of 85.6% and overall survival of 93.5% (13). With additional follow-up, the treatment results remain excellent with a 10-year overall survival rate of 91.0% for all patients, 96.1% for low-risk patients, and

86.0% for standard/high-risk patients. Cognitive outcomes have not been systematically investigated or reported.

Demographic and clinical factors are associated with cognitive late effects in childhood ALL. Intensive treatment has been the most reliable predictor of increased risk (6–9,14–16). Younger age at treatment has been associated with worse cognitive outcomes, most likely resulting from greater vulnerability of the developing brain to neurotoxic agents (6,16–18). However, it is unclear whether this relationship is specific to children receiving cranial irradiation or also holds true for those receiving chemotherapy alone (16). Sex may also be associated with cognitive changes following ALL therapy, with girls more likely to experience deleterious effects (19,20). The mechanism for sex-specific risk is not fully understood but may result from differences in cerebral myelination (21,22). Furthermore, the literature is divided as to whether increased risk in girls is limited to children receiving cranial irradiation (23,24), and sex differences may vary depending on cognitive ability assessed (25). Few studies have been able to examine these demographic and clinical risk factors in a large cohort of prospectively studied patients who received homogeneous treatment and had comprehensive cognitive evaluations.

The first objective of this study was to systematically evaluate cognitive outcomes in a radiation-naïve sample treated with contemporary risk-adapted therapy. The second objective was to investigate the predictive value of treatment intensity, age at treatment, and sex with respect to cognitive outcomes. Based on the existing literature, our primary hypothesis was that patients would perform well on global measures of cognitive ability, such as intellectual functioning; however, a subset of them would show evidence of difficulties on measures of attention, particularly on performance-based measures of sustained attention including indices of processing efficiency, which may be more sensitive to central nervous system-directed therapy (14,18,25,26). Secondarily, we predicted that higher treatment intensity and younger age at diagnosis would be risk factors for cognitive problems, whereas female sex would not reliably predict risk when looking across a range of cognitive skills.

Patients and Methods

Patients

All participants were sequentially enrolled on an institutional treatment protocol for ALL, Total Therapy Study XV (ClinicalTrials.gov, NCT00137111), which includes serial cognitive assessment (13). Children were assigned to low-risk or combined standard/high-risk groups based on comprehensive biological and clinical risk classification, which included blast cell immunophenotype and genotype, presenting clinical features, and early treatment response (13). Beginning with remission induction, all patients received ITMHA as central nervous system-directed therapy (13 to 18 treatments in low-risk group and 16 to 25 treatments in standard/high-risk group). During consolidation therapy, HDMTX was given intravenously every other week for four cycles at 2.5 g/m² for low-risk patients and 5.0 g/m² for standard/high-risk patients. During continuation treatment, methotrexate was given intravenously weekly at 40 mg/m² together with daily mercaptopurine for 3 weeks, followed by pulse therapy with vincristine plus dexamethasone at 8 mg/m² per day for 5 days for low-risk patients

and at 12 mg/m² per day for 5 days for standard/high-risk patients at week 4. This treatment continued for 120 weeks for girls and 146 weeks for boys, interrupted by two reinduction treatments. At the time of cognitive testing, patients had received no ITMHA for approximately 72 weeks, no HDMTX for approximately 120 weeks, and no corticosteroids for approximately 20 weeks. No patients received prophylactic cranial irradiation.

Children aged 1 to 18 years were enrolled on the St Jude Total Therapy XV protocol between 2000 and 2007. They were excluded from current analysis if they were previously diagnosed with a developmental disorder with known cognitive sequelae (eg, Down syndrome, *n* = 10), did not speak English as a primary language (*n* = 16), or were missing psychological data (*n* = 43; included children with refractory or progressive disease, testing refusals, missed testing appointments, or scheduling problems). The study was approved by the Institutional Review Board at St Jude Children's Research Hospital. Written informed consent, with assent from the patient as appropriate, was obtained prior to participation.

Cognitive Assessment

Children were tested 120 weeks after completion of consolidation therapy (week 120) using measures standardized on large representative normative samples with demonstrated reliability and validity. All measures were individually administered by trained, master's level psychological examiners under the supervision of a licensed psychologist within the Psychology Clinic. Participants were administered an age-appropriate Wechsler Intelligence Scale [Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) for patients aged <6 years (27), the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) for patients aged 6–16 years (28), and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) for patients aged >16 years (29)]. All Wechsler Intelligence Scales yield an age-standardized Full Scale Intelligence Quotient. The majority of participants (59%) were administered the WISC-III, which allows for derivation of Freedom from Distractibility and Processing Speed indices to examine attention and processing speed, respectively. Academic skills were assessed for participants at least 6 years of age using the Wechsler Individual Achievement Test [WIAT, Word Reading, Spelling, and Math Reasoning (30)]. All Wechsler scores have a normative mean of 100 and SD of 15.

Participants at least 6 years of age also were administered the Conners' Continuous Performance Test (CPT), a computerized measure of sustained attention (31). The CPT provides scores for Omission errors (failing to respond to targets), Reaction Time (processing speed), Reaction Time Variability, *d'* (vigilance), and β (risk taking). All scores are age-standardized; for Omission errors, a percentile score is derived, and for the other indices, a *T* score is derived, with a normative mean of 50 and SD of 10. The Conners' Parent Rating Scale (CPRS) (32) was also administered as a real-world indicator of attention abilities. CPRS Learning, Impulsive-Hyperactive, and Hyperactive scales were of interest for this study. These scales are age- and sex-standardized.

To assess learning and memory, the age-appropriate California Verbal Learning Test [CVLT-Child, CVLT-C for participants 6–16 years of age (33) and CVLT-Adult, CVLT-A for participants \geq 17 years of age (34)] was administered. This verbal memory measure requires the child to recall a list of 15 (CVLT-C) or 16 (CVLT-A)

words after each of five exposure trials, after exposure to an interference list, and after short and long delays. Age-standardized scores are provided. The Total recall score is the number of words recalled across five trials and is converted to a T score with a normative mean of 50 and SD of 10. In addition to this global score, variables representing rate of new learning with additional list exposure (Learning Slope), words recalled following a short delay (Short Delay Free Recall), and words recalled following a long delay (Long Delay Free Recall) were also examined. These scores were converted to Z scores, with a normative mean of 0 and SD of 1.

In addition to testing completed at week 120, an Estimated Intelligence Quotient was derived for each participant at study baseline using an abbreviated administration of the Wechsler Intelligence Scale. This score is computed from the Information, Similarities, and Block Design subtests from the WPPSI-R, WISC-III, or WAIS-III using a formula provided by Sattler (35). For children younger than three-and-a-half years of age at study baseline, for whom there is not an age-appropriate Wechsler Intelligence Scale, the Bayley Scales of Infant Development, Second Edition [BSID-II (36)] was administered. The BSID-II yields a global Mental Development Index. Both the Estimated Intelligence Quotient and Mental Development Index have an age-standardized mean of 100 and SD of 15. These scores were provided to characterize the sample at baseline.

Statistical Analyses

Analyses of demographic and clinical variables were performed to characterize the group and compare participants with and without cognitive data to establish group representativeness. For each cognitive measure, the percentage of the sample performing below the average range was calculated. Below-average performance was operationalized as a score more than 1 SD discrepant from the normative sample. χ^2 analysis was used to compare these percentages with the expected 16%, based on the normative sample, to identify measures for which there is an excess of below-average performers.

To evaluate effects of treatment risk arm (low, standard/high), age at diagnosis (<5, ≥5 years), and sex, the mean of each cognitive measure for each subgroup was compared with the normative mean using a one-sample *t*-test. Further, cognitive scores among treatment risk arm, sex, and age at diagnosis subgroups were compared directly using Wilcoxon rank sum tests. Univariate logistic regression analyses were used to estimate the effect of risk arm, age at diagnosis, and sex on the probability of below-average performance. Finally, multivariable logistic regression models were used to investigate the independent effect of relevant clinical variables on probability of below-average performance, including cumulative dexamethasone dose (mg/m²), cumulative HDMTX dose (g/m²), cumulative ITMHA dose (mL; 1 mL consisted of 1 mg MTX, 2 mg hydrocortisone, and 3 mg cytarabine), age at diagnosis (<5, ≥5 years), and sex. The Hosmer–Lemeshow Goodness-of-Fit Test was used to test for goodness of fit for logistic regression models. Given the large range of cumulative chemotherapy exposures, odds ratios (OR) were based on doses grouped into therapeutically meaningful units (100 mg for dexamethasone, 50 mL for ITMHA, and 5 g for HDMTX); these units roughly correspond to 2 weeks of dexamethasone treatment, 4–5 ITMHA doses, and 1–2 doses of HDMTX, respectively. All independent variables were entered and retained in each multivariate model.

All tests of statistical significance were two-sided. All *P*-values were adjusted within each test battery using the Holm–Bonferroni step-down method to address risk for Type I error. Analyses were conducted using SAS version 9.2 (<http://www.sas.com>; SAS Institute, Cary, NC).

Results

Group Characteristics

The study cohort was on average 6 years of age at the time of diagnosis, largely white, and balanced by sex and treatment risk arm (Table 1). Of 408 patients enrolled on the treatment protocol at St Jude Children’s Research Hospital, 339 participated in at least one cognitive assessment and 243 participated in the week 120 assessment. There were no statistically significant differences among the 339 patients participating in cognitive assessments, the 243 patients with a week 120 cognitive assessment, or the 69 patients without any cognitive assessment on relevant demographic (eg, age, sex, ethnicity) or clinical (eg, treatment risk arm) factors, suggesting that cognitive outcomes were representative of the entire group. Sample size varied for analyses based on age range for cognitive measures, subgroups of interest, and missing data (see Supplementary Table 1, available online).

Cognitive Performance

The results of χ^2 analyses revealed that the entire ALL group did not differ statistically significantly from the normative sample with respect to percentage of below-average performers on

Table 1. Patient demographic and clinical characteristics*

Characteristics	N (%)	Mean (SD)	Range
Sex			
Boys	131 (53.91)		
Girls	112 (46.09)		
Ethnicity			
White	194 (79.84)		
African American	39 (16.05)		
Other	10 (4.12)		
Risk arm			
Low	126 (51.85)		
Standard/high	117 (48.15)		
Age at diagnosis, y	243	6.56 (4.39)	1.02–18.73
Baseline IQ (EIQ) †	117	101.42 (15.46)	64.00–142.00
Baseline Bayley MDI ‡	33	92.12 (14.85)	50.00–116.00
HDMTX dose, g/m ²			
Low-risk arm	126	11.68 (2.14)	3.56–18.04
Standard/high-risk arm	117	18.61 (3.64)	7.40–29.30
ITMHA dose, mL			
Low-risk arm	126	150.08 (69.75)	94.00–856.00
Standard/high-risk arm	117	204.59 (50.12)	80.00–375.00
Dex dose, mg/m ²			
Low-risk arm	126	1008.18 (177.96)	175.50–1302.59
Standard/high-risk arm	117	1212.61 (374.11)	60.34–1690.13

* HDMTX = high-dose methotrexate; ITMHA = intrathecal methotrexate, hydrocortisone and ara-C; Dex = dexamethasone.

† EIQ = estimated IQ based on the Block Design, Similarities and Information subtests from the age-appropriate Wechsler scale.

‡ MDI = Mental Development Index from the Bayley Scales of Infant Development, Second Edition, administered to children up to three-and-a-half years of age in absence of an age-appropriate Wechsler scale.

measures of intellectual functioning (Wechsler scales, Full Scale Intelligence Quotient, Standard Score [SS] = 95.95, % below average = 22.94, 95% confidence interval [CI] = 17.68 to 28.91, $P = .12$), academic skills (WIAT, Math Reasoning, SS = 100.26, % below average = 11.66, 95% CI = 7.17 to 17.60, $P = .80$; Word Reading, SS = 100.77, % below average = 11.73, 95% CI = 7.21 to 17.71, $P = .80$; Spelling, SS = 98.92, % below average = 16.56, 95% CI = 11.21 to 23.18, $P = 1.00$), or verbal memory (CVLT-Total [T] = 50.15, % below average = 15.19, 95% CI = 9.98 to 21.75, $P = 1.00$; Learning Slope, $Z = -.24$, % below average = 17.95, 95% CI = 12.27 to 24.89, $P = 1.00$; Short Delay Free Recall, $Z = 0.05$, % below average = 10.26, 95% CI = 5.98 to 16.12, $P = .72$; Long Delay Free Recall, $Z = -.04$, % below average = 16.03, 95% CI = 10.65 to 22.74, $P = 1.00$). However, the entire ALL group differed statistically significantly from normative expectations on the measure of sustained attention (CPT Omissions, % = 84.00, % below average = 67.31, 95% CI = 59.35 to 74.59, $P < .001$; Hit Reaction Time, $T = 48.97$, % below average = 26.92, 95% CI = 20.14 to 34.60, $P < .018$; Variability, $T = 58.70$, % below average = 46.15, 95% CI = 38.15 to 54.31, $P < .001$; d' , $T = 59.98$, % below average = 44.87, 95% CI = 36.91 to 53.03, $P < .001$; β , $T = 71.73$, % below average = 63.46, 95% CI = 55.39 to 71.02, $P < .001$), with greater than 40% of the sample performing below the average range on 4 out of 5 indices.

Treatment Intensity. One-sample t -tests indicated that patients on the low-risk arm performed statistically significantly better than the normative sample on Processing Speed (WISC-III) as well as Word Reading, Spelling, and Math Reasoning (WIAT, Table 2). However, patients on the low-risk arm had statistically significantly worse performance than the normative group with respect to sustained attention, including Omission errors, Reaction Time Variability, d' , and β on the CPT. In contrast, patients on the standard/high-risk

arm had statistically significantly worse scores than the normative sample on Full Scale Intelligence Quotient, WISC-III Freedom from Distractibility and Processing Speed, and WIAT Spelling, in addition to worse performance than the normative group with respect to Omission errors, Reaction Time Variability, d' , and β on the CPT. Parents also reported statistically significantly higher levels of Learning Problems on the CPRS for children on the standard/high-risk arm (Table 2). Wilcoxon rank sum tests indicated that patients on the low-risk arm performed statistically significantly better than patients on the standard/high-risk arm on all Wechsler indices and all WIAT areas (Table 3). Parents also rated low-risk patients as having statistically significantly fewer problems with Hyperactivity and Learning Problems than standard/high-risk patients. Consistent with these findings, univariate logistic regression revealed a greater probability of below-average performance for patients treated on the standard/high-risk arm relative to the low-risk arm for Processing Speed (WISC-III: 27.14% vs 6.25%, $P = .009$), all WIAT scores (Math Reasoning: 18.60% vs 3.90%, $P = .008$; Word Reading: 20.00% vs 2.60%, $P = .007$; Spelling: 27.91% vs 3.90%, $P = .001$), as well as Hyperactivity (23.00% vs 9.84%, $P = .018$) and Learning Problems (35.00% vs 16.39%, $P = .005$) on the CPRS (Figure 1).

Age at Diagnosis. One-sample t -tests revealed that children diagnosed at a younger age (<5 years) had statistically significantly worse scores than the normative sample on Full Scale Intelligence Quotient (Wechsler FSIQ), WISC-III Freedom from Distractibility (Wechsler FFD), and all indices of sustained attention (CPT) (Table 2). Parents also rated these participants as having statistically significantly greater Learning Problems on the CPRS (Table 2). Children diagnosed at an older age (≥ 5 years) had statistically significantly worse scores than the normative sample on Omission errors, Reaction Time Variability, d' , and β on the CPT and Learning Slope on the CVLT (Table 2).

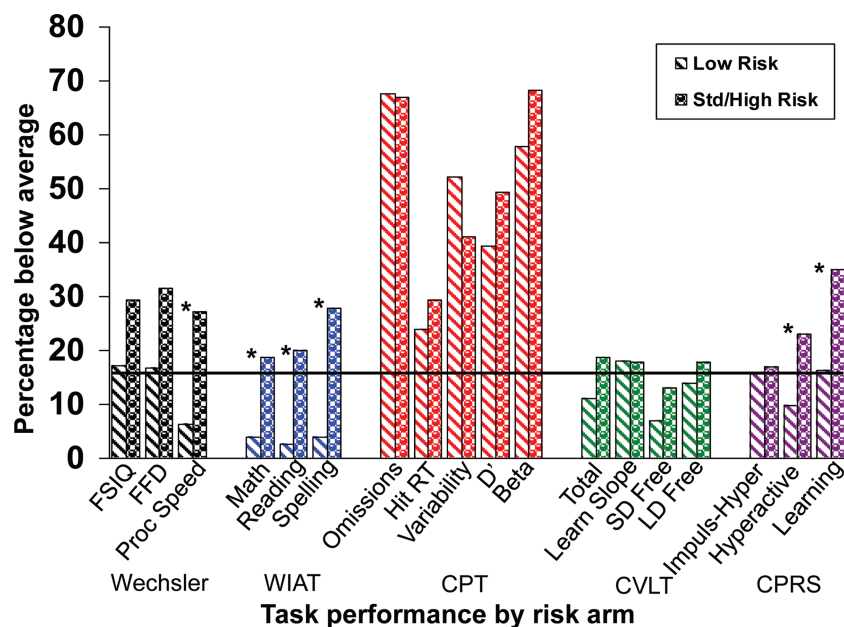


Figure 1. Performance related to treatment risk arm. **Black line** indicates the expected rate of below-average scores (16%). The asterisk signifies a statistically significant difference in rate of below-average performance between low- and standard/high-risk arms based on univariate logistic regression. All statistical tests were two-sided. WIAT = Wechsler Individual Achievement Test; CPT = Conners' Continuous Performance Test; CVLT = California Verbal Learning Test; CPRS = Conners' Parent Rating Scale; FSIQ = Full Scale Intelligence Quotient; FFD = Freedom From Distractibility Index; RT = reaction time; SD = short delay; LD = long delay; Proc Speed = processing speed; Impuls-Hyper = Impulsivity-Hyperactivity Index.

Table 2. Subgroup performance relative to normative sample*

Test	Treatment risk arm						Age at diagnosis						Sex					
	Low			Standard/high			<5 years			≥5 years			Boys			Girls		
	Mean (95% CI)	Pt	Mean (95% CI)	Pt	Mean (95% CI)	Pt	Mean (95% CI)	Pt	Mean (95% CI)	Pt	Mean (95% CI)	Pt	Mean (95% CI)	Pt	Mean (95% CI)	Pt		
Wechsler, SS†																		
FSIQ	98.1 (95.5 to 100.7)	.32	93.5 (90.3 to 96.7)	<.001	94.1 (91.3 to 97.0)	<.001	97.8 (94.8 to 100.7)	.27	95.3 (92.5 to 98.0)	.003	96.7 (93.6 to 99.8)	.12						
FFD	98.8 (95.5 to 102.1)	.47	93.3 (89.7 to 96.9)	<.001	93.7 (89.0 to 98.4)	.02	96.9 (94.1 to 99.8)	.12	95.3 (92.1 to 98.5)	.01	96.9 (93.0 to 100.8)	.23						
Proc Speed	104.8 (101.1 to 108.4)	.04	95.3 (91.1 to 99.6)	.03	101.5 (96.0 to 107.0)	.59	99.1 (95.7 to 102.6)	.62	97.1 (93.5 to 100.8)	.12	103.8 (99.0 to 108.6)	.23						
WIAT, SS																		
Math	103.4 (100.6 to 106.2)	.017	97.4 (94.0 to 100.8)	.14	100.8 (97.0 to 104.6)	1.00	100.0 (97.2 to 102.9)	1.00	101.1 (98.1 to 104.1)	.96	99.1 (95.7 to 102.6)	.83						
Reading	105.5 (102.1 to 108.8)	.005	96.5 (93.2 to 99.8)	.08	102.7 (97.8 to 107.7)	.81	99.9 (97.1 to 102.7)	1.00	99.9 (96.6 to 103.2)	.96	102.0 (98.4 to 105.6)	.83						
Spelling	104.3 (101.5 to 107.2)	.007	94.1 (91.0 to 97.2)	<.001	101.4 (97.2 to 105.6)	1.00	97.8 (95.2 to 100.5)	.33	96.9 (94.0 to 99.8)	.11	101.7 (98.3 to 105.2)	.83						
CPT, T‡																		
Omissions, %	82.7 (77.9 to 87.5)	<.001	85.1 (81.1 to 89.2)	<.001	81.2 (74.1 to 88.3)	<.001	85.0 (81.6 to 88.3)	<.001	84.0 (80.1 to 87.9)	<.001	84.0 (78.9 to 89.1)	<.001						
Hit RT	50.8 (47.7 to 53.8)	.63	47.5 (44.5 to 50.5)	.10	45.4 (41.1 to 49.7)	.038	50.2 (47.7 to 52.7)	.88	49.7 (46.9 to 52.5)	.85	47.9 (44.5 to 51.3)	.22						
Variability	58.4 (55.2 to 61.6)	<.001	59.0 (56.0 to 61.9)	<.001	60.3 (57.1 to 63.5)	<.001	58.1 (55.5 to 60.8)	<.001	57.5 (54.8 to 60.2)	<.001	60.4 (56.9 to 64.0)	<.001						
d'	59.4 (57.0 to 61.7)	<.001	60.5 (58.2 to 62.8)	<.001	59.4 (56.4 to 62.3)	<.001	60.2 (58.2 to 62.2)	<.001	58.9 (57.2 to 60.7)	<.001	61.5 (58.3 to 64.6)	<.001						
β	68.0 (63.7 to 72.3)	<.001	74.9 (70.6 to 79.1)	<.001	63.6 (59.2 to 67.9)	<.001	74.5 (70.9 to 78.2)	<.001	71.6 (68.0 to 75.3)	<.001	71.8 (66.6 to 77.1)	<.001						
CVLT, Z§																		
Total (T)	50.9 (48.4 to 53.3)	.94	49.5 (46.7 to 52.4)	1.00	46.0 (42.6 to 49.4)	.09	51.7 (49.5 to 54.0)	.37	49.2 (46.7 to 51.6)	.83	51.6 (48.6 to 54.6)	.59						
Learning Slope	-0.2 (-0.5 to 0.1)	.43	-0.3 (-0.5 to 0.0)	.08	-0.1 (-0.6 to 0.3)	1.00	-0.3 (-0.5 to 0.1)	.013	-0.3 (-0.5 to 0.0)	.11	-0.2 (-0.5 to 0.1)	.37						
SD Free Recall	0.2 (-0.0 to 0.4)	.43	-0.1 (-0.3 to 0.2)	1.00	-0.1 (-0.4 to 0.2)	1.00	0.1 (-0.1 to 0.3)	.61	-0.1 (-0.4 to 0.1)	.83	0.3 (0.0 to 0.6)	.14						
LD Free Recall	0.1 (-0.2 to 0.4)	.94	-0.1 (-0.4 to 0.2)	1.00	-0.3 (-0.8 to 0.1)	.37	0.1 (-0.2 to 0.3)	.61	-0.1 (-0.4 to 0.1)	.83	0.1 (-0.2 to 0.4)	.59						
CPRS, T‡																		
Impulse-Hyper	48.6 (46.8 to 50.3)	.22	51.8 (49.5 to 54.1)	.13	51.2 (49.1 to 53.2)	.46	48.8 (46.8 to 50.8)	.47	49.6 (47.5 to 51.6)	.97	50.5 (48.5 to 52.5)	1.00						
Hyperactive	48.1 (46.4 to 49.9)	.10	52.8 (50.2 to 55.4)	.08	51.3 (49.2 to 53.4)	.46	49.0 (46.8 to 51.3)	.47	50.8 (48.6 to 52.9)	.97	49.6 (47.4 to 51.8)	1.00						
Learning	50.3 (48.2 to 52.3)	.79	56.8 (53.6 to 60.1)	<.001	54.3 (51.5 to 57.1)	.008	52.1 (49.5 to 54.6)	.32	54.1 (51.3 to 56.9)	.01	52.3 (49.8 to 54.7)	.21						

* FSIQ = Full Scale Intelligence Quotient; FFD = Freedom from Distractibility Index; WIAT = Wechsler Individual Achievement Test; CPT = Conners' Continuous Performance Test; RT = Reaction Time; CVLT = California Verbal Learning Test; SD = Short Delay; LD = Long Delay; CPRS = Conners' Parent Rating Scale. Proc Speed = processing speed; Impulse-Hyper = Impulsivity-Hyperactivity Index; d' = vigilance; β = risk taking; SS = standard score.

† P-values are based on a one-sample t-test compared with the published normative mean. They have been adjusted using the Holm-Bonferroni step-down method to account for multiple comparisons and reduce the risk of a Type I error. All tests of statistical significance were two-sided.

‡ Scores are reported as SS, which have a normative mean of 100 and SD of 15; T-scores, which have a normative mean of 50 and SD of 10; and Z-scores, which have a normative mean of 0 and SD of 1.

§ Indices on the CPT and CPRS are reverse coded such that a higher score is indicative of worse performance or greater problems.

Wilcoxon rank sum tests revealed that patients diagnosed at a younger age performed statistically significantly worse than children diagnosed at an older age on the Total score for the CVLT (Table 3). Furthermore, the younger age at diagnosis group had a statistically significantly less impulsive response style (β) on the CPT (Table 3). Univariate logistic regression did not reveal a greater probability for below-average performance on any cognitive measure for patients diagnosed at a younger age (Figure 2).

Sex. One-sample *t*-tests revealed that male participants had statistically significantly worse scores than the normative sample on FSIQ and WISC-III Freedom from Distractibility, and Omission errors, Reaction Time Variability, d' , and β (CPT, Table 2). Parents also rated boys as having statistically significantly greater Learning Problems on the CPRS. Girls performed statistically significantly worse than the normative sample on Omission errors, Reaction Time Variability, d' , and β on the CPT (Table 2). Wilcoxon rank sum tests revealed that girls performed statistically significantly better than boys on Processing Speed (WISC-III, Table 3). Univariate logistic regression did not reveal any differences in risk for below-average performance based on sex for any cognitive measure (Figure 3).

Multivariable Models. Multivariable logistic regression models, accounting for sex and cumulative dose of ITMHA, MTX, and dexamethasone, revealed that participants treated at a younger age

(<5 years) were at a statistically significantly increased risk (three- to fourfold) for below-average performance on Reaction Time (CPT, OR = 3.91, 95% CI = 1.65 to 9.30, $P = .010$) and Long Delay Free Recall (CVLT, OR = 4.64, 95% CI = 1.69 to 12.71, $P = .01$; Table 4). Multivariable models did not identify any statistically significant, independent risk for sex, cumulative dexamethasone, cumulative ITMHA, or cumulative HDMTX dose on any of the cognitive outcome variables.

Given that below-average performance on the CPT was the most common finding, post hoc analyses were conducted to evaluate the relationship between this performance measure of attention and parent report of attention problems. Pearson correlation coefficients revealed a small but statistically significant relationship between Reaction Time Variability on the CPT and Hyperactivity on the CPRS ($r = .18$, $P = .037$) and trends for relationships between Omission errors on the CPT and Hyperactivity on the CPRS ($r = .15$, $P = .078$) and Learning Problems on the CPRS ($r = .14$, $P = .093$).

Discussion

Overall, study findings were consistent with a priori hypotheses. Omission of prophylactic cranial irradiation from ALL treatment resulted in generally well-preserved cognitive abilities for the

Table 3. Subgroup comparison by risk arm, age at diagnosis, and sex*

Test	By treatment risk arm†		By age at diagnosis‡		By sex	
	Difference of means (95% CI)	<i>P</i> ‡	Difference of means (95% CI)	<i>P</i> ‡	Difference of means (95% CI)	<i>P</i> ‡
Wechsler, SS§						
FSIQ	4.6 (0.6 to 8.7)	.03	-3.6 (-7.7 to 0.4)	.37	-1.5 (-5.6 to 2.7)	.34
FFD	5.5 (0.7 to 10.4)	.03	-3.3 (-8.6 to 2.1)	.67	-1.6 (-6.6 to 3.4)	.34
Proc Speed	9.4 (3.8 to 15.0)	.003	2.4 (-4.1 to 8.8)	.67	-6.7 (-12.5 to -0.8)	.03
WIAT, SS						
Math	6.0 (1.6 to 10.4)	.007	0.7 (-4.1 to 5.6)	1.00	1.9 (-2.6 to 6.5)	.68
Reading	9.0 (4.3 to 13.6)	.001	2.9 (-2.4 to 8.1)	1.00	-2.1 (-7.0 to 2.8)	.68
Spelling	10.2 (6.0 to 14.4)	<.001	3.5 (-1.3 to 8.4)	1.00	-4.8 (-9.3 to -0.3)	.06
CPT, TI						
Omissions (%)	-2.4 (-8.6 to 3.7)	.30	-3.8 (-10.8 to 3.3)	.25	0.0 (-6.2 to 6.3)	.74
Hit RT	3.3 (-1.0 to 7.6)	.80	-4.8 (-9.6 to 0.1)	.11	1.8 (-2.5 to 6.2)	1.00
Variability	-0.5 (-4.9 to 3.8)	.80	2.2 (-2.8 to 7.1)	.35	-2.9 (-7.3 to 1.4)	.63
d'	-1.1 (-4.4 to 2.2)	.80	-0.8 (-4.6 to 3.0)	.52	-2.6 (-5.9 to 0.8)	1.00
β	-6.9 (-12.9 to -0.9)	.15	-11.0 (-17.7 to -4.2)	.025	-0.2 (-6.4 to 6.0)	1.00
CVLT, Z						
Total (T)	1.4 (-2.4 to 5.2)	1.00	-5.7 (-9.8 to -1.6)	.006	-2.4 (-6.3 to 1.4)	.30
Learning Slope	0.1 (-0.3 to 0.4)	1.00	0.1 (-0.2 to 0.5)	.49	-0.0 (-0.4 to 0.3)	.91
SD Free Recall	0.3 (-0.1 to 0.6)	1.00	-0.2 (-0.6 to 0.2)	.15	-0.4 (-0.8 to -0.0)	.08
LD Free Recall	0.2 (-0.2 to 0.6)	1.00	-0.4 (-0.9 to 0.0)	.15	-0.3 (-0.7 to 0.1)	.30
CPRS, T						
Impulse-Hyper	-3.2 (-6.1 to -0.4)	.05	2.4 (-0.5 to 5.2)	.25	-0.9 (-3.8 to 1.9)	1.00
Hyperactive	-4.7 (-7.7 to -1.6)	.02	2.3 (-0.8 to 5.3)	.24	1.2 (-1.9 to 4.3)	1.00
Learning	-6.6 (-10.2 to -2.9)	.02	2.3 (-1.5 to 6.0)	.37	1.8 (-2.0 to 5.6)	1.00

* FSIQ = Full Scale Intelligence Quotient; FFD = Freedom from Distractibility Index; WIAT = Wechsler Individual Achievement Test; CPT = Conners' Continuous Performance Test; RT = Reaction Time; CVLT = California Verbal Learning Test; SD = Short Delay; LD = Long Delay; CPRS = Conners' Parent Rating Scale; Proc Speed = processing speed; Impulse-Hyper = Impulsivity-Hyperactivity Index; d' = vigilance; β = risk taking; SS = standard score.

† Treatment risk arm: low vs standard high; age: <5 y vs \geq 5 y.

‡ *P*-values are based on Wilcoxon rank sum tests comparing subgroups. They have been adjusted using the Holm-Bonferroni step-down method to account for multiple comparisons and reduce the risk of a Type I error. All tests of statistical significance were two-sided.

§ Scores are reported as mean differences based on SS, which have a normative mean of 100 and SD of 15; T-scores, which have a normative mean of 50 and SD of 10; and Z-scores, which have a normative mean of 0 and SD of 1.

|| Indices on the CPT and CPRS are reverse coded such that a higher score is indicative of worse performance or greater problems.

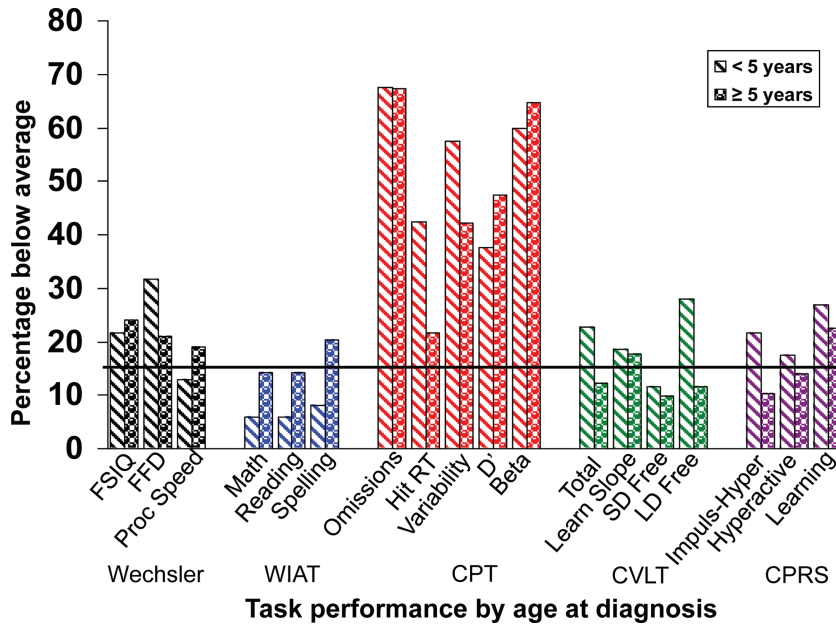


Figure 2. Performance related to age at diagnosis. **Black line** indicates the expected rate of below-average scores (16%). All statistical tests were two-sided. WIAT = Wechsler Individual Achievement Test; CPT = Conners' Continuous Performance Test; CVLT = California Verbal Learning Test; CPRS = Conners' Parent Rating Scale; FSIQ = Full Scale Intelligence Quotient; FFD = Freedom From Distractibility Index; RT = reaction time; SD = short delay; LD = long delay; Proc Speed = processing speed; Impuls-Hyper = Impulsivity-Hyperactivity Index.

group as a whole relative to normative expectations. The entire sample performed well on global measures of cognitive ability without evidence of excess impairment on measures of intellectual functioning, academic abilities, and learning and memory. This contrasts with historical experience with patients receiving 18–24 Gy of cranial irradiation (4,5,7,9,14,37). Problems with sustained attention emerged as the most prominent deficit, with below-average performance in approximately 40% of the sample

irrespective of sex, age at treatment, or treatment intensity. This limited association among attention measures and treatment and demographic factors suggests other sources for variability, such as genetic polymorphisms related to pharmacokinetics or pharmacodynamics of chemotherapy.

Higher treatment intensity with chemotherapy was associated with worse performance on measures of processing speed and academics, as well as greater parent report of learning problems.

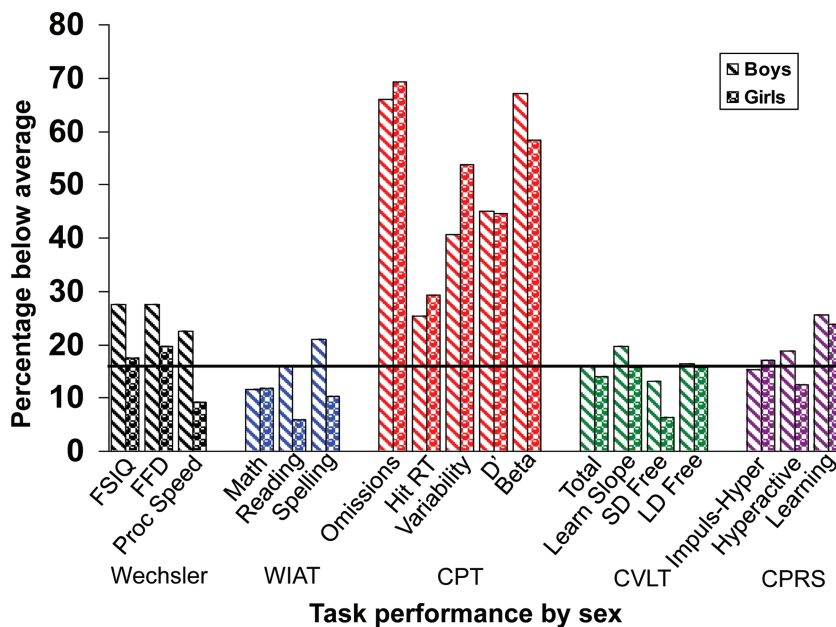


Figure 3. Performance related to sex. **Black line** indicates the expected rate of below-average scores (16%). All statistical tests were two-sided. WIAT = Wechsler Individual Achievement Test; CPT = Conners' Continuous Performance Test; CVLT = California Verbal Learning Test; CPRS = Conners' Parent Rating Scale; FSIQ = Full Scale Intelligence Quotient; FFD = Freedom From Distractibility Index; RT = reaction time; SD = short delay; LD = long delay; Proc Speed = processing speed; Impuls-Hyper = Impulsivity-Hyperactivity Index.

Table 4. Multivariable logistic regression of patient and clinical characteristics and cognitive performance*

Test	Age at diagnosis†			Sex			Cumulative dexamethasone‡			Cumulative ITMHA†			Cumulative HDMTX†		
	OR (95% CI)	P†	P†	OR (95% CI)	P†	P†	OR (95% CI)	P†	P†	OR (95% CI)	P†	P†	OR (95% CI)	P†	P†
Wechsler, SS															
FSIQ	1.09 (0.57 to 2.10)	1.00	.38	0.60 (0.31 to 1.16)	.38	.68	0.98 (0.88 to 1.09)	.68	.37	1.21 (0.95 to 1.53)	.37	.37	1.16 (0.79 to 1.71)	.46	.46
FFD	2.63 (1.04 to 6.65)	.12	.40	0.68 (0.28 to 1.65)	.40	.57	0.94 (0.83 to 1.06)	.57	.51	1.18 (0.73 to 1.91)	.51	.51	1.62 (0.91 to 2.89)	.22	.22
Proc Speed	1.18 (0.36 to 3.85)	1.00	.38	0.45 (0.14 to 1.37)	.38	.37	0.90 (0.78 to 1.03)	.37	.37	1.48 (0.89 to 2.48)	.37	.37	1.84 (0.94 to 3.60)	.22	.22
WIAT, SS															
Math	0.56 (0.14 to 2.16)	.80	.41	1.60 (0.55 to 4.65)	.41	.58	0.96 (.83 to 1.10)	.58	.23	1.58 (0.95 to 2.62)	.23	.23	1.44 (0.78 to 2.67)	.74	.74
Reading	0.57 (0.15 to 2.19)	.80	.41	0.40 (0.12 to 1.34)	.41	.49	0.90 (0.78 to 1.04)	.49	.39	1.40 (0.84 to 2.34)	.39	.39	1.31 (0.69 to 2.46)	.74	.74
Spelling	0.44 (0.14 to 1.41)	.51	.41	0.52 (0.20 to 1.38)	.41	.58	0.93 (0.82 to 1.06)	.58	.46	1.19 (0.76 to 1.86)	.46	.46	1.37 (0.79 to 2.38)	.74	.74
CPT, T															
Omissions, %	1.03 (0.46 to 2.30)	1.00	1.00	1.28 (0.62 to 2.65)	1.00	1.00	1.05 (0.95 to 1.17)	1.00	1.00	1.02 (0.69 to 1.51)	1.00	1.00	1.05 (0.67 to 1.65)	1.00	1.00
Hit RT	3.91 (1.65 to 9.30)	.01	1.00	1.38 (0.62 to 3.07)	1.00	1.00	0.94 (0.84 to 1.05)	1.00	1.00	1.29 (0.84 to 1.96)	1.00	1.00	1.54 (0.94 to 2.52)	.42	.42
Variability	1.78 (0.83 to 3.86)	.56	.77	1.65 (0.83 to 3.27)	.77	1.00	0.99 (0.90 to 1.10)	1.00	1.00	0.85 (0.58 to 1.24)	1.00	1.00	1.29 (0.84 to 2.00)	.75	.75
d'	0.73 (0.34 to 1.59)	1.00	1.00	1.09 (0.55 to 2.16)	1.00	1.00	0.97 (0.88 to 1.07)	1.00	1.00	1.18 (0.82 to 1.71)	1.00	1.00	1.03 (0.67 to 1.58)	1.00	1.00
β	0.00	1.00	1.00	0.00	1.00	1.00	0.84 (0.42 to 1.67)	1.00	1.00	2.90 (0.25 to 33.88)	1.00	1.00	0.05 (0.00 to 4.14)	.72	.72
CVLT, Z															
Total (T)	3.02 (1.11 to 8.19)	.09	1.00	1.12 (0.42 to 3.02)	1.00	.88	1.06 (0.91 to 1.22)	.88	1.00	1.12 (0.66 to 1.90)	1.00	1.00	1.78 (1.01 to 3.14)	.19	.19
Learning Slope	1.03 (0.40 to 2.66)	.96	1.00	0.75 (0.31 to 1.84)	1.00	.88	1.07 (0.93 to 1.23)	.88	1.00	1.00 (0.62 to 1.62)	1.00	1.00	0.80 (0.46 to 1.40)	.44	.44
SD Free Recall	1.88 (0.56 to 6.35)	.62	1.00	0.48 (0.14 to 1.70)	1.00	.88	0.92 (0.80 to 1.07)	.88	1.00	1.25 (0.70 to 2.25)	1.00	1.00	1.54 (0.80 to 2.93)	.44	.44
LD Free Recall	4.64 (1.69 to 12.71)	.01	1.00	0.98 (0.37 to 2.61)	1.00	.80	0.92 (0.81 to 1.05)	.80	.94	1.38 (0.81 to 2.33)	.94	.94	1.51 (0.87 to 2.64)	.44	.44
CPRS, T															
Impulse-Hyper	2.51 (1.13 to 5.60)	.07	1.00	0.91 (0.43 to 1.92)	1.00	.52	0.91 (0.79 to 1.04)	.52	1.00	0.94 (0.68 to 1.30)	1.00	1.00	1.10 (0.71 to 1.71)	.66	.66
Hyperactive	1.69 (0.78 to 3.67)	.37	.73	0.63 (0.28 to 1.37)	.73	1.00	1.00 (0.87 to 1.14)	1.00	1.00	1.28 (0.98 to 1.69)	1.00	1.00	1.26 (0.81 to 1.95)	.62	.62
Learning	1.45 (0.76 to 2.75)	.37	1.00	0.93 (0.49 to 1.76)	1.00	1.00	0.98 (0.88 to 1.10)	1.00	1.00	1.04 (0.83 to 1.31)	1.00	1.00	1.40 (0.97 to 2.02)	.23	.23

* FSIQ = Full Scale Intelligence Quotient; FFD = Freedom from Distractibility Index; WIAT = Wechsler Individual Achievement Test; CPT = Conners' Continuous Performance Test; RT = Reaction Time; CVLT = California Verbal Learning Test; SD = Short Delay; LD = Long Delay; CPRS = Conners' Parent Rating Scale, Proc Speed = processing speed; Impulse-Hyper = Impulsivity-Hyperactivity Index; d' = vigilance; β = risk taking; SS = standard score, OR = odds ratio, CI = confidence interval. Odds ratios represent the effects of being <5 years old at the time of diagnosis (referent = ≥5y), female (referent = male), cumulative dexamethasone (per 100 mg/m²), cumulative ITMHA (per 50 mL) and cumulative HDMTX (per 5 g/m²). Dexamethasone, ITMHA, and HDMTX were categorized into therapeutically meaningful units that roughly correspond to 2 wk of dexamethasone treatment, 4–5 ITMHA doses, and 1–2 doses of HDMTX, respectively.

† All clinical factors, age at diagnosis (<5 vs ≥5 y), sex, cumulative dexamethasone (per 100 mg/m²), ITMHA (per 50 mL), and HDMTX (per 5 g/m²), were included in final multiple logistic regressions.

‡ P-values have been adjusted using the Holm–Bonferroni step-down method to account for multiple comparisons and reduce the risk of a Type I error. All tests of statistical significance were two-sided.

Hence, additional follow-up with potential therapeutic intervention is warranted, especially for half of our patients who received intensive chemotherapy. Younger age at treatment also remained predictive of worse performance on selective indices of sustained attention and memory. The effect of sex was negligible and in the opposite direction of the existing literature that suggests female sex as a risk factor. It may be that sex differences are specific to assessed skill and less likely to be found on language-based measures, for which there is evidence of developmental advantages for girls (37–39).

It is important to note that not all statistically significant findings have clinical impact. Using clinical thresholds to classify average and below-average performers based on normative expectations assists in interpreting study findings. The statistically significantly elevated rate of impairment on a computerized measure of sustained attention, coupled with parent report of attention and learning problems, suggests that attention difficulties are of noteworthy magnitude and affect real-world functioning. These findings corroborated those of a previous study (26), which included a subset of patients from this study, demonstrating similar proportions of below-average performers on a different measure of attention and working memory, with performance related to leukoencephalopathy on neuroimaging.

Current findings should be interpreted in the context of study limitations. Data analyses were cross-sectional, examining cognitive outcomes two-and-a-half years following remission induction. Longitudinal studies including longer term outcomes would allow for further examination of persistence and/or exacerbation of deficits over time. Early emerging attention problems may result in later emerging declines in intellectual functioning and academic achievement (40). It will also be important to compare the cognitive findings of this study with those from other contemporary trials using lower doses of cranial irradiation (eg, 12 Gy), once those results become available. The current study utilized gold standard assessment measures with large normative samples; however, inclusion of a medical control group would allow for isolation of effects of central nervous system-directed treatment from other illness-related experiences (eg, prolonged absences from school). Finally, ecological measures, such as school grades or provision of special education services, would allow for fuller understanding of the clinical impact of cognitive late effects.

The findings of this study highlight the benefits of risk-adapted therapy omitting cranial irradiation but also indicate that treatment with chemotherapy alone is not without risks. Attention as a core and primary cognitive late effect of modern therapy is consistent with the existing literature (14,41,42) as well as findings implicating vulnerability of cerebral white matter to central nervous system-directed therapy (43,44). Post-mortem histological findings (45), with convergent support from structural and functional neuroimaging studies (46,47), suggest that frontal-subcortical pathways continue to develop into the third decade of life, as indicated by ongoing myelination and pruning. Given protracted developmental myelination of the prefrontal cortices and dependence of attention on these brain regions, these skills may be particularly vulnerable to treatment-related neurotoxicity (26,48).

White matter abnormalities in the frontal lobes have been reported in leukemia patients during treatment with MTX (44), and leukoencephalopathy during active therapy appears related to attention and working memory problems detected at completion of therapy (26). Transient changes in white matter may be the result of demyelination, which could lead to decreased axonal density and brain atrophy. Reddick et al. (43) found that ALL survivors who receive chemotherapy alone have white matter volumes larger than ALL patients who receive cranial irradiation but smaller than that of healthy sibling control participants. In this same study (43), smaller white matter volumes were associated with larger deficits in attention, IQ, and academic achievement. In a more recent diffusion tensor imaging study (49), the nine survivors of childhood ALL treated only with chemotherapy had persistently lower white matter volume in frontal lobes than 14 healthy control participants. Furthermore, this reduction in white matter volume corresponded to deficits in attention, visual-constructional skills, mental flexibility, and mathematics.

Current findings indicate that monitoring for late effects and caregiver education should focus on attention abilities early in the survivorship period. Furthermore, development of interventions that address cognitive late effects is imperative. There is encouraging empirical support for emerging pharmacologic and nonpharmacologic remediation approaches targeting attention concerns (50–52).

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