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ORIGINAL REPORT

White Matter Anisotropy in Post-Treatment Childhood Cancer Survivors: Preliminary Evidence of Association With Neurocognitive Function

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A B S T R A C T

Purpose
We aim to determine if the loss of white matter fractional anisotropy (FA), measured by diffusion tensor magnetic resonance imaging (DTI), in post-treatment childhood medulloblastoma (MED) and acute lymphoblastic leukemia (ALL) survivors correlate with intelligence quotient (IQ) scores.

Materials and Methods
MED and ALL survivors (n = 30; 20 male, 10 female; age range, 6.0 to 22.1 years; mean, 13.1 years) were recruited for DTI and IQ tests. In this cross-sectional study, age-matched normal control (n = 55; 32 male, 23 female; age range, 6.0 to 23 years; mean, 12.1 years) DTI was obtained to compute percentage difference in white matter FA (ΔFA%) for each patient compared with the age-matched control group. Multivariate regression analysis was performed to determine the relationships between ΔFA%, age at treatment, irradiation dose, time interval from treatment, and full-scale IQ (FSIQ), verbal IQ (VIQ), and performance IQ (PIQ). Receiver operating characteristics curves were used to determine the best ΔFA% cutoffs for predicting FSIQ, VIQ, and PIQ of less than 85.

Results
ΔFA% had a significant effect on FSIQ (adjusted $r^2 = 0.439$; $P < .001$), VIQ (adjusted $r^2 = 0.237$; $P = .028$), and PIQ (adjusted $r^2 = 0.491$; $P < .001$) after adjusting for the effects of age at treatment, irradiation dose, and time interval from treatment. The best ΔFA% value to predict less than 85 scores in FSIQ, VIQ, and PIQ was −3.3% with specificities of 100% and sensitivities ranging from 77.8% to 87.5%.

Conclusion
Our preliminary findings suggest that white matter FA may be a clinically useful biomarker for the assessment of treatment-related neurotoxicity in post-treatment childhood cancer survivors.

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INTRODUCTION

Treatment-induced neurotoxicity is a major cause of neurobehavioral morbidity in childhood cancer survivors affecting diverse aspects of cognitive function, especially attention, memory, and processing speed, which, in turn, affect intelligence quotient (IQ) and academic achievement.[1-7] With therapeutic advancements and improving long-term survivals, there is a greater and more urgent need for attention to neurocognitive outcomes, an important domain contributing to the quality of life of these children.

The assessment of treatment-induced neurotoxicity using conventional magnetic resonance neuroimaging techniques have been limited, with most studies reporting a lack of correlation between the presence of leukoencephalopathy on conventional magnetic resonance imaging (MRI) and clinical symptoms or neurocognitive tests.[8-11] Advanced MRI techniques have shown more promising results. Volumetric measurements of normal appearing white matter in medulloblastoma (MED) survivors have been found to be reduced compared with normal controls,[12] and the severity of volume loss correlates with young age at cranial irradiation,[12] cranial irradiation dose, and IQ scores.[5,6,12] This supports the fact that cerebral white matter is the neuroanatomic substrate for treatment-induced neurotoxicity. Also, magnetic resonance spectroscopy studies have generally shown a reduction in *N*-acetyl aspartate ratios in the white matter of childhood acute lymphoblastic leukemia (ALL) children, although no correlation has been found with neurocognitive scores.[13,14]

We have used a new sequence in MRI, diffusion tensor MRI (DTI), to measure the loss of fractional anisotropy (FA) in the white matter of childhood cancer survivors.[15,16] DTI is a technique that is able to quantitate the diffusion of water molecules in the brain. In white matter, the diffusion process is highly directional because of axonal fibers running in parallel, making this technique advantageous for the assessment of white matter.[17] This property, termed diffusion anisotropy, can be quantified by the index FA. When white matter microstructure is disrupted because of pathology, the abnormality can be detected and quantified by the loss of FA. Compared with volumetric measurements, this method potentially has the advantage of more sensitive detection of subtle and early changes that occur in the microstructure and organization of white matter fiber tracts. We have shown that white matter FA (WMFA) is less in childhood MED survivors compared with normal control patients,[15,16] and that the difference correlates with known risk factors of neurotoxicity,[18] suggesting that FA may be used as a biomarker of treatment-induced white matter damage reflecting the status of tissue microstructure and architecture. In a cross-sectional study of childhood MED and ALL survivors, we aim to determine if FA measurement correlates with neurocognitive function, by the assessment of IQ scores.

MATERIALS AND METHODS

Patient Demographics

Consecutive MED and ALL survivors who were free of the primary disease, completed treatment at least 1 year ago, and were at least 6 years of age were recruited from the Pediatric Oncology Unit of our hospital for DTI and IQ tests. Informed consent was obtained from the patient or parent and the study was approved by the hospital institutional review board. A total of 30 patients (20 male, 10 female; age range, 6.0 to 22.1 years; mean age, 13.1 years) were recruited, of which 12 were MED survivors and 18 were ALL survivors. All the MED survivors belonged to our previous cohort studied for the association of FA with risk factors of neurotoxicity.[18] IQ scores were not analyzed then.

All MED survivors (9 male, 3 female; age range, 6 to 20.6 years; mean, 11.8 years) underwent tumor resection, craniospinal irradiation, and chemotherapy. The whole brain was irradiated with lateral opposing fields 23.4 to 40 Gy in 1.8 to 2 Gy daily fractions. Afterward, additional boost was given to the posterior cranial fossa with reduced lateral opposing fields or with three-dimensional conformal radiotherapy. Three patients had posterior cranial fossa boost with three-dimensional conformal radiotherapy. Total dose to the posterior cranial fossa ranged from 50 to 55.8 Gy. Total craniospinal irradiation dose was 23.4 Gy (n = 3), 30.6 Gy (n = 3), 36 Gy (n = 5), and 40 Gy (n = 1). The variation in dosage is, in part, because of the change of the protocol in recent years and also, in part, because of the differences in their disease status. Chemotherapy regime was vincristine, cyclophosphamide, cisplatin and VP16 (baby Pediatric Oncology Group protocol) for children diagnosed before 2000 or CCNU (lomustine), cisplatin, and vincristine (CCV protocol) for children diagnosed after 2000.

All ALL survivors (11 male, 7 female; age range, 6.8 to 22 years; mean, 13.9 years) were treated with standardized intrathecal and systemic chemotherapy regimes. Patients received intrathecal methotrexate and high-dose methotrexate in doses varying from 2 to 5 g/m^2 for three to four doses. Before October 1997, chemotherapy was according to the HKALL93 protocol (based on the United Kingdom Medical Research Council protocols for childhood ALL, UKALLX1). From October 1997, the chemotherapy regime was altered to the HKALL97 protocol (based on the Berlin-Frankfurt-Munster study group protocol, ALL-BFM 95). The cranial irradiation dose for high-risk patients was 18 Gy in the HKALL93 protocol and 12 Gy in the HKALL97 protocol. Nine ALL survivors underwent irradiation for CNS prophylaxis and/or CNS disease (6 males, 3 females; age range, 7.4 to 22 years; mean, 14.8 years) and nine did not (5 males, 4 females; age range, 6.8 to 17.7 years; mean, 13.1 years). Cranial irradiation dose was 12 Gy (n = 2), 18 Gy (n = 5), and 24 Gy (n = 2, for CNS involvement).

Patient demographic data is summarized in Table 1. Fifty-five healthy age-matched children (32 male, 23 female; age range, 6.0 to 23 years; mean, 12.1 years) were selected as controls for DTI scans after institutional review board approval and informed consent was obtained from the subjects, patients, or parents. These subjects were volunteer healthy control subjects or patients who underwent MRI of the brain for clinical indications such as headache or congenital sensorineural hearing loss and were subsequently confirmed to have no neurologic deficit by clinical examination and normal MRI scans. The control subjects were imaged with the same DTI protocol as the patients and were divided into four groups by age: Group A (n = 13; age range, 6.0 to 8.9 years; mean, 7.7 years), Group B (n = 18; age range, 9.0 to 11.9 years; mean, 10.2 years), Group C (n = 11; age range, 12.0 to 14.9 years; mean, 13.6 years), and Group D (n = 13; age range, 15.0 to 23.0 years; mean, 17.9 years) for analysis (see below for ΔFA% calculation).

Data Acquisition

MRI was performed using a Signa 1.5 Tesla imager (General Electric Medical Systems, Milwaukee, WI) with a standard head coil. DTI data was acquired using single-shot spin-echo echo-planar imaging with TR = 10,000 ms, TE = 100 ms, acquisition matrix = 128 × 128 and field of view = 28 cm. Using a slice thickness of 5 mm with 1.5 mm gap, images were acquired through the entire brain (18 or 19 images). Diffusion-sensitizing gradient encoding was applied in 25 directions by using a diffusion-weighted factor b = 1,200 s/mm^2, and one image was acquired without use of a diffusion gradient, ie, b = 0 s/mm^2. The DTI imaging time was approximately 5 minutes.

Image Processing

The DTI data were processed using FUNCTOOL (GE Medical Systems, USA) to obtain the FA map. All image manipulations were done using SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UK) and MATLAB 6.5 (The MathWorks Inc, Natick, MA). Computation of the quantitative index, mean WMFA from the FA map was performed for each patient and control subject as described previously.[18] The mean WMFA of the

Table 1. Showing Patient Demographics, WMFA, ΔFA%, and Treatment Protocols of 30 ALL and MED Patients

Tumor Type	WMFA		ΔFA%		Age at MRI (years)		Age at Rx (years)		Interval (years)		RT Dose (Gy)		Chemotherapy Protocol
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Range	Mean	
ALL without RT, n = 9	0.355	0.011	−0.34	2.55	13.06	4.00	6.68	6.32	6.38	4.29	0		HKALL93/97
ALL with RT, n = 9	0.351	0.014	−1.51	4.10	14.83	4.67	6.47	4.35	8.39	4.74	12-24	18	HKALL93/97
MED, n = 12	0.336	0.022	−4.37	6.25	11.75	4.87	8.52	3.57	3.25	2.26	23.4-40	32	bPOG/CCV

Abbreviations: WMFA, white matter fractional anisotropy; ΔFA%, percentage difference in white matter FA; ALL, acute lymphoblastic leukemia; MED, medulloblastoma; FA, fractional anisotropy; MRI, magnetic resonance imaging; Rx, treatment; RT, radiotherapy; SD, standard deviation.

control subjects were grouped into the respective four age groups (Group A-D) and the mean WMFA of each age group was obtained.

Δ *Fractional Anisotropy (ΔFA%) Calculation*

As it is known that WMFA increases nonlinearly with age, the corresponding age-matched control group mean WMFA was used as a reference value to calculate the percentage difference in WMFA (ΔFA%) of each patient. The same reference WMFA value was used in the calculation of ΔFA% for multiple patients, depending on patient age. These reference values were required for comparison in our cohort as these values are scanner and sequence specific and cannot be quoted from the literature. ΔFA% for each patient was computed by (WMFA of patient – WMFA of the age-matched control group)/WMFA of age-matched control group × 100%. As this is not a longitudinal study, note that ΔFA% used in this study does not represent change within an individual but rather reflects a difference in FA of each individual compared with the corresponding age-matched control group.

Neuropsychologic Tests

IQ scores were obtained for all patients within 0 to 476 days of the DTI scans, with 22 patients (73.3%) having had IQ tests performed within 4 months of DTI scans. All but two IQ tests were performed within 1 year of the DTI scans. We used the Hong Kong Wechsler Intelligence Scales for Children (HK-WISC) for subjects younger than 16 years of age and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) for those 16 years of age and older. The HK-WISC is an adaptation of the WISC taking into consideration the cultural background and range of experience of local Hong Kong children. Verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ) were assessed.

Statistical Analysis

We used the Mann-Whitney *U* test to compare age, educational level, and socioeconomic status (according to the definition by the United Kingdom office of population consensus and surveys 1991) and Fisher's exact test to compare sex differences between the control and patient groups. Analysis of variance (ANOVA) was performed to compare neurocognitive measures, ΔFA%, and patient demographic factors between the three treatment groups, ALL without irradiation, ALL with irradiation, and MED survivors. We performed posthoc tests among the three treatment groups using Bonferroni corrections. To test for trend of ΔFA% over the three treatment groups, we used linear contrast. Normality assumption of the ANOVA analysis was checked and was met. Multiple linear regression analysis was used to study the effects of irradiation dose and age at treatment on ΔFA% after the cubic root transformation. The transformation was made because of inadequate normality before transformation. To determine the relationships between independent variables—sex, education level, socioeconomic status, and known neurotoxicity risk factors—age at treatment, irradiation dose and time interval from treatment, and ΔFA% and dependent variables—FSIQ, VIQ, and PIQ—a two-stage multivariate regression analysis was performed to account the correlation among the dependent variables. The independent variables were clustered into two groups. Group 1 included sex, education level, and socioeconomic status. Group 2 included known neurotoxicity risk factors, age at treatment, irradiation dose and time interval from treatment, and ΔFA%. The two groups were defined such that variables in group 1 are general factors that may affect IQ and group 2 are variables that have been shown to affect IQ and ΔFA% (ie, risk factors of neurotoxicity) in this type of patient group. In stage 1, a multivariate analysis was performed to examine the effect of each variable in group 1. In stage 2, a multivariate analysis was performed on all variables in group 2 as well as those variables significant in stage 1.

We also tested the unadjusted effects of ΔFA% on the IQ scores using ΔFA% as the only independent variable. All regression models were checked for adequacy by using the standardized residuals. Normal assumptions were met. Receiver operating characteristics curves were used to determine the best ΔFA% cutoffs for predicting a FSIQ, VIQ, and PIQ of less than 85. Specifically, the best cutoff value was taken as the one that maximized the Youden index, ie, sensitivity + specificity −1. We computed the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of the best ΔFA% cutoffs.

All statistical analyses were performed using the statistical package SPSS for Windows (Version 11.0, SPSS, Chicago, IL). A *P* value of less than .05 was considered to indicate statistical significance.

RESULTS

Control and Patient Group Demographics

There were no significant differences found between age (Mann-Whitney *U* test, $P = .316$), sex (Fisher's exact test, $P = .492$), educational levels (Mann-Whitney *U* test, $P = .899$), and socioeconomic status (Mann-Whitney *U* test, $P = .306$) between the control and patient groups.

Mean WMFA and ΔFA%

The mean WMFA of Groups A, B, C, and D control patients were 0.348 (standard deviation [SD], 0.016), 0.355 (SD, 0.010), 0.359 (SD, 0.012), and 0.358 (SD, 0.007), respectively. The mean WMFA and mean ΔFA% of all 30 patients was 0.346 (SD, 0.019) and −2.30% (SD, 4.94%), respectively. Mean WMFA and mean ΔFA% of the three treatment groups are summarized in Table 1. There were no significant differences in age at treatment between the three treatment groups but MED survivors had a significantly shorter time interval from treatment compared with the ALL survivors (ANOVA, $P = .014$). We found a level of significance that suggested a trend toward significant differences in ΔFA% between the three treatment groups with MED survivors having the largest ΔFA%, ALL survivors with irradiation having slightly smaller ΔFA%, and ALL survivors without irradiation having the least ΔFA% (ANOVA, $P = .066$). Multiple linear regression analyses found that irradiation dose (effect, −0.040; SE, 0.016; $P = .018$) and age at treatment (effect, 0.106; SE, 0.048; $P = .035$) had a significant effect on the cubic root of ΔFA%.

IQ Scores

Mean FSIQ, VIQ, and PIQ of all 30 patients was 106.03 (SD, 17.05), 110.57 (SD, 15.77), and 99.57 (SD, 17.25), respectively. IQ scores and subtest scores of the three treatment groups are summarized in Table 2. By ANOVA analysis, there were no significant differences in IQ scores between the three treatment groups, although MED survivors had the lowest scores in FSIQ, VIQ and the verbal subtests, information, and arithmetic, followed by ALL survivors with irradiation and ALL survivors without irradiation (Table 2). FSIQ scores were below average (< 85) in five patients (five of 30, 16.67%), of which three were MED survivors (three of 12, 25%) and two were ALL survivors (two of 18, 11.11%, one with and one without irradiation). VIQ scores were below average (< 85) in three patients (three of 30, 10%), of which two were MED survivors and one was an ALL survivor (without irradiation). PIQ scores were below average (< 85) in six patients (six of 30, 20%), of which four were MED survivors (four of 12, 30%) and two were ALL survivors (two of 18, 11.11%, one with and one without irradiation). Evaluation of the IQ subtests revealed that at least one below average subtest score (< 7) was found in 10 ALL survivors (10 of 18, 55.6%) and six MED survivors (six of 12, 50%). The percentage frequencies of below average scores for each subtest were as follows: information, 16.7%; similarities, 3.3%; arithmetic, 6.7%; vocabulary, 14.3% and comprehension, 3.3%; picture completion, 3.3%; picture arrangement, 10%; block design, 10%; object assembly, 16.7%; and coding/digit symbol, 34.5%.

Table 2. Showing the IQ Scores of 30 ALL and MED Survivors

Characteristics	ALL Without RT (n = 9)			ALL With RT (n = 9)			MED (n = 12)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Full scale IQ	109.3	17.6	75-139	107.6	13.0	84-125	102.4	17.9	68-123
Verbal IQ	114.9	17.0	84-150	109.8	13.7	92-132	107.9	14.9	80-123
Performance IQ	100.0	15.1	70-122	104.1	13.0	77-125	95.8	19.8	62-119
Verbal subtests									
Information	10.3	1.6	7-12	9.9	3.2	5-16	8.8	2.5	5-13
Digit span	13.2	7.0	9-19	13.0	6.5	9-18	11.8	6.1	7-15
Vocabulary	10.7	5.6	5-17	10.8	6.1	5-17	11.4	5.2	8-14
Arithmetic	12.0	3.3	8-17	11.0	2.5	7-15	9.8	3.5	3-17
Comprehension	12.0	2.2	8-16	10.7	3.7	7-19	11.5	3.4	5-16
Similarities	13.1	2.8	8-18	10.9	3.8	6-16	13.4	3.4	8-19
Performance subtests									
Picture completion	10.0	1.6	7-12	11.2	1.7	8-14	9.3	2.6	4-13
Picture arrangement	11.3	3.6	5-17	10.1	1.9	8-13	10.3	3.6	3-16
Block design	11.3	3.1	6-17	11.9	3.2	7-18	10.1	4.3	3-16
Object assembly	9.7	2.9	5-16	9.6	3.0	5-13	10.2	3.8	4-17
Coding/digit symbol	7.3	2.3	5-12	9.6	4.5	5-16	7.7	2.4	4-11

Abbreviations: IQ, intelligence quotient; ALL, acute lymphoblastic leukemia; MED, medulloblastoma; RT, radiotherapy; SD, standard deviation.

Statistical Analysis for ΔFA% Versus IQ Scores

Multivariate regression analysis with ΔFA% as the only independent variable found significant correlations with FSIQ (Fig 1; adjusted $r^2 = 0.434$; $P < .001$), VIQ (Fig 2; adjusted $r^2 = 0.234$; $P = .004$), and PIQ (Fig 3; adjusted $r^2 = 0.515$; $P < .001$). Note that the overall significance of ΔFA% with the three IQ scores was significant (Wilk's Lambda test, $P < .001$). In stage 1 of multivariate regression analysis using sex, educational level, and socioeconomic status as independent variables, we found that these variables were all not significant factors affecting IQ scores (Wilk's lambda test, $P = .686$, $P = .490$, and $P = .232$, respectively). Therefore, these variables were excluded from further multivariate analysis. In stage 2, after adjusting for the effects of age at treatment, irradiation dose and time interval from treatment, ΔFA% remained as a significant factor of FSIQ (adjusted $r^2 = 0.439$; $P < .001$), VIQ (adjusted $r^2 = 0.237$; $P = .028$), and PIQ (adjusted $r^2 = 0.491$; $P < .001$; Table 3).

Using 85 as a cutoff for below average IQ score, receiver operating characteristic curve analysis showed that the best ΔFA% value to predict less than 85 scores in FSIQ, VIQ, and PIQ was −3.3%. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for predicting FSIQ less than 85, VIQ less than 85, and PIQ less than 85 using ΔFA % = −3.3% are presented in Table 4.

DISCUSSION

In a cohort of childhood post-treatment MED and ALL survivors, we found that ΔFA% (difference between patient FA and age-matched healthy control group FA normalized to the control group FA) of the white matter is significantly correlated with FSIQ, VIQ, and PIQ before and after adjusting for age at treatment, irradiation dose, and time interval since treatment. In addition, a ΔFA% cutoff of −3.3% provided a high specificity (100%), high negative predictive value (100%), and low negative likelihood ratio (0) for FSIQ and PIQ of less than 85. Together with high positive likelihood ratios, our results

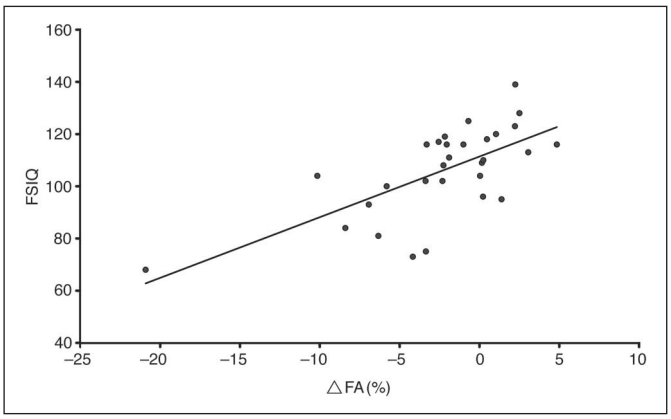

Fig 1. Scatter plot of FSIQ (full-scale intelligence quotient) and ΔFA% (percentage difference in white matter fractional anisotropy).

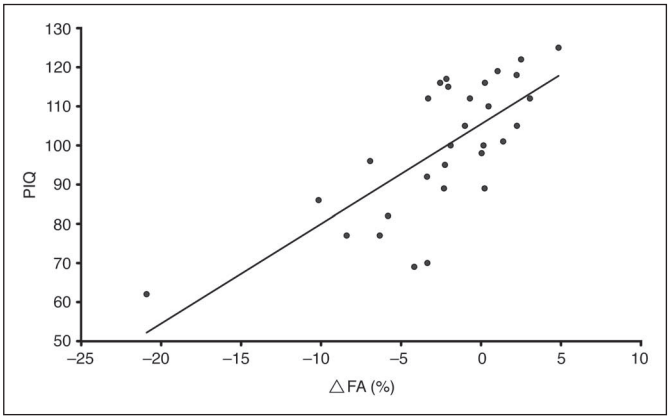

Fig 2. Scatter plot of PIQ (performance intelligence quotient) and ΔFA% (percentage difference in white matter fractional anisotropy).

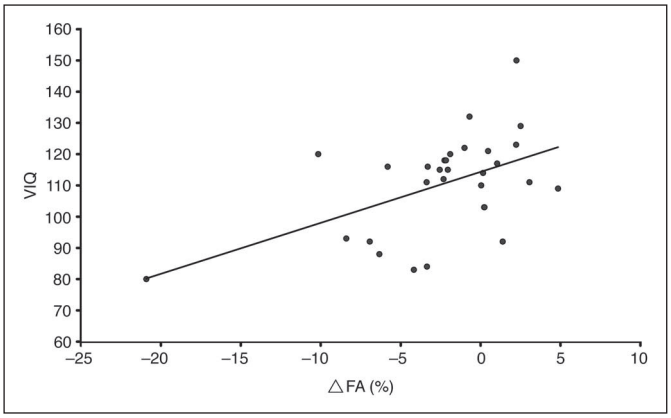

Fig 3. Scatter plot of VIQ (verbal intelligence quotient) and ΔFA% (percentage difference in white matter fractional anisotropy).

suggest that FA is a clinically useful indicator of cognitive outcome in this cohort of childhood cancer survivors. Positive predictive values were found to be moderate and this can, in part, be explained by the low prevalence of IQ scores less than 85 in our cohort.

It has been shown that white matter FA increases nonlinearly with age with the steepest increase occurring in the first few years of life, reaching asymptote at about 6 years in the internal capsule and corpus callosum and at about 8 years in the peripheral white matter of the centrum semiovale.[19-22] This is attributed to several factors, including myelination, and increases in the number of axons, axonal diameter, and fiber coherence. Hence, we have used age-matched patient controls to derive the ΔFA% for each patient.

The association of DTI indices with cognitive function has been shown in both normal and diseased populations. Nagy et al[23] found that the development of cognitive abilities in childhood is correlated with maturation of white matter; specifically, working memory and reading abilities were found to correlate with increased FA in the superior and inferior left frontal lobe and the left temporal lobe, respectively. Peng et al[24] studied children with early chronic malignant phenylketonuria and found that VIQ, PIQ, and FSIQ were related to alteration of diffusion indices in the parieto-occipital white matter. Similar correlations have been found in minimal cognitive impairment and Alzheimer's disease,[25] ischemic leukoaraiosis,[26] and relapsing-remitting multiple sclerosis.[27] In our cohort of childhood cancer survivors, apart from white matter damage from cranial irradiation and chemotherapy, contributory causes of cognitive decline in MED survivors include the primary effects of the tumor in the cerebellum, cerebellar resection,[28,29] and its complications such as posterior fossa syndrome and hydrocephalus;[30] and in ALL survivors, cortical atrophy and mineralizing microangiopathy are known sequelae of intrathecal methotrexate chemotherapy, which affect cognition.[31] Therefore, white matter FA, which could be an indicator of myelin and/or axonal integrity, only partially accounts for cognitive function in our cohort.

We note that the IQ scores of our cohort are relatively high compared with other studies, especially the MED survivors. Mulhern et al[12] and Palmar et al[34] found the IQ scores in MED survivors to be between 80 and 85. The IQ scores of ALL survivors have been found to be generally higher and often within the normal range.[31] This is presumably partly because of the lower cranial irradiation dose in these patients. However, most studies have found some decline in one or more aspects of cognitive function when individual subsets scores are assessed.[31] Since the cognitive impairment in ALL survivors is relatively mild and difficult to detect, this may be evident only when a matching control group IQ is used for comparison.[32,33] High IQ scores in our cohort may reflect selection bias, a relatively high age at diagnosis and treatment of our MED group (mean age at diagnosis, 8.5 years, which is older than in most studies), and conservative irradiation doses. In our cohort, the lack of a significant difference in the IQ scores between MED survivors and ALL survivors may be because IQ tests were performed at a shorter interval since treatment in the former group, as it has been shown that IQ scores progressively decline with interval since treatment.[4,34,35] The subtest with most frequent below average score in our cohort was digit symbol/coding (34.5%). This subtest is a test of psychomotor performance and involves motor persistence, sustained attention, response speed, and visuomotor coordination. It is considered a sensitive test of brain damage and tends to be affected regardless of the locus of the lesion and is in keeping with the diffuse white matter damage found after whole brain irradiation.

Our study is limited by a relatively small, heterogeneous cohort with varied treatment protocols and disease processes. Our findings may, therefore, only be specific to this cohort of patients and should not be generalized to other types of cohorts. In addition, the small subject numbers may result in the lack of power for determination of the effect of some factors in the multivariate regression analysis. The

Table 3. Showing Multivariate Regression Analysis of the Relationships Between Independent Variables; ΔFA% and Neurotoxicity Risk Factors; Age at Treatment, Irradiation Dose and Time Interval From Treatment and Dependent Variables; Full-Scale IQ, Verbal IQ, and Performance IQ

		Full-Scale IQ			Performance IQ			Verbal IQ		
Variables	*P** (overall significance)	Effect Estimate	95% CI	*P*	Effect Estimate	95% CI	*P*	Effect Estimate	95% CI	*P*
Unadjusted analysis		adjusted $r^2 = 0.434$			adjusted $r^2 = 0.515$			adjusted $r^2 = 0.234$		
ΔFA%	< .001	2.323	1.336 to 3.311	< .001	2.546	1.621 to 3.472	< .001	1.631	0.568 to 2.694	.004
Adjusted analysis		adjusted $r^2 = 0.439$			adjusted $r^2 = 0.491$			adjusted $r^2 = 0.237$		
ΔFA	.001	2.064	0.924 to 3.204	< .001	2.600	1.502 to 3.699	< .001	1.254	0.023 to 2.484	.028
Age at Rx	.308	0.753	−0.480 to 1.987	.220	0.323	−0.866 to 1.511	.581	0.796	−0.535 to 2.127	.230
RT dose	.531	−0.033	−0.426 to 0.361	.866	0.137	−0.242 to 0.516	.464	−0.127	−0.551 to 0.298	.545
Interval	.934	−0.369	−1.696 to 0.957	.571	−0.191	−1.469 to 1.087	.761	−0.399	−1.830 to 1.032	.571

Abbreviations: ΔFA%, percentage difference in white matter FA; IQ, intelligence quotient; ΔFA, difference in fractional anisotropy; Rx,treatment; RT, radiotherapy.
*By Wilk's lambda test.

Table 4. Showing Sensitivity, Specificity, PPV, NPV, LR+, and LR− of Full-Scale IQ < 85, Verbal IQ < 85, and Performance IQ < 85 When ΔFA% = −3.3%

	Full-Scale IQ		Verbal IQ		Performance IQ	
Variable	%	95% CI	%	95% CI	%	95% CI
Sensitivity	84	63.9 to 95.5	77.8	57.7 to 91.4	87.5	67.6 to 97.3
Specificity	100	47.8 to 100	100	29.2 to 100	100	54.1 to 100
PPV	55.6	21.2 to 86.3	33.3	7.5 to 70.1	66.7	29.9 to 92.5
NPV	100	83.9 to 100	100	83.9 to 100	100	83.9 to 100
LR+	6.3	2.5 to 15.3	4.5	2.2 to 9.1	8.0	2.8 to 23.1
LR−	0		0		0	

Abbreviations: PPV, positive predictive value; NPV,negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; IQ, intelligence quotient; ΔFA%, percentage difference in white matter FA.

age ranges applied to the control subjects in this study are arbitrary and were selected such that they were reasonably small. The use of mean FA reference values of an age-range, albeit small, instead of exact age-match is another limitation that has been discussed in our previous publication.[18] The cross-sectional nature of the study does not allow the assessment of developmental trends in IQ and FA. In a prospective study, if FA decline is found to herald IQ deterioration and is able to indicate damage before the completion of treatment, it may be used as a parameter to effect change in treatment strategy. Also, two patients had a prolonged time lag of more than 1 year between IQ test and DTI, which may have affected the accuracy of our results. Finally, in the assessment of cognitive function, we did not evaluate more specific tests to tap specific cognitive abilities, which have been reported to decline after cranial irradiation, for example, memory and learning, attention and information processing speed. These tests may be more sensitive to the detection of cognitive decline and it may be possible that some of these tests have a stronger correlation with ΔFA%. Nevertheless, our preliminary observations warrant prospective, larger scale studies and further research in this area.

In conclusion, our findings suggest that DTI, using FA as a biomarker, may be a clinically useful tool for the assessment of treatment-related neurotoxicity and can be used as an adjunct to IQ scores. Longitudinal studies should be performed with close time points after treatment to determine the patterns of FA change and if loss of FA can be used to predict subsequent IQ decline. Apart from the assessment of neurotoxicity, this biomarker may potentially be useful in the assessment of timing and application of neurotoxic treatments and to test the effectiveness of neuroprotective drugs.

REFERENCES

1. Packer RJ, Sposto R, Atkins TE, et al: Quality of life in children with primitive neuroectodermal tumors (medulloblastoma) of the posterior fossa. Pediatr Neurosci 13:169-175, 1987

2. Johnson DL, McCabe MA, Nicholson HS, et al: Quality of long-term survival in young children with medulloblastoma. J Neurosurg 80:1004-1010, 1994

3. Walter AW, Mulhern RK, Gaijar A, et al: Survival and neurodevelopmental outcome of young children with medulloblastoma at St. Jude Children's Research Hospital. J Clin Oncol 17:3720-3728, 1999

4. Spiegler BJ, Bouffet E, Greenberg ML, et al: Change in neurocognitive functioning after treatment with cranial radiation in childhood. J Clin Oncol 22:706-713, 2004

5. Mulhern RK, White HA, Glass JO, et al: Attentional functioning and white matter integrity among survivors of malignant brain tumors of childhood. J Int Neuropsychol Soc 10:180-189, 2004

6. Reddick WE, White HA, Glass JO, et al: Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. Cancer 97:2512-2519, 2003

7. Mulhern RK, Reddick WE, Palmer SL, et al: Neurocognitive deficits in medulloblastoma survivors and white matter loss. Ann Neurol 46:834-841, 1999

8. Ball WS, Prenger EC, Ballard ET: Neurotoxicity of radio/chemotherapy in children: Pathologic and MR correlation. AJNR Am J Neuroradiol 13:761-776, 1992

9. Curran WJ, Hecht-Leavitt C, Schut L, et al: Magnetic resonance imaging of cranial radiation lesions. Int J Radiat Oncol Biol Phys 13:1093-1098, 1987

10. Constine LS, Konski A, Ekholm S, et al: Adverse effects of brain irradiation correlated with MR and CT imaging. Int J Radiat Oncol Biol Phys 15:319-330, 1988

11. Tsuruda JS, Kortman KE, Bradley WG, et al: Radiation effects on cerebral white matter: MR evaluation. AJR Am J Roentgenol 149:165-171, 1987

12. Mulhern RK, Palmer SL, Reddick WE, et al: Risks of young age for selected neurocognitive deficits in medulloblastoma are associated with white matter loss. J Clin Oncol 19:472-479, 2001

13. Chu WCW, Chik KW, Chan YL, et al: White matter and cerebral metabolite changes in children undergoing treatment for acute lymphoblastic leukemia: Longitudinal study with MR imaging and H MR spectroscopy. Radiology 229:659-669, 2003

14. Chan YL, Roebuck DJ, Yuen MP, et al: Long-term cerebral metabolite changes on proton magnetic resonance spectroscopy in patients cured of acute lymphoblastic leukemia with previous intrathecal methotrexate and cranial irradiation prophylaxis. Int J Radiat Oncol Biol Phys 50:759-763, 2001

15. Khong PL, Kwong DLW, Chan GCF, et al: Diffusion-tensor imaging (DTI) for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: A pilot study. AJNR Am J Neuroradiol 24:734-740, 2003

16. Leung LHT, Ooi GC, Kwong DL, et al: White-matter diffusion anisotropy after chemo-irradiation: A statistical parametric mapping study and histogram analysis. Neuroimage 21:261-268, 2004

17. LeBihan D, Mangin JF, Poupon C, et al: Diffusion tensor imaging: Concepts and applications. J Magn Reson Imag 13:534-546, 2001

18. Khong PL, Leung LH, Chan GCF, et al: White matter anisotropy in childhood medulloblastoma survivors: Association with neurotoxicity risk factors. Radiology 236:647-652

19. Nomura Y, Sakuma H, Tagami T, et al: Diffusional anisotropy of the human bran assessed with diffusion-weighted MR: Relation with normal brain development and aging. AJNR Am J Neuroradiol 15:231-238, 1994

20. Morriss MC, Zimmerman RA, Bilaniuk LT, et al: Changes in brain water diffusion during childhood. Neuroradiology 41:929-934, 1999

21. Mukherjee P, Miller JH, Shimony JS, et al: Normal brain maturation during childhood: Developmental trends characterized with diffusion-tensor MR imaging. Radiology 221:349-358, 2001

22. Philip JV, Mukherjee P, Neil JJ, et al: White matter maturation in older children demonstrated with diffusion tensor MRI. Proc Intl Soc Mag Reson Med 9:409, 2001

23. Nagy Z, Westerberg H, Klingberg T, et al: Maturation of white matter is associated with the development of cognitive functions during childhood. J Cogn Neurosci 16:1227-1233, 2004

24. Peng SSF, Tseng WYI, Chien YH, et al: Diffusion tensor images in children with early-treated, chronic, malignant phenylketonuric: Correlation with intelligence assessment. AJNR Am J Neuroradiol 25:1569-1574, 2004

25. Kantarci K, Jack CR, Xu YC, et al: Mild cognitive impairment and Alzheimer disease: Regional diffusivity of water. Radiology 219:101-107, 2001

26. O'Sullivan M, Morris RG, Huckstep B, et al: Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. J Neurol Neurosurg Psychiatry 75:441-447, 2004

27. Rovaris M, Iannucci G, Falautano M, et al: Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: An exploratory study with diffusion tensor MR imaging. J Neurol Sci 195:103-109, 2002

28. Steinlin M, Imfeld S, Zulauf P, et al: Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. Brain 126:1998-2008, 2003

29. Riva D, Giorgi C: The cerebellum contributes to higher functions during development: Evidence from a series of children surgically treated for posterior fossa tumours. Brain 123:1051-1061, 2000

30. Mabbott DJ, Spiegler BJ, Greenberg ML, et al: Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. J Clin Oncol 23:2256-2263, 2005

31. Moleski M: Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. Arch Clin Neuropsychol 15:603-630, 2000

32. Ochs J, Mulhern R, Fairclough D, et al: Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial radiation or parenteral methotrexate: A prospective study. J Clin Oncol 9:145-151, 1991

33. Giralt J, Ortega JJ, Olive T, et al: Long-term neuropsychologic sequelae of childhood leukemia: Comparison of two CNS prophylactic regimens. Int J Radiat Oncol Biol Phys 24:49-53, 1992

34. Palmer SL, Goloubeva O, Reddick WE, et al: Patterns of intellectual development among survivors of pediatric medulloblastoma: A longitudinal analysis. J Clin Oncol 19:2302-2308, 2001

35. Palmer SL, Gaijar A, Reddick WE, et al: Predicting intellectual outcome among children treated with 35-40 Gy craniospinal irradiation for medulloblastoma. Neuropsychology 17:548-555, 2003

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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CORRECTIONS

Author Corrections

The February 20, 2006, article by Khong et al, entitled "White Matter Anisotropy in Post-Treatment Childhood Cancer Survivors: Preliminary Evidence of Association With Neurocognitive Function" (J Clin Oncol 24:884-890, 2006), contained an error in the spelling of the eighth author's name. It was originally given as Grainne McAlanon and should have been Grainne McAlonan. The authors apologize to the readers for the mistake.

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The August 1, 2010, article by Konstantinopoulos et al entitled "Gene Expression Profile of *BRCA*ness That Correlates With Responsiveness to Chemotherapy and With Outcome in Patients With Epithelial Ovarian Cancer" (J Clin Oncol 28: 3555-3561), contained errors.

In Figure 2b, patients 1, 2, and 4 were incorrectly labeled as revertant. Also, patient 3 was originally labeled as BRCA-2 mutation/BRCA-2 revertant, whereas the label should have read **BRCA-1 mutation and BRCA-2 mutation/BRCA-1 mutation and BRCA-2 revertant.**

In the Abstract, under Results, the first sentence contained an error and should have read: "The BRCAness profile accurately predicted **platinum responsiveness** in eight out of 10 patient-derived tumor specimens, and between PARP-inhibitor sensitivity and resistance in four out of four Capan-1 clones**.**"

In the Methods section, under Patient Samples, the second sentence of the first paragraph should have read: "The first included six EOC patients with BRCA-1/-2 germline mutations, **three of whom** have been previously described."

In the Results section, under BRCAness Profile Distinguishes Between Platinum-Sensitive and Platinum-Resistant Tumor Biopsy Samples, the third sentence of the first paragraph should have read: "**One of these patients** was previously reported to have reversion of the BRCA genotype upon development of platinum resistance." In the same paragraph, the last sentence should have read: "Thus, these samples afforded us with an opportunity to determine how the BRCAness profile correlated with **platinum responsiveness**."

In the same section, in the last paragraph, references to revertant (functional) BRCA gene status should have been removed.

In the legend for Figure 2b, the last sentence should have read: "The BRCAness profile accurately distinguished between platinum sensitivity and platinum resistance in eight out of 10 tumor specimens."

In the Acknowledgments section, the following text should have been included: "and Elizabeth Swisher, MD, for her assistance in clarifying the BRCA mutation status of patients shown in Figure 2."

In the Appendix, under Patient Samples, the following text in the first paragraph should have been omitted: "In each case, the development of platinum resistance was associated with reversion to functional BRCA1 and BRCA2 protein.[23,30]"

The online version has been corrected in departure from the print. The authors apologize to the readers for the mistakes.

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Journal Correction

The October 1, 2010, article by Bianchini et al, entitled "Molecular Anatomy of Breast Cancer Stroma and Its Prognostic Value in Estrogen Receptor–Positive and –Negative Cancers" (J Clin Oncol 28: 4316-4323), contained errors.

The labels for the y-axes of Figure 3 were originally given as B-Cell Cluster Score, and should have been **B-cell/plasma cell Metagene Score**. Also, the labels for the x-axes were inadvertently transposed, and should have read: **ER- No Relapse, ER- Relapse, ER+ No Relapse, ER+ Relapse.**

The online version has been corrected in departure from the print. *Journal of Clinical Oncology* apologizes to the authors and readers for the mistakes.

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