Neuro-Oncology

19(12), 1673–1682, 2017 | doi:10.1093/neuonc/nox135 | Advance Access date 19 July 2017

Posterior fossa syndrome and long-term neuropsychological outcomes among children treated for medulloblastoma on a multi-institutional, prospective study

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Abstract

Background. Patients treated for medulloblastoma who experience posterior fossa syndrome (PFS) demonstrate increased risk for neurocognitive impairment at one year post diagnosis. The aim of the study was to examine longitudinal trajectories of neuropsychological outcomes in patients who experienced PFS compared with patients who did not.

Methods. Participants were 36 patients (22 males) who experienced PFS and 36 comparison patients (21 males) who were matched on age at diagnosis and treatment exposure but did not experience PFS. All patients underwent serial evaluation of neurocognitive functioning spanning 1 to 5 years post diagnosis.

Results. The PFS group demonstrated lower estimated mean scores at 1, 3, and 5 years post diagnosis on measures of general intellectual ability, processing speed, broad attention, working memory, and spatial relations compared with the non-PFS group. The PFS group exhibited estimated mean scores that were at least one standard deviation below the mean for intellectual ability, processing speed, and broad attention across all time points and for working memory by 5 years post diagnosis. Processing speed was stable over time. Attention and working memory declined over time. Despite some change over time, caregiver ratings of executive function and behavior problem symptoms remained within the average range.

Conclusion. Compared with patients who do not experience PFS, patients who experience PFS exhibit greater neurocognitive impairment, show little recovery over time, and decline further in some domains. Findings highlight the particularly high risk for long-term neurocognitive problems in patients who experience PFS and the need for close follow-up and intervention.

Key words

brain tumor | medulloblastoma | neuropsychological outcomes | posterior fossa syndrome

Medulloblastoma is the most common pediatric malignant brain tumor.[1,2] Five-year survival rates are 70%–85% with treatment that includes surgical resection, risk-adapted radiation treatment, and chemotherapy.[3] Medulloblastoma arises in the posterior fossa region and the extent of the surgical resection is a good prognostic marker.[4] Thus, neurosurgeons will often strive for a gross total resection whenever possible. However, a

Importance of the study

Medulloblastoma patients who experience PFS demonstrate worse neuropsychological functioning at one year post diagnosis; however, the long-term neurobehavioral consequences of PFS have not been comprehensively evaluated. Our study is the first to prospectively examine the longitudinal trajectories of neuropsychological outcomes in pediatric medulloblastoma patients who experienced PFS compared with patients who did not experience PFS but were matched on treatment and age at diagnosis.

consequence of surgery in this brain region is posterior fossa syndrome (PFS), sometimes referred to as cerebellar mutism. PFS occurs in up to 29% of medulloblastoma patients following surgery.[5,6]

Patients with PFS generally present with diminished speech or mutism that can be accompanied by ataxia, hypotonia, emotional lability, and other neurobehavioral abnormalities.[7–10] Presentation is variable, with a delayed onset of anywhere from 1 to 6 days following surgery and a limited symptom duration of between 1 day and 4 months.[8] Recovery is often spontaneous but can be followed by a period of speech dysarthria.[7,8] Many patients have long-term speech difficulties[7,11–13] and are at increased risk for psychosocial problems following treatment.[14]

PFS may result from bilateral damage to the proximal efferent cerebellar pathways along the dentorubrothalamocortical pathway.[15–17] Damage anywhere along the dentorubrothalamocortical pathway may lead to a speech disorder, and damage to the dentate nuclei, in particular, may cause mutism. Cerebellar pathways also play a role in higher-order functions. Adults with acquired cerebellar lesions demonstrate persistent impairments in executive function, visual-spatial organization, linguistic processing, and affect regulation.[18] Subsequent studies have suggested a similar pattern of cognitive impairment in children who experienced cerebellar lesions.[19,20]

Declines in neurocognitive functioning are well documented in children treated for medulloblastoma.[21–24] Treatment-related risk factors (eg, younger age, higher dose of radiation) are associated with worse outcomes over time; attention, working memory, and processing speed are particularly vulnerable.[25] PFS is also associated with worse neurocognitive outcomes in survivors.[26–28] Medulloblastoma patients who experienced PFS demonstrated significantly poorer neurocognitive function at 12 months post diagnosis compared with patients who did not experience PFS.[28] However, the long-term neurobehavioral consequences of PFS have yet to be examined.

The present study examined the longitudinal trajectory of attention, working memory, processing speed, visual-spatial ability, and overall intellectual ability over 5 years in patients who experienced PFS compared with patients, matched on age at diagnosis and treatment exposure (high vs average risk), who did not experience PFS. Caregiver reports of executive functioning and behavior problem symptoms were also examined. We hypothesized that functioning in these areas would be statistically lower over time in patients who experienced PFS compared with patients who did not experience PFS.

Methods

Patient Population

Out of 327 participants with histologically confirmed medulloblastoma enrolled on an ongoing institutional review board–approved multisite clinical trial (SJMB03) for patients with newly diagnosed embryonal brain tumor, 77 (24%) experienced PFS. Thirty-six participants who experienced PFS were included in the present study. Thirty-eight were excluded because they did not participate in any cognitive testing due to medical status restricting assessment ($n = 1$), lack of English proficiency ($n = 2$), refusing informed consent ($n = 7$), refusing testing ($n = 2$), ineligibility (due to blindness and preexisting intellectual disability; $n = 2$), taken off study ($n = 7$), patient dying ($n = 10$), or multiple reasons across different time points ($n = 7$). In addition, patients were excluded for providing data at only one time point ($n = 2$) and another provided only partial data ($n = 1$).

Thirty-six comparison participants were selected by identifying patients who did not experience PFS who matched the PFS patients on age at diagnosis and disease risk status (average vs high). Since disease risk status dictated treatment, patients were also matched on treatment intensity (described below). Comparison participants were also matched on sex and race when possible.

All participants provided informed consent at one of 9 participating institutions, which all followed the same protocol-driven medical treatment. Patients underwent surgical resection and were classified as having average risk medulloblastoma (≤1.5 cm^2 residual tumor and no metastatic disease) or high-risk medulloblastoma (>1.5 cm^2 residual disease and/or metastatic disease localized to the neuraxis) according to a modified Chang staging system.[29] Following surgery, a diagnosis of PFS was made by the treating physician if clinical features were present (eg, diminished speech or mutism, ataxia, hypotonia, emotional lability). Patients were treated with postsurgical risk-adapted craniospinal photon irradiation (CSI) that was initiated within 31 days of surgery. Patients with high-risk disease received CSI (M0–1, 36 Gy; M2–3, 36–39.6 Gy) and supplemental photon irradiation to the tumor bed using conformal treatment methods (total dose, 55.8 Gy). When appropriate, local sites of metastasis received supplemental photon irradiation (total dose, 50.4–54 Gy). Patients with average risk disease received 23.4 Gy CSI and supplemental conformal photon irradiation to the tumor bed to 55.8 Gy. The clinical target volume to the tumor

bed was 1.0 cm for all patients. Following radiation therapy, at approximately 12 weeks post treatment initiation, all patients received 4 cycles of high-dose chemotherapy (cyclophosphamide, cisplatin, and vincristine) with stem cell support.

Cognitive and Academic Assessment

Protocol-driven cognitive assessments were scheduled to be conducted at baseline (after surgical resection and within 2 weeks of radiation therapy) and at 1, 3, and 5 years post diagnosis at all participating institutions. At St Jude Children's Research Hospital, patients were evaluated at baseline and annually for 5 years post diagnosis. The baseline assessment was scheduled for shortly after surgery, and thus many of the participants who experienced PFS were not well enough to complete it. Therefore, baseline data were excluded from the analyses. Data were randomly missing at other time points for a variety of reasons (see Appendix). To be included in the present study, participants had to provide data at 2 or more time points in order to examine change in functioning over time.

Measures

The following scores from the Woodcock–Johnson Tests of Cognitive Abilities, Third Edition (WJIII)[30] were examined in the present study: General Intellectual Ability (GIA), Processing Speed cluster (PS), Broad Attention cluster (BA), Working Memory cluster (WM), and the Spatial Relations subtest score (SR). The WJIII has a population mean of 100 with a standard deviation of 15 points. Lower scores indicate poorer performance. The following scores from the Behavior Rating Inventory of Executive Function (BRIEF),[31] a caregiver-report questionnaire measuring child executive functioning, were utilized in the present study: Behavior Regulation Index (BRI) and Metacognitive Index (MI). Two versions of the Child Behavior Checklist (CBCL),[32] a caregiver-report questionnaire measuring child behavioral and emotional problems, were used. The CBCL/1½–5 is for children 1½ to 5 years of age, while the CBCL/6–18 is for children aged 6 to 18 years; the present study utilized the Internalizing (INT), Externalizing (EXT), and Total Problems (TP) index scores. For all questionnaires, the population mean is 50 with a standard deviation of 10 points. Higher scores indicate more problems.

Statistical Analysis

Linear mixed-effect models (LMMs) using PROC MIXED procedures in SAS 9.2 were used because they allow for missing data and maximize all data available to fit the slope. LMMs were fitted to examine the average rate of change over time (slope) and differences in estimates of slope between the PFS group and the non-PFS group. Differences in estimated scores at 1, 3, and 5 years post diagnosis were also examined by setting modifications in the LMM. For each outcome, a matched pair was included in the analysis if both the PFS case and the matched non-PFS comparison case provided data from at least 2 time points; otherwise, both cases from the matched pair were excluded from the analysis of that particular outcome. All analyses performed were 2-tailed and a significance threshold alpha level of $P = 0.05$ was used.

Results

Demographic and Clinical Comparisons

Table 1 includes demographic and clinical characteristics for the PFS patients who were included in the present analyses versus PFS patients from the source population who were excluded due to not completing cognitive testing. The PFS group included was significantly more racially diverse; however, no differences in sex or age at diagnosis were found. The excluded PFS patient group included significantly more high-risk patients compared with the included PFS group. Table 2 includes demographic and clinical characteristics for the PFS group compared with the matched non-PFS comparison group included in the study. No differences in sex, race, age at diagnosis, or risk were found. There was a significant group difference in the number of surgeries such that PFS patients underwent slightly more surgeries.

Table 1 Comparisons between participants included in the current study who experienced PFS and participants who experienced PFS but were excluded from the current study

Variable	Included Patients Who Experienced PFS ($N = 36$)	Excluded Patients Who Experienced PFS ($N = 41$)	*P*-value
Age at diagnosis, M (SD)	8.4 (2.7)	8.7 (3.1)	0.57
Race, % (*n*)			
White	69.4 (25)	85.4 (36)	<0.05
Black	8.3 (3)	4.9 (2)	
Asian	11.1 (4)	4.9 (2)	
Other	11.1 (4)	2.4 (1)	
Risk, % (*n*)			
Average	83.3 (30)	48.8 (20)	<0.01
High	16.7 (6)	51.2 (21)	
Sex, % (*n*)			
Female	38.9 (14)	31.7 (13)	0.51
Male	61.1 (22)	68.3 (28)	

Note. Participants with PFS came from the following institutions: Children's Hospital of Philadelphia ($n = 1$), Duke University Medical Center ($n = 7$), Hospital for Sick Children ($n = 10$), Lady Cilento Children's Hospital ($n = 10$), Royal Children's Hospital, Melbourne ($n = 4$), St Jude Children's Research Hospital ($n = 33$), Sydney Children's Hospital ($n = 1$), Texas Children's Hospital ($n = 11$).

Table 2 Comparisons between participants who experienced PFS and matched participants who did not experience PFS

Variable	Experienced PFS (*N* = 36)	Did Not Experience PFS (*N* = 36)	*P*-value
Age at diagnosis, M (SD)	8.4 (2.7)	8.3 (2.6)	0.95
Race, % (*n*)			
White	69.4 (25)	83.3 (30)	0.17
Black	8.3 (3)	5.6 (2)	
Asian	11.1 (4)	5.6 (2)	
Other	11.1 (4)	5.6 (2)	
Risk, % (*N*)			
Average	83.3 (30)	83.3 (30)	1.00
High	16.7 (6)	16.7 (6)	
Surgeries (*SD*)	1.64 (1.25)	1.28 (0.45)	0.04
Sex, % (*N*)			
Female	38.9 (14)	41.7 (15)	0.81
Male	61.1 (22)	58.3 (21)	

Performance-Based Measures

Results from the LMM of performance-based measures are in Table 3. Examination of estimated mean scores (intercepts) at specific time points revealed significant group differences on all estimated WJIII scores for the GIA, PS, BA, WM, and SR at 1, 3, and 5 years post diagnosis such that the PFS group demonstrated significantly lower scores compared with the non-PFS group (see Fig. 1). Furthermore, the PFS group had estimated mean scores that were at least one standard deviation below the mean across all time points for GIA, PS, and BA and by 5 years post diagnosis for WM. For SR, both groups had scores within the average range.

Results for GIA indicated that both groups demonstrated a slight increase in scores. However, neither group's rate of change over time was significantly different from zero, nor was there a significant difference in rate of change between groups. Change over time in PS was not significantly different from zero in either group, and there was no significant difference in rate of change between groups. Both groups' PS scores remained low over time. The BA and WM showed significant and nearly significant decline for both groups, respectively. The BA rate of decline was nearly significantly different between groups, but the WM rate of decline was not significantly different between groups. Increase over time on the SR was significant for the PFS group, but not significantly different from zero for the non-PFS group. The rate of change was not significantly different between groups.

Caregiver-Report Measures

Results from the LMM of caregiver-report measures are in Table 4. Higher scores on caregiver-report measures indicate more problems. All caregiver-report measures remained within the average range over time. On BRI and MI, estimated scores were significantly different between groups at 1 year post diagnosis; but not at other time points (see Fig. 2). On BRI, the non-PFS group demonstrated significant increase over time. However, the PFS group did not demonstrate change that was significantly different from zero, nor was there a significant group difference in rate of change over time. On MI, the non-PFS group demonstrated significant increase over time; however, the PFS group did not show change that was significantly different from zero. The rate of change over time was only near a significant difference between groups.

On INT, there was no significant difference between estimated scores at any time points (see Fig. 2). Results from INT indicated that neither group demonstrated change over time that was significantly different from zero, and there was no significant group difference in the rate of change over time. On EXT, there was a significant group difference in estimated scores at 1 and 3 years post diagnosis; however, estimated scores at 5 years post were not significantly different (see Fig. 2). Neither group demonstrated change over time that was significantly different from zero, and there was no significant group difference in rate of change over time. On TP, there was a significant group difference in estimated scores at 1 year post diagnosis and a near significant group difference at 3 years post diagnosis; however, estimated scores at 5 years post diagnosis were not significantly different (see Fig. 2). The non-PFS group demonstrated a near significant increase in scores over time, but the PFS group did not demonstrate change over time that was significantly different from zero. There was only a near significant group difference in rate of change in scores over time.

Discussion

This is the first study to prospectively examine longitudinal trajectories of cognitive and behavioral outcomes in pediatric medulloblastoma patients who experienced PFS compared with medulloblastoma patients, matched on age at diagnosis and treatment exposure, who did not experience PFS. Examination focused on attention, working memory, processing speed, and visual-spatial skills, which have been found to be vulnerable in medulloblastoma patients. Trajectories of cognitive development over 5 years post diagnosis were worse in patients who experienced PFS compared with patients who did not. On average, patients who experienced PFS demonstrated cognitive scores that were lower at 1 year post diagnosis and either demonstrated no significant recovery or continued to decline over time.

The degree of impairment varied depending on the skill measured. Processing speed was the most impaired skill for patients in either group. Participants who experienced PFS exhibited impaired (>2 SD below mean) processing speed and below-average intellectual ability at 1 year post, and scores remained low over time. Given that motor impairment is part of PFS, it is possible that participants who experienced PFS had more difficulty on processing speed tests, in part because these tests included a motor

Table 3 Results for linear-mixed effect models using performance-based measures

WJIII Measures		*N* (obs)	Effect	Estimate	SE	*P*-value
WJIII GIA	No PFS	33 (120)	Intercept	103.57	3.27	<0.01
			Time	0.36	0.41	0.39
	PFS	33 (112)	Intercept	82.42	3.30	<.01
			Time	0.27	0.44	0.54
	Difference in slope		Time*PFS	–0.09	0.60	0.88
	Difference at Year 1		PFS vs No PFS	–21.15	4.64	<0.01
	Difference at Year 3		PFS vs No PFS	–21.42	4.29	<0.01
	Difference at Year 5		PFS vs No PFS	–21.60	4.47	<0.01
WJIII PS	No PFS	34 (130)	Intercept	83.70	3.28	<0.01
			Time	0.38	0.53	0.47
	PFS	34 (117)	Intercept	64.39	3.34	<0.01
			Time	–0.41	0.55	0.46
	Difference in slope		Time*PFS	–0.79	0.76	0.30
	Difference at Year 1		PFS vs No PFS	–19.31	4.68	<0.01
	Difference at Year 3		PFS vs No PFS	–21.68	4.11	<0.01
	Difference at Year 5		PFS vs No PFS	–23.26	4.40	<0.01
WJIII BA	No PFS	29 (110)	Intercept	100.21	3.72	<0.01
			Time	–0.97	0.54	0.08
	PFS	29 (99)	Intercept	83.76	3.78	<0.01
			Time	–2.39	0.58	<0.01
	Difference in slope		Time*PFS	–1.43	0.80	0.08
	Difference at Year 1		PFS vs No PFS	–16.45	5.30	<0.01
	Difference at Year 3		PFS vs No PFS	–20.73	4.76	<0.01
	Difference at Year 5		PFS vs No PFS	–23.58	5.04	<0.01
WJIII WM	No PFS	35 (137)	Intercept	105.12	3.16	<0.01
			Time	–0.84	0.50	0.09
	PFS	35 (117)	Intercept	92.61	3.26	<0.01
			Time	–1.57	0.54	<0.01
	Difference in slope		Time*PFS	–0.73	0.74	0.32
	Difference at Year 1		PFS vs No PFS	–12.51	4.54	0.01
	Difference at Year 3		PFS vs No PFS	–14.70	3.98	<0.01
	Difference at Year 5		PFS vs No PFS	–16.16	4.26	<0.01
WJIII SR	No PFS	36 (139)	Intercept	103.88	2.05	<0.01
			Time	0.29	0.45	0.52
	PFS	36 (122)	Intercept	91.47	2.12	<0.01
			Time	1.03	0.48	0.04
	Difference in slope		Time*PFS	0.74	0.66	0.27
	Difference at Year 1		PFS vs No PFS	–12.41	2.95	<0.01
	Difference at Year 3		PFS vs No PFS	–10.20	2.24	<0.01
	Difference at Year 5		PFS vs No PFS	–8.72	2.63	0.01

Note. WJIII = Woodcock-Johnson Tests of Cognitive Abilities, Third Edition; WJIII BA = Broad Attention; WJIII GIA = General Intellectual Ability; WJIII PS = Processing Speed; WJIII SR = Spatial Relations subtest; WJIII WM = Working Memory; Standard score mean is 100 with a standard deviation of 15 points.

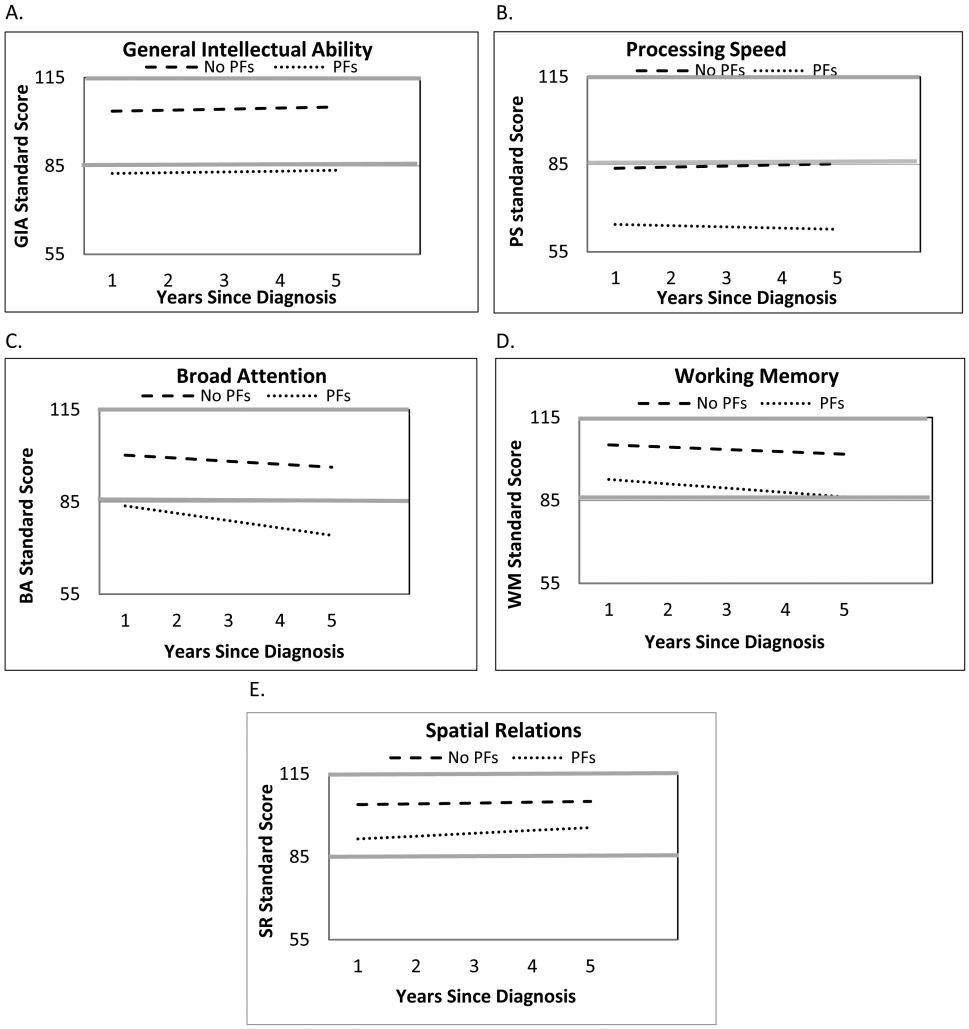

Fig. 1 Estimated change in standard scores on performance-based measures over time (years), specifically: (A) General Intellectual Ability, (B) Processing Speed, (C) Broad Attention, (D) Working Memory, and (E) Spatial Relations. Population mean is 100 with a standard deviation of 15 points. The gray bars mark a standard deviation above and below the mean. Group differences were statistically significant ($P \leq 0.01$) for all outcomes at 1, 3, and 5 years post diagnosis. There were no statistically significant group differences in change over time (slope).

component (marking items with a pencil). Participants who did not experience PFS exhibited low average range processing speed and average range intellectual ability at 1 year post diagnosis that remained stable over time. Participants in both groups demonstrated trajectories of decline in attention and working memory; however, participants who did not experience PFS demonstrated only near significant decline, and scores remained in the average range over time. Participants who experienced PFS demonstrated lower scores at 1 year post diagnosis that significantly declined to low average and impaired (>2 SD below mean) by 5 years post diagnosis for working memory and attention, respectively. Patients who experience PFS may demonstrate worse attention and working memory due to greater disruption in the fronto-cerebellar pathways sustained during surgery compared with patients who did not experience PFS.[33–37] However, surgical guidelines for minimizing risk while maintaining survival are currently unknown. Our results suggest that the early brain insult sustained by patients who experience PFS may contribute to an acute decline in attention, processing speed, and working memory with very little recovery over time.

Findings with regard to visual-spatial ability were less discrepant. All participants exhibited average range scores over time. Prior work indicates that individuals with cerebellar lesions exhibit difficulties primarily on the planning and organizational aspects of visual-spatial drawing and constructional tasks.[19,38] Average range performance in the current study may be due to the use of a multiple choice spatial-relations measure that minimized planning and organizational requirements and placed no demands on drawing and constructional ability.

Caregiver ratings of participant executive function in daily life did not show the same patterns of change over

Table 4 Results for linear mixed-effects models using caregiver-report measures

Caregiver Report Measures		*N* (obs)	Effect	Estimate	SE	*P*-value
BRIEF BRI	No PFS	30 (116)	Intercept	44.58	2.03	<0.01
			Time	0.91	0.44	0.04
	PFS	30 (103)	Intercept	50.53	2.14	<0.01
			Time	−0.15	0.48	0.75
	Difference in slope		Time*PFS	−1.07	0.65	0.10
	Difference at Year 1		PFS vs No PFS	5.95	2.95	<0.05
	Difference at Year 3		PFS vs No PFS	2.75	2.28	0.23
	Difference at Year 5		PFS vs No PFS	0.62	2.66	0.82
BRIEF MI	No PFS	30 (116)	Intercept	43.56	2.18	<0.01
			Time	2.01	0.47	<0.01
	PFS	30 (103)	Intercept	49.83	2.29	<0.01
			Time	0.68	0.51	0.19
	Difference in slope		Time*PFS	−1.33	0.69	0.06
	Difference at Year 1		PFS vs No PFS	6.27	3.16	<0.05
	Difference at Year 3		PFS vs No PFS	2.28	2.45	0.35
	Difference at Year 5		PFS vs No PFS	−0.37	2.86	0.90
CBCL INT	No PFS	32 (119)	Intercept	52.41	2.10	<0.01
			Time	0.22	0.48	0.64
	PFS	32 (108)	Intercept	56.08	2.18	<0.01
			Time	−0.43	0.50	0.39
	Difference in slope		Time*PFS	−0.65	0.69	0.35
	Difference at Year 1		PFS vs No PFS	3.66	3.02	0.23
	Difference at Year 3		PFS vs No PFS	1.70	2.30	0.46
	Difference at Year 5		PFS vs No PFS	0.39	2.75	0.89
CBCL EXT	No PFS	32 (119)	Intercept	44.73	1.75	<0.01
			Time	−0.04	0.39	0.91
	PFS	32 (108)	Intercept	50.28	1.82	<0.01
			Time	−0.61	0.42	0.15
	Difference in slope		Time*PFS	−0.56	0.57	0.33
	Difference at Year 1		PFS vs No PFS	5.55	2.52	0.03
	Difference at Year 3		PFS vs No PFS	3.86	1.94	<0.05
	Difference at Year 5		PFS vs No PFS	2.73	2.30	0.24
CBCL TP	No PFS	32 (119)	Intercept	45.89	1.95	<0.01
			Time	0.77	0.44	0.08
	PFS	32 (108)	Intercept	53.69	2.02	<0.01
			Time	−0.46	0.46	0.33
	Difference in slope		Time*PFS	−1.22	0.64	0.06
	Difference at Year 1		PFS vs No PFS	7.81	2.81	0.01
	Difference at Year 3		PFS vs No PFS	4.14	2.16	0.06
	Difference at Year 5		PFS vs No PFS	1.70	2.56	0.51

Note. BRIEF = Behavior Inventory of Executive Function; BRIEF BRI = Behavior Regulation Index; BRIEF MI = Metacognitive Index; CBCL = Childhood Behavior Checklist; CBCL EXT = Externalizing Problems Index; CBCL INT = Internalizing Problems Index; CBCL TP = Total Problems Index. Standard score mean is 50 with a standard deviation of 10 points.

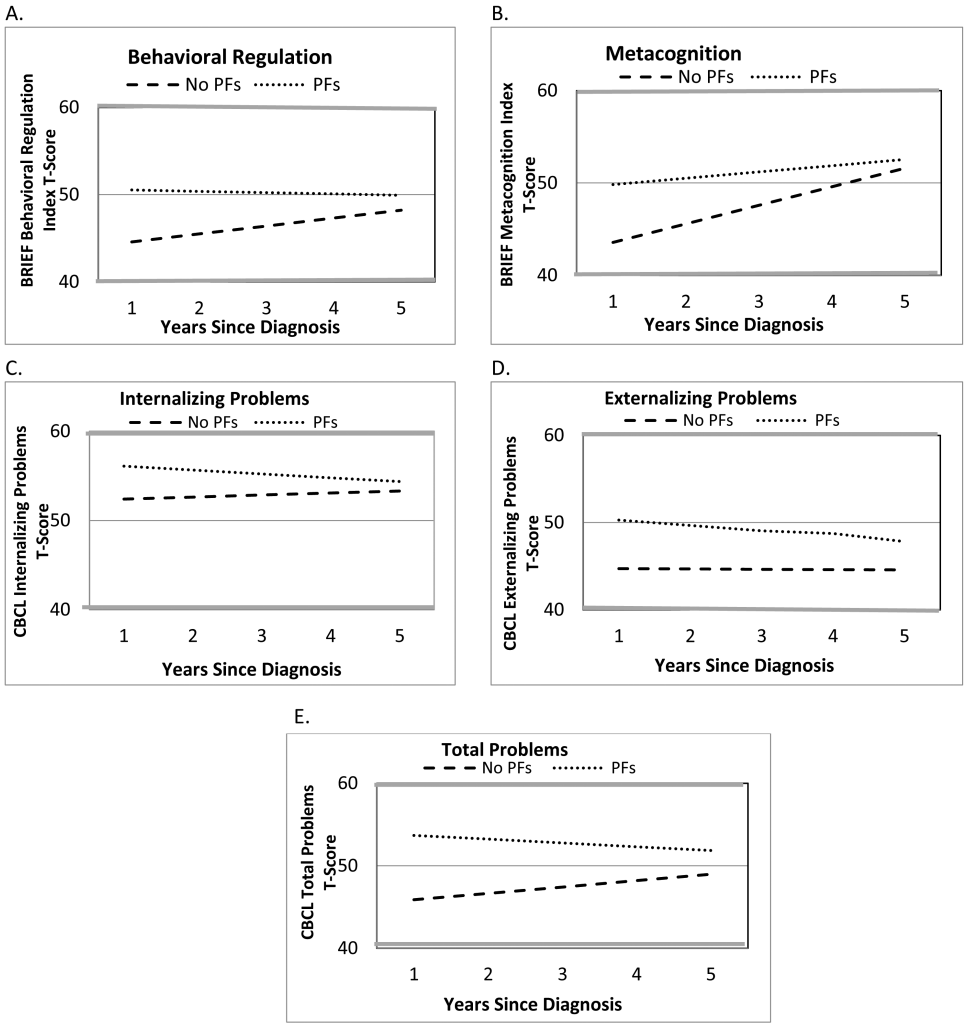

Fig. 2 Estimated change in standard scores on caregiver report measures over time (years), specifically: (A) BRIEF Behavior Regulation, (B) BRIEF Metacognition Index, (C) CBCL Internalizing Problems, (D) CBCL Externalizing Problems, and (E) CBCL Total Problems. Standard score mean is 50 with a standard deviation of 10 points. The gray bars mark a standard deviation above and below the mean. Group differences were statistically significant ($P < 0.05$) at 1 year post diagnosis for BRIEF Behavior Regulation, BRIEF Metacognitive Index, and CBCL Total Problems. Group differences were statistically significant ($P < 0.05$) at 1 and 3 years post diagnosis for CBCL Externalizing Problems. There were near statistically significant group differences ($P = 0.06$) in change over time (slope) for BRIEF Metacognitive Index and CBCL Total Problems only.

time as performance-based measures. Caregivers of all participants reported average behavior regulation over time. Caregivers of participants who experienced PFS rated their children as exhibiting average range metacognition over time. Caregivers of participants who did not experience PFS rated their children as exhibiting a slight increase in metacognitive problems over time; however, scores remained within the average range. Caregiver ratings of executive function provide an estimate of a child's abilities in real-world situations, and thus are qualitatively different than performance-based measures administered in a more structured setting. Other studies have found a lack of direct correspondence between parent report and performance-based behavior measures of executive function.[27,39–42] Lack of convergence across measurement types may be due, in part, to parents accommodating to the difficulties their children exhibit in daily life and no longer viewing them as problematic.[43] However, it is also possible that some children who perform poorly on performance-based measures do not demonstrate these same impairments in daily life. Our results highlight the importance of using multiple methods of measurement, as difficulties would not have been apparent if only the caregiver report were used.

Caregiver ratings of participant behavior problem symptoms indicated that symptoms remained within the normal range over time for both groups. Caregiver report of symptoms was significantly higher at 1 year

post diagnosis for caregivers of participants who experienced PFS, suggesting that caregivers of participants who experienced PFS likely viewed participants as experiencing symptom elevation around the time of diagnosis that then gradually improved over time. This slightly higher rate of behavior problem symptoms is consistent with the report of emotional lability that often occurs as part of PFS.

Although this is the only study to provide important findings on longitudinal cognitive outcomes in pediatric medulloblastoma patients who experienced PFS compared with patients who did not experience PFS, a few limitations must be acknowledged. First, diagnostic criteria for PFS were not specified in the protocol, and thus a diagnosis of PFS was based on the judgment of the treating physician. Given the variable presentation, future studies should specify criteria for determining a PFS diagnosis such as those put forth in the recently published consensus paper.[44] In addition, a large number of patients were excluded because they did not participate in cognitive testing. Consequently, few high-risk patients were included in this study. High-risk patients tend to demonstrate poorer cognitive function, presumably because they received higher dose radiation.[26] Thus, the current results may underestimate the severity of cognitive decline in patients who receive higher doses of radiation. However, the stability of intellectual ability and processing speed found across both groups in our study is notable and consistent with findings by Moxon-Emre et al, who also found stable IQ over time in patients who received low-dose radiation.[45] Finally, the absence of baseline measurements limits our ability to assess between group differences prior to treatment. However, examination of caregiver education years as a proxy or indirect estimation of baseline functioning indicated no significant differences between the PFS (M = 13.70, SD = 2.44) and matched non-PFS groups (M = 14.58, SD = 1.90) ($P = 0.11$).

In summary, medulloblastoma patients who experience PFS are at greater risk for neurocognitive problems that occur early and persist over time compared with patients who did not experience PFS but had the same treatment exposure. Furthermore, given that most patients on the study received lower dose radiation, our results suggest that PFS is a greater predictor of neurocognitive impairment than low-dose radiation. Thus, patients who experience PFS should be monitored closely and provided with intervention as early as possible. Interventions found to be effective for children with acquired brain injuries may be appropriate.[46] Future studies should closely document the diagnosis and course of PFS and systematically examine how these variables relate to a range of long-term neuropsychological outcomes. In addition, surgical guidelines that minimize risk while maintaining survival should be further explored.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

Funding

This work was supported in part by the National Cancer Institute through a Cancer Center Support (CORE) grant (P30-CA21765), the Noyes Brain Tumor Foundation, Musicians Against Childhood Cancer (MACC), and the American Lebanese Syrian Associated Charities (ALSAC).

Conflict of interest statement. None.

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