

Neurocognitive and Psychological Functioning of Children with an Intracranial Germ Cell Tumor

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Purpose

This study was conducted to investigate the neurocognitive functioning of children with intracranial germ cell tumor (IGCT) prior to receiving proton beam therapy (PBT), and to identify differential characteristics of their neurocognitive functioning depending on tumor location. As a secondary object of this study, neurocognitive functions were followed up at 1-2 years after PBT to examine early post-treatment changes.

Materials and Methods

Between 2008 and 2014, 34 children with IGCT treated who received PBT at National Cancer Center, Korea were enrolled in this study. Standardized neurocognitive tests of intelligence, memory, and executive functioning were performed with baseline psychological assessments using the Child Behavior Checklist (CBCL). Follow-up assessments after PBT were conducted in 20 patients (T2). The results were analyzed based on the locations of tumors, which included the suprasellar, pineal gland, basal ganglia, and bifocal regions.

Results

The neurocognitive function of IGCT patients was significantly lower than that of the normal population in performance intelligence quotient ($p=0.041$), processing speed ($p=0.007$), memory ($p < 0.001$), and executive functioning ($p=0.010$). Patients with basal ganglia tumors had significantly lower scores for most domains of neurocognitive functioning and higher scores for CBCL than both the normal population and patients with IGCT in other locations. There was no significant change in neurocognitive function between T1 and T2 for all types of IGCT patients in first 1-2 years after PBT.

Conclusion

Tumor location significantly affects the neuropsychological functioning in patients with IGCT. Neuropsychological functioning should be closely monitored from the time of diagnosis in IGCT patients.

Key words

Brain neoplasms, Germ cell tumor, Cognitive function

Introduction

Intracranial germ cell tumors (IGCT), which are the most common types of brain tumors in Asian children and adolescents [1,2], are typically found in the suprasellar area and pineal gland, and less commonly in the basal ganglia. Pure germinomas are very sensitive to radiotherapy and chemotherapy, and show excellent prognosis with 5-year overall survival rates of $\geq 90\%$ following radiotherapy with or with-

out chemotherapy [3-5]. Non-germinomatous germ cell tumors (NGGCT) have less favorable prognosis than pure germinoma; however, the 5-year survival rate has reached 60%-80%, even for NGGCT after aggressive multimodal therapy was adopted [6-8]. The improvement in survival rates of patients with IGCTs has raised questions regarding the impact of these tumors on neuropsychological functioning and the quality of life of long-term survivors.

Radiotherapy has generally been thought to contribute to poor neurocognitive functions and quality of life of IGCT

patients [9,10]. However, most studies of the neurocognitive functioning of IGCT patients have analyzed the long-term effects of radiotherapy by measuring neurocognitive functions at a specific time after treatment without performing pre-treatment assessments [11-13]. Hence, it is difficult to conclude that radiation therapy is solely responsible for the neurocognitive decline in these patients.

Merchant et al. [4] evaluated the long-term changes in neurocognitive functioning relative to a baseline assessment and found that there were no significant differences in the intelligence quotient (IQ) of the patients before and after radiotherapy. However, they reported that the IQ of the patients was consistently in low to average range from the time of diagnosis to the follow-up assessment. In contrast, several studies have revealed that the pre-treatment neurocognitive functioning of children with brain tumors was not markedly different from that of an age-matched normal population [14,15]. These findings, together with those of a study by Merchant et al. [4] have led the authors to hypothesize that the changes in neurocognitive functioning before starting radiotherapy may be specific to IGCT. Therefore, we investigated whether tumor location causes differences in neuropsychological functioning in patients with IGCT patients treated with proton beam therapy (PBT).

Materials and Methods

1. Study design and patients

Neurocognitive function tests were performed since 2008 as a part of hospital work up for the patients who were going to have PBT. However, analysis of the accumulated result of the tests and also, expanded performance of the neurocognitive function test in a prospective manner as a research project was approved by Institutional Review Board (IRB) in 2014 (IRB number: NCC2014-0044). Since then, all patients with IGCT undergoing PBT were referred to a clinical psychologist after providing informed consent to evaluate their neuropsychological functions before starting PBT (T1, baseline evaluation) and yearly after completion of PBT (T2, T3, etc.). The primary objective of this study was to determine the factors affecting the baseline neuropsychological functions. Additionally, because early follow-up results were available in some of the patients, changes in neuropsychological functions at 1-2 years after PBT were evaluated as a secondary objective.

Between June 2008 and November 2014, 40 children with an IGCT underwent PBT at the National Cancer Center, South Korea, and were referred for baseline evaluation. Of

the 40 patients who underwent PBT, three who refused to undergo the neurocognitive and psychological tests and three who had previously received radiotherapy were excluded. Therefore, baseline data were analyzed for 34 patients. Follow-up assessments (T2) were conducted in 20 patients at a median of 15.0 months (range, 6.0 to 28.8 months) after PBT. Fourteen patients were not included in follow-up assessments because three patients refused to undergo the follow-up tests, seven were lost to follow-up, and four were followed up for < 1 year.

2. Treatment

All patients received four cycles of chemotherapy before PBT according to the Korean Pediatric Neuro-Oncology protocol. According to this protocol, the radiation field and dose are determined by the tumor histology, initial tumor markers, tumor extent, and response to neoadjuvant chemotherapy. Patients with germinoma received four cycles of chemotherapy with alternating carboplatin/etoposide (course A) and cyclophosphamide/VP-16 (course B) before radiotherapy. Patients with NGGCT received four cycles of chemotherapy consisting of carboplatin, etoposide, and bleomycin alternating with cyclophosphamide, etoposide, and bleomycin. Patients with pure germinoma received a whole ventricle irradiation (WVI) dose of 19.8 Gy followed by a primary site boost of 10.8 Gy in patients with a complete response to chemotherapy, and a 19.8 Gy boost in patients with a partial response. Patients with disseminating germinoma received a craniospinal irradiation (CSI) dose of 25.2 Gy. Patients with NGGCT received CSI at a dose of 36 Gy for localized disease or 39.6 Gy for disseminated disease. A primary site boost was given up to a total dose of 55.8-59.4 Gy depending on the extent of the residual tumor and the limitations imposed by the organs at risk. A boost target volume was created with a 1.5 cm margin around the primary tumor volume, and in the case of bifocal tumors (involving both suprasellar and pineal glands), the whole ventricle was included in boost volume. In the case of basal ganglia tumors, the boost target volume was same as that of the tumors in other locations, but because the remnant white matter change after chemotherapy precluded clear response evaluations, most patients with basal ganglia tumor received high-end of dose ranges. In all patients, PBT was used in passive scattering (double scattering) mode.

3. Assessment of neurocognitive function and emotional and behavioral problems

To measure general intellectual functions, the Korean Wechsler Intelligence Scale for Children, third edition (KWISC-III) and The Korean Wechsler Adult Intelligence

Scale (K-WAIS) were used for children of 6 to 15 years and children aged ≥ 16 years, respectively [16,17]. The KWISC-III can yield full-scale IQ (FIQ), verbal IQ (VIQ), performance IQ (PIQ) scores, verbal comprehension, perceptual organization (PO), freedom from distractibility (FD), and processing speed (PS), while K-WAIS only provides FIQ, VIQ, and PIQ. The standard scores of all measures are a mean of 100 and a standard deviation (SD) of 15. The Rey-Kim Memory Test and Kim's Frontal Lobe Executive Neuropsychological Test were used to assess the children's memory and frontal lobe executive functions, respectively [18,19]. These tests provide the memory quotient (MQ) and the executive IQ (EIQ), respectively.

The Korean version of the Child Behavior Checklist (K-CBCL) [20] was used to assess emotional and behavioral problems. The standard test scores are normalized T scores with a mean of 50 and a SD of 10. Higher scores indicate greater problems.

4. Statistical analyses

PASW ver. 18 (SPSS Inc., Chicago, IL) was used for all analyses. All test scores were compared to age-matched standardized normative values using t tests. The effects of clinical factors on neurocognitive and psychological functioning were analyzed using t tests or analysis of variance (ANOVA). Differences in neurocognitive and psychological functioning between tumor locations were examined using ANOVA and χ^2 tests. The changes in neurocognitive functioning between T1 and T2 were examined using repeated-measures ANOVA and the differences between T1 and T2 were analyzed using pairwise comparison tests according to the tumor location. Statistical significance was defined as p-values of < 0.05 .

Results

1. Patient, treatment, and tumor characteristics

The clinical and tumor characteristics of the patients are summarized in Table 1. Overall, 66% of the patients were male, and the median age at T1 was 12.3 years (range, 7.3 to 18.4 years). There were eight patients with suprasellar tumors (22.9%), 10 with pineal gland tumors (28.6%), six with basal ganglia tumors (17.1%), and 10 with bifocal tumors involving both the suprasellar and pineal gland (31.4%). About 60% of patients had hydrocephalus and underwent procedures for treatment. Twenty patients (58.8%) received CSI or whole brain irradiation and the other 14 patients received WVI. The median radiation dose applied to the pri-

Table 1. Patient characteristics at baseline

Characteristic	No. (%)
Sex	
Male	23 (67.6)
Female	11 (32.4)
Age at diagnosis (yr)	
Mean \pm SD	12.3 \pm 3.1
Median (range)	12.0 (7.0-18.1)
Age at first evaluation (yr)	
Mean \pm SD	12.6 \pm 3.1
Median (range)	12.3 (7.3-18.4)
Interval between diagnosis and first evaluation (mo)	
Mean \pm SD	3.9 \pm 1.3
Median (range)	3.7 (0.5-8.0)
Tumor location	
Suprasellar	8 (23.5)
Pineal gland	10 (29.4)
Basal ganglia	6 (17.6)
Bifocal ^{a)}	10 (29.4)
Diagnosis	
Germinoma	18 (52.9)
NGGCT or mixed IGCT	16 (47.1)
Hydrocephalus	
Yes	21 (61.8)
No	13 (38.2)
Procedure for hydrocephalus^{b)}	
Yes	20 (58.8)
No	14 (41.2)
Surgery extent	
GTR	3 (8.8)
NTR or STR	4 (11.8)
Biopsy only	24 (70.6)
No surgery	3 (8.8)
Radiation field	
CSI+primary site	19 (55.9)
WBI+primary site	1 (2.9)
WVI+primary site	14 (41.2)
Radiation dose, median (range, Gy)	
Germinoma	30.6 (30.0-45.0)
NGGCT	54.6 (30.6-55.8)
Total patients	39.6 (30.0-55.8)

SD, standard deviation; NGGCT, non-germinomatous germ cell tumor; IGCT, intracranial germ cell tumor; GTR, gross total resection; NTR, near total resection; STR, subtotal resection; CSI, craniospinal irradiation; WBI, whole brain irradiation; WVI, whole ventricle irradiation. ^{a)}Suprasellar and pineal gland involvement, ^{b)}Ventriculoperitoneal shunt, external ventricular drainage, and ventriculostomy.

Table 2. Baseline neurocognitive functioning according to tumor location

Variable	No.	Total patients	p-value ^{a)}	Suprasellar	p-value ^{b)}	Pineal gland	p-value ^{b)}	Basal ganglia	p-value ^{b)}	Bifocal	p-value ^{a)}	p-value ^{a)}	One-way ANOVA		Post hoc comparison
													df	p-value	
FIQ	34	96.74±21.36	0.379	110.50±17.98	0.143	92.70±25.60	0.391	76.83±8.66	0.001	101.70±15.69	0.740	3,30	0.016	BG < suprasellar	
VIQ	33	101.36±19.13	0.685	112.00±20.84	0.178	99.80±18.78	0.974	83.33±10.52	0.012	106.30±16.21	0.250	3,29	0.033	BG < suprasellar	
PIQ	33	91.55±22.80	0.041	107.57±14.67	0.221	86.10±36.46	0.183	73.83±10.82	0.002	96.40±15.59	0.484	3,29	0.035	BG < suprasellar	
VC	29	102.17±18.72	0.537	112.25±16.74	0.077	96.63±20.56	0.657	83.80±13.24	0.052	109.13±12.30	0.074	3,25	0.020	BG < suprasellar	
PO	29	96.83±21.48	0.433	110.25±17.54	0.142	87.25±27.44	0.230	82.00±11.38	0.024	102.25±14.45	0.673	3,25	0.044	BG, pineal < suprasellar	
FD	28	99.39±19.35	0.869	102.86±17.06	0.673	102.88±26.51	0.768	84.40±7.47	0.010	102.25±16.26	0.707	3,24	0.312	-	
PS	29	86.59±24.61	0.007	104.88±14.95	0.387	82.63±25.48	0.095	67.00±17.85	0.014	84.50±26.24	0.139	3,25	0.039	BG < suprasellar	
MQ	32	84.75±19.35	0.000	86.50±23.85	0.153	90.78±16.13	0.125	81.50±16.51	0.041	79.33±20.92	0.018	3,28	0.633	-	
EIQ	23	84.52±26.18	0.010	86.83±19.93	0.167	104.14±14.65	0.482	60.60±24.80	0.024	78.20±29.82	0.177	3,19	0.024	BG < pineal	

Values are presented as mean±standard deviation. FIQ, full-scale intelligence quotient (IQ); BG, basal ganglia; VIQ, verbal IQ; PIQ, performance IQ; VC, verbal comprehension; PO, perceptual organization; FD, freedom of distractibility; PS, processing speed; MQ, memory quotient; EIQ, executive IQ. ^{a)}Comparison with normal population.

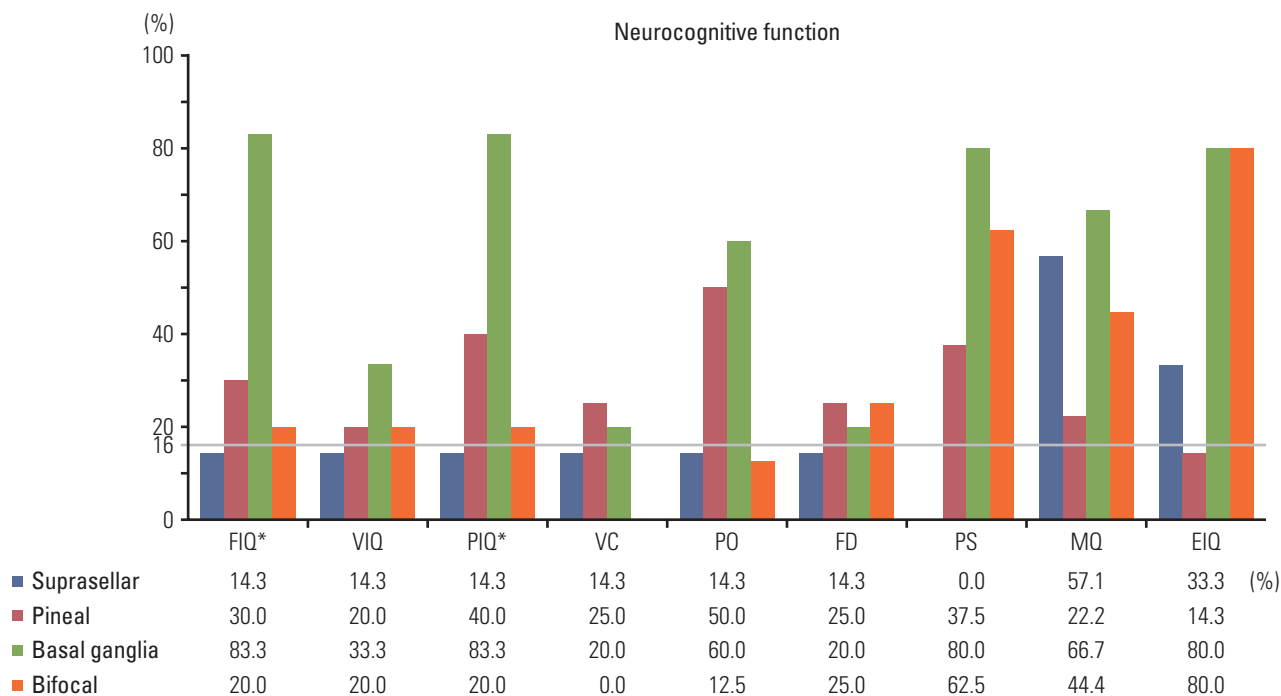
mary tumor was 30.6 Gy (range, 30.0 to 45.0 Gy) for patients with pure germinoma and 55.8 Gy (range, 30.6 to 55.8 Gy) for patients with NGGCT. Two patients diagnosed with pure germinomas received 45 Gy of radiotherapy because one patient had residual disease after chemotherapy and the other had a high β human chorionic gonadotropin level at initial diagnosis. Three patients with NGGCT had mature teratoma as a nongerminoma component and received 30.6 to 39.6 Gy. Several clinical variables, including the presence of hydrocephalus, endocrine symptoms (i.e., polydipsia and polydipsia), visual symptoms (i.e., double vision, visual disturbance, and strabismus), and the duration of symptoms (time from initial signs to tumor diagnosis) were closely related to tumor locations. Suprasellar tumor had more endocrine symptoms ($p < 0.001$), while pineal tumor was associated with hydrocephalus ($p=0.008$) and visual symptoms ($p=0.140$). No significant differences in the duration of symptoms were found according to the tumor locations, but tumors in pineal gland had a shorter duration than the other tumors (mean±SD, 4.0±3.77 months in basal ganglia vs. 12.37±13.53 in suprasella, 7.67±8.2 in basal ganglia and 11.1±11.25 in bifocal tumor; $p=0.273$). Therefore, we did not conduct further analyses investigating the effects of these variables on neuropsychological functioning.

2. Neurocognitive and psychological functioning at baseline (T1) and effect of tumor location

Baseline neurocognitive and psychological functioning did not show any differences between patients with pure germinomas and those with NGGCTs. To evaluate the effects of tumor location, patients were grouped into four subgroups; suprasellar, pineal gland, basal ganglia, and bifocal. Tumor location was not associated with tumor histology.

Table 2 shows the baseline neurocognitive functioning of the patients. The mean scores for MQ and EIQ were lower than those for the normal population ($p=0.041$ and $p < 0.001$, respectively). Although the patients also had slightly lower scores for PIQ and PS than the normal population, the values were still within the normal range (range, 85 to 115). When analyzed by tumor location, patients with basal ganglia tumor had lower scores than the normal population for all domains. One-way ANOVA showed that all neurocognitive functioning domains, except for the FD and MQ, differed significantly by tumor location ($p=0.016$ to $p=0.044$). *Post hoc* comparison revealed significant differences in each domain between patients with basal ganglia tumors and those with suprasellar tumors. When the frequencies of scores lower than one SD within each tumor location were compared with the expected 16% of the general population, they were greatest for patients with basal ganglia tumors on all neurocognitive domains (Fig. 1A).

A



B

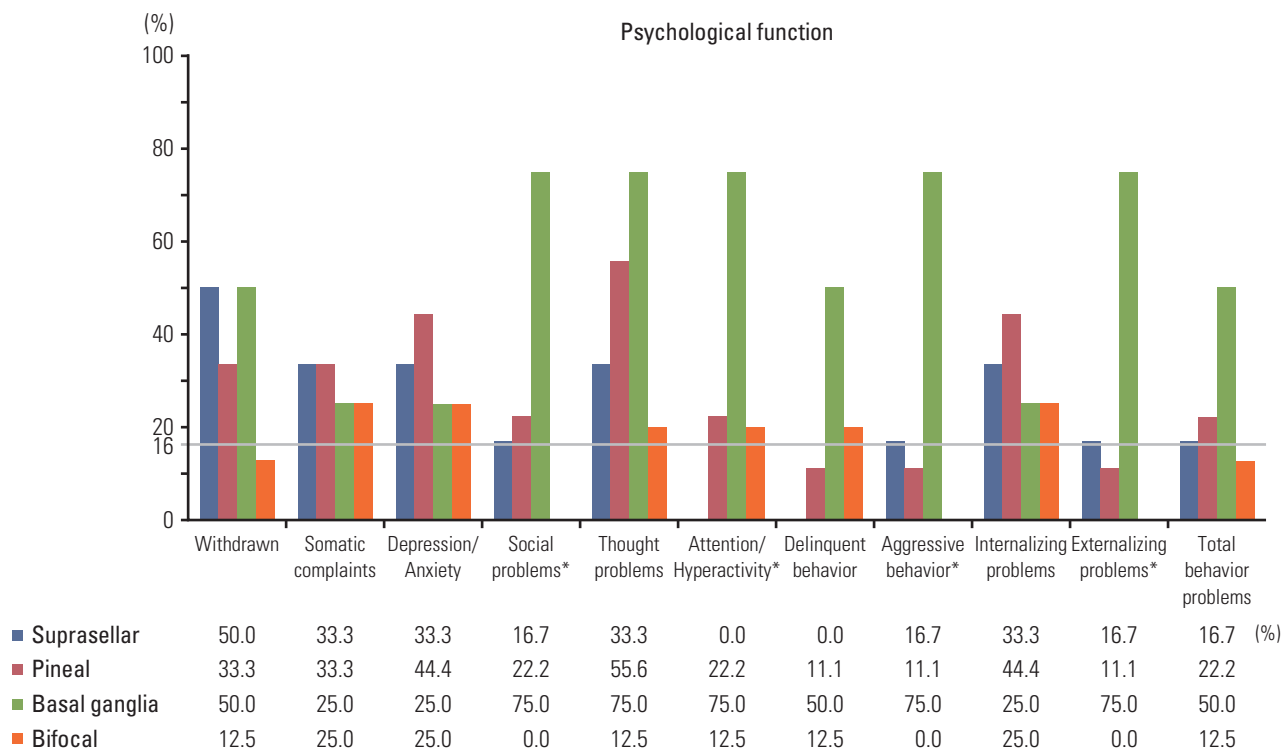


Fig. 1. Proportions of patients with impairments in each neurocognitive (A) and psychological (B) domain. FIQ, full-scale intelligence quotient (IQ); VIQ, verbal IQ; PIQ, performance IQ; VC, verbal comprehension; PO, perceptual organization; FD, freedom of distractibility; PS, processing speed; MQ, memory quotient; EIQ, executive IQ. *p < 0.05.

Table 3. Psychological functioning according to tumor location

Variable	GCTs (n=27)	p-value ^{a)}	Suprasellar (n=6)	p-value ^{a)}	Pineal gland (n=9)	p-value ^{a)}	Basal ganglia (n=4)	p-value ^{a)}	Bifocal (n=8)	p-value ^{a)}	ANOVA p-value	Post hoc comparison
Internalizing problems	54.89±10.26	0.020	58.00±8.25	0.063	55.11±13.68	0.295	57.75±3.78	0.026	50.88±9.55	0.803	0.579	-
Externalizing problems	48.74±10.62	0.543	49.67±9.14	0.932	47.11±9.44	0.385	63.25±5.85	0.020	42.63±8.70	0.048	0.008	Pineal, bifocal < BG
Total behavior problems	52.33±10.15	0.243	54.00±8.41	0.297	52.67±9.94	0.444	62.25±5.32	0.019	45.75±9.94	0.266	0.050	Bifocal < BG
Withdrawn	56.19±13.17	0.022	63.50±18.05	0.126	55.56±14.81	0.293	56.50±11.03	0.324	51.25±5.88	0.566	0.411	-
Somatic complaints	54.85±9.21	0.011	59.00±6.00	0.014	53.11±9.68	0.363	58.25±5.38	0.055	52.00±11.64	0.642	0.436	-
Depression / Anxiety	53.85±10.32	0.063	53.83±12.56	0.488	55.22±11.86	0.223	54.25±8.06	0.369	52.13±9.39	0.542	0.950	-
Social problems	56.07±9.52	0.003	53.33±6.51	0.265	56.11±9.33	0.085	68.75±7.18	0.014	51.75±8.07	0.559	0.016	Bifocal < BG
Thought problems	54.78±9.52	0.015	53.67±9.14	0.371	56.78±9.22	0.058	63.00±11.46	0.108	49.25±6.61	0.758	0.096	-
Attention / Hyperactivity	53.78±11.05	0.087	49.33±6.31	0.806	55.89±9.44	0.098	69.00±8.68	0.022	47.13±9.22	0.407	0.003	Suprasellar, bifocal < BG
Delinquent behavior	49.11±7.70	0.554	48.71±7.06	0.552	47.89±7.64	0.431	59.25±0.96	0.000	46.13±6.77	0.150	0.026	Bifocal < BG
Aggressive behavior	49.59±10.77	0.846	50.00±9.45	1.000	47.33±9.35	0.417	64.25±7.93	0.037	44.50±8.99	0.127	0.013	Pineal, bifocal < BG

Values are presented as mean±standard deviation. Higher scores mean greater problems. GCT, germ cell tumor; BG, basal ganglia. ^{a)}Comparison with normal population.

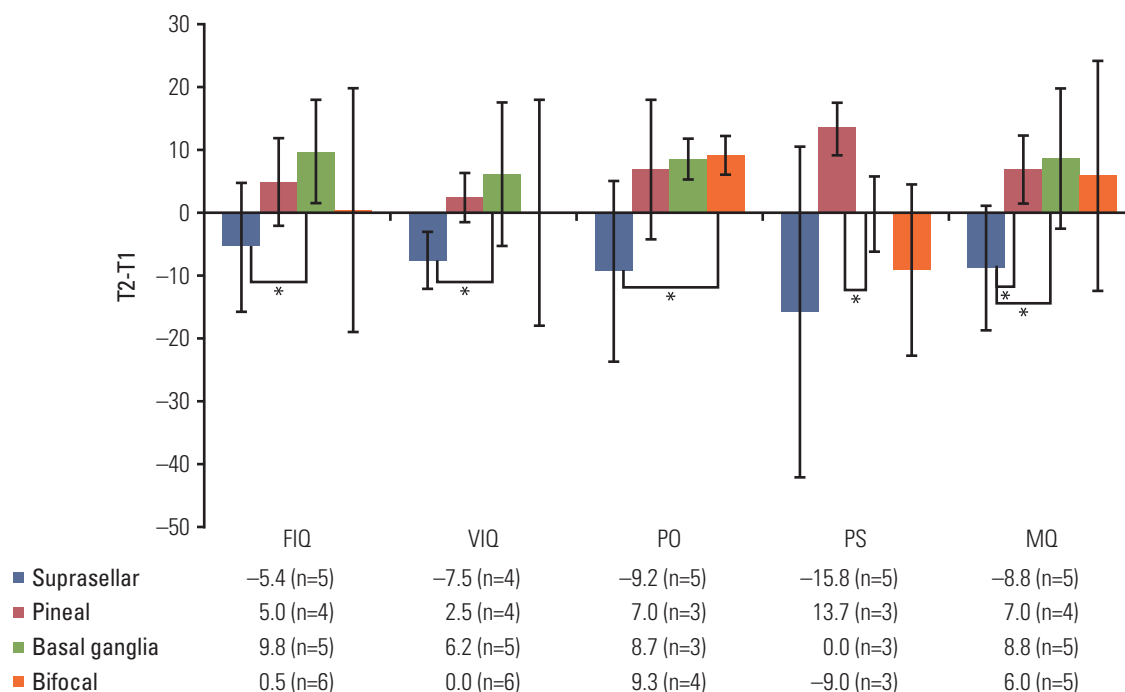


Fig. 2. Changes in neurocognitive functioning from baseline (T1) to 1-2 years after proton beam therapy (T2) according to tumor location. The y axis represents the difference between T2 and T1; therefore, a negative value of T2-T1 indicates decreased functions. FIQ, full-scale intelligence quotient (IQ); VIQ, verbal IQ; PO, perceptual organization; PS, processing speed; MQ, memory quotient; T2-T1, difference between T1 and T2. *p < 0.05. Bars indicate standard deviation.

Table 4. Effect of radiation field and dose on cognitive functions

Variable	Radiation field			Radiation dose, Gy		
	T2-T1 difference (mean±SD)		p-value	T2-T1 difference (mean±SD)		p-value
	CSI	WVI		≤ 39.6	> 39.6	
FIQ	-0.80±17.79 (n=10)	5.30±6.04 (n=10)	0.327	4.41±9.14 (n=12)	-1.00±18.14 (n=8)	0.387
VIQ	-3.22±15.06 (n=9)	4.00±8.38 (n=10)	0.207	1.58±9.66 (n=12)	-1.14±16.50 (n=7)	0.653
PIQ	0.22±23.60 (n=9)	6.30±8.87 (n=10)	0.458	7.33±14.37 (n=12)	-3.29±20.69 (n=7)	0.203
VC	1.14±8.63 (n=7)	2.63±9.23 (n=8)	0.754	1.10±8.95 (n=10)	3.60±8.79 (n=5)	0.617
PO	-4.00±14.85 (n=6)	8.25±6.34 (n=8)	0.078	4.80±11.30 (n=10)	-2.00±14.68 (n=5)	0.336
FD	-7.83±9.02 (n=6)	5.00±14.44 (n=8)	0.081	2.00±14.60 (n=10)	-6.75±9.91 (n=4)	0.297
PS	-12.67±24.30 (n=6)	1.38±14.27 (n=8)	0.199	-3.78±20.43 (n=9)	-6.20±20.61 (n=5)	0.836
MQ	1.80±16.31 (n=10)	4.44±10.50 (n=9)	0.684	5.09±10.11 (n=11)	0.25±17.65 (n=8)	0.458
EIQ	2.60±19.97 (n=5)	4.38±14.88 (n=8)	0.857	0.50±16.30 (n=10)	14.33±12.66 (n=3)	0.208

SD, standard deviation; CSI, craniospinal irradiation; WVI, whole ventricle irradiation; FIQ, full-scale intelligence quotient (IQ); VIQ, verbal IQ; PIQ, performance IQ; VC, verbal comprehension; PO, perceptual organization; FD, freedom of distractibility; PS, processing speed; MQ, memory quotient; EIQ, executive IQ.

Table 3 shows the results of the K-CBCL. In all patients combined, the mean scores for all domains were within the normal ranges for the general population (range, 40 to 60). Basal ganglia tumor patients had significantly higher scores for externalization problems, total behavioral problems, social problems, attention/hyperactivity, delinquent behaviors, and aggressive behaviors when compared with the normal population. Patients with a basal ganglia tumor more frequently had scores greater than one SD for most subscales of the K-CBCL when compared with the expected 16% of the normal population (Fig. 1B). Overall, 75% of the parents of patients with basal ganglia tumors reported that their children displayed attention/hyperactivity problems, aggressive behaviors, thought problems, social problems, and externalization problems.

3. Neurocognitive and psychological functioning at 1-2 years after PBT (T2)

At 1-2 years after PBT, most scores of the neurocognitive test and the CBCL were not significantly different from those of the normal population, except for the MQ (mean, 88.6; $p=0.045$). The T2 scores for all domains of neurocognitive functioning and the CBCL were not significantly different from those at T1. However, in patients with a suprasellar tumor, the test scores tended to decrease between T1 and T2, except for MQ and EIQ. In contrast, the scores for most domains increased between these times in patients with pineal, basal ganglia, or bifocal tumors. In pairwise comparisons between T1 and T2, differences were found as follows: suprasellar vs. basal ganglia for FIQ; suprasellar vs. pineal gland for VIQ; suprasellar vs. bifocal for PO; pineal gland vs. basal ganglia for PS; suprasellar vs. pineal gland and basal ganglia for MQ (Fig. 2). CBCL scores were not analyzed according to tumor location because of the small sample size of T2 ($n=13$).

We also examined the potential effects of the radiation field and dose on neurocognitive functioning at T2 (Table 4). Patients who received CSI tended to have lower scores at T2 than at T1, whereas those who received WVI tended to have higher scores at T2 than at T1. However, these changes were not statistically significant. There were no significant differences in neurocognitive functioning scores between patients who received higher doses (> 39.6 Gy) and those who received lower doses (≤ 39.6 Gy).

Discussion

In this study, children with IGCT displayed significantly lower PIQ, PS, MQ, and EIQ scores than an age-matched normal population. Deficits in attention and memory, including slow speed processing, are the most commonly reported problems in childhood brain tumor survivors in general and are commonly attributed to cranial irradiation [21,22]. The deficits in memory function caused by cranial irradiation are now known to represent a component of diffuse global dysfunction of brain function associated with white matter changes [21,23] rather than isolated memory disturbances [24]. However, our data revealed disturbances in memory function were present even before radiotherapy was started. Wilkening et al. [25] specifically examined memory function in IGCT and observed amnesia in 38% of patients. They also reported that amnesia was not related to the presence of hydrocephalus or history of cranial radiotherapy, and that low memory function was not associated with global decreases in IQ, which are sometimes observed in younger children with other tumors, such as medulloblastoma [14,15]. Williams and Pennybacker [26] examined brain tumor patients with memory impairment and found that most of their tumors were located in a deep, midline position. They also reported that patients with tumors involving periventricular structures had more frequent memory loss than those with tumors in frontal locations.

The effects of tumor location on neurocognitive functioning observed in the present study were consistent with those reported by Liang et al. [11], who found that IGCT arising in the basal ganglia is associated with worse neuropsychological outcomes than tumors arising in other locations. We showed that poor neurocognitive functioning of patients with basal ganglia tumors persists after treatment, but tends to improve within the early follow-up period, although the mean scores at T2 still remained poor relative to the normal population. According to Liang et al. [11], the impaired neurocognitive function in the patients with basal ganglia tumors was likely to be life-long. In contrast to these authors, who only assessed neurocognitive aspects in children, we also examined psychological functioning in patients with basal ganglia tumors. We found that children with tumors located in the basal ganglia showed various behavioral issues, as reflected in the results of CBCL compared to patients with tumors in other locations. The basal ganglia have extensive connections with the cerebral cortex, especially the frontal cortex. In addition to motor function, the basal ganglia play various roles in cognition, memory, and emotion through connections with the limbic cortex [27,28], and disruption of these functions may cause externalization of symptoms of patients with basal ganglia tumors.

Notably, we observed tendencies for FIQ, VIQ, perceptual organization, and MQ to decrease between T1 and T2 in patients with suprasellar tumors. In contrast, these scores tended to increase between T1 and T2 in patients with tumors in the other sites. Although we only observed these changes over a relatively short time, the results appear to agree with those reported by Mabott et al. [13], who found a decline in the average PS and delayed visual memory, especially in patients with suprasellar tumors. Dennis et al. [29] reported impaired memory in children with hormone deficiencies. In the present study, patients with suprasellar tumors tended to have decreases in neurocognitive functioning, and the changes in memory function in suprasellar patients were significantly greater than those in children with pineal or basal ganglia tumors. All of the patients with suprasellar tumors had hormone deficiencies, which may have contributed to neurocognitive deficiencies. The boost field applied to suprasellar tumors must target a larger volume of the medial temporal lobes because of the anatomical proximity relative to tumors in the pineal gland [30]. A longer follow-up period is needed to determine if differences in the temporal dose–volume histograms have long-term effects on the neurocognitive functioning of children with IGCT.

It should be noted that our study was limited in that we analyzed a relatively small number of patients, and only 20/34 patients were assessed at T2. However, this study is a preliminary report of an ongoing prospective study and the

first to report the short-term neurocognitive outcomes of PBT in children with IGCT. It should also be noted that we assessed the psychological status of children as well as neurocognitive functioning before and after treatment. Because the study included children with histories of chemotherapy and surgery, the results do not represent the neuropsychological state of the child at initial diagnosis. Nevertheless, the timing of the baseline examination before radiotherapy seems reasonable considering the practical limitations of performing neuropsychological evaluation upon diagnosis of IGCT. Further analysis of longitudinal changes in neurocognitive functions after PBT will be available after longer follow-up with more patients.

In conclusion, neuropsychological functioning in patients with IGCT may be primarily influenced by tumor location itself, and does not change in the short term after treatment. However, further study is needed to evaluate the long-term effects of PBT on neurocognitive function.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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