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Title: *Long-term outcome and social-intellectual ability of patients with basal ganglia germinoma*

Running title: Basal ganglia germinoma outcomes

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Abbreviations:

ADHD: attention deficit hyperactivity disorder

AFP: α-fetoprotein

BG: basal ganglia

β-hCG: β-subunit human chorionic gonadotropin

CSF: cerebrospinal fluid

FI: focal irradiation

IGCT: intracranial germ cell tumor

IQ: intelligence quotient

KPS: Karnofsky Performance Status

MRI: magnetic resonance imaging

OS: overall survival

RBE: relative biological effectiveness

RFS: recurrence-free survival

WBI: whole-brain irradiation

1 WISC-III: Wechsler Intelligence Scale for Children, third edition

2 WVI: whole-ventricular irradiation

3

Abstract

Background

In this study, we aimed at delineating the still ambiguous clinical characteristics and long-term outcomes of basal ganglia (BG) germinoma from the aspect of recurrence-free survival as well as social and intellectual activity.

Methods

We retrospectively reviewed medical records and imaging data for 12 patients with BG germinoma diagnosed and treated between 1996–2020, collecting the most recent status via medical records or telephone from the patients.

Results

The tumors involved the right and left sides or bilateral locations in 3, 7, and 2 cases, respectively. The median follow-up period was 179 months. Six patients exhibited onset-neuropsychological symptoms, e.g., cognitive decline or behavior disorder. We evaluated the intelligence quotient (IQ) in 10 patients and observed significantly lower IQ scores in 6 patients with neuropsychological symptoms. While patients with right-sided lesions displayed average IQ levels (median 106), those with left-sided or bilateral lesions had reduced IQ (median 67). A complete response was achieved by primary chemoradiotherapy in all patients. While 3 patients who underwent focal or whole-ventricle irradiation experienced recurrence, none was observed in patients who received whole-brain irradiation (WBI).

Concerning the neurocognitive outcomes, 3 and 6 patients with unilateral right and left lesions were living self-independently (KPS ≧ 70), while the 3 remaining patients (1 with left and 2 with bilateral lesions) in a dependent status (KPS < 70).

Conclusions

WBI is crucial for disease control in BG germinoma. Furthermore, lesion laterality might affect neuropsychological symptoms including IQ at diagnosis and neurocognitive outcomes in BG germinoma.

Introduction

Germinoma is the most common and least malignant intracranial germ cell tumor (IGCT), usually located in the midline, i.e., in the pineal gland and neurohypophysis. The IGCT rate is higher among Asian than among Western populations, displaying an overall male predominance, usually occurring in adolescents and young adults [1,2].

The third most common IGCT location is the basal ganglia (BG), accounting for approximately 10% of all cases [1-4]. Interestingly, BG IGCT reportedly correlates with PI3K/mTOR pathway mutations and chromosomal instabilities, whereas MAPK pathway mutations are common in most germinomas [5]. Considering the distinct molecular characteristics of BG IGCT, BG germinoma could exhibit unique clinical and biological properties compared with pineal or neurohypophyseal germinoma. The common clinical history of slowly progressive hemiparesis and other symptoms (e.g., precocious puberty and diabetes insipidus) could equally characterize patients with BG germinoma [6,7]. In addition, neuropsychological symptoms (e.g., cognitive decline, personality change, and behavior disorders) have been described related to this condition [8,9]. However, the frequency of such neuropsychological symptoms might be underestimated due to specific evaluation requirements.

As BG germinoma symptoms are peculiar, its clinical characteristics should be evaluated via an integrated approach. In this study, we reviewed BG germinoma symptom onset, diagnosis, and treatment outcome in our institution, aiming at defining BG germinoma clinical characteristics by

analyzing the initial symptoms, with a particular focus on neuropsychological symptoms, and long-term outcomes, including recurrence rate and neurocognitive function (e.g., workability).

Materials and methods

Patient population

The institutional review board of Hokkaido University Hospital for Clinical Research approved this study (No. 020-0369). We retrospectively reviewed patients diagnosed and treated with IGCT in our institution between 1996–2020 and investigated those with basal ganglia lesions at presentation, pathologically diagnosed with pure germinoma and germinoma with syncytiotrophoblastic giant cells, also including patients clinically diagnosed with germinoma without histological confirmation. Clinical diagnosis was based on tumor markers, especially β-subunit human chorionic gonadotropin (β-hCG) in serum or cerebrospinal fluid (CSF), and radiological appearance. Patient numbers were determined in order of occurrence. The exclusion criteria were the presence of non-germinomatous components (including teratoma, choriocarcinoma, yolk sac tumor, or embryonal carcinoma) within the obtained pathological specimen and, based on a previous study, marked β-hCG (>2000 mIU/mL) or α-fetoprotein (AFP) (>10 ng/mL) increase [10,11].

Examination and diagnosis

We performed a retrospective review of medical records (locations; initial symptoms; comorbidities; days from symptom onset to diagnosis; treatment including surgery, chemotherapy and radiation therapy; recurrence; recurrence-free survival [RFS]; overall survival [OS]), laboratory data (including tumor marker levels such as β-hCG and AFP in the serum as well as CSF), and magnetic resonance imaging (MRI) results. Our MRI evaluation included routine conventional multiplanar brain scans with and without gadolinium contrast.

Clinical psychologists performed our intelligence and neuropsychological disorder evaluation, describing these symptoms as initial ones according to the American Psychological Association Dictionary of Psychology (https://dictionary.apa.org/). Neuropsychological symptoms were considered impairments of cognition and behavior associated with various neurological disorders. For intelligence quotient (IQ) evaluation, we used the Wechsler Intelligence Scale for Children third edition (WISC-III) [12] or the Tanaka–Binet test [13], i.e., the standardized Japanese version of the Stanford–Binet test [14]. We performed these evaluations during the initial treatment. For the neurocognitive outcome assessment, we collected the academic history, most recent Karnofsky performance status (KPS), and most recent occupation via medical records or directly from the patients via telephone surveys. For the eventual social status assessment, we established two groups denoted

as “dependent” and “self-independent” statuses (KPS ≧ 70 and < 70, respectively).

Statistical analysis

We performed the statistical analyses using GraphPad Prism 8.43 (GraphPad Software, Inc., San Diego, CA, USA). We used the Mann–Whitney U and Kruskal–Wallis tests for the comparisons between the two and among the three groups, respectively. We evaluated the RFS using the Kaplan–Meier method and performed the comparisons using the log-rank test. We considered P-values of $p < 0.05$ significant.

Results

Patient demographics

We identified 12 patients with IGCT in the BG during the study period. Table 1 presents the clinical characteristics of these patients encapsulated by time series. Ten and two patients suffered from unilateral (i.e., 3 right- and 7 left-side) and bilateral lesions, respectively. Two patients were diagnosed with multifocal lesions: in one case, it involved the neurohypophysis and in the other, the pineal gland. BG germinoma predominantly occurred in males (1 female vs 11 males). Their ages ranged between 8–19 years (median: 14.5 years; mean: 13.6 years). We obtained a histological diagnosis of germinoma in 9 cases. The remaining three cases were clinically diagnosed as germinoma with mild (< 100 mIU/mL) serum β-hCG level increase.

Neuropsychological comorbidities included attention deficit hyperactivity disorder (ADHD) and Down syndrome in patients #10 and #12, respectively. All 12 patients were right-handed.

Clinical presentation

In this series, hemiparesis, particularly slow progressing motor weakness, was the most common initial symptom (11/12 patients, 92%). Dysarthria was observed in 2 patients (17%). Patient #4, concurring with a neurohypophyseal lesion, exhibited diabetes insipidus and panhypopituitarism as well. No case involved hydrocephalus either clinically or radiologically.

Cognitive decline, including academic problems (i.e., the inability to acquire the necessary grade-level knowledge), was registered in 5 patients (42%). In addition, patient #7, displaying personality change and behavior disorder, was socially impaired at the initial diagnosis (8.3%). Six patients displayed such neuropsychological symptoms (50%). Moreover, 2 patients exhibited comorbidity with other psychiatric diseases such as ADHD and Down syndrome in patients #10 and #12, respectively. Concerning the time from symptom to diagnosis, we observed no significant difference between patients with and without neuropsychological symptoms (medians: 8 and 6.5 months; ranges: 2–14 and 1–35 months, respectively; Supplementary Figure 1).

Intelligence evaluation, neuropsychological symptoms, and disease laterality

Of the 12 patients, IQ was evaluated during the primary treatment in the case of 10 patients. We used the Tanaka–Binet intelligence scale and WISC-III to evaluate patient #1 and the other 9 patients, respectively. One patient (#4) did not undergo IQ testing owing to the lack of apparent neuropsychological symptoms. In addition, patient #12 could not be tested due to Down syndrome.

The IQ scores of 6 patients with neuropsychological symptoms (patients #1, 3, 5, 6, 7, and 11; median: 66) were significantly lower than those of patients without neuropsychological symptoms (patients #2, 8, 9, 10; median 104; Figure 1A). Neuropsychological symptoms at the onset are associated with IQ. Figure 1B presents the IQ scores according to disease laterality (except for 3 patients without intelligence evaluation). Patients with unilateral right-sided lesions did not tend to exhibit low IQ score levels (median: 106; range: 100–111). However, patients with left or bilateral lesions displayed relatively low IQ scores (median: 67; range: 57–102) considering that IQ scores could be defined with a median and mean of 100. As all participants were right-handed, the basal ganglia lesion of the dominant side might affect their IQ levels.

Treatment and recurrence

Table 2 summarizes the treatments and outcomes of the patients. The median follow-up was 179 months. All chemotherapy protocols involved 3 or 4 courses of platinum-based regimens: carboplatin

450 mg/m^2 on day 1 and etoposide 150 mg/m^2 on days 1–3 (CARE regimen), and/or ifosfamide 900 mg/m^2, cisplatin 20 mg/m^2, and etoposide 60 mg/m^2 on days 1–5 (ICE regimen). Nine and three patients were treated according to the ICE and CARE regimens, respectively. The CARE protocol was switched to the ICE protocol in the middle of the treatment in the case of patient #11 due to poor response to CARE chemotherapy, supplemented with boost irradiation. Salvage surgery was applied to remove the residual lesion in the case of this patient, but no viable cells could be observed. Salvage surgery was not required in the case of any other patient.

Following chemotherapy, the patients were administered a reduced dose and volume of irradiation (X-ray or proton beam therapy). At the beginning of this treatment series, 4 patients received focal or whole-ventricular irradiation (FI or WVI, respectively) as described previously [15]. The remaining 8 patients received whole-brain irradiation (WBI), as described previously [10]. Patients #1–10 underwent X-ray radiation while patients#11 and #12 received proton beam radiotherapy after the introduction of this approach. A previous study determined the relative biological effectiveness (RBE) value as 1.1, which was used for treatment planning [16]. The dose fractionation for FI, WVI, or WBI ranged from 23.4 to 25.2 Gy in 1.8 Gy fractions or 24 Gy in 2 Gy fractions as shown in table 2. Additionally, patient #11 received a boost of 27 Gy (RBE) in 15 fractions.

The initial treatment resulted in complete response in all patients, although 3 of 4 patients who received FI with or without WVI experienced recurrence. All recurrence was observed in the extra

field. In contrast, we observed no recurrence among WBI-treated patients. The log-rank test indicated a significant difference in RFS between the patients who underwent WBI or FI/WVI (Figure 2; p = 0.02). All patients are currently alive.

Neurocognitive outcomes

Table 2 summarizes the neurocognitive outcomes, academic history, recent occupation, and KPS. Patients #1, #3, and #7 were assigned a "dependent" status. Among them, patients #1 and #3 had tumor recurrence. Concerning lesion laterality, patients #1 and #7 displayed bilateral, while patient #3 unilateral left-side lesions. Conversely, the remaining 6 patients with left-sided lesions were considered "independent." All 3 patients with unilateral right-side lesions (patients #2, #8, and #10) were also classified as "independent" and socially and intellectually preserved in that they could graduate at least from high school (usually considered as the minimum requirement in Japan). These outcomes were not related to the clinical latency period or time from symptom to diagnosis, but patient #3 displayed a longer period than other patients with unilateral left-sided lesions.

Discussion

General clinical profiles of BG germinoma

Although germinoma is the most common germ cell tumor, it is less common in the BG than in the

pineal gland and neurohypophysis [1-4]. The majority of them occur unilaterally, and their symptoms are often documented as hemiparesis with ipsilateral brainstem atrophy, representing Wallerian degeneration [17]. Additionally, BG germinoma is characterized by a myriad of other symptoms such as precocious puberty, diabetes insipidus [6,7], and neuropsychological symptoms [8,9]. A previous study described that 12 among 43 patients with BG germinoma (27.9%) exhibited cognitive decline or behavior disorder [18]. In our series, we detected neuropsychological symptoms in 6 (50%) of 12 patients. So far, few studies have investigated the cognitive function of BG germinoma due to specific and detailed evaluation requirements [8,9]. Specifically, studies investigating the correlation between BG germinoma-related cognitive functions and anatomical features are scarce. Therefore, we focused on the relationship between neuropsychological symptoms and clinical characteristics, with a particular interest in disease laterality.

IQ- and neuropsychological symptom-associated laterality

First, patients with BG germinoma who presented with neuropsychological symptoms tended to display reduced IQ scores at diagnosis, as described in Figure 1A. IQ was originally considered to be associated with learning abilities and cognitive functions [19,20]. Therefore, IQ might reflect neuropsychological symptoms (Figure 1A). It is well-recognized that BG germinomas are often coupled with neuropsychological problems [7,21]. The basal ganglia reportedly maintain mutual

connections with the cortex [22]. In our series, all patients were right-handed, with lesions involved in the left, presumably dominant side of the brain, associated with neurocognitive dysfunctions. IQ tended to correlate with laterality and dominant-side involvement (Figure 1B). Notably, the IQ scores of patients with bilateral lesions were significantly lower than those of patients with unilateral lesions. Wataya et al. also reported that bilateral BG germinoma significantly affected cognitive symptoms [23].

Thus far, no research has focused on the association between BG germinoma laterality and neuropsychological symptoms. However, IQ deterioration with dominant-side lesions might imply a potential association between laterality and neuropsychological symptoms [24].

Potential WBI-mediated BG germinoma control

At the beginning of this series, patients received FI or WVI but often experienced recurrence (3/4 cases, 75%). In addition, we observed all recurrences in the out-of-field region. Therefore, we modified the BG germinoma radiotherapy protocol from FI or WVI to WBI [10,15]. They suggestibly invade the deep brain tissue widely, with potential recurrence in the extraventricular areas [6]. After the WBI treatment of BG germinoma, we observed no recurrence. Therefore, BG germinoma recurrence rate appears to be lower if treated with WBI than with FI or WVI.

Potential association between laterality and neurocognitive outcomes

Accurate neurocognitive outcome evaluation requires multiple assessments of neuropsychological symptoms; we used 3 factors (academic history, recent occupation, and KPS) to detect severe disability. In our series, 3 patients with severe disability displayed bilateral or left-sided lesions, whereas all patients with only right-sided lesions had favorable outcomes.

Although one patient displayed specific symptoms (personality change and behavior disorder in patient #7) that reduced sociality, long clinical latency in the other two patients with left-sided or bilateral lesions (patients #1 and #3) might have caused severe neuropsychological disorders. However, patient #8, with a right-sided lesion, displayed significantly longer clinical latency and the related neurocognitive outcome was markedly better than that of patients with left-sided or bilateral lesions. Although the comparison of the time from symptom to diagnosis between patients with or without neuropsychological symptoms did not indicate an association between clinical latency and initial neuropsychological symptoms, the former might be a neurocognitive dysfunction-associated factor, especially in patients with dominant-side lesions. Previously, the time from onset to diagnosis was reported as a prognosis-affecting factor in patients with IGCT [25]. However, our results suggest that the neurocognitive outcome of BG germinoma, rather than the diagnostic delay, may affect disease laterality.

Limitations

This study has certain limitations that need to be addressed. First, due to the retrospective nature of the study, the lack of precocious puberty description limited a full BG germinoma clinical characterization difficult. Second, radiotherapy-related cognitive declines could be unclear and radiation-induced neurotoxicity might develop over time. Moreover, we could not detect such progressive changes, and these should thus be investigated in the future. Third, IQ and symptoms were insufficient to assess the neuropsychological functions. In addition, one patient in this study underwent a different test battery because of age, which might result in misinterpretation. Furthermore, neuropsychological function should be assessed at follow-up. A comprehensive evaluation including neurocognitive, emotional/behavioral, and adaptive functional aspects as well as quality of life should be performed at certain points.

To clarify the clinical behavior of BG germinoma, future research should aim at compensating for the design- and small sample size-related limitations of this study.

Conclusions

We performed a retrospective examination of 12 BG germinoma cases. Reduced-dose WBI could control BG germinoma in the long term. Moreover, disease laterality could be an important risk factor affecting BG germinoma neuropsychological symptoms and outcomes.

Glossary

ADHD	Attention deficit hyperactivity disorder
BG	Basal ganglia
IGCT	Intracranial germ cell tumor
IQ	Intelligence quotient
KPS	Karnofsky performance status
MRI	Magnetic resonance imaging
RBE	Relative biological effectiveness
RFS	Recurrence-free survival
WBI	Whole-brain irradiation

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Author contributions

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Data Acquisition: M.O, S.Y, R.S, Y.I, H.M, Y.T, M.S, Y.C, T.M, and T.H

Final editing and approval of the manuscript: M.O, S.Y, R.S, Y.I, H.M, Y.T, M.S, Y.C, K.N, T.M, T.H, H.A, A.M, and M.F

Supervision: H.A, A.M, and M.F

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Declaration of interest

The authors declare no conflict of interest or financial disclosures concerning the materials or methods used in this study or the findings specified in this article.

Declaration of generative AI in scientific writing

During the preparation of this work, no generative AI or AI-assisted technologies were used.

References

1. Makino K, Nakamura H, Yano S, Kuratsu J-I. Incidence of Primary Central Nervous System Germ Cell Tumors in Childhood: A Regional Survey in Kumamoto Prefecture in Southern Japan. *Pediatric Neurosurgery.* 2013;49(3):155-158.
2. Takami H, Perry A, Graffeo CS, et al. Comparison on epidemiology, tumor location, histology, and prognosis of intracranial germ cell tumors between Mayo Clinic and Japanese consortium cohorts. *Journal of Neurosurgery.* 2021;134(2):446-456.
3. Murray MJ, Horan G, Lowis S, Nicholson JC. Highlights from the Third International Central Nervous System Germ Cell Tumour symposium: laying the foundations for future consensus. *ecancermedicalscience.* 2013;7.
4. Ogawa K, Shikama N, Toita T, et al. Long-term results of radiotherapy for intracranial germinoma: a multi-institutional retrospective review of 126 patients. *Int J Radiat Oncol Biol Phys.* 2004;58(3):705-713.
5. Takami H, Fukuoka K, Fukushima S, et al. Integrated clinical, histopathological, and molecular data analysis of 190 central nervous system germ cell tumors from the iGCT Consortium. *Neuro Oncol.* 2019;21(12):1565-1577.
6. Sonoda Y, Kumabe T, Sugiyama S, et al. Germ cell tumors in the basal ganglia: problems of early diagnosis and treatment. *J Neurosurg Pediatr.* 2008;2(2):118-124.
7. Li B, Feng J, Chen L, et al. Relapse pattern and quality of life in patients with localized basal ganglia germinoma receiving focal radiotherapy, whole-brain radiotherapy, or craniospinal irradiation. *Radiotherapy and Oncology.* 2021;158:90-96.
8. Liang SY, Yang TF, Chen YW, et al. Neuropsychological functions and quality of life in survived patients with intracranial germ cell tumors after treatment. *Neuro-Oncology.* 2013;15(11):1543-1551.
9. Lv W, Feng J, Chen L, Liu S, Qiu X. Behavior Disorder and Social Function Impairment in Children with Basal Ganglia Germ Cell Tumors. *Neuropsychiatric Disease and Treatment.* 2021;Volume 17:91-98.
10. Kamoshima Y, Sawamura Y. Update on current standard treatments in central nervous system germ cell tumors. *Curr Opin Neurol.* 2010;23(6):571-575.
11. Kanamori M, Kumabe T, Saito R, et al. Optimal treatment strategy for intracranial germ cell tumors: a single institution analysis. *J Neurosurg Pediatr.* 2009;4(6):506-514.
12. Nicholson CL. *Interpretation of the WISC-III and Its Subtests [microform] / Charles L. Nicholson and Charles L. Alcorn.* [Washington, D.C.]: Distributed by ERIC Clearinghouse; 1993.
13. Education TIf. Tanaka-Binet Intelligence Scale. *Tokyo: Taken Publisher.* 1987.
14. Carvajal H, Gerber J. 1986 Stanford-Binet Abbreviated Forms. *Psychological Reports.*

1987;61(1):285-286.
15. Aoyama H, Shirato H, Ikeda J, Fujieda K, Miyasaka K, Sawamura Y. Induction Chemotherapy Followed by Low-Dose Involved-Field Radiotherapy for Intracranial Germ Cell Tumors. *Journal of Clinical Oncology.* 2002;20(3):857-865.
16. Maeda K, Yasui H, Matsuura T, et al. Evaluation of the relative biological effectiveness of spot-scanning proton irradiation in vitro. *J Radiat Res.* 2016;57(3):307-311.
17. Ozelame RV, Shroff M, Wood B, et al. Basal ganglia germinoma in children with associated ipsilateral cerebral and brain stem hemiatrophy. *Pediatric Radiology.* 2006;36(4):325-330.
18. Graham RT, Abu-Arja MH, Stanek JR, et al. Multi-institutional analysis of treatment modalities in basal ganglia and thalamic germinoma. *Pediatric Blood & Cancer.* 2021;68(10).
19. Adam A, Kiosseoglou G, Abatzoglou G, Papaligoura Z. A comparison of three-factor structure models using WISC-III in Greek children with learning disabilities. *Annals of General Psychiatry.* 2018;17(1).
20. Diaz-Asper CM, Schretlen DJ, Pearlson GD. How well does IQ predict neuropsychological test performance in normal adults? *Journal of the International Neuropsychological Society.* 2004;10(01).
21. Helie S, Chakravarthy S, Moustafa AA. Exploring the cognitive and motor functions of the basal ganglia: an integrative review of computational cognitive neuroscience models. *Front Comput Neurosci.* 2013;7:174-174.
22. Leisman G, Braun-Benjamin O, Melillo R. Cognitive-motor interactions of the basal ganglia in development. *Front Syst Neurosci.* 2014;8:16.
23. Wataya T, Ishizaki R, Kitagawa M, Tashiro Y. Germinoma in the bilateral basal ganglia presented with cognitive deterioration. *Child's Nervous System.* 2015;31(6):953-958.
24. Knecht S. Handedness and hemispheric language dominance in healthy humans. *Brain.* 2000;123(12):2512-2518.
25. Phi JH, Kim S-K, Lee YA, et al. Latency of intracranial germ cell tumors and diagnosis delay. *Child's Nervous System.* 2013;29(10):1871-1881.

Figure captions

Figure 1. Intelligence quotient (IQ) scatterplot of patients with basal ganglia germinoma at initial diagnosis. IQ was evaluated during the initial treatment.

(A) Grouping based on overall neuropsychological symptoms (NPS). The IQ of patients with NPS (n = 6; median = 66; range: 57–91) was significantly lower than that of those without NPS (n = 4; median = 104; range: 100–111), as confirmed by the Mann–Whitney U test ($p = 0.01$).

(B) Grouping based on disease laterality. We observed a significant difference between groups, as confirmed by the Kruskal–Wallis test ($p = 0.04$). IQ values of patients with right-side lesions (Rt.) were higher than those of patients with bilateral lesions (Bil.); IQ values of patients with left-side lesions (Lt.) widely varied.

The bar indicates IQ means ± SD.

Figure 2. Kaplan–Meier plots of recurrence-free survival (RFS) among 12 patients with basal ganglia germinoma.

RFS was stratified by radiation therapy: whole-brain irradiation (WBI) or focal/focal plus whole-ventricle irradiation (F / WV + F). We observed a significant difference between treatment groups based on a log-rank test ($p = 0.02$).

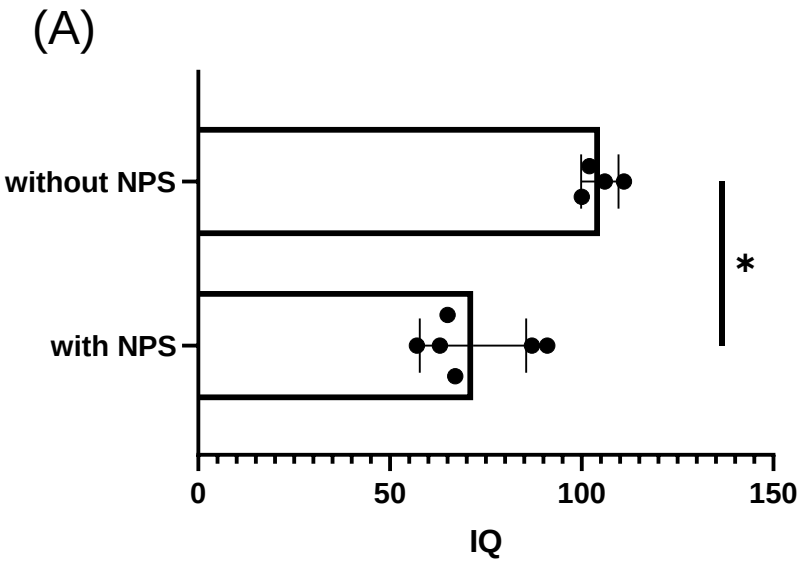
Supplementary Material

Supplementary Figure 1. Scatter plot of the time from onset to diagnosis in patients with basal ganglia germinoma.

Groups were based on overall neuropsychological symptoms (NPS). No significant difference between patients with NPS (median = 8 months; range 2–14) and without NPS (median = 6.5 months; range: 1–35) were observed, as confirmed using the Mann–Whitney U test ($p = 0.86$).

The bar indicates the mean time from onset to diagnosis.

Figure 1



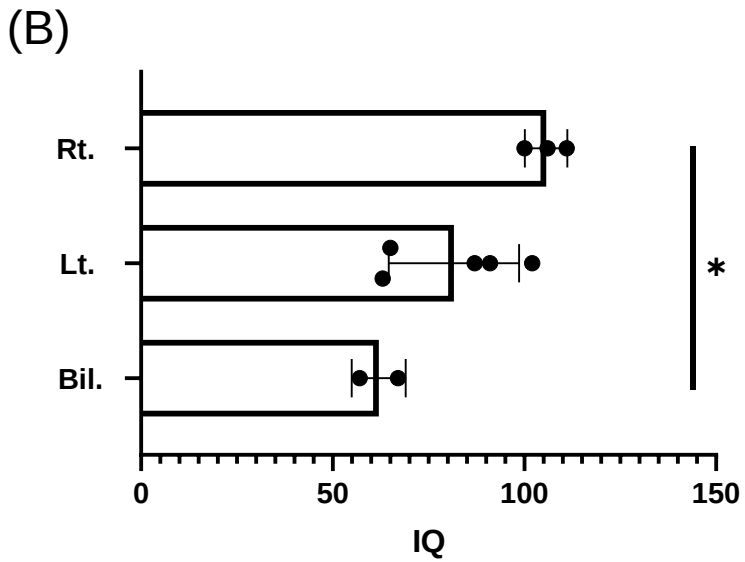
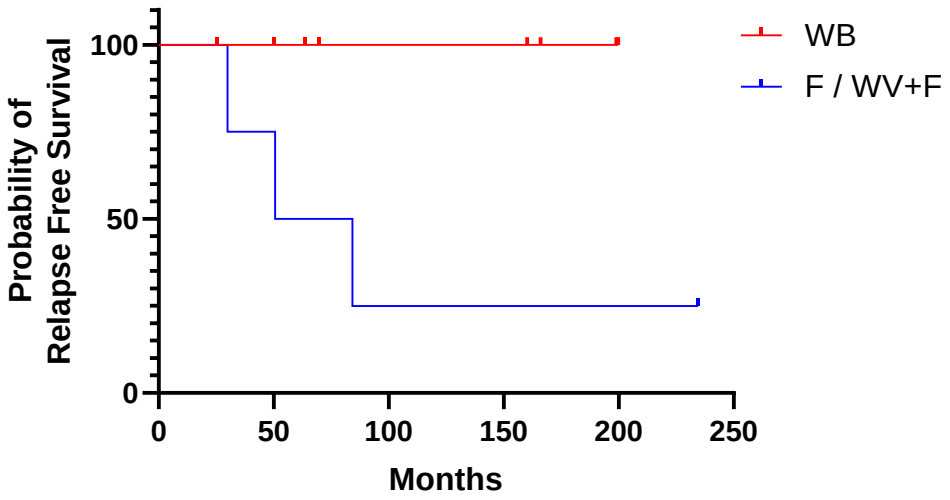


Figure 2


Probability of
Relapse Free Survival
100
50
0
0
50
100
150
200
250
Months
WB
F / WV+F

Supplement Figure 1

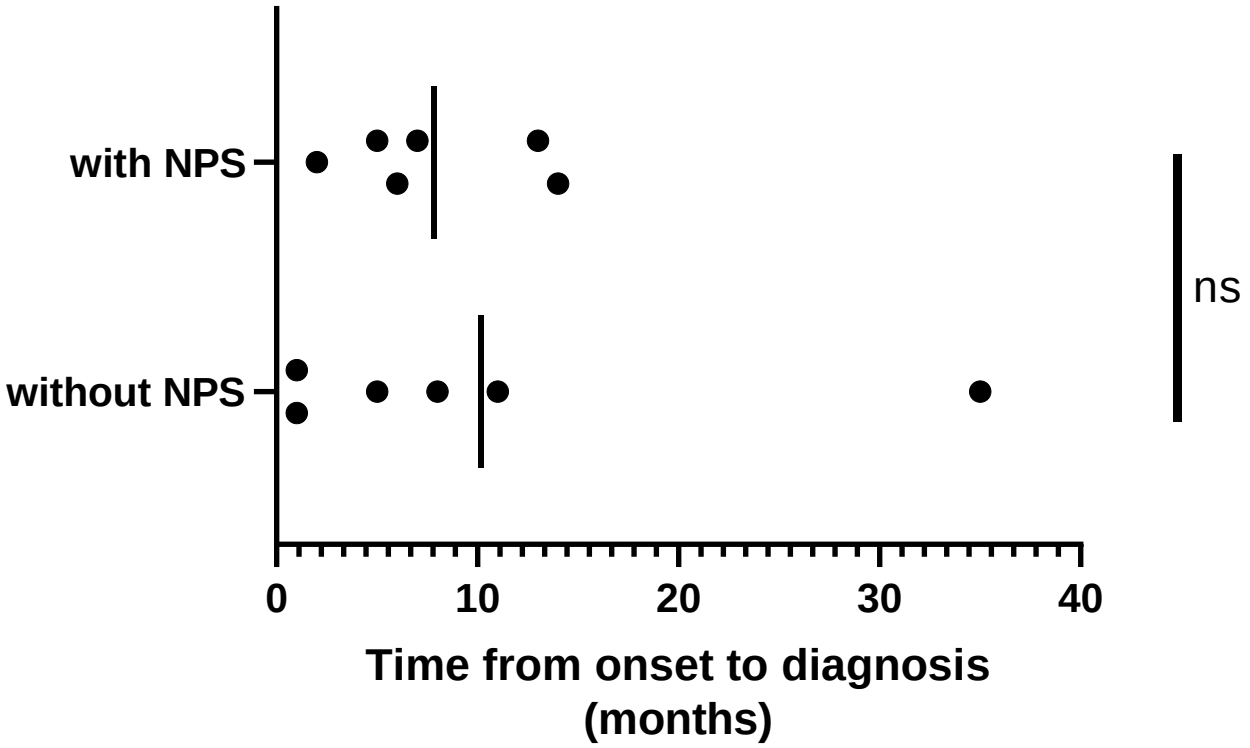


Table 1. Clinical characteristics of germinoma in the basal ganglia at diagnosis

Case No.	Age (yrs), Sex	Tumor Location	Side	Comorbidity	Initial Symptoms	IQ	Time from Symptom to Dx (months)
1	19, M	BG	Bil.	None	hemiparesis, cognitive decline, dysarthria	57*	13
7	13, M	BG	Bil.	None	personality change, behavior disorder	67	7
3	12, M	BG	Lt.	None	hemiparesis, motor aphasia, academic problem	87	14
4	19, F	BG + NH	Lt.	None	DI, Visual disturbance, panhypopituitarism	NA	1
5	15, M	BG	Lt.	None	hemiparesis, academic problem	63	2
6	13, M	BG	Lt.	None	hemiparesis, academic problem	65	5
9	15, M	BG	Lt.	None	hemiparesis, dysarthria	102	5
11	14, M	BG	Lt.	None	hemiparesis, academic problem	91	6
12	8, M	BG + P	Lt.	Down synd.	hemiparesis	ND	11
2	15, M	BG	Rt.	None	hemiparesis	106	1
8	16, M	BG	Rt.	None	hemiparesis	100	35
10	9, M	BG	Rt.	ADHD	hemiparesis	111	8

ADHD: Attention deficit hyperactivity disorder, Dx: diagnosis, BG: basal ganglia, P: pineal, NH: neurohypophysis, Bil: bilateral, Rt: right, Lt: left, synd: syndrome, DI: diabetes insipidus, IQ: intelligence quotient, NA: not applicable, ND: not detected *Only this patients was evaluated by Tanaka-Binet test.

Table 2. Treatments and outcomes of germinoma in the basal ganglia

Case No.	Age(yrs), Sex	Tumor Location	Side	Time from Symptom to Dx (months)	Chemo (No. of courses)	Radi (dose, Gy)	Salvage Surgery	RFS (months)	OS (months)	Academic History (Graduated)	Recent Occupation	Recent KPS
1	19, M	BG	Bil.	13	ICE (4)	F (24)	No	50	192	Special support education school	Receiving disability support	60
7	13, M	BG	Bil.	7	ICE (4)	WB (25.2)	No	No rec	69	Junior high school	Receiving disability support	50
3	12, M	BG	Lt.	14	ICE (4)	WV+F (24)	No	29	244	Junior high school	None	50
4	19, F	BG + NH	Lt.	1	ICE (4)	WV+F (24)	No	No rec	234	Technical school	None	90
5	15, M	BG	Lt.	2	ICE (4)	WB+F (25.2)	No	No rec	199	Graduate school	Full time job	90
6	13, M	BG	Lt.	5	CARE (4)	WB (25.2)	No	No rec	63	Junior College	ND	90
9	15, M	BG	Lt.	5	ICE (3)	WB (25.2)	No	No rec	166	University	Full time job	90
11	14, M	BG + P	Lt.	6	CARE(3) →ICE (3)	WB+F (23.4+27[RBE])	Yes*	No rec	50	High school	Full time job	90
12	8, M	BG + P	Lt.	11	CARE (3)	WB (23.4[RBE])	No	No rec	25	Elementary school (in school)	Student	80
2	15, M	BG	Rt.	1	ICE (3)	F (24)	No	84	225	High school	Part time job	90
8	16, M	BG	Rt.	35	ICE (4)	WB (25.2)	No	No rec	199	High school	Full time job	80
10	9, M	BG	Rt.	8	ICE (4)	WB (25.2)	No	No rec	160	Graduate school (in school)	Student	100

Chemo: chemotherapy, Radi: radiotherapy, Rec: recurrence, BG: basal ganglia, P: pineal, NH: neurohypophysis, Dx: diagnosis, RBE: relative biological effectiveness, RFS: recurrence free survival, OS; overall survival, F: focal irradiation, WV: whole ventricle irradiation, WB: whole brain irradiation, KPS: Karnofsky performance status, ND: not detected, * no viable tumor cells were observed.