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Neuropsychological functions and quality of life in survived patients with intracranial germ cell tumors after treatment

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Background. The notable survival chances of intracranial germ cell tumors (icGCTs) lead to a rising concern over long-term neurocognitive outcome. Yet, prior evidence related to this issue fails to provide a comprehensive examination of the effects of tumor location and radiotherapy. We attempt to explore their impacts on the neuropsychological functions and life quality in children with icGCT after multimodality treatments.
Methods. A retrospective review of 56 patients diagnosed with icGCTs at age <20 and treated at the Taipei Veterans General Hospital was provided. Intelligence, memory, visual organization, attention, and executive function were assessed by neurocognitive tests; adaptation to life, emotional and behavioral changes, interpersonal relationships, and impact on the family were evaluated by parent-report instruments. Effects of tumor locations (germinomas and nongerminomatous malignant germ cell tumors in the pineal, suprasellar, and basal ganglia) and irradiation on these measurements were examined.
Results. Patients with tumors in the basal ganglia region had lower full-scale IQs than those with tumors in the pineal or suprasellar regions. Subscores of intelligence scale and short-term retention of verbal and visual stimuli showed evident group differences, as did the quality of life and adaptive skills, particularly in psychosocial domains. Patients treated with whole-ventricular irradiation had better outcomes. Extensive irradiation field and high irradiation dosage influenced intellectual functions, concept crystallization, executive function, and memory.
Conclusions. Tumor location and irradiation field/dosage appear to be the crucial factors related to certain neuropsychological, emotional, and behavioral dysfunctions that in turn alter the quality of life in children with icGCTs who survive after treatment.

Keywords: basal ganglia, intracranial germ cell tumors, neurocognitive functions, quality of life, whole ventricular irradiation.

Primary intracranial germ cell tumors (icGCTs) are a specific entity of brain tumors with a variety of histological types and different degrees of malignancy. Intracranial GCTs make up 11.2%–15.3% of primary intracranial tumors in Asian children[1–3] compared with 3.6% in the US.[4] Being the third most common type of brain tumors in the pre-adult stage,[5–7] they attract much attention from pediatric neuro-oncologists in Taiwan. Intracranial GCTs predominantly occur in the pineal, suprasellar, basal ganglia, and cerebral ventricular regions. Further, these tumors also develop at multiple sites such as synchronous pineal and suprasellar tumors; in some rare cases, they involve diffusely along the ventricular wall.[5,8]

Treatment strategy for icGCTs relies on multiple factors. With histological verification, it could be adjusted according to the therapeutic classification of GCTs initiated by the Japan Pediatric Brain Tumor Study Group.[8,9] In this

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classification, mature teratoma is a benign tumor that can be cured simply by radical resection. Germinomas are highly sensitive to radiotherapy (RT). For localized tumor, complete remission and high overall survival rate can be obtained by using decreased-dosage whole ventricular irradiation (WVI) and primary boost (PB) to the tumor site.[9–11] Along with chemotherapy, whole brain irradiation (WBI) is given to tumors with multiple sites,[9] and craniospinal axis irradiation (CSI) is delivered to disseminated tumors.[12] However, CSI had been applied to both localized and disseminated intracranial germinomas.[13] The intermediate prognosis group includes immature teratoma and mixed tumors mostly composed of germinoma and immature teratoma. For intracranial immature teratoma, initial radical excision is preferred. The adjuvant treatments for localized tumor include WVI with higher PB and chemotherapy.[9] The poor prognosis group involves the yolk sac tumor, choriocarcinoma, embryonal carcinoma, and mixed tumors composed mainly of these components. Extensive field radiation (ie, CSI) with high-dose PB and ifosfamide/carboplatin/etoposide chemotherapy are suggested.[9]

Due to the improved therapeutic strategies in recent decades, knowing the survival rate no longer meets the need for integrated care of these patients; evaluation of quality of life and neuropsychological functioning are in demand. The age at diagnosis of icGCTs is mostly in older childhood and adolescence, which are the critical periods for cognitive and social development as well as for intensive elementary or high school education. Therefore, investigation of improving the psychosocial functions of these patients is urgently needed. Previous research[14] on icGCTs reported declines in working memory, visual memory, and processing speed. However, risks for other neuropsychological disturbances related to irradiation, hormone deficiencies, neuro-ophthalmological defects, and hydrocephalus remain unclear, particularly for tumors in the basal ganglia region.

The pediatric neuro-oncology team at the Taipei Veterans General Hospital (VGHTPE) has conducted multidisciplinary research to broaden our understanding of icGCTs. This study aimed for a comprehensive examination of various aspects of psychosocial functioning, quality of life, and adaptive behavior across different settings. We considered that a systematic comparison among different tumor locations and irradiation regimens was relatively sparse in Asia. This study provides a clinical review of patients with icGCTs in the pineal, suprasellar, and basal ganglia regions in an attempt to correlate the neurobehavioral findings with localization of the tumor, RT, and prognostic outcome. Moreover, we seek supporting evidence for the efficacy of reduced-dosage WVI with PB to balance survival in nondisseminated germinomas and protection of neuropsychological functions and quality of life.

Materials and Methods

Participants

Fifty-six children and adolescents (43 males) treated for icGCT within the last 20 years at the VGHTPE were randomly selected into this review study regardless of tumor malignancy, prognosis, or life achievement. The mean age at diagnosis was 11.9 years (range, 3.2–19.9 y). The mean age at neuropsychological evaluation was 17.7 years (range, 8.9–29.1 y). The mean follow-up time was 6.9 years (range, 1.7–17.9 y). The tumor locations included pineal ($n = 20$), suprasellar ($n = 14$), and basal ganglia ($n = 22$). Tumor diagnoses consisted of germinoma ($n = 35$), mature teratoma ($n = 1$), and nongerminomatous malignant germ cell tumors (NG-MGCTs; $n = 20$). Thirty-nine patients received different extents of tumor resection based on no data ($n = 1$), biopsy ($n = 13$), partial/subtotal resection ($n = 14$), and near total/gross total excision ($n = 11$) (Table 1).

The primary irradiation field and dosage varied according to tumor diagnosis, CSF dissemination, tumor marker, prognosis group classification, and residual tumor after adjuvant treatment. The irradiation fields comprise tumor bed irradiation (TBI), gamma knife radiosurgery, WVI with PB, WBI with PB, and CSI with PB (Table 2). For localized germinomas, since the 2000s we have limited the irradiation field to WVI + PB with adjusted radiation dosage ranging 24–30 Gy to the ventricles and 30 Gy to the tumor bed. The 7 recurrent cases were all germinomas. The tumors relapsed after chemotherapy in 2 patients, after TBI in 3 patients, after gamma knife radiosurgery in 1 patient, and after WVI in 1 patient. Salvage irradiation therapy for tumor recurrence was given (3 CSI + PB, 2 CSI + chemotherapy, 1 CSI, 1 WBI). Table 2 shows further details for average RT dosage and field of primary RT applied to icGCTs in different tumor locations.

Neither differences in the length of interval between treatment and neuropsychological evaluation ($F = 0.01$, $P = .98$) nor age at RT ($F = 0.08$, $P = .92$) was evident as a function of tumor location. However, time after RT varied significantly by irradiation regimens ($P < .05$). Patients receiving WBI had longer intervals ($M = 9.92$) than patients receiving CSI ($M = 5.76$), TBI ($M = 5.67$), or WVI ($M = 2.87$), due partly to the transition of treatment strategies at VGHTPE. [11] Histological constitution or extent of resection did not differ by tumor location ($P > .05$).

Materials and Procedures

Patients were referred by the Division of Pediatric Neurosurgery and received neuropsychological assessments of intelligence, memory, visual organization, attention, and executive function. The Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV) and the Wechsler Adult Intelligence Scale -Third Edition (WAIS-III) were conducted for different age groups. The memory tasks included the Digit Span Test and the Spatial Span Test of the Wechsler Memory Scale-Third Edition (WMS-III) for auditory and spatial working memory, the Word List of the WMS-III for verbal short-term memory, and the Rey Complex Figure Test and Recognition Trial for visual constructional memory. The vigilance task of the Gordon Diagnostic System was used

Table 1. Medical characteristics of study population

Location of icGCTs				**No. of Cases**
Pineal				20
Pineal				14
Synchronous pineal and suprasellar				6
Suprasellar/neurohypophyseal				14
Basal ganglia				22
Diagnosis of icGCT				
	Total	Pineal	Suprasellar	Basal ganglia
Germinoma	35	9	10	16
Mature teratoma	1	1	0	0
NG-MGCT	20	10	4	6
Immature teratoma	4	3	1	0
Yolk sac tumor, pure	1	0	0	1
Mixed GCT	13	7	1	5
Diagnosed by tumor markers	1	0	1	0
Unclassified	1	0	1	0
Surgical excision				
	No data	Biopsy	Partial/subtotal	Near total/gross total
Pineal ($n = 20/20$)	0	8	7	5
Suprasellar ($n = 7/14$)	0	3	4	0
Basal ganglia ($n = 12/22$)	1	2	3	6

Table 2. Primary RT and/or chemotherapy for icGCTs in different locations

Treatment Modality			
	Location		
	Pineal $n = 20$	**Suprasellar $n = 14$**	**Basal Ganglia $n = 22$**
CMT alone	1	1	0
RT alone	7	9	12
GKRS	1	0	0
RT + CMT	11	4	10
Primary RT field			
	No. of cases/primary RT dose + PB dose (Gy) by location		
	Pineal	Suprasellar	Basal ganglia
TBI	7/41.3 (25–54)	2/42 (30–54)	9/32 (28–50.4)
TBI + GKRS	1	0	0
TBI + WBI	1	0	0
WVI + PB	6/28.3 (24–30.6) + 38 (30–54)	8/23.8 (23.2–24) + 30.1 (29.3–30.6)	6/23.9 (23.4–24) + 33.9 (30–50)
WBI + PB	0	1/30.1 + 50	3/34.9 (26–38.8) + 50 (50–50.6)
GKRS	1	0	0
CSI + PB	3/25 (22.5–30.6) + 54.2 (52.5–55)	2/28.5 (27–30) + 52.2 (50.4–54)	3/28.4 (26.8–30) + 50.8 (50–51.5)
CSI + PB + GKRS	1	0	0

Abbreviations: CMT, chemotherapy; GKRS, gamma knife radiosurgery.

to evaluate patients' self-modulation in sustaining attention and impulse control. The Computerized Wisconsin Card Sorting Test (WCST) Computer Version 4 was conducted to assess the executive function for reasoning flexibility and strategy shift.

The Chinese Adaptive Behavior Assessment System–Second Edition (ABAS-II) for children from 6 to 17 years and adults from 18 to 84 years and the Child Health Questionnaire 50-item Parent Form (CHQ-PF50) for children and adolescents from 6 to 18 years were gathered through parent reports.

During the routine follow-up at our clinic, the examiner began with a brief interview before administration of the neuropsychological tests. A brief break was permitted

Table 3. Overall results of neuropsychological measures grouped by tumor location

Measure	Basal ganglia, *M* (*SD*)	Pineal, *M* (*SD*)	Suprasellar, *M* (*SD*)
Intelligence (WISC-IV/WAIS-III)			
Full scale IQ[a]	80.81 (20.70)***	102.25 (16.36)	101 (14.67)
Verbal comprehension[a]	91.05 (15.81)*	106.20 (15.35)	100.79 (15.39)
Perceptual reasoning[a]	89.95 (22.01)*	103.55 (17.33)	104.86 (14.30)
Working memory[a]	87.74 (19.20)*	103.45 (15.83)	99.21 (16.48)
Processing speed[a]	71.89 (17.14)	81.95 (17.04)	86.57 (18.36)
Memory			
Working memory (Digit/Spatial Span tests of WMS-III)			
Forward digit span[b]	9.61 (3.33)	10.50 (2.88)	9.29 (2.87)
Backward digit span[b]	7.72 (3.46)	9.85 (3.62)	10.64 (2.85)
Forward spatial span[b]	7.47 (3.68)**	10.24 (2.14)	11.10 (2.77)
Backward spatial span[b]	8.07 (3.49)*	10.88 (3.35)	11.50 (2.59)
Verbal short-term memory (Word List test of WMS-III)			
Immediate recall[b]	4.94 (3.70)*	7.16 (4.18)	8.36 (4.78)
Delayed recall[b]	6.4 (3.96)	7.11 (4.29)	8.93 (4.31)
Recognition[b]	7.50 (3.94)	9.32 (3.37)	9.93 (2.73)
Visual constructional memory (RCFT)			
3-Min immediate recall[c]	32.67 (12.57)	38.00 (17.93)	40.31 (10.27)
30-Min delayed recall[c]	30.83 (12.66)	35.78 (16.39)	39.85 (13.30)
Recognition[c]	31.17 (13.17)*	44.61 (17.02)	48.08 (8.61)
Attention (GDS)			
Correct[b]	8.67 (4.34)	8.88 (4.17)	8.70 (3.53)
Commission[b]	10.27 (2.37)	9.88 (2.62)	9.90 (2.56)
Latency[b]	9.07 (1.75)	8.76 (2.39)	8.10 (2.60)
Executive function (WCST)			
Category completed	4.91 (1.38)	5 (1.5)	5.64 (0.81)
Perseverative error[a]	93.91 (15.25)*	100 (19.24)	110.27 (13.60)
Nonperseverative error[a]	92.55 (12.34)	92.50 (18.50)	101.27 (15.56)
Visual organization (RCFT)			
Copy trial of RCFT[d]	4 out of 12	10 out of 19	3 out of 13

Abbreviations: RCFT,Rey Complex Figure Test; GDS, Gordon Diagnostic System.
[a]$M = 100$, $SD = 15$, deviation score.
[b]$M = 10$, $SD = 3$, scale score.
[c]$M = 50$, $SD = 10$, *T*-score.
[d]Number of subjects who fall below the critical point (percentile rank < 16).
*$P < .05$, **$P < .01$, ***$P < .001$.

as the patient requested. After the assessment, the examiner would discuss the preliminary findings with the family to verify the ecological validity of the assessment results. A few participants were not administered all the tests due to time constraints; therefore, the number of patients in different measures may vary.

Statistical Analysis

The test results were represented by either deviation score (mean [*M*] = 100, *SD* = 15), scale score ($M = 10$, $SD = 3$), *Z* score ($M = 0$, $SD = 1$), or *T* score ($M = 50$, $SD = 10$) based on age-related norms published in the test manuals. The overall effects of tumor location and radiation field on cognitive outcomes were explored by using 1-way analyses of variance or the Kruskal–Wallis test followed by post hoc comparison with the Mann–Whitney *U*-test. The impacts of the presence or absence of hydrocephalus and surgical resection combined with chemotherapy were also taken into account. Pearson's correlation tests were conducted for detecting the relationships among irradiation dosage, neuropsychological performance, and quality of life. Group differences were regarded as significant at $P < .05$.

Results

Neuropsychological Evaluation

Neuropsychological data grouped by tumor location are displayed in Table 3. Statistical analysis showed that full-scale IQ (FSIQ) differed significantly by tumor location, $F(2, 52) = 9.01$, $P < .001$, as did performance in verbal comprehension ($F = 4.72$, $P < .05$), perceptual

reasoning ($F = 3.59$, $P < .05$), and working memory ($F = 4.24$, $P < .05$). Patients with tumors in the basal ganglia exhibited lower scores in most intelligence tasks than patients with pineal and suprasellar tumors. In the verbal and spatial memory tasks, patients with basal ganglia tumors showed a general decline in memory functioning, as did a few cases with tumors in the pineal region; patients with suprasellar tumors were least affected. The basal ganglia group performed significantly worse than the suprasellar group in immediate recall of an unrelated word list, $Z = -1.98$, $P < .05$, as well as delayed recognition of the embedded items of a previously presented complex figure, $F(2, 40) = 5.21$, $P < .05$. Group divergence of both forward spatial span, $F = 5.68$, $P < .01$, and backward spatial span, $F = 4.35$, $P < .05$, indicated that patients with basal ganglia tumors had less capacity to retain spatial information for further manipulation than patients with pineal and suprasellar tumors.

The Rey Complex Figure Test demands many cognitive abilities and is sensitive to mild neuropsychological impairment. Lower scores obtained from the pineal group revealed mild to moderate disturbances in visual-perceptual and visuomotor integration. However, a constructional strategy prevailed in the sample: most patients either (i) began with the overall contour without explicitly differentiating the central rectangle and internal details or (ii) juxtaposed details one by one without an organized structure.[15]

We also appraised the risk for late adverse effects associated with irradiation. A significant effect of radiation field was disclosed in overall intellectual performance, $\chi^2 = 8.30$, $P < .05$; patients receiving WVI ($M = 102.24$, $SD = 16.97$) had higher FSIQs than the group receiving WBI ($M = 71.29$, $SD = 27.16$). The difference between the CSI ($M = 90.75$, $SD = 16.36$) and WVI groups, though present, was not statistically meaningful. A significant correlation between FSIQs and RT dosage of the PB to the tumor bed was detected in patients with basal ganglia tumors, $r = -0.54$, $P < .05$. Verbal comprehension also changed as a function of radiation field, $\chi^2 = 8.69$, $P < .05$, indicating that mean verbal comprehension scores of the CSI group ($M = 94.50$, $SD = 15.64$) and WBI group ($M = 83.40$, $SD = 22.77$) fell significantly behind the WVI group ($M = 105.95$, $SD = 13.91$). Furthermore, radiation field yielded a significant result in delayed verbal recognition, $Z = -2.80$, $P < .05$; (WBI: $M = 5.50$, $SD = 3.70$ vs WVI: $M = 10.20$, $SD = 2.07$). Performance on the WCST task indicated that the TBI and WBI groups committed more nonperseverative errors than the WVI group, $\chi^2 = 8.25$, $P < .05$, showing poor use of feedback information and fluctuating in their choice of sorting principle.

A marginal effect of tumor location was detected in information processing speed, $F(2, 50) = 3.15$, $P = .05$, as was the effect of radiation field $Z = -1.89$, $P = .05$, showing that the WVI group ($M = 86.43$, $SD = 18.24$) seemed to spare greater mental processing speed than the CSI group ($M = 73.08$, $SD = 16.24$). The mean accuracy in the vigilance task of the study sample was modestly below that of the normal population. Further, the average response latency in this task was significantly longer ($M = 8.71$, $SD = 2.21$) than that of the normative sample, $t = -3.77$, $P < .01$. Taken together, the neurobehavioral changes provide evidence that mental tardiness in pediatric brain tumor patients, as a common sequelae, could cause their unsuccessful reaction to the rapidly changing information.

Adaptive Function and Quality of Life

The current findings revealed a significant difference in the general adaptive composite scores, $F(2, 34) = 4.48$, $P < .05$. Survivors with icGCTs in the basal ganglia had poorer outcome of overall adaptive functioning falling within the borderline range. Conversely, patients with pineal and suprasellar tumors had outcomes comparable to the normal sample. Similarly, tumor location affected 3 general domains (see Table 4 for a summary of the results in different adaptive measures): conceptual skills ($F = 5.88$, $P < .01$), social skills ($F = 3.63$, $P < .05$), and practical skills ($F = 4.10$, $P < .05$). Patients with basal ganglia tumors displayed significantly worse performance in communication, functional academics, self-directing, leisure, and self-care skills than the other 2 groups ($Ps < .05$).

Likewise, children and adolescents with basal ganglia tumors were rated the lowest in the Psychosocial Summary Scale and the Physical Summary Scale of the quality of life assessment, and these scores were significantly below the normative mean ($Ps < .05$). Conversely, patients with pineal and suprasellar tumors had measures within the subaverage range in both physical and psychosocial domains. A significant difference was shown between the basal ganglia and the pineal groups in the psychosocial domain, $Z = -2.09$, $P < .05$, and between patients receiving WBI ($M = 32.63$, $SD = 13.35$) and WVI ($M = 45.06$, $SD = 10.51$), $Z = -1.98$, $P < .05$. (See Table 5 for details of results obtained on different quality of life measures.) Psychosocial outcomes were evidently affected by tumor location in Role Limitations–Behavior/Emotion, Behavior, and Self-esteem ($Fs < 4.93$, $Ps < .05$). For instance, the survivors treated for basal ganglia tumors put in extra effort to meet academic requirements and were more likely to be disturbed by their emotional or behavioral problems when engaging in school activities. And the parents reported lower ratings of patients' satisfaction with abilities, looks, family/peer relationships, and life. Moreover, WBI was associated with worse physical outcome compared with the other treatment groups, particularly in physical functioning ($\chi^2 = 8.15$, $P < .05$) and bodily pain ($\chi^2 = 7.61$, $P < .05$). Patients receiving WBI also developed poorer self-concept ($M = -2.3$, $SD = 1.36$) than the CSI group ($M = -0.47$, $SD = 1.01$) and WVI group ($M = -0.71$, $SD = 1.06$).

FSIQs were strongly correlated with the Psychosocial Summary Scale ($r = 0.62$, $P < .001$), the Physical Summary Scale ($r = 0.60$, $P < .001$), and the general adaptive composite scores ($r = 0.72$, $P < .001$). Furthermore, the general adaptive composite scores were significantly correlated with the Psychosocial Summary Scale ($r = 0.70$, $P < .001$) and the Physical Summary Scale ($r = 0.52$, $P < .01$).

Table 4. Overall results of adaptive behavior by tumor location analysis

ABAS-II Domain	Basal Ganglia, *M* (*SD*)	Pineal, *M* (*SD*)	Suprasellar, *M* (*SD*)
General adaptive composite[a]	79.14 (25.81)*	99.85 (16.58)	101.30 (18.58)
Concept skill[a]	82.50 (23.30)**	104.77 (14.73)	102.80 (14.68)
Communication[b]	7.33 (3.99)*	10.92 (3.07)	10.30 (2.54)
Functional academics[b]	6.71 (4.21)**	11.50 (2.68)	10.80 (2.66)
Self-direction[b]	6.93 (4.07)*	11.00 (2.92)	10.60 (3.75)
Social skill[a]	80.50 (25.14)*	98.69 (13.90)	100.30 (21.24)
Leisure[b]	6.86 (4.47)*	10.54 (2.63)	10.80 (3.16)
Social[b]	6.71 (4.41)	9.31 (2.81)	9.40 (4.53)
Practical skill[a]	77.73 (24.58)*	96.38 (18.45)	99.50 (18.91)
Community use[b]	7.33 (4.34)	10.08 (3.57)	9.50 (3.84)
Home living[b]	6.57 (4.24)	8.92 (3.00)	9.80 (3.26)
Health and safety[b]	6.07 (3.83)**	9.77 (3.19)	10.30 (2.91)
Self-care[b]	6.00 (4.75)*	9.69 (3.68)	10.20 (3.23)

[a]$M = 100$, $SD = 15$, deviation score.
[b]$M = 10$, $SD = 3$, scale score.
*$P < .05$, **$P < .01$.

Table 5. Quality of life measurement and scores

Quality of Life Domain	Basal Ganglia, *M* (*SD*)	Pineal, *M* (*SD*)	Suprasellar, *M* (*SD*)
Physical health summary[a]	35.30 (15.14)	41.88 (14.34)	42.90 (14.35)
Physical Functioning[b]	−1.77 (2.00)	−0.73 (1.66)	−0.52 (1.36)
Role limitation–Physical[b]	−2.13 (1.75)	−0.81 (1.61)	−0.67 (1.77)
General health[b]	−1.07 (1.09)	−0.64 (0.77)	−0.99 (1.00)
Bodily pain[b]	−0.01 (0.78)	0.44 (1.07)	−0.02 (1.33)
Psychosocial health summary[a]	36.72 (12.78)*	46.77 (12.27)	43.93 (9.45)
Behavior[b]	−0.82 (1.23)*	0.46 (1.08)	0.02 (0.90)
Role limitation–Emotion/Behavior[b]	−2.11 (1.80)*	−0.69 (1.52)	−0.49 (1.40)
Mental health[b]	−0.59 (1.38)	0.20 (1.35)	0.35 (0.79)
Self-esteem[b]	−1.68 (1.32)*	−0.32 (1.16)	−1.09 (0.81)
Involved both physical and psychosocial domains			
Parent impact–Emotion[b]	−1.28 (1.40)	−1.09 (1.71)	−1.28 (1.59)
Parent impact–Time[b]	−1.17 (1.22)	−1.10 (1.94)	−0.74 (1.66)

[a]$M = 50$, $SD = 10$, *T*-score.
[b]$M = 0$, $SD = 1$, *Z*-score.
*$P < .05$.

We further analyzed the roles of time after RT, fraction dose, and RT age, which have been extensively discussed. Yet, the present study falls short of detecting such impacts. None of the newly included predictors could significantly explain the variance of patients' neuropsychological performance and living functioning. Furthermore, the results of neither analyses of covariance nor correlation tests indicated that the length of RT interval, fraction dose, and RT age functioned as evident covariates that would cast significant influences on our primary results.

Discussion

This study examined multiple neurocognitive and psychosocial functions of patients who survived icGCTs in Taiwan. Long-term outcome of icGCTs has been well documented in the last decade,[14,16–19] yet a number of novel findings of the present study are worth noting. First of all, patients with tumors in the basal ganglia were subject to diverse changes in cognition, affection, and behavior. Their FSIQs, along with performance in verbal comprehension, perceptual reasoning, working memory, and short-term retention of previously acquired information, were significantly inferior to those of patients with tumors in the pineal and suprasellar regions. Evidence from various assessments conjointly corroborates a role of the basal ganglia in control of behavior, emotion, and cognition. Patients with icGCTs suffered a significant decline in information processing speed and exhibited difficulty in copying a complex figure based on organized strategies that, in turn, resulted in poor

reproduction in the later recall trials. Mild to moderate memory disorder or executive dysfunction could underlie the problematic production.

Radiation volume appears to be another crucial factor affecting intellectual functioning. Extensive volume of radiation (such as CSI or WBI) was related to cognitive declines. This is evident in patients receiving >30 Gy to the whole brain and >50 Gy to the tumor site who manifested moderate to severe defects in several neurocognitive domains, including FSIQ, verbal memory, and executive functions, relative to those treated with WVI or TBI. Verbal comprehension entailing crystallized concepts of facts, semantic knowledge, and verbal discourse were also susceptible to the effects caused by CSI or WBI.

Our primary finding suggests that tumor location, particularly in the basal ganglia, plays a critical role in prognosis. The basal ganglia subserves roles from motor control to integration of drives and experiences.[20–23] Mood and behavioral syndromes reported after lesions of this region can be divided into 2 categories[20]: abulic/akinetic syndromes and disinhibition syndromes. The former is related to malfunctioning of the anterior cingulate pathway, which connects the limbic cortices with other brain areas to select environmental stimuli based on emotion, motivation, and spontaneity.[24,25] Compromising this pathway results in indifference to basic instincts, reduced spontaneous motor skills and verbalization (delayed and laconic responses), and initiation difficulty. The disinhibition syndromes may be associated with the orbitofrontal circuit innervating the basal ganglia to integrate mood, instincts, and behaviors under situational or social restraints or to direct goal behavior after appraisal of environmental factors and strategies. Disruption of this circuit could result in disinhibition and impulsivity,[20,25,26] as exemplified by a few cases prone to socially inappropriate (sexual or aggressive) and risk-taking behaviors, emotional distress, and easily reacting with tantrum.

Disinhibition may also appear in forms of dysexecutive syndromes due to dorsolateral prefrontal dysfunction, such as deficits in reasoning flexibility, maintaining or shifting attention, and suppressing distractive responses, as well as showing repetitive, compulsive, or stereotyped behaviors.[20,25,26] For example, a case showed difficulties in suppressing irrelevant stimuli and shifting strategy based on external feedbacks. The ill construction and poor retrieval of complex figures implicate deficient memory and visuospatial processing. This conjecture seemed to receive further support from the ABAS-II finding that patients with basal ganglia tumors exhibited more problems in implementing goal-directed behaviors.

Of the above implications, the basal ganglia is likely to participate in a wide range of cognitive activities.[22,25,27,28] This notion is based on anatomical findings of its profuse reciprocal interconnections with other brain regions, including the prefrontal, orbitofrontal, sensorimotor, limbic/paralimbic cortices, diencephalic structures, and midbrain, [29,30] which are involved in higher-order cognitive abilities.[21,22,26,31,32] This view possibly explains part of the reason that general cognitive decline was detected only in patients with basal ganglia tumors, given that the other tumor sites do not have such wide connections to various cortical areas.

Other risk factors detrimental to neurocognitive functions, including tumor histology, adjuvant treatment, and hydrocephalus, also deserve consideration. As treatment strategy depends mainly on histology, prognostic features may vary with different subtypes of GCTs. An increasing body of research has been dedicated to the refinement of adjuvant RT. Some investigators documented stable and average intelligence in a group of patients treated with CSI,[16,33] yet others reported significant declines in intellectual functioning, visual-motor integration, visual and verbal memory, and executive functioning following irradiation in childhood.[34–36] To disambiguate these discrepant findings, the present study analyzed the role of the treatment factors.

Overall, patients subjected to WVI spared the neurocognitive functioning more than those with CSI and WBI, particularly in FSIQ, short-term retention of verbal information, and reasoning flexibility. The adverse impacts probably have to do with extensive radiation along the neuraxis in altering or disrupting the growth of white matter (ie, demyelination and necrosis) and leading to "delayed effects" on neuropsychological functions.[37,38] A few exceptional cases ($n = 4$) were identified in the pineal group, as they preserved normal intelligence within the average to high average level. The mean dose applied to the craniospinal axis was 25.1 Gy. Unlike the clear results of radiation field, radiation dosage yielded relatively minor effects in the present study, with the exception that a significant correlation was obtained for patients with basal ganglia tumors, as their FSIQs negatively correlated with the radiation doses applied to the tumor site. The current findings seemed to corroborate our recent proposal that adjusting radiation volume to the whole ventricular system with a lower PB (<36 Gy) was sufficient for nondisseminated intracranial germinomas, and such treatment predicted better quality of life.[11] Prior research investigating the late-delayed effects of irradiation has suggested that time after radiotherapy,[39] fraction dose, and age at radiotherapy are important factors. Our study using a cohort design on a selected sample has limitation in exploring their potential impacts. However, neither the regression analysis nor the correlation tests indicated them as valid predictors or covariates.

Persistent memory disturbances sometimes occur with icGCTs. Hydrocephalus was identified as a potential risk factor. Patients with concurrent hydrocephalus showed poorer performance in delayed recall of the word list and complex figure than those without such a complication ($Ps < .05$). The built-up intracranial pressure due to obstruction of the third ventricle or surgical resections may cause considerable damage to diencephalic structures such as the fornix, thalamus, hypothalamus, basal forebrain, mammillary bodies, and mammillothalamic tract, which are implicated in memory processes.[40–42] Similarly, some cases with tumor cells infiltrating into the brain structures surrounding the third ventricle might also show amnesia-like syndromes.[43–46] Our data indicated that patients with tumors in the basal ganglia

and pineal regions were more vulnerable to memory difficulties. Six out of 20 patients with pineal tumors showed disproportionately mild to moderate decline in memory functioning based on their normal IQ scores—among these patients, concurrent hydrocephalus was often identified in the diagnosed stage. On the other hand, a significant correlation between the FSIQs and verbal memory scores in patients with basal ganglia tumors was detected. Thus, memory disturbances in this group might be a problem secondary to general cognitive dysfunction.[47]

Finally, this study intended to address the issue of whether living adaptation and quality of life were somehow related to neuropsychological functioning in survivors of icGCTs. Our data showed this to be the case. According to both the ABAS-II and CHQ-PF50, patients with basal ganglia tumors encountered more frustration in daily functioning than the other groups. This outcome agrees with the neuropsychological testing results that a number of strong correlations exist among the FSIQ, Physical Summary Scale, Psychosocial Summary Scale, and general adaptive composite scores. These findings implicate overall intelligence to be a useful prognosis indicator, as it involves many facets of human cognition, including novel problem solving, procedural knowledge, and crystallized concepts developed through education. Specific defects in any of the neurocognitive domains may underlie adaptation difficulties across various settings and result in unfavorable impacts on quality of life. For instance, mild executive dysfunction might lead to poor adaptive skills in self-care, problem solving, and implementation of multiple errands. We did detect a moderate correlation between test performance of WCST and general adaptive composite, $r = 0.46$, $P < .05$. Impaired spatial working memory in patients with basal ganglia tumors is also considered supporting evidence for the reduced dorsolateral prefrontal cortex functioning that involved execution, monitoring, and manipulation of remembered items in working memory. As many studies addressed the shortcomings of such tasks to provide an analogue of the real world, the preliminary findings presented hopefully would solicit more research to examine this issue by adopting different multitasking tests.

Some limitations of the present study should be noted. First, since our clinical data were gathered retrospectively, the lack of presurgical-postsurgical comparison makes our empirical findings fall short of disambiguating neurocognitive changes as a result of the tumor per se, the subsequent treatments, or interaction of the two. Bearing this in mind, we have begun to establish a data bank of preintervention baselines for recently treated children in our institute. Second, unlike the traumatic brain injuries with acute changes in neuropsychological functions, cognitive declines that result from radiotherapy may not be obvious at the start but develop over years. The present study could not reveal such progressive changes, as it was a cohort design within a limited time span rather than a longitudinal one. Only through examination of a few cases that received the neuropsychological assessments more than once in our sample were we able to reconstruct the possible deterioration path over time. Third, although we failed to detect significant effects of the length of RT interval and RT age, these variables were implicated in cognitive deficits. For instance, a correlation of -0.227 was found between FSIQ and time after RT ($P = .098$). Other factors relevant to psychosocial dysfunction or learning disability remain unexplored, such as hormonal deficiency and visual defects. These factors should be carefully pursued in the future.

Albeit that there were these limitations of a less than perfect design and unevenly distributed sample sizes within certain conditions, the present study has generated rich information entailing insights into the relationship among neurocognitive, emotional/behavioral, and adaptive functions and quality of life. It also provides a comprehensive comparison across tumor locations and treatments. It justifies neuropsychological assessment for patients with CNS GCTs and evaluation of their quality of life, both of which may lead to improvement in therapeutic protocol, transdisciplinary intervention, and after-treatment rehabilitation.

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