Prognostic factors related to intratumoral hemorrhage in pediatric intracranial germ cell tumors

Ju-Ting Chen[a,b], Han-Jui Lee[c,d], Yi-Wei Chen[d,e], Muh-Lii Liang[d,f], Hsin-Hong Chen[d,f], Yi-Yen Lee[d,f], Jiing-Feng Lirng[c,d], Chao-Bao Luo[c,d], Feng-Chi Chang[c,d,*], Wan-Yuo Guo[c,d]

[a]Department of Diagnostic Radiology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, ROC; [b]College of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan, ROC; [c]Department of Radiology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [e]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [f]Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Certain types of pediatric intracranial germ cell tumors (PIGCTs) are prone to intratumoral hemorrhaging (TH) and associated with poor survival outcome. However, the impact of TH on the functional prognosis of patients with PIGCTs has not been well studied. This study aimed to evaluate the clinical and MR findings in PIGCT patients with TH to identify the factors related to patient survival and functional outcome.

Methods: This study included 17 patients diagnosed with PIGCT and TH between 2002 and 2016 and evaluated TH-associated clinical and MR findings. The modified Rankin scale (mRS) was used to evaluate functional outcome, which was poor when mRS ≧ 3. The volumes of hematomas and tumors were manually tracked within each brain magnetic resonance imaging slice.

Results: Among the 17 patients, 6 (35.3%) died and 9 (52.9%) had poor functional outcome. Regarding the functional outcome, the mean hematoma volume to tumor volume ratio (HTVR) was 8.5 ± 3.9% in the favorable outcome group and 42.3 ± 27.8% in the poor outcome group (p = 0.001). For the survival outcome, the mean HTVR was 15.7 ± 16.1% in the living group and 46.0 ± 31.5% in the deceased group (p = 0.016). The cutoff point of the receiver operating characteristics curve for HTVR to predict death and poor functional outcome was 19.27% and 16.8%, respectively.

Conclusion: Our study demonstrated that patients with larger HTVR had significantly worse functional and survival outcomes than those with smaller HTVR. We suggest that early and aggressive treatment for PIGCTs in patients with large HTVR can improve their long-term prognosis.

Keywords: Brain; Germ cell tumors; Pediatric MRI; Tumoral hemorrhage

1. INTRODUCTION

The occurrence of pediatric intracranial germ cell tumors (PIGCTs) is significantly higher in Asia than in the West.[1,2] Survival of patients with PIGCTs is mainly determined by their histology types.[3] The 10-year survival rate of patients with pure germinoma can be as high as 92.7%. In contrast, patients with certain types of germ cell tumors (yolk sac tumor, embryonal carcinoma, or choriocarcinoma) have 3-year survival rates as low as 27.3%.[4]

Intracranial tumoral bleeding is rare in pediatric patients. Patients with choriocarcinoma and nongerminomatous germ cell tumors (NGGCTs) with choriocarcinoma elements are notorious for being at high risk of tumoral hemorrhage (TH) and poor survival.[5] However, the influence of TH on functional and survival outcomes of PIGCTs has not been well studied.[2] The purpose of this study was to identify the factors affecting functional and survival outcomes of PIGCT patients with TH. To achieve this goal, we evaluated clinical and magnetic resonance imaging (MRI) findings in these patients. By more aggressively managing these factors, we would expect to improve the long-term prognosis of these pediatric patients.

2. METHODS

The protocol of this retrospective study was approved by our institutional review board, giving us access to the clinical records and radiological images of the patients with PIGCTs.

2.1. Patients and clinical findings

There were 116 pediatric patients diagnosed with intracranial germ cell tumors in our institute between 2002 and 2016. Seventeen of these patients also had TH at the time of their initial diagnosis. TH was diagnosed by pathological examination in 13 patients and by clinical and MR results in 4 patients. Clinical findings, including demographic features, chief clinical symptoms, final diagnosis, and functional and survival outcomes of treatment, were evaluated (Table 1). Any recurrence of diseases or complications of treatment were recorded. The

*Address correspondence: Dr. Feng-Chi Chang, Department of Radiology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: fcchang374@gmail.com (F.-C. Chang).

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Table 1

Demographic features of the 17 pediatric patients with hemorrhagic intracranial germ cell tumors

Characteristics	Number	%
Age, y	11.1 ± 4.3 (4-19)	…
Sex		
Male/Female	12/5	70.6/29.4
Initial symptoms		
Headache	9	52.9
Vomiting	5	29.4
Blurred vision	5	29.4
Limb weakness	3	17.6
Diabetes insipidus	2	11.8
Acute symptoms[a]	10	58.8
Diagnosis		
Germinoma	7	41.2
Yolk sac tumor	1	5.9
Choriocarcinoma	1	5.9
Mixed GCT	8	47.0
Tumor MRI features		
Location		
Pineal	6	35.3
Suprasellar	3	17.6
Pineal and suprasellar	3	17.6
Basal ganglion	4	23.5
Other	1	5.9
Tumor composition		
Solid/Mixed/Cystic	8/8/1	47.1/47.1/5.9
Initial CSF seeding	6	35.3
T1WI		
High/Iso/Low	1/13/3	5.9/76.5/17.6
T2WI		
High/Iso/Low	0/16/1	0.0/94.1/5.9
Enhancement		
Strong/Weak	15/2	88.2/11.8
DWI: restriction		
Yes/no	13/1	92.9/7.1
Intratumoral location of hematomas		
Intracystic/Solid	9/8	52.9/47.1
Stage of hematomas		
Hyperacute	1	5.9
Acute	4	23.5
Early subacute	12	70.6
Tumor volume, cm^3	23.0 ± 15.7 (1.8-53.7)	…
Hematoma volume, cm^3	6.5 ± 7.7 (0.1-25.5)	…
Hematoma/Tumor volume, %	26.4 ± 26.4 (4.8-88.6)	…
Treatment		
Operation	14	82.4
Chemotherapy	14	82.4
Radiotherapy	17	100
Tumor recurrence	4	23.5
Recurrence interval, y	1.2 ± 0.6 (0.8-2.0)	…
Survival outcome		
Alive	11	64.7
Dead	6	35.3
Survival time, y	5.6 ± 4.2 (0.8-15.2)	…
Functional outcome		
mRS ≦ 2	8	47.1
mRS ≧ 3	9	52.9

[a]Acute symptoms indicate clinical symptoms that are due to increased intracranial cerebral pressure or intracranial herniation. Stage of hematoma: hyperacute, 1 (T1 Iso, T2 high); acute, 2 (T1 Iso, T2 low); early subacute, 3 (T1 high, T2 low); late subacute, 4 (T1 high, T2 high); chronic, 5 (T1 and T2 low).
CSF = cerebrospinal fluid; DWI = diffusion-weighted image; GCT = germ cell tumor; MRI = magnetic resonance imaging; mRS = modified Rankin scale; T1WI = T1-weighted image; T2WI = T2-weighted image.

modified Rankin scale (mRS) was used to assess functional outcome. "Poor outcome" was defined as mRS ≧ 3, and "favorable outcome" was defined as mRS ≦ 2.[6]

2.2. MRI findings

The MR images of the brain and spine were acquired on 1.5T MR scanners (Signa HD & Excite TwinSpeed; GE Healthcare, Waukesha, WI). The sequences included a T1-weighted image, FLAIR, T2-weighted image, and 3D-contrast-enhanced T1-weighted image. Diffusion MR images with b = 0 and b = 1000 s/mm^2 were available for 14 patients. All patients also underwent contrast-enhanced spinal MRI to elucidate whether any seeding by the tumor had occurred during the initial diagnosis and subsequent follow-up period. The intervals between acute symptoms onset and the time of the MR image examination were recorded. The pretreatment scans were analyzed. The clinical and MR follow-ups were conducted every 3 months in the first 2 years after treatment and every 6 to 12 months thereafter.

Imaging studies were retrospectively reviewed by two neuroradiologists (with 3 and 20 years experience), and final decisions on diagnosis, tumor location, volume, component, signal change, enhancement characteristics, and the location and stage of the hematoma were reached by consensus. The tumor was defined as "solid" when <25% of its volume was cystic; "cystic" when >75% of its volume was cystic; and "mixed" when between 25% and 75% of its volume was cystic. Intratumoral hemorrhaging was diagnosed from clinical and MR findings and/or pathological examination. On the basis of MR gradient-echo imaging or susceptibility-weighted imaging, intra-THs were classified as either intracystic or solid. Intracystic hemorrhage was indicated by blood inside cystic structures, including fluid-fluid levels within smooth-in-contour enhanced cyst walls (Figure 1). Solid hemorrhage was indicated by hematoma within the solid portion of the tumor (Figure 2). Hemorrhage was classified according to temporal change on T1-/T2-weighted images into five stages: hyperacute (T1 iso, T2 iso to high), acute (T1 iso, T2 low), early subacute (T1 high, T2 low), late subacute (T1 high, T2 high), and chronic (T1 and T2 low).[7] If the MR signals of hemorrhage stage were mixed, the correlation of the most recent stage with clinical symptoms would be analyzed. The volume of hematomas and tumors was manually traced in each brain MRI slice and was calculated by multiplying the thickness of the slice by the areas of the hematoma and tumor, respectively. If there were multiple sites of hemorrhage, the total volume of the hematomas would be calculated by summing the volumes of hemorrhage at these sites. The total hematoma volume was also expressed relative to total tumor volume for better comparison between different tumor sizes and different ages of the children.[8] We used the hematoma volume to tumor volume ratio (HTVR) for evaluating the functional and survival outcomes.

2.3. Statistical analysis

The statistical analysis was performed using SPSS for Windows (version 18). For univariate analysis, the nonparametric methods and χ^2 test were used to assess differences in categorical variables. Receiver operating characteristic (ROC) curves were used to explore the characteristics of diagnostic tests by graphing the false positive rate (1-specificity) on the horizontal axis and the true positive rate (sensitivity) on the vertical axis with various cutoff values. A p value of 0.05 was considered to indicate a statistically significant difference among the test populations.

3. RESULTS

3.1. Patients and clinical findings

The demographic features of the 17 PIGCT patients with TH are shown in Table 1. Their mean age at diagnosis was 11.1 years (11.1 ± 4.3 [4-19]). Their diagnoses included germinoma (n = 7 [41.2%]), mixed GCT (n = 8 [47%]), yolk sac tumor (n = 1 [5.9%]), and choriocarcinoma (n = 1 [5.9%]).

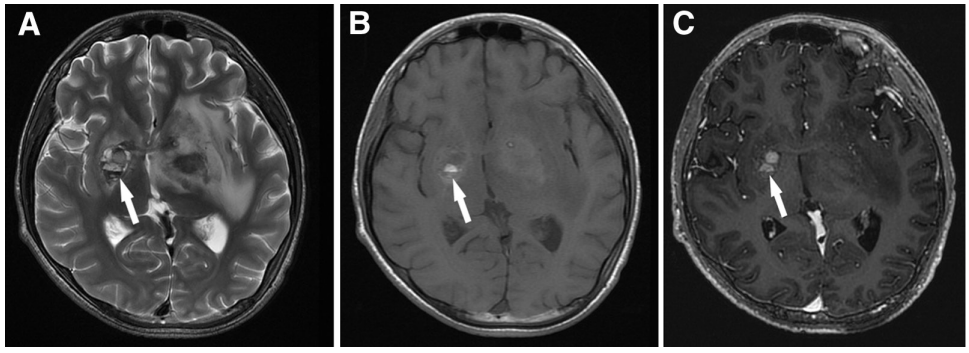

Fig. 1 A 9-y-old boy with germinomas of the bilateral basal ganglia. The axial MRI of the brain showed multiple early subacute intracystic hematomas in the germinoma of right basal ganglion. The largest subacute hematoma located in the right basal ganglia presented with hyperintensity on T1WI (A, arrow) and hypointensity on T2WI (B, arrow). Strong enhancement of the solid part of the tumor and cystic wall of the hematoma were also found (C, arrow). MRI, magnetic resonance imaging; T1WI, T1-weighted image; T2WI, T2-weighted image.

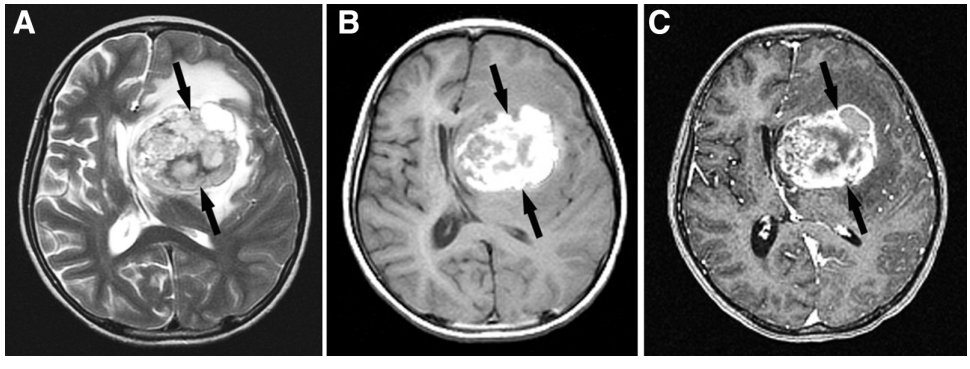

Fig. 2 An 8-y-old girl with yolk sac tumor of the left basal ganglion. Axial MRI of the brain showed the tumor associated with a large early subacute intratumoral hematoma. The hematoma had hyperintensity on T1WI (A, arrows) and mixed hypointensity on T2WI (B, arrows). Strong enhancement was noted (C, arrows). Note the significant perifocal edema and subfalcine herniation. MRI, magnetic resonance imaging; T1WI, T1-weighted image; T2WI, T2-weighted image.

Acute symptoms, such as signs of acutely increased intracranial pressure, were observed in 10 (58.8%) patients, and non-emergent symptoms, such as diabetes insipidus or lethargy, were observed in 7 patients.

The mean follow-up period was 5.6 ± 4.2 (0.8-15.2) years. The overall survival rate and 5-year survival rate for the 17 patients were 11/17 (64.7%) to date and 12/17 (70.6%), respectively. Within a mean period of 3.3 ± 2.9 (0.8-8.8) years, four patients died from tumor recurrence, one from tumor progression, and one from a radiation-related secondary tumor. The functional outcomes of all 17 patients were characterized as either poor in 9 (52.9%) or favorable in 8 (47.1%).

3.2. MR findings

The MR findings of the 17 PIGCT patients with TH are presented in Table 1. The average interval between symptom onset and MR examination was 5.9 days (5.9 ± 4.0 [2-14]). Subarachnoid seeding or metastasis was noted initially in six cases (35.3%). The mean volumes of the tumors and hematomas were 23 cm^3 (23.0 ± 15.7 [1.8-53.7]) and 6.5 cm^3 (6.5 ± 7.7 [0.1-25.5]), respectively. The mean HTVR was 26.4% (26.4 ± 26.4 [4.8-88.6]).

Hematomas were intracystic for nine patients (52.9%) and within solid tumor for eight (47.1%). In one case, the TH extended to the solid tumor surface and entered the ventricle. Two of the 17 (11.8%) patients had multiple stages of hematoma, which indicated repeated bleeding. The mean tumor volume, mean hematoma volume, and HTVR were 18.7 cm^3, 4.5 cm^3, and 22.6% for the germinoma group and 26.0 cm^3, 7.9 cm^3, and 29.1% for the NGGCT group and were slightly but not statistically significantly larger in the NGGCT group (p = 0.380, 0.360, and 0.631, respectively).

3.3. Statistical analysis

3.3.1. Functional and survival outcomes

The statistical analysis of factors potentially affecting functional and survival outcomes is shown in Table 2.

Regarding clinical functional outcome, the poor outcome group had significantly larger mean hematoma volume (10.4 ± 8.9 versus 2.2±1.8 cm^3 in the favorable group; p = 0.021) and mean HTVR (42.3 ± 27.8% versus 8.5 ± 3.9%; p = 0.001).

Regarding the survival outcome, the deceased group had significantly larger mean HTVR (46.0 ± 31.5% versus 15.7 ± 16.1% in the living group; p = 0.016).

3.3.2. ROC curve analysis

The results of ROC curve analysis for predicting poor outcome are shown in Table 3. For hematoma volume, the estimated area under the curve was 0.83 (p = 0.021) for predicting the poor functional outcome (mRS ≧ 3), and the cutoff value was estimated to be 5.6 cm^3, with 67% sensitivity and 100% specificity. The areas under the curve for HTVR as an indicator of poor functional and survival outcome were 0.97 (p = 0.001) and 0.86 (p = 0.012); the cutoff value, sensitivity, and specificity were 16.8%, 89%, and 100% for the patients with mRS≧3 and 19.3%, 83%, and 82% for the deceased group, respectively.

4. DISCUSSION

The incidence of spontaneous bleeding of PIGCT has been rarely reported, and it is in the range of 9.4% to 14.3%.[9,10] In the study by Liang et al,[10] hemorrhage was identified in the tumors of 13 NGGCT patients, whereas none was observed in

Table 2

Analysis of the survival and clinical outcomes of the 17 pediatric patients with intracranial germ cell tumors

	Survival outcome			Clinical outcome		
1	Alive (N = 11)	Death (N = 6)	*p*	Favorable (mRS ≦ 2; N = 8)	Poor (mRS ≧ 3; N = 9)	*p*
Tumor pathology						
Germinoma	6	1	0.304	4	3	0.637
Nongerminoma	5	5		4	6	
Tumor location						
Midline (pineal and suprasellar regions)	7	5	0.600	7	5	0.294
Other	4	1		1	4	
Tumor component						
Solid	4	4	0.335	3	5	0.637
Cystic and mixed	7	2		5	4	
Initial seeding						
Y	4	2	1.000	3	3	1.000
N	7	4		5	6	
Acute symptoms						
Y	6	4	1.000	5	5	1.000
N	5	2		3	4	
Stage of hematomas						
Acute	3	2	1.000	3	2	0.620
Subacute	8	4		5	7	
Location of intratumoral hematoma						
Intracystic	7	2	0.335	6	3	0.153
Solid	4	4		2	6	
Tumor volume, cm^3	23.7 ± 17.4	21.8 ± 13.4	1.000	23.7 ± 18.2	22.4 ± 14.2	0.923
Volume of hematomas, cm^3	4.5 ± 7.2	10.2 ± 7.7	0.088	2.2 ± 1.8	10.4 ± 8.9	0.021*
Hematoma/Tumor ratio, %	15.7 ± 16.1	46.0 ± 31.5	0.016*	8.5 ± 3.9	42.3 ± 27.8	0.001**

*$p < 0.05$, **$p < 0.01$.

mRS = modified Rankin scale; $p = p$ value for χ^2, Fisher exact test, or t test.

Table 3

Results of receiver operating characteristic curve analyses for predicting poor clinical outcome (mRS ≧ 3) and poor survival outcome (Death) in the 17 patients with hemorrhagic intracranial germ cell tumors

	Cutoff	Sensitivity	Specificity	AUC	*p*
Poor clinical outcome (mRS ≧ 3)					
Tumor volume, cm^3	23.2	0.44	0.75	0.514	0.923
Hematoma volume, cm^3	5.6	0.67	1	0.833	0.021*
Ratio of hematoma/tumor volume, %	16.8	0.89	1	0.972	0.001**
Poor survival outcome (death)					
Tumor volume, cm^3	18.7	0.67	0.55	0.500	1.000
Hematoma volume, cm^3	3.1	0.83	0.64	0.758	0.088
Ratio of hematoma/tumor volume, %	19.3	0.83	0.82	0.864	0.016*

*$p < 0.05$, **$p < 0.01$.

AUC = area under receiver operating characteristic curve; mRS = modified Rankin scale.

the tumors of 19 germinoma patients. We found 17 cases of PIGCT with TH (7 with germinomas and 10 with NGGCTs) in a total of 116 cases of PIGCT (14.7%). Although NGGCTs (compared with germinomas) had larger tumor and hematoma volumes, and a larger percentage of them were hemorrhagic, the difference in size was not statistically significant. This result suggested that spontaneous bleeding can occur in both germinomas and NGGCTs.

Patients with germinomas have better prognosis than those with NGGCTs.[4,11] The 5-year survival rate of patients with pure germinomas ranges from 89.2% to 93.3%.[11,12] NGGCTs are less radiosensitive than germinomas, and the 5-year survival rates are lower, that is, 50% to 70.6%.[11,12] In our studies, the 5-year survival rate was 85.7% for germinoma patients with TH and 60% for NGGCT patients with TH. The survival outcomes of both groups were similar to that reported in the literature. These findings suggested that TH by itself does not significantly influence survival. Consequently, we looked at other potential outcome predictors, such as hematoma volume.

It was unclear in the past whether TH influences the functional and survival outcomes of patients with PIGCT. In this study, functional and survival outcomes were significantly worse for patients with larger HTVR. Patients with larger hematoma volume also had worse functional outcomes. Poor functional outcome was predicted when hematoma size was >5.6 cm^3, or mean HTVR was >16.8% (Table 3). These findings suggested that the hematoma volume had a significant influence on the outcomes of PIGCT patients with TH. Therefore, we recommend using hematoma volume and HTVR for predicting functional and survival outcomes in these patients. These results might be explained by acute hematoma expansion causing irreversible direct damage to the adjacent brain tissue, or tumor-induced compression of the brain causing acute increased

intracranial pressure (IICP) and obstructive hydrocephalus.[13] The larger the hematoma volume, the greater its effect on brain parenchyma and acute IICP. Repeated tumor bleeding might also enlarge hematoma volume and aggravate brain damage. Another possible mechanism affecting the outcome of patients with TH is injury secondary to hematoma-related inflammatory changes. Free radicals and cytokines involved in this inflammatory process can injure the brain tissue adjacent to hematomas.[14] We suggested that these patients should receive aggressive treatments, such as surgical intervention or irradiation as soon as possible.

The peak incidence of PIGCT is around 10 to 12 years of age.[15] In our studies, the mean age was 11.1 years. The previously reported male predominance of GCTs[16] was also observed here. In our studies, TH was found in tumors located in pineal gland, suprasellar region, and basal ganglia. Hence, there is no age, sex, or tumor location predilection for spontaneous TH. That said, some clinical features of PIGCT with HT were clearly different from those of without TH (Table 1). For example, diabetes insipidus was only noted in two patients (11.8%) of this study.

Although there was no statistical significance (p = 0.102), we found that intracystic hematomas were smaller than solid hematomas. We hypothesize that intracystic hematomas are structurally confined, limiting their adjacent extension and size expansion. These confined intracystic hematomas might resolve with tumor control by irradiation. In contrast, vascular hematomas within solid tumors have no defined cystic wall barrier. This intratumoral hematoma may expand even beyond the tumor surface and have a significant mass effect possibly justifying early surgical intervention.

The limitations of this retrospective study included small number of patients, diverse MR patterns of TH, and lack of a single therapeutic strategy. These limitations made statistical analysis difficult. We suggest a prospective, multicenter study to evaluate more cases. A study using comprehensive imaging techniques, such as MR perfusion imaging, may be beneficial in evaluating the disease process before and after therapy.

In conclusion, our study demonstrated that (1) functional and survival outcomes were significantly worse for patients with larger HTVRs than those with smaller ones; (2) tumors with hematomas >5.6 cm^3 or mean HTVR >16.8% increased risk of poor functional outcome (mRS ≧ 3); and (3) mean HTVR >19.3% predicted poor survival outcome after treatment. In PIGCT patients with TH, early and aggressive treatment (such as radiotherapy) is recommended to improve the clinical outcomes of those with large hematoma volume and large HTVR.

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