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Original Article

Prognostic implications of distinctive imaging characteristics in primary intracranial germ cell tumors: A retrospective analysis

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ABSTRACT

Purpose: Primary central nervous system (CNS) germ cell tumors (GCTs) are rare brain tumors that encompass two subtypes: germinomas and non-germinomatous germ cell tumors (NGGCTs), NGGCTs have less favorable outcome and require multi-modality treatment. Biopsy is recommended for disease diagnosis, the specimen may not adequately reflect the entire tumor. This study aimed to assess distinct imaging characteristics to differentiate between GCT subgroups and to identify possible initial image and subgroup features that influence survival.
Method: This retrospective study, conducted from January 2006 to March 2023, analyzed patient data and MRI findings of primary CNS GCTs. It evaluated tumor characteristics including cysts, seeding, multifocality, and hemorrhage. Tumor volumes and apparent diffusion coefficient (ADC) values of both tumoral and normal-appearing contralateral white matter were measured. These factors were correlated with overall and 5-year survival rates.
Results: This study included 51 participants with CGTs, comprising 19 germinoma and 32 NGGCTs cases. GCTs with hemorrhage had worse overall ($P = 0.03$) and 5-year ($P = 0.01$) survival rates. No survival difference between germinoma and non-hemorrhagic NGGCT. NGGCTs were more likely to bleed ($P < 0.001$) than germ cell tumor, especially those with choriocarcinoma or yolk sac tumor components ($P = 0.001$). The ADC ratios of germinomas were significantly lower than those of NGGCTs ($P = 0.03$ for whole tumor; $P < 0.01$ or solid part), The ADC ratios of choriocarcinoma were also lower than mixed tumor ($P = 0.01$; $P = 0.02$).
Conclusion: Hemorrhage indicates worse prognosis. Intratumoral hemorrhage and ADC ratios differentiate germinoma from NGGCTs. Larger cohorts and advanced MR techniques are needed for future study.

1. Introduction

Primary central nervous system germ cell tumors (GCTs) are rare neoplasms primarily observed in pediatric and young adult populations with distinct geographical differences in the incidence of GCT [1]. In Western countries, GCTs account for 1%–3% of brain tumors, whereas in East Asia, they make up 8%–15% [2].

Five histological types of GCTs are recognized by the WHO—germinoma; teratoma (mature or immature); yolk sac tumor; choriocarcinoma; and embryonal carcinoma. Tumors of more than one histological subtype are classified as mixed GCTs [1].

Abnormally elevated levels of serum or cerebrospinal fluid (CSF) tumor markers, such as α-fetoprotein (AFP) and human chorionic gonadotropin (β-HCG) are utilized in diagnosing GCTs [2]. AFP is predominantly secreted by yolk sac tumors; lower levels may be detected in embryonal carcinomas and mixed GCTs. β-HCG is primarily secreted by choriocarcinomas; lower levels may be detected in embryonal carcinomas, immature teratomas, and mixed GCTs [2].

Of the histological types, germinoma is the predominant form (60–70% of cases) followed by mixed GCTs, while each of the non-germinomatous GCTs (NGGCTs) other than teratoma is extremely rare [1]. Most GCTs arise in the midline pineal region (40%–60%) or suprasellar region (30%–40%), while some occur simultaneously in both locations (bifocal) (2%–26%) and rarely in the basal ganglia and other sites [2]. Radiographically observable tumors in the pineal region include GCT, pineal parenchymal tumors, and astrocytoma [3], while

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common tumors seen in the suprasellar region include craniopharyngioma, suprasellar macroadenoma, GCT, and Langerhans cell histiocytosis [4]. The age of the patient and various imaging features may aid in distinguishing tumor types; however, histopathological examination is usually necessary to conclude the final diagnosis [3,4].

The survival of patients with GCTs is mainly determined by the histological type of the tumor [5]. The 5-year overall survival rate is approximately 90%–95% for germinoma since it is a chemo- and radio-sensitive tumor [1,6]. In contrast, for NGGCTs, the 3-year survival rate has been reported as low as 27.3% [5]; it has improved over the decades with the 5-year progression-free survival improving to over 70% [1]. The treatment approach varies between germinoma and NGGTs [1,2]. Radiation therapy alone or radiation therapy covering the entire ventricular system along with chemotherapy have both been proposed for germinoma [1,6]. However, combined chemotherapy and radiotherapy is strongly recommended for NGGCTs, except for mature teratomas [1].

Although the tumor is usually located centrally, tumor biopsy for pathology diagnosis is still recommended [1,2]. Together with imaging, serum/CSF tumor markers, and histopathological characteristics, a prompt diagnosis can be established and the appropriate treatment can be initiated [1]. Due to the central location of these tumors, biopsy specimens are usually tiny, and may not adequately reflect the entire tumor [1]. We aimed to investigate if magnetic resonance imaging (MRI) features can help differentiate germinoma from NGGCTs since the prognosis and treatment of these two groups of tumors vary. Previous literature reviews have attempted to use image features, such as intra-tumoral cysts [7–10], hemorrhage [11], calcification [8], and apparent diffusion coefficient (ADC) values [10,12]; however, the diagnostic value of these features varies. To the best of our knowledge, no study has discussed the potential imaging differences in subgroups of NGGCT.

Additionally, we aimed to determine if particular imaging features can help in predicting the prognosis at the time of the initial diagnosis.

2. Methods

2.1. Patients

This retrospective study included data between January 2006 and March 2023. The informed consent was waived. It included patients who had undergone both pre-treatment MRI and surgical biopsy at our hospital. Patient data, including age, sex, tumor marker levels, and pathology reports were extracted from the hospital's electronic medical records. Pathology reports and serologic tumor markers were reviewed simultaneously. At our hospital, serum/CSF β-hCG >100 IU/L or AFP (>10 ng/mL) was considered abnormal.

2.2. MRI

MRI scans were performed using a 1.5-T scanner. T1-weighted images and T2-weighted images were acquired with a field of view (FOV) of 200 mm and a slice thickness of 5 mm. Post-contrast T1-weighted images were obtained with an FOV of 200 mm and a slice thickness of 3–5 mm. The diffusion-weighted imaging (DWI) parameters were as follows: echo time (TE) = 60–75 ms; repetition time (TR) = 4000–5000 ms; FOV = 200 mm; and slice thickness = 5 mm. Diffusion was measured in three orthogonal directions using three b-values (0, 500, and 1000 s/mm^2. ADC maps were calculated by the MRI scanners using DWI sequences based on Fick's law. Susceptibility-weighted imaging (SWI) was acquired with the following parameters: TR/TE = 49/40 ms, flip angle = 15°, rectangular FOV = 200 mm, slice thickness = 2 mm, and iPAT factor = 2.

The MR images were reviewed on a picture archiving and communication system workstation (EBM Technologies) by a single radiologist with 14 years of experience. The evaluation included several tumor characteristics; the presence of cystic components, which were categorized as either exclusively large (≥1 cm) or exclusively small (<1 cm) (Fig. 1); and the presence of blood-fluid layering or short T1 and short T2, which suggest subacute hematoma. Intratumoral ADC values were measured using the region of interest (ROI) method.

The ROI was identified manually, and its size ranged from more than 20 mm^2. Two types of tumoral ROIs were obtained. For the entire tumor, an ROI was achieved by selecting the slice with the largest tumor diameter on the axial view, and a circular or ovoid ROI was placed to be as large as possible but not exceed the tumor's margin. For the solid part of the tumor, a circular or ovoid ROI was placed on the axial view by selecting the slice with the largest solid tumor, excluding large cysts and hemorrhages. However, due to the potential risk of including numerous tiny cysts, their complete exclusion from the ROIs was not feasible. The ADC ratios (ADC tumor/ADC White Matter) were obtained by comparing the ADC value of the tumor to that of the normal-appearing central white matter in the contralateral unaffected parietal lobe (Fig. 2).

The tumor volume was assessed using ROI-based volumetry. The reviewer analyzed all image series within a single MRI study for each patient to determine the precise tumor margins. The entire tumor region was delineated with a non-ellipsoidal shape. A three-dimensional (3D) ROI-based volume was calculated by summing all tumor areas in each slice and multiplying by the slice profile (5-mm slice thickness plus 1-mm gap).

All ROIs were delineated by a radiologist (Radiologist 1) who saved snapshots of the delineations. Another radiologist (Radiologist 2) reviewed these delineations, and the final ROI selection was determined by consensus between the two radiologists (Radiologist 1 & 2). To detect calcification within a lesion, we utilized computed tomography (CT) images taken around the same time as the MRI before treatment.

2.3. Statistical analysis

A comparison between the two groups was conducted using the Mann–Whitney *U* test to analyze continuous variables, including age and ADC ratios. Fisher's exact probability test was used to analyze categorical variables, such as sex, presence of hemorrhage, calcification, and the presence or absence of cysts. Statistical significance was defined as a P-value<0.05. All statistical analyses were performed using Stata 12 (StataCorp LP).

3. Results

3.1. Patient demographics

Overall, 51 participants diagnosed with intracranial GCTs were recruited in this study, including 19 patients (16 males) aged 11–49 years (mean ± standard deviation [SD]: 19 ± 10 years) diagnosed with germinoma. Of them, 7 (36.8%) patients had bifocal tumors (combined suprasellar and pineal regions), while others had a single tumor in the pineal region (n = 6, 31.6%), suprasellar region (n = 4, 21%), basal ganglia (n = 1; 5.3%), and periventricular region (n = ; 2.3%). Additionally, 3 (15.8%) patients had tumor seeding during the initial diagnosis.

Overall, 32 patients (28 males) aged 18 ± 6.6 years were diagnosed with NGGCTs. Of them, 22 patients had choriocarcinoma (19 males; mean age: 18 ± 7.1 years; β-hCG: 145.7 ± 357.5 IU/L), six patients had mixed GCTs (6 males; mean age: 17.3 ± 5.1 years; β-hCG: 148.5 ± 227.8 IU/L, AFP: 60.0 ± 21.1 ng/mL), two patients had embryonal carcinomas (two males; mean age: 18.5 ± 1.5 years; β-hCG: 6.9 ± 6.9 IU/L; AFP: 3.0 ± 2.8 ng/mL), and two patients had yolk sac tumors (one male; mean age: 10 ± 1 years; AFP: 3787 ± 5277 ng/mL). Of them, 8 (15.8%) patients had multifocal tumors (combination of either suprasellar, pineal, or basal ganglia regions), while others had single tumors, including the pineal region (n = 16, 50%), the suprasellar region (n = 4, 12.5%), and

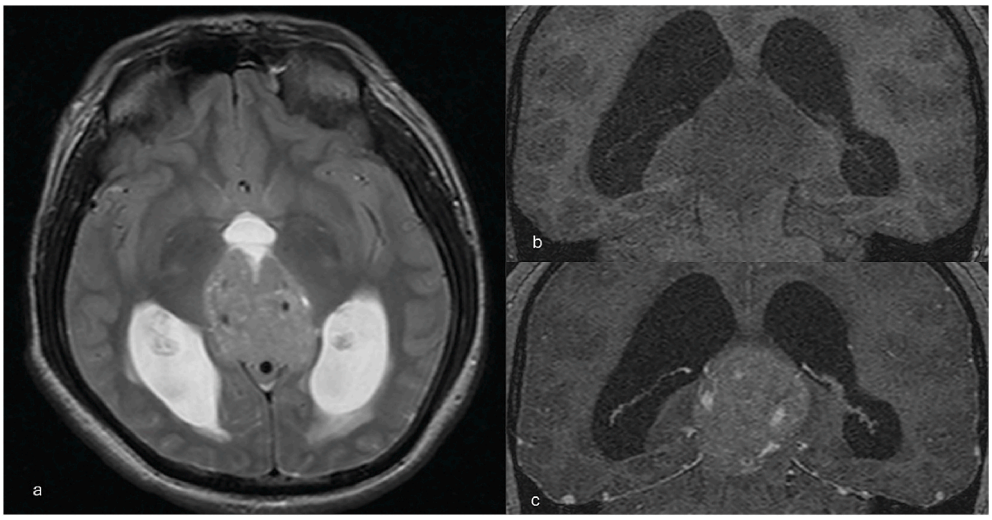

Fig. 1a. A 22-year-old male with a germinoma in the pineal region exhibits numerous tiny high signal intensity foci on the T2-weighted axial image (a). These tiny lesions display low T1 signal intensity (b) and do not enhance on the T1 post-contrast image (c), indicating cystic components. All the cystic components are smaller than 1 cm, so we categorize this tumor as a small cystic tumor.

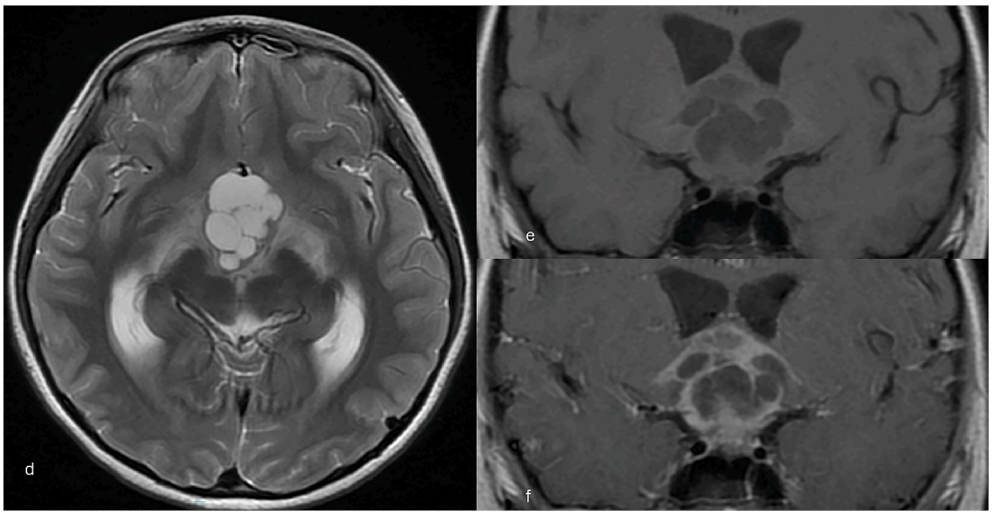

Fig. 1b. A 13-year-old female with a germinoma in the suprasellar region exhibits a lesion with multiple large high signal intensity components on the T2-weighted image (d), which display low T1 signal intensity (e) and only marginally enhance on the T1 post-contrast image (f), indicating cystic components. All the cystic components are greater than 1 cm, so we categorize this tumor as a tumor with big cysts.

the basal ganglia (n = 4, 12.5%). Furthermore, 3 (9.3%) patients had tumor seeding during the initial diagnosis.

There were no significant differences in terms of sex (P = 1), age (P = 0.97), multifocal tumors (P = 0.53), or tumor seeding (P = 0.66) between the germinoma and NGGCT groups (Table 1).

3.2. Imaging features and measurements

Of the 19 patients diagnosed with germinoma, 9 (47.4%) patients had internal calcification within the lesion, none had intra-tumoral hemorrhage, 10 (52.6%) patients had exclusively small cysts, 3 (15.8%) patients had exclusively large cysts, and 17 (89.4%) patients had cysts of any sizes (including patients with exclusively large, small, and mixed cysts). The mean tumor volume was 19.9 ± 14.4 cm^3 (mean ± standard deviation). The ADC ratio of the whole tumor and only the solid part was 1.36 ± 0.61 and 0.87 ± 0.15, respectively.

Of 32 patients with NGGCTs, 19 (59.4%) patients had internal calcifications and all the calcified lesions were found in the pineal gland. Additionally, 11 (37.5%) patients had intra-tumoral hemorrhage, 14 (43.8%) patients had exclusively small cysts, 5 (15.6%) patients had exclusively large cysts, and 24 (75%) patients had cysts of any sizes. The mean tumor volume was 15.1 ± 11.5 cm^3. The ADC ratio of the whole tumor and only the solid part was 1.66 ± 0.60 and 1.28 ± 0.44, respectively.

No significant differences were observed in the distribution of calcification (P = 0.39) or the presence of cysts, including exclusively small cyst (P = 0.57), exclusively large cyst (P = 1), or cysts of any sizes (P = 0.29). However, a significant difference was found in the presence of intra-tumoral hemorrhage (P < 0.001) as well as the ADC ratio of the whole tumor (P = 0.03) and only the solid part (P < 0.001) between the two groups (Table 2).

3.3. Subgroup analysis

When considering hemorrhage, GCTs without hemorrhage demonstrated better overall survival (8/11 vs. 39/40, respectively; number of survivors/total patients; P = 0.03) and 5-year survival (3/6 vs. 29/30, respectively; P = 0.01) rate than GCTs with hemorrhage. There was no

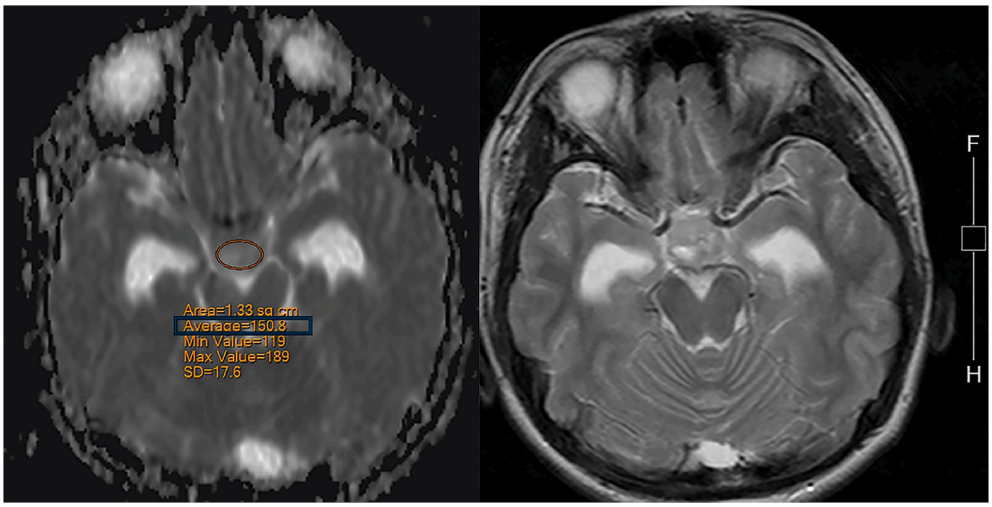

Fig. 2a. A 13-year-old male with a suprasellar germinoma. To measure the ADC value of the "whole tumor," the slice with the largest tumor diameter on the axial view was selected. An ovoid region of interest (ROI) was then placed on the ADC map, aiming to be as large as possible without exceeding the tumor's margin. We utilized the average value in the measurement data (the rectangular box in the image, which is presented identically in Fig. 2b and c). The T2-weighted image at the same level served as a reference.

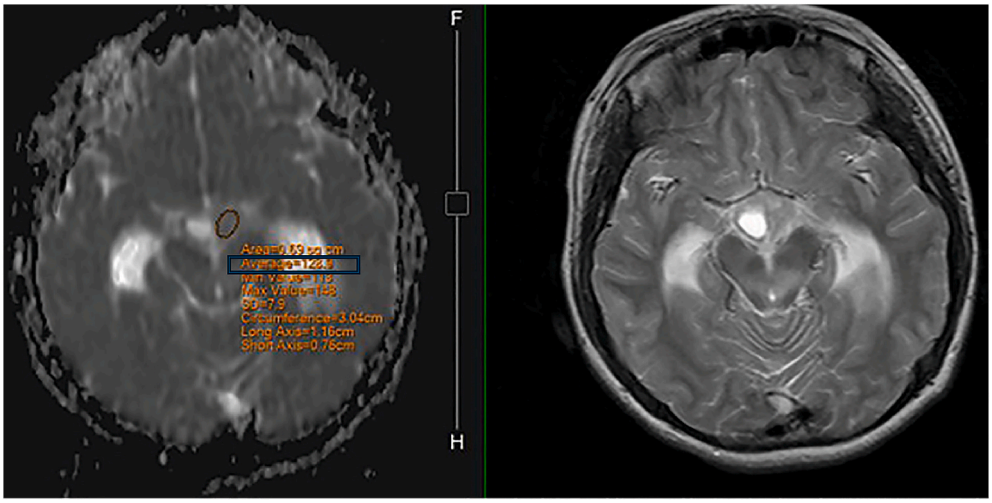

Fig. 2b. In this same patient, to measure the ADC value of the "solid part", the ROI was carefully positioned in the solid tumor area on the ADC map, intentionally excluding the sizable cystic region. The T2-weighted image served as a reference to enhance visibility of the tumor boundaries and cysts.

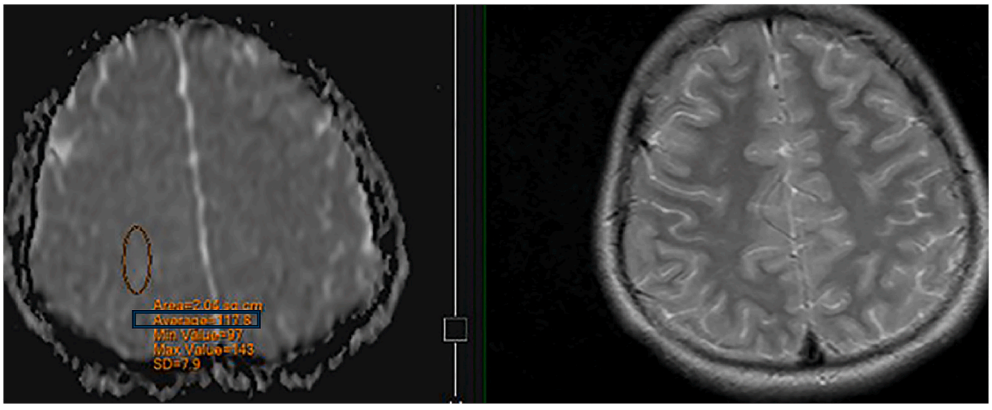

Fig. 2c. In the same patient, the ROI was positioned on the contralateral normal-appearing parietal white matter on the ADC map. A T2-weighted image was used as a reference to avoid signal contamination or interference caused by interstitial edema associated with hydrocephalus.

Table 1
Demographics of germ cell tumor patients.

Table 1	Gender	Age	Multi-focal	Seeding	Serum	
	F:M	(Years old)			AFP[a] (ng/ml)	β-hCG[b] (IU/L)
Germinoma, (n = 19)	3:16	19 ± 10	7 (36.8%)	3 (15.8%)	WNL	WNL
NGGCTs (n = 32)	4:28	18 ± 6.6	8(25%)	3 (9.3%)		
Choriocarcinoma (n = 22)	3:19	18 ± 7.1	6 (27.3%)	2 (9.1%)	WNL	145.7 ± 357.5
Mixed GCTs (n = 6)	0:6	17.3 ± 5.2	2 (33.3%)	1(16.7%)	60.0 ± 21.1	148.5 ± 227.8
Yolk sac tumor (n = 2)	1:1	10 ± 1	0	0	3787 ± 5277	WNL
Embryonal carcinoma (n = 2)	0:2	18.5 ± 1.5	0	0	6.9 ± 6.9	3.0 ± 2.8
P value: Germinoma v.s. NGGCTs	1	0.97	0.53	0.66		

NGGCTs: non-germinomatous germ cell tumors GCTs: germ cell tumors WNL: Within normal limit.
[a] AFP: α-fetoprotein.
[b] β-hCG: β-human chorionic gonadotropin.

Table 2
Image findings of Germ Cell Tumor Patients.

	Volume (cm^3)	Cysts[a]			Calcification	Hemorrhage	ADC ratio[b]	
		Small cyst	Large cyst	All sized cysts			Whole	Solid
Germinoma, N = 19	19.9 ± 14.4	10 (52.6%)	3 (15.8%)	17 (89.4%)	9 (47.4%)	0 (0%)	1.36 ± 0.61	0.87 ± 0.15
NGGCTs; N = 32	15.1 ± 11.5	14 (43.8%)	5(15.6%)	24 (75%)	19 (59.4%)	11 (37.5%)	1.66 ± 0.60	1.28 ± 0.44
Choriocarcinoma; N = 22	11.7 ± 9.8	8	3	14	12	6	1.41 ± 0.43	1.10 ± 0.23
Mixed GCTs; N = 6	19.7 ± 9	3	2	6	3	3	2.26 ± 0.7	1.56 ± 0.52
Yolk sac tumor; N = 2	13.7 ± 4.5	1	0	2	2	2	2.18 ± 0.32	2.10 ± 0.34
Embryonal carcinoma; N = 2	39.4 ± 8.7	2	0	2	2	0	1.98 ± 0.24	1.69 ± 0.29
P value: Germinoma v.s. NGGCTs	0.19	0.57	1	0.29	0.39	<0.001	0.03	<0.001

NGGCTs: non-germinomatous germ cell tumors.
GCTs: germ cell tumors.
[a] Small cyst: tumors exclusively comprised of cysts <1 cm; Large cyst: exclusively≧1 cm; All-sized cysts: cysts of any size.
[b] The ADC ratio = ADC of tumor/ADC of contralateral unaffected white matter.

significant difference in the tumor volume (21.6 ± 12.3 vs.15.5 ± 12.7 cm^3, respectively; P = 0.16), ADC ratio of the whole tumor (1.7 ± 10.4 vs. 1.58 ± 0.71, respectively; P = 0.58) and only the solid part (1.21 ± 0.38 vs. 1.14 ± 0.38, respectively; P = 0.61) of a tumor. Additionally, tumor hemorrhage was not related to tumor seeding (1/11 vs. 5/40, respectively; number of seeding tumors/total tumors; P = 1) or multifocal (3/11 vs. 12/40, respectively; number of multifocal tumors/total tumors; P = 1) (Table 3A).

Furthermore, 19 patients with germinoma and 21 patients with NGGCTs did not have tumoral hemorrhage. Between these two groups, germinomas had a larger tumor volume (19.9 ± 14.4 vs. 11.6 ± 9.6 cm^3, respectively; P = 0.04). However, there was no significant in the overall (19/19 vs. 20/21, respectively; P = 1) and 5-year survival (15/15 vs. 14/15, respectively; P = 1) rates despite histological differences. Additionally, there was also no difference in the presence of tumor seeding (3/19 vs. 2/21, respectively; P = 0.65), multifocal (7/19 vs. 2/21, respectively; P = 0.15) of tumor or ADC ratios of whole (1.36 ± 0.61 vs.1.43 ± 0.62, respectively; P = 0.16) and only the solid part (0.87 ± 0.15 vs.1.14 ± 0.38, respectively; P = 0.91) of a tumor (Table 3B).

When considering histopathological components, we observed that

Table 3
Subgroup analysis of germ cell tumor patients.

	Hemorrhagic GCTs	P value	Germinoma	P value	Choriocarcinoma/yolk sac components	P value	Choriocarcinoma	P value
	vs. Non-hemorrhagic GCTs (A)		vs. non-hemorrhagic NGGCTs (B)		vs. non-Choriocarcinoma/yolk sac components (C)		vs. Mixed GCTs (D)	
Overall survival[a]	8/11 vs. 39/40	0.03	19/19 vs. 20/21	1	26/30 vs.21/21	0.13	20/22 vs. 4/6	0.19
5-year survival[a]	3/6 vs. 29/30	0.01	15/15 vs. 14/15	1	15/19 vs.16/16	0.11	10/12 vs. 4/6	0.57
Hemorrhage		NA	0 vs. 0	1	55% vs.0	0.001	27.3% vs.60%	0.29
Volume(cm^3)[b]	21.6 ± 12.3 vs. 15.5 ± 12.7	0.16	19.9 ± 14.4 vs. 11.6 ± 9.6	0.04	15.1 ± 11.8 vs. 19.3 ± 13.8	0.25	11.7 ± 9.8 vs. 19.7 ± 0.9	0.08
Whole ADC ratio[b]	1.7 ± 10.4 vs. 1.58 ± 0.71	0.58	1.36 ± 0.61 vs. 1.43 ± 0.62	0.16	1.52 ± 0.58 vs. 1.73 ± 0.76	0.11	1.41 ± 0.43 vs 2.26 ± 0.7	0.01
Solid ADC ratio[b]	1.21 ± 0.38 vs. 1.14 ± 0.38	0.61	0.87 ± 0.15 vs. 1.14+-/ 0.38	0.91	1.15 ± 0.37 vs. 1.15 ± 0.4	1	1.10 ± 0.23 vs. 1.56 ± 0.52	0.02
Seeding[a]	1/11 vs. 5/40	1	3/19 vs. 2/21	0.65	3/30 vs. 3/21	0.68	2/22 vs.1/6	0.53
Multi-focal[a]	3/11 vs. 12/40	1	7/19 vs.2/21	0.15	8/30 vs.7/21	0.76	6/22 vs. 2/6	1

GCTs: Germ Cell Tumors.
NGGCTs: Non-germinomatous germ cell tumors.
The ADC ratio = ADC of tumor/ADC of contralateral unaffected white matter.
[a] Number of patients with (Factor)/Total number of patients in this group.
[b] mean ± standard deviation.

in those with choriocarcinoma or yolk sac tumor components (n = 30; 22 patients with choriocarcinoma, two with yolk sac tumor, and six with mixed GCTs), there was a notable trend with a significantly higher incidence of tumor bleeding (n = 11) compared with those without these components (21 patients, with no reported bleeding) (P = 0.001). There was no significant difference in the prevalence of tumor seeding (3/30 vs. 3/21, respectively; P = 0.68) or multifocal (8/30 vs.7/21, respectively; P = 0.76) between the two groups. Additionally, there was no significant difference between the overall survival rate (26/30 vs. 21/21, respectively; P = 0.13), 5-year survival rate (15/19 vs. 16/16, respectively; P = 0.11), tumor volume (15.1 ± 11.8 vs. 19.3 ± 13.8 cm^3, respectively; P = 0.25), or ADC ratios of the whole (1.52 ± 0.58 vs. 1.73 ± 0.76, respectively; P = 0.11) and only the solid tumor part (1.15 ± 0.37 vs.1.15 ± 0.4, respectively; P = 1) (Table 3C).

When comparing between subgroups of NGGCTs, we observed significant differences in the ADC ratio of whole (1.41 ± 0.43 vs. 2.26 ± 0.7, respectively; P = 0.01) and solid tumor part (1.10 ± 0.23 vs. 1.56 ± 0.52, respectively; P = 0.02) between choriocarcinoma and mixed GCTs. However, there were no significant differences in the overall survival (20/22 vs. 4/6, respectively; P = 0.19), 5-year survival rate (10/12 vs. 4/6, respectively; P = 0.57), tumor volume (11.7 ± 9.8 vs. 19.7 ± 0.9 cm^3, respectively; P = 0.08), hemorrhage (27.3% vs. 60%, respectively; P = 0.29), tumor seeding (2/22 vs. 1/6, respectively; P = 0.53), or the presence of multifocal tumors (6/22 vs. 2/6, respectively; P = 1) between these two groups (Table 3D).

Additional patients are needed to conduct a robust subgroup analysis for yolk sac tumors and embryonal carcinomas since the sample size in our study is limited.

3.4. Factors affecting survival

In the cohort of 19 patients with germinoma, 15 individuals had completed follow-up of over 5 years without any recorded deaths, while four patients are yet to complete 5 years of follow-up. In the NGGCT group, which comprised 32 patients, 28 patients were still alive, with 17 of them having survived for more than 5 years. Four patients died in the second month, second year, fourth year, and fourth year of follow-up, respectively. The first three patients had concomitant tumor bleeding at the time of diagnosis.

The overall survival rate (8/11 vs. 39/40, respectively; number of survivors/total patients) and 5-year survival rate (3/6 vs. 29/30, respectively) between those with and without tumoral hemorrhage were significant (P = 0.03 and P = 0.01, respectively) (Table 4).

Factors, such as multifocal location (P = 0.57 and P = 0.58, respectively) and tumor seeding (P = 0.4 and P = 0.47, respectively) did not affect the overall and 5-year survival rate. Additionally, there was no significant difference in the tumor volume (P = 0.6 and P = 0.61, respectively), ADC ratio of the whole tumor (P = 0.55 and P = 0.75, respectively) or only the solid part (P = 0.18 and P = 0.39, respectively) between survivors and those who died during the overall and 5-year follow-up periods (Table 4).

Table 4
Factors influencing germ cell tumor patient survival.

Finding	Overall Survival	P value	5-year Survival	P value
Bleeding[a] (+vs. -)	8/11 vs. 39/40	0.03	3/6 vs. 29/30	0.01
Multiple location[a] (+vs. -)	13/15 vs. 34/36	0.57	10/12 vs. 22/24	0.58
Seeding[a] (+vs. -)	5/6 vs. 42/45	0.4	4/5 vs. 28/31	0.47
Whole ADC ratio[b](Sur vs. Mor) [c]	1.60 ± 0.67 vs.1.80 ± 0.54	0.55	1.68 ± 0.72 vs.1.80 ± 0.54	0.75
Solid ADC ratio[b] (Sur vs. Mor) [c]	1.13 ± 0.38 vs.1.4 ± 0.35	0.18	1.22 ± 0.41 vs.1.4 ± 0.35	0.39
Tumor volume (cm^3) (Sur vs. Mor) [c]	16.6 ± 12.9 vs.20.1 ± 10.6	0.6	16.6 ± 12.7 vs.20.1 ± 10.6	0.61

[a] Number of patients with (Factor)/Total number of patients in this group.
[b] The ADC ratio = ADC of tumor/ADC of contralateral unaffected white matter.
[c] (Sur vs. Mor) = (Survival vs. Mortality).

4. Discussion

In Taiwan, intracranial GCTs make up approximately 10% of brain tumors in the preadult population [10]. This incidence is significantly higher compared to that in Western countries, where GCTs account for only approximately 1% of primary brain tumors in pediatric and young adult patients. This discrepancy in incidence suggests a potential racial predisposition to GCTs [1,2]. Intracranial GCTs encompass a range of tumors with diverse histology, and they demonstrate varying responses to treatment. It is crucial to differentiate between germinomas and NGGCTs because the diagnosis significantly affects the choice of radiation field and chemotherapy regimens and, ultimately, patient survival. The treatment strategies and outcomes differ between these two types of tumors [13].

Previous studies involving MRI often had limited sample sizes [7,8,12] or a lack of analysis of NGGCT subgroups [10]. Since the imaging features of NGGCT subgroups may vary, it is imperative to further explore and elucidate these characteristics to enhance our knowledge in this area.

In our study, we frequently observed the presence of cystic components in both the germinoma (17/19 patients) and NGGCT groups (24/32 patients), irrespective of their cyst sizes. This finding contrasts with those of previous studies, which reported a higher incidence of cystic components in NGGCTs [7,9,10]. The disparity in results is likely due to the utilization of improved MRI techniques in our study, which provided higher resolution and allowed for the detection of small cystic components in both germinomas and NGGCTs.

In patients with NGGCTs, our study revealed a significantly higher likelihood of hemorrhage when compared to patients with germinoma (P < 0.001). This finding aligns with those of previously reported studies by Wu et al., in 2017 and Chen et al., in 2019 [5,10]. Furthermore, there was a significant likelihood (P = 0.003) of hemorrhage in patients with choriocarcinoma or yolk sac tumor components [14–16]. Intracranial choriocarcinomas have been characterized as ovoid or irregular masses with a large hemorrhagic component on MRI [14]. Both choriocarcinomas and yolk sac tumors are prone to bleeding due to their abundant or fragile blood supply and tendency to erode blood vessels [14–16]. Overall, our findings reinforce the existing body of literature of a higher likelihood of hemorrhage in NGGCTs, including choriocarcinomas and yolk sac tumors, compared to germinomas.

Additionally, intratumoral hemorrhage was found to be associated with reduced survival time. Limited previous reports have discussed the role of tumor hemorrhage in the survival of patients with intracranial GCTs [5,17]. The poor prognosis of patients with hemorrhagic intracranial GCTs can be attributed to several factors, including intraventricular hemorrhage-related hydrocephalus and the ensuing cerebral inflammation caused by hemorrhage. We did not measure the intratumoral hemorrhage volume because of the difficulty in measuring the hemorrhage volume released into the ventricles. Large-scale studies are needed to explore the underlying factors that contribute to this difference and to better understand the implications of hemorrhagic events in intracranial germ cell tumors.

Consistent with previous studies [10,12], our study revealed significantly lower ADC ratios in germinomas than NGGCTs, in both the overall tumors (P = 0.03) and only the solid portion (P < 0.001). This could be related to lymphocyte infiltration resulting in high cellularity in germinomas, which in turn results in low ADC [3,7,18]. Additionally, we discovered significant differences in the ADC ratios within subgroups of NGGCTs. Specifically, choriocarcinomas demonstrated significantly lower ADC ratios than mixed GCTs, both in the overall tumor (P = 0.01) and only in their solid parts (P = 0.02). This finding has not been

described in prior literature. As this study was retrospective and conducted at a single institution, although the patient population was relatively large compared to those of prior studies, the sample size was still limited for conducting robust scientific analyses within certain subgroups of NGGCTs. Multicenter studies might enable us to obtain a larger pool of patients, which may help us gain a deeper understanding of this disease. Furthermore, due to the inclusion of images spanning from 2006 to 2023, advanced MR techniques such as diffusion tensor imaging, MR spectroscopy, or perfusion could not be obtained for all patients in this study. Advanced imaging techniques may potentially help us better elucidate the differences in imaging characteristics between germinomas, NGGCTs, and their subgroups.

5. Conclusions

Our study revealed a higher incidence of hemorrhagic events in NGGCTs compared to germinoma. Tumors containing choriocarcinoma or yolk sac tumor components are more prone to hemorrhage. Patients with hemorrhage had lower overall and 5-year survival rates, and hemorrhage was the only factor that affected survival in this study.

Both the ADC ratio of the whole tumor and only the solid part were significantly lower in germinomas compared to NGGCTs. Therefore, ADC ratios can help in distinguishing between germinomas and NGGCTs, while other imaging features such as cysts, calcifications, or hemorrhage are not quite useful. Additionally, both the ADC ratio of the whole tumor and only the solid part were significantly lower in choriocarcinomas than in mixed GCTs. To gain a more comprehensive understanding of imaging differences in GCTs, future evaluations would benefit from a larger patient cohort or the use of advanced MR techniques.

Statements and declarations

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The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the National Taiwan University Hospital approved this study.

Informed consent

The informed consent of this retrospective study was waived by the Research Ethics Committee D of the National Taiwan University Hospital (NTUH-REC No.202305131RINB).

Other declarations

None of the material in this manuscript has been published previously or is currently under consideration for publication elsewhere.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2024.05.016.

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