RESEARCH

Comparison of different predominant lesions in intracranial bifocal germ cell tumors to predict neuroendocrine outcomes

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Abstract

Purpose: Intracranial germ cell tumors frequently arise from the midline of the brain, occasionally presenting as bifocal diseases. The predominant lesion might affect clinical characteristics and neuroendocrine outcomes.

Method: A retrospective cohort study involving 38 patients with intracranial bifocal germ cell tumors was performed.

Result: Twenty-one patients were assigned to the sellar-predominant group, while the other 17 patients were assigned to the non-sellar-predominant group. Differences in gender ratio, age, manifestation, the incidence of metastasis, the incidence of elevated tumor markers, human chorionic gonadotropin levels in serum and in cerebrospinal fluid, diagnostic method, and tumor type were not significant between the sellar-predominant group and the non-sellar-predominant group. Before treatment, the sellar-predominant group had a higher incidence of adenohypophysis hormone deficiencies and central diabetes insipidus than those of the non-sellar-predominant group, without significant differences. After multidisciplinary therapy, the sellar-predominant group also had a higher incidence of adenohypophysis hormone deficiencies and central diabetes insipidus than those of the non-sellar-predominant group. The differences in the hypothalamic–pituitary–adrenal (HPA) axis impairment ($P = 0.008$), hypothalamic–pituitary–thyroid (HPT) axis impairment ($P = 0.048$), and hypothalamic–pituitary–gonad (HPG) axis impairment ($P = 0.029$) were significant between sellar-predominant group and non-sellar-predominant group, while the others were not. At median 6 (3, 43) months of follow-up visit, sellar-predominant group had a higher incidence of adenohypophysis hormone deficiencies than those of non-sellar-predominant group. The differences in the HPA impairment ($P = 0.002$), HPT impairment ($P = 0.024$), and HPG impairment ($P < 0.000$) were significant, while the others were not. Further comparison of the neuroendocrine function between different subtypes of sellar-predominant patients indicated that the differences in adenohypophysis hormone deficiencies and central diabetes insipidus were not significant between the two subtype groups.

Conclusion: Bifocal patients with different predominant lesions present similar manifestations and neuroendocrine disorders before treatment. Non-sellar-predominant patients would have better neuroendocrine outcomes after tumor treatment. The distinction of the predominant lesion in patients with bifocal intracranial germ cell tumor plays a valuable role in predicting neuroendocrine outcomes, as well as in optimizing long-term neuroendocrine management during survival time.

Key Words

- intracranial germ cell tumor
- bifocal germ cell tumor
- hypothalamic–adenohypophysis axis
- hypothalamic–neurohypophyseal axis
- neuroendocrinology

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Introduction

Intracranial germ cell tumors (iGCTs) are rare malignancies of the central nervous system that probably arise from primordial germ cells (1, 2, 3, 4) or transform from endogenous brain cells (5, 6), which usually develop along the midline of the brain as well as in the bifocal regions. Bifocal lesions are considered the special image feature of iGCT (7), commonly involving the sellar and pineal regions, rarely as the sellar and basal ganglia lesions (8). Neuroendocrine disorders may probably be due to the tumor mass effect in sellar area as well as to the related treatment. Neuroendocrine disorders affect the initial presentations, the safety during the period of neurosurgery and chemoradiotherapy, and complications and sequelae. However, it is unclear what factors affect or predict neuroendocrine outcomes.

The tumor mass effect manifests as a crucial factor affecting endocrinopathies in iGCT patients. Tumors located in the sellar area may involve adjacent neuroendocrine organs that affect the regulation of hormone synthesis and secretion, as well as in the diffuse neuroendocrine system. Pre-treatment image, to some extent, reflects tumor mass effect and the involvement with neuroendocrine organs. However, for those bifocal patients, it has not been discussed whether the different predominant lesion possesses different neuroendocrine characteristics. It is unclear whether the sellar-predominant bifocal iGCT patients are similar to sellar solitary ones, while non-sellar-predominant bifocal iGCT patients are not. Furthermore, with the advantage of the neurosurgery and chemoradiotherapy techniques, iGCTs are still considered curable diseases with a 5-year event-free survival of more than 90% in localized germinomas and more than 70% in non-germinomatous germ cell tumors (9). It is also unclear whether identifying predominant lesions in bifocal iGCT can predict neuroendocrine outcomes and guide long-term neuroendocrine management of patients.

Previous studies have described the images in the sellar region of patients with bifocal lesions as five categories and six types (10). However, the role of this complex image classification on neuroendocrine outcomes is unclear. The distinction of the predominant lesion in bifocal iGCT patients has a wide applicability. We considered that a giant pineal mass or a basal ganglia mass with pituitary stalk involvement was a typical non-sellar-predominant type. On the contrary, iGCTs with hypothalamus and/or pituitary involvement with a limited lesion in the pineal gland or the basal ganglia mass were considered to be the predominant type. To explore the characteristics and neuroendocrine outcomes of bifocal GCTs with different predominant lesions, this article was performed. Further comparison between different subtypes of sellar-predominant bifocal iGCT patients would also be performed.

Subject and methods

This study included 38 patients who were diagnosed with iGCTs between January 2015 and December 2022 at the Beijing Tiantan Hospital. The inclusion criteria were: (i) the defined diagnosis based on human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) in serum and cerebrospinal fluid (CSF), histological features and patterns, and the response to chemotherapy or radiotherapy; (ii) the pre-treatment brain images indicating a sellar lesion; and (iii) the completion of the multidisciplinary treatment for iGCT. The exclusion criteria were (i) a history of chromosomal abnormalities or other malignant tumors; (ii) loss of physical examinations due to mental disorders or severe physical disabilities; and (iii) incomplete revaluation of neuroendocrine function.

Medical records were compiled, including general characteristics, clinical manifestations, neuroimaging features, laboratory examination, tumor markers, diagnostic methods, therapeutic strategies, and outcomes. The symptom interval was defined as the time span from its occurrence to its diagnosis. Tumor markers were measured using an electrochemiluminescence immunoassay. Hormone levels were measured by an immunochemiluminometric assay. Common biochemical parameters were measured using an autoanalyzer. Pre-treatment-enhanced magnetic resonance imaging (MRI) was divided into sellar predominance and non-sellar predominance. Sellar predominance was divided into two subtypes: subtype 1 means tumors located in the intrasellar site or with a pituitary stalk involvement (Fig. 1A) and subtype 2 means tumors located in the third ventricle or with an extension to the pituitary stalk or intrasellar site (Fig. 1B). Non-sellar predominance means the isolated lesion was located on the floor of the third ventricle or pituitary stalk (Fig. 1C). Therapeutic strategies for iGCTs were platinum-based induction chemotherapy (ifosfamide, 1.5 g/m^2, d1–3; etoposide, 70 mg/m^2; d1–3; and cisplatin, 30 mg/m^2; d1–3) every 4 weeks for two cycles following radiotherapy (whole-brain for

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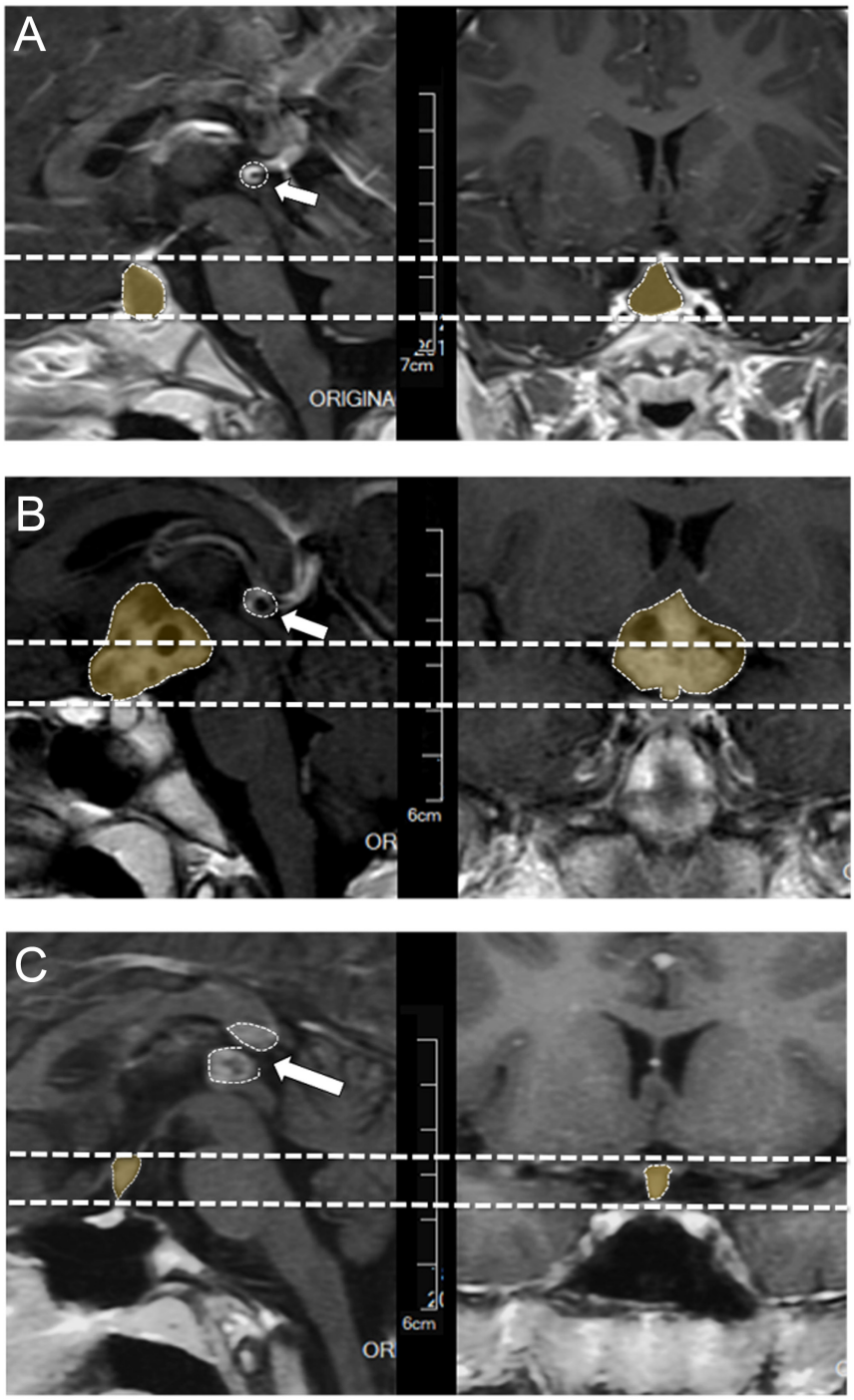

Figure 1
Different imaging grades for patients with bifocal intracranial germ cell tumors. Each lesion was marked by white dotted lines: (A) the neuroimaging features of sellar-predominant subtype 1, (B) neuroimaging features of sellar-predominant subtype 2, and (C) neuroimaging features of non-sellar-predominant patients.

metastasis-free lesions or craniospinal irradiation for metastasis lesions) and then an additional two cycles of chemotherapy. Alternative neurosurgery included a ventriculoperitoneal shunt (VPS) operation for increased pressure hydrocephalus, transcranial or transsphenoidal biopsy for diagnosis, and transcranial or transsphenoidal surgery for removing residual after chemoradiotherapy.

Neuroendocrine disorders were evaluated before treatment, after tumor elimination, and at the last follow-up visit. Central diabetes insipidus (CDI): presentation of polyuria (>50 mL/kg d or 3.5 L/day) with elevated plasma osmolality (300 mOsm/kg H_2O) and decreased urine osmotic pressure (<600 mOsmol/L) mOsm/kg H_2O) and negative urine glucose. Impairment to hypothalamic–pituitary–adrenal axis (HPA): basal

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cortisol level <3 μg/dL indicated impaired HPA function while the basal cortisol level >15 μg/dL excluded it. If basal cortisol levels ranged from 3 to 15 μg/dL, the circadian rhythm of adrenocorticotropic hormone and cortisol (08:00, 16:00, and 24:00 h) was monitored. If the circadian rhythm of the adrenocorticotropic hormone and cortisol disappeared, the level of the adrenocorticotropic hormone was low or normal, indicating that HPA was potentially damaged. Impairment to hypothalamic–pituitary–thyroid axis (HPT): the basal free thyroxine level was below the reference values (7.64–16.3 pmol/L), while the thyroid-stimulating hormone level was lower, normal, or slightly higher than the reference values (0.49–4.91uIU/mL). Impairment to growth hormone–insulin-like growth factor-1 (GH/IGF1): children with growth retardation or adults with obvious hypometabolic syndrome had IGF1 levels below 2 S.D. than their peers and had additional pituitary hormone deficiencies. Impairment to hypothalamic–pituitary-–gonad axis (HPG) axis: adolescents (males aged 14–18 years, females aged 13–18 years) had follicle-stimulating hormone, luteinizing hormone levels, and sex steroid hormones below the Tanner stage 2 reference values or bone age was below the actual age of 2 years. Adults (over 18 years) were below the adult reference values. Hyperprolactinemia (HPRL): the basal prolactin levels were greater than 17 ng/mL in males or 20 ng/mL in females. Slightly elevated basal prolactin levels were repeatedly evaluated on another day.

The results of the continuation variable were presented by mean and standard deviation (mean ± S.D.) and median and range (interquartile range). The independent sample *t*-test and the Wilcoxon rank sum test were performed. Qualitative variables were presented by number and percentage (*n*, %). Fisher's exact test was performed. A *P*-value less than 0.05 was considered statistically significant. SPSS 22.0 software (IBM) was used for statistical analysis.

Table 1 Characteristics of patients included.

	Sellar predominance	Non-sellar predominance	All	*P*
Gender (*n*, %)				0.460
Male	14 (66.7%)	14 (82.4%)	28 (73.7%)	
Female	7 (33.3%)	3 (17.6%)	10 (26.3%)	
Age (years)	14.48 ± 4.96	13.18 ± 5.03	13.89 ± 4.97	0.431
Manifestation (*n*, %)				
Polydipsia and polyuria	16 (76.2%)	11 (64.7%)	27 (71.1%)	0.491
Headache	3 (14.3%)	4 (23.5%)	7 (18.4%)	0.678
Dyskinesia	4 (19.0%)	3 (17.6%)	7 (18.4%)	0.999
Nausea	3 (14.3%)	2 (11.8%)	5 (13.2%)	0.999
Fatigue	4 (19.0%)	1 (5.9%)	5 (13.2%)	0.355
Visual impairment	3 (14.3%)	1 (5.9%)	4 (10.5%)	0.613
Growth retardation	4 (19.0%)	0 (0.0%)	4 (10.5%)	0.113
Hypogonadism	3 (14.3%)	1 (5.9%)	4 (10.5%)	0.613
Precocity	1 (4.8%)	1 (5.9%)	2 (5.3%)	0.999
Delayed puberty	2 (9.5%)	0 (0.0%)	2 (5.3%)	0.492
SIs (months)	5 (3.12)	1 (1,9)	3 (1,25.5)	0.075
Metastasis (*n*, %)	6 (28.6%)	2 (11.8%)	8 (21.1%)	0.257
Markers (*n*, %)	11 (52.4%)	9 (52.9%)	20 (52.6%)	1.000
hCG (U/L)	10.6 (5.1, 26.3)	76.7 (3.9, 453.5)	12.6 (4/9, 117, 4)	0.491
AFP (U/L)	12 (8.4, 167, 27)	-	12 (8.4, 167, 27)	-
hCG(CSF) (U/L)	7.7 (4.6, 62.0)	11.9 (6.6, 184)	9.8 (6.3, 82.7)	0.432
Diagnostic method (*n*, %)				0.730
Pathology	7 (33.3%)	7 (41.20%)	14 (36.8%)	
Chemotherapy	14 (66.7%)	10 (58.8%)	24 (63.3%)	
Type (*n*, %)				0.515
GE	10 (90.9%)	4 (66.7%)	14 (82.4%)	
NGGCT	2 (33.3%)	1 (9.1%)	3 (7.9%)	
Surgery (*n*, %)				0.793
None	12 (57.10%)	10 (58.80%)	22 (57.9%)	
Biopsy	7 (33.30%)	4 (23.50%)	11 (28.9%)	
Resection	1 (4.80%)	2 (11.80%)	3 (7.9%)	
VPS	1 (4.80%)	1 (5.90%)	2 (5.3%)	

AFP, alpha-fetoprotein; CSF, cerebrospinal fluid; GE, germinomas; hCG, human chorionic gonadotropin; NGGCT, non-germinomatous germ cell tumors; SIs, symptom intervals; VPS, ventriculoperitoneal shunt.

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This study protocol was reviewed and approved by IRB of Beijing Tiantan Hospital, Capital Medical University, approval number (KY2022-024-01). Informed consent was obtained from all participants (or their parents/legal guardian/next of kin) to participate in the study.

Results

Characteristics of patients included

A total of 38 patients (28 males and 10 females) were included, with a mean age of 13.89 ± 4.97 years old. A total of 21 patients (14 males and 7 females) were assigned to the sellar-predominant group, while the other 17 (14 male and 3 females) were assigned to the non-sellar-predominant group. Eleven patients of the non-sellar-predominant groups were sellar and pineal bifocal lesions, while the other six patients were basal ganglia and sellar lesions.

Manifestations were mostly common in polydipsia and polyuria (71.1 %), followed by headache (18.4%), hemiparesis (18.4%), nausea (13.2%), and fatigue (13.2%). All patients included received an assessment of hCG and AFP levels in serum and 15 patients synchronously in CSF. A total of 20 (52.6%) patients had elevated tumor marker levels. Among patients with elevated tumor markers, the median hCG was 20 (52.6%) U/L in serum and 9.8 (6.3, 82.7) in CSF. Median AFP was 12 (8.4, 167, 27) U/L in serum, while none of the patients included had elevated AFP levels in CSF. A total of 14 (36.8%) patients were diagnosed with iGCT through pathologic results and the other 24 (63.3%) patients through clinical methods. All patients included received radiation therapy combined with adjuvant chemotherapy. Additionally, 2 (5.3%) patients received hydrocephalus VPS surgery prior to chemoradiotherapy, 11 (28.9%) patients received biopsy, 3 (7.9%) received transcranial or transsphenoidal tumor resection operation, and the other 22 (57.9%) patients did not receive any neurosurgery therapy.

Comparison of the characteristics between sellar-predominant patients and non-sellar-predominant patients

There were no significant differences in gender ratio ($P=0.460$), age ($P=0.431$), manifestation of CDI ($P=0.491$), headache ($P=0.678$), hemiparesis ($P=0.999$), nausea ($P=0.999$), fatigue ($P=0.355$), visual impairment ($P=0.613$), growth retardation ($P=0.113$),

Table 2 Neuroendocrine disorders of patients with different predominant lesions.

	Pre-multidisciplinary treatment				Post-multidisciplinary treatment				Final follow-up			
	Sellar	Non-sellar	All		Sellar	Non-sellar	All		Sellar	Non-sellar	All	
Predominance	*n* = 21	*n* = 17	*n* = 38	*P*	*n* = 21	*n* = 17	*n* = 38	*P*	*n* = 11	*n* = 11	*n* = 11	*P*
HPA	13 (61.9%)	7 (41.2%)	20 (52.6%)	0.328	15 (71.4%)	4 (23.5%)	19 (50.0%)	0.008	9 (81.8%)	1 (9.1%)	10 (45.5%)	0.002
HPT	14 (66.7%)	7 (46.7%)	21 (58.3%)	0.310	15 (71.4%)	6 (35.3%)	21 (55.3%)	0.048	10 (90.9%)	4 (36.4%)	14 (63.6%)	0.024
GH/IGF1	15 (93.8%)	9 (69.2%)	24 (82.8%)	0.144	18 (85.7%)	9 (60.0%)	27 (75.0%)	0.122	10 (90.9%)	8 (80.0%)	18 (85.7%)	0.586
HPG	11 (84.6%)	3 (37.5%)	14 (66.7%)	0.056	8 (61.5%)	1 (10.0%)	9 (39.1%)	0.029	9 (90.0%)	1 (11.1%)	11 (57.9%)	0.000
HPRL	14 (66.7%)	7 (41.2%)	21 (55.3%)	0.190	8 (38.1%)	2 (11.8%)	10 (26.3%)	0.136	4 (36.4%)	1 (9.1%)	5 (22.7%)	0.311
CDI	19 (90.5%)	14 (82.4%)	33 (86.8%)	0.640	18 (85.7%)	12 (70.6%)	30 (78.9%)	0.426	11 (100.0%)	11 (100.0%)	22 (100.0%)	-

CDI, central diabetes insipidus; GH, growth hormone; HPA, hypothalamus–pituitary–adrenal axis; HPG, hypothalamic–pituitary–gonadal axis; HPRL, hyperprolactinemia; HPT, hypothalamus–pituitary–thyroid axis; IGF1, insulin-like growth factor-1.

hypogonadism ($P=0.613$), delayed puberty ($P=0.492$), precocity ($P=0.999$), SIs ($P=0.075$), incidence of metastasis ($P=0.257$), incidence of elevated tumor markers ($P=0.999$), hCG levels in serum ($P=0.491$) and in CSF ($P=0.432$), diagnostic method ($P=0.730$), tumor type ($P=0.515$), and surgery method ($P=0.793$) between the sellar-predominant group and the non-sellar-predominant group (Table 1).

Comparison of the neuroendocrine function between sellar-predominant patients and non-sellar-predominant patients

Before treatment, the sellar-predominant group had a higher incidence of HPA (61.9%), HPT (66.7%), GH/IGF1 (93.8%), HPG (84.6%), HPRL (66.7%), and CDI (90.5%) than those of the non-sellar-predominant group (41.2, 46.7, 69.2, 37.5, 41.2, and 82.4%, respectively), without significant differences ($P=0.328$, 0.310, 0.144, 0.056, 0.190, and 0.640, respectively). The multidisciplinary therapy period to eliminate iGCT lasted a of mean 8.7 ± 2.6 months. After multidisciplinary therapy, the sellar-predominant group had a higher incidence of HPA (71.4%), HPT (71.4%), GH/IGF1 (85.7%), HPG (61.5%), HPRL (38.1%), and CDI (85.7%) than those of the non-sellar-predominant group (23.5, 35.3, 60.0, 10.0, 11.8, and 70.6%, respectively). The differences in the HPA impairment ($P=0.008$), HPT impairment ($P=0.048$), and HPG impairment ($P=0.029$) were significant between the sellar-predominant group and the non-sellar-predominant group, while GH/IGF1 impairment ($P=0.122$), HPRL ($P=0.136$), and CDI ($P=0.426$) were not significant. A total of 22 patients received a median of 6 (3, 43) months of follow-up, of which 11 of them were in the sellar-predominant group and the other 11 were in the non-sellar-predominant group. At the last follow-up visit, the sellar-predominant group had a higher incidence of HPA (81.8%), HPT (90.9%), GH/IGF1 (90.9%), HPG (90.0%), and HPRL (36.4%) than those of non-sellar-predominant group (9.1, 36.4, 80.0%, 11.1, and 9.1%, respectively). The differences in the HPA impairment ($P=0.002$), HPT impairment ($P=0.024$), and HPG impairment ($P < 0.000$) were significant between the sellar-predominant group and the non-sellar-predominant group, while the GH/IGF1 impairment ($P=0.586$) and HPRL ($P=0.311$) were not significant. All patients had CDI regardless of the predominant lesion (Table 2).

Except for three patients who received transcranial or transsphenoidal tumor resection operation, the differences in HPA impairment ($P=0.006$) and HPT

Table 3 Neuroendocrine disorders of sellar-predominant patients with different subtypes.

	Pre-multidisciplinary treatment				Post-multidisciplinary treatment				Final follow-up			
Subtype	1 ($n=7$)	2 ($n=14$)	All ($n=21$)	*P*	1 ($n=7$)	2 ($n=14$)	All ($n=21$)	*P*	1 ($n=2$)	2 ($n=9$)	All ($n=11$)	*P*
HPA	3 (42.9%)	10 (71.4%)	13 (61.9%)	0.346	4 (57.1%)	11 (78.6%)	15 (71.4%)	0.354	1 (50.0%)	8 (88.9%)	9 (81.8%)	0.345
HPT	3 (42.9%)	11 (78.6%)	14 (66.7%)	0.156	4 (57.1%)	11 (78.6%)	15 (71.4%)	1.354	1 (50.0%)	9 (100.0%)	10 (90.9%)	0.182
GH/IGF1	5 (83.3%)	10 (100.0%)	15 (93.8%)	0.375	5 (71.4%)	13 (92.9%)	18 (85.7%)	0.521	1 (50.0%)	9 (100.0%)	10 (90.9%)	0.182
HPG	4 (80.0%)	7 (87.5%)	11 (84.6%)	1.000	2 (40.0%)	6 (75.0%)	8 (61.5%)	0.293	1 (100.0%)	9 (100.0%)	10 (100.0%)	-
HPRL	4 (57.1%)	10 (71.4%)	14 (66.7%)	0.638	2 (28.6%)	6 (42.9%)	8 (38.1%)	0.656	0 (0.0%)	4 (44.4%)	4 (36.4%)	0.491
CDI	5 (71.4%)	14 (100.0%)	19 (90.5%)	0.100	6 (85.7%)	12 (85.7%)	18 (85.7%)	1.000	2 (100.0%)	9 (100.0%)	11 (100.0%)	-

CDI, central diabetes insipidus; GH, growth hormone; HPA, hypothalamus–pituitary–adrenal axis; HPG, hypothalamic–pituitary–gonadal axis; HPRL, hyperprolactinemia; HPT, hypothalamus–pituitary–thyroid axis; IGF1, insulin-like growth factor-1.

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impairment ($P=0.044$) were also significant between the sellar-dominant group and the non-sellar-predominant group at the end of multidisciplinary therapy. Similarly, differences in HPA impairment ($P=0.005$), HPT impairment ($P=0.020$), and HPG impairment ($P=0.000$) were also significant between the sellar-predominant group and the non-sellar-predominant group at the final follow-up visit (Supplementary Table 1, see section on supplementary materials given at the end of this article).

Comparison of the neuroendocrine function between different subtypes of sellar-predominant patients

Among 21 patients in sellar-predominant group, 7 of them were further assigned to subgroup 1 and the other 14 patients to subgroup 2. Before multidisciplinary treatment for iGCT, the differences in HPA impairment ($P=0.346$), HPT impairment ($P=0.156$), GH/IGF1 impairment ($P=0.375$), HPG impairment ($P=0.999$), HPRL ($P=0.638$), and CDI ($P=0.999$) were not significant between the two subtype groups. Similarly, in the end of multidisciplinary treatment, the differences in HPA impairment ($P=0.354$), HPT impairment ($P=0.354$), GH/IGF1 impairment ($P=0.521$), HPG impairment ($P=0.293$), HPRL ($P=0.656$), and CDI ($P=0.999$) were not significant between two subtype groups. A total of 11 patients received a median of 18 (3, 54) months of follow-up visit, of which 2 of them were in subtype 1 group and the other 9 were in subtype 2 group. At the last follow-up visit, the differences in the HPA impairment ($P=0.345$), HPT impairment ($P=0.182$), GH/IGF1 impairment ($P=0.182$), and HPRL ($P=0.491$) were not significant. Besides, all sellar-predominant patients had HPG impairment and CDI (Table 3).

Discussion

This study focuses on the potential relationship between image features and neuroendocrine outcomes of bifocal iGCT patients. Based on the characteristics of patients with different predominant lesions, this study aimed at optimizing neuroendocrine management during the period of multidisciplinary therapy and the following survival time. The comparison of the neuroendocrine outcomes between patients with different predominant lesions before multidisciplinary therapy, after multidisciplinary therapy, and at the last follow-up visit indicated that (i) bifocal iGCT patients initially had neuroendocrine disorders regardless of the predominant lesion but (ii) non-sellar bifocal patients may have better neuroendocrine outcomes after multidisciplinary therapy. These two results remain after excluding the three patients who underwent surgical resection. The differences in neuroendocrine outcomes between patients with different predominant lesions seem less related to the multidisciplinary strategy.

Neuroendocrine disorders are commonly seen in iGCT patients with sellar involvement, including those non-sellar-predominant patients. In this study, the ratio of sellar-predominant bifocal patients and non-sellar-predominant ones is nearly 5:4, indicating that the evaluation of neuroendocrine function and relevant hormone replacement for non-sellar-predominant bifocal patients deserves more concern. Before multidisciplinary therapy for iGCT, patients with both the sellar-predominant and non-sellar-predominant lesion presented with hypothalamic adenohypophysis and neurohypophysis disorders. Both sellar predominant and non-sellar predominant manifested as polydipsia and polyuria, nausea, and fatigue, without statistical significance. Differences in HPA impairment, HPT impairment, GH/IGF1 impairment, HPG impairment, HPRL, and CDI were not significant between different predominant groups. According to the similarity of initial neuroendocrine function, the multidisciplinary therapy team, including the oncology, radiology, and neurosurgery departments, should pay more attention to the evaluation of the neuroendocrine function of those non-sellar-predominant patients. The proper exogenous hormone replacement treatments are needed for all iGCT patients with sellar involvement to ensure the safety of tumor treatment, regardless of the predominant lesion.

Neuroendocrine function varied during multidisciplinary therapy. After treatment and during follow-up, partial adenohypophysis disorders might spontaneously relieve in the non-sellar-predominant patients, leaving constant neurohypophysis disorders. During survival time, sellar-predominant patients had a higher incidence of HPA impairment, HPT impairment, GH/IGF1 impairment, HPG impairment, HPRL, and CDI than those of non-sellar-predominant patients. The differences in HPA impairment, HPT impairment, and HPG impairment were significant. These differences suggested that sellar-predominant patients tend to have similar neuroendocrine outcomes to isolated sellar lesions, while the non-sellar-predominant patients do not. Based on the differences in long-term neuroendocrine outcomes, the multidisciplinary

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therapy team should consider constant exogenous hormone replacement treatment for sellar-predominant lesions, and reduced hormone replacement dose for non-sellar-predominant patients. To explore therapeutic influence, the comparison of neuroendocrine outcomes between the sellar-predominant group and the non-sellar-predominant group was repeated excluding the three patients who received surgery resection. The results also indicated that non-sellar-predominant patients have a greater potential for spontaneous improvement. In fact, iGCTs generally do not need to be removed by neurosurgery, which reduces surgery-related endocrinopathy (9). In addition, the high sensitivity of iGCTs to radiation makes it possible for the preservation of the neuroendocrine function during the therapy for tumors (11, 12, 13, 14). However, previous studies which discussed original therapeutic strategies in bifocal iGCT rarely focused on neuroendocrine outcomes.

The distinction of the predominant lesion in patients with bifocal iGCT plays a valuable role in predicting neuroendocrine outcomes during the survival time. However, further comparison between different subtypes of sellar-predominant patients did not indicate a significant difference. It is suggested that the current image subtype is insufficient to predict long-term neuroendocrine outcomes. In fact, previous studies have discussed the image classification of sellar GCT; however, the image classification of sellar iGCT has not achieved a consensus. A previous study involving 38 patients with solitary sellar GCT divided the image into three categories mainly based on the location of sellar turcica and the third ventricle (15). Tumors located on the floor of the third ventricle to the third ventricle were classified as type 1, those located in the pituitary stalk were classified as type 2, and those located in the sellar turcica were classified as type 3. Type 2 means easy to delayed diagnosis or misdiagnose due to the indistinct pituitary stalk and type 3 means difficult to differentiate from craniopharyngioma in the early stage. This study described the typical morphology of the sellar GCT with obvious limitations as follows. Firstly, type 1 and 3 images of this study are not the commonly seen iGCT images. Lastly, this study did not compare the influence of tumor mass on endocrine glands and hormone levels. However, another study involving 22 solitary sellar iGCT and 20 bifocal iGCT patients classified the morphology of GCT in the sellar into five categories (10), based mainly on the relationship between the direction of tumor growth and the floor of the third ventricle and the turcica sellar. Type 1: a localized lesion at the floor of the third ventricle, type 1a without pituitary stalk involvement while 1b with. Type 2: a localized lesion at the floor of the third ventricle with growing toward the third ventricle and pituitary stalk. Type 3: a lesion located at the floor of the third ventricle with growing toward the sellar turcica. Type 4: a lesion located at the floor of the third ventricle, limited to the upper end of the pituitary stalk. Type 5: an isolated pituitary stalk lesion. This study suggested that sellar lesions located between the floor of the third ventricular and the upper part of the pituitary stalk were the most common image classification, while isolated pituitary stalk lesions are rare. Besides, this study indicated that the prognosis of bifocal iGCTs is worse than that of solitary iGCTs. This study described more systematical morphological features of the sellar GCTs but also had some limitations. First, the image classification of type 6 is relatively complex and subjective. For example, both type 1a and type 4 images were located on the floor of the third ventricle with an identifiable pituitary stalk. The difference depends only on approximate tumor mass rather than a precision volume Secondly, the study proposed the controversial point that multidisciplinary treatment for bifocal tumors should refer to metastasis iGCTs. However, most research on iGCTs still considers that the dose and field of radiotherapy and relevant chemotherapy depend on tumor metastasis or not. Finally, this study did not compare the neuroendocrine outcomes among patients with different image type.

We focused on the structure of the hypothalamus, pituitary stalk, and pituitary gland to describe the potential damage of tumors on neuroendocrine organs rather than directly comparing lesions' volume. The subtypes in this study were mainly based on the extension of tumor growth, dividing into the involvement of the pituitary gland area (subtype 1) or both the pituitary gland and the hypothalamus area (subtype 2). This type scheme would be more rationale for revealing the damage of neuroendocrine organ damage. In the present study, although the differences in neuroendocrine outcomes are not significant between subtypes 1 and 2, it could be predicted that patients with the subtype 1 and 2 images would have better neuroendocrine outcomes than those with non-sellar patients. Combined with the previous study on pituitary stalk GCT (16), this study indicated that a limited sellar iGCT located in the pituitary and the floor of the third ventricle, including solitary and bifocal lesions, has the potential to spontaneously improve neuroendocrine outcomes. Hence, it is valuable evidence to support the role of sellar lesion image in predicting neuroendocrine outcomes and in administrating

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individual hormone replacement treatment. In the future, if more research concerns on the image features, a new image classification might be discussed. Sellar iGCT image classification may be comparable to the image classification of craniopharyngioma, involving tumor growth, extent, and the relationship to surrounding brain structure. However, craniopharyngioma is a type of tumor that is primarily dependent on neurosurgery, while iGCT is dependent on radiotherapy and chemotherapy. The potential role of image classification might be different between these two sellar diseases.

IGCTs have a high overall survival rate regardless of the controversy about synchronous (17) or metastatic occurrence (10, 18, 19, 20) of bifocal lesions. Hence, the command of improving the quality of life of those survivors deserves more attention. This study, primarily based on hypothalamic neurohypophysis and adenohypophysis, indicates that identifying predominant lesions in bifocal iGCT can predict the neuroendocrine outcomes of patients, and guide their long-term neuroendocrine management to some extent. In future prospective studies, neuroendocrine-related disorders need to be further explored, not only concentrating on pituitary target hormone levels, but also on hypothalamic function, optic and oculomotor nerve function, cavernous sinus and other factors affecting quality of life.

This study has certain limitations. First, this study only included 32 patients who may not reflect some potential risk factors for neuroendocrine function. Regression analysis of multiple related factors prefers if future patients are sufficient. Next, although irrelevant to the predominant lesion in bifocal iGCTs, the new subtype of the sellar iGCT image should be considered to predict the neuroendocrine outcomes of iGCT patients with sellar involvement. Finally, as a retrospective design, this study did not mention the final height, puberty development, and the quality of life. All these long-term outcomes are valuable for survivors and require future prospective research to explore.

Conclusion

Patients with bifocal iGCTs with sellar involvement initially present with neuroendocrine disorders regardless of the predominant lesion. However, non-sellar-predominant patients would have better neuroendocrine outcomes than those sellar-predominant ones after tumor treatment. The distinction of the predominant lesion in patients with bifocal iGCTs plays a valuable role in predicting neuroendocrine outcomes, as well as in optimizing long-term neuroendocrine management during survival time.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-23-0168.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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