The enigma of bifocal germ cell tumors in the suprasellar and pineal regions: synchronous lesions or metastasis?

Clinical article

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Object. Intracranial germ cell tumors (GCTs) frequently present with bifocal lesions in both the suprasellar and pineal areas. The pathogenesis of these bifocal GCTs has been the subject of controversy. Bifocal GCTs may be caused by synchronous tumors or by metastatic spread of tumor cells from one site to the other. The prognosis associated with bifocal GCTs has also been a cause of concern.

Methods. The authors constructed a single-institution patient cohort comprising 181 patients with intracranial GCTs. The clinical characteristics of bifocal GCTs were compared with those of suprasellar and pineal GCTs.

Results. Bifocal GCTs were observed in 23 patients (12.8%). Eighteen patients presented with bifocal GCTs that were diagnosed as germinomas, but 5 patients exhibited mixed GCTs. Analyses of age distributions and comparisons of tumor sizes were compatible with a model of a metastatic origin of bifocal GCTs. Eleven patients (47.8%) presenting with bifocal GCTs exhibited tumor seeding at presentation. Tumor seeding was significantly associated with bifocal lesions (p < 0.001). Patients with bifocal germinomas showed significantly shorter event-free survival and overall survival than did those presenting with germinomas from a single site of origin.

Conclusions. Bifocal GCTs are not restricted to germinomas, as had been previously reported, but do include mixed GCTs. The authors hypothesize that bifocal GCTs may result from the metastatic spread of suprasellar or pineal GCTs. The bifocal presentation of germinomas may be a poor prognostic sign and should alert clinicians to the possibility of a disseminated disease.
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Key Words • **intracranial tumor** • **bifocal germ cell tumor** •
suprasellar tumor • **pineal tumor** • **metastasis** • **oncology**

Intracranial GCTs are a heterogeneous group of brain tumors that differ from neuroepithelial tumors in many aspects. Intracranial GCTs have been suggested to originate from heterotopic germ cells, as Teilum proposed.[6,24] The development of GCTs is strongly associated with the patient's sex and age.[7] However, the most intriguing characteristic of GCTs might be their peculiar predilection for a specific location. Intracranial GCTs develop predominantly in the midline around the third ventricle, specifically in the suprasellar and pineal regions.[26] The reason for the specific localization of intracranial GCTs has not been elucidated.

The simultaneous occurrence of both suprasellar and pineal GCTs has been described as a bifocal GCT.[4,22] The bifocal occurrence of GCTs has been considered to be almost pathognomonic of germinomas, and some clinicians

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This article contains some figures that are displayed in color online but in black-and-white in the print edition.

have argued that biopsy of these lesions is not necessary.[11] The pathogenesis of bifocal GCTs is quite controversial.[13] Suprasellar and pineal regions are the most common sites of origin for intracranial GCTs, and therefore, bifocal GCTs could be regarded as synchronous tumors. However, considering that intracranial GCTs, especially germinomas, readily metastasize along the ventricular walls, the presence of bifocal lesions raises concerns for the metastatic spread of the disease.

In this study, we constructed a large patient cohort of intracranial GCTs. We compared the clinical and epidemiological characteristics of bifocal GCTs with those of GCTs located solely in the suprasellar or pineal regions. Epidemiological data and the seeding patterns of GCTs supported the hypothesis that bifocal GCTs arise from metastasis from a single site, rather than from synchronous tumor development.

Methods

Data Sources

The Institutional Review Boards of the Seoul National University Hospital and the Seoul National University College of Medicine approved this study protocol. We searched our institution's electronic databases of patients who were diagnosed with intracranial GCTs. The databases nonselectively included all patients admitted to the Seoul National University Children's Hospital and the Seoul National University Hospital. We limited our search to the period between January 1998 and December 2010, as the radiological and clinical records for patients enrolled before 1998 were not fully digitalized and many of them were not available for review. We excluded metastatic GCT to the brain. Within the study period, 181 patients were clinically diagnosed as having intracranial GCTs. These patients constituted the entire cohort of intracranial GCTs for our analyses. Information regarding patient characteristics, such as age and sex, and disease characteristics, including tumor size, location, tumor markers, pathology, and the presence of tumor seeding, was collected from the electronic medical record. Detailed information regarding patients' treatment was supplemented by operation, chemotherapy, and radiotherapy records, which were not fully available electronically, from each department concerned. The outcome of the treatment was confirmed by the electronic medical record, and death certificate information was obtained from the National Statistical Office and the Ministry of Public Administration and Security.

Database Construction

We developed a structured data extraction form, and data were entered via double entry. Clinical data stored in the electronic medical record and paper records were reviewed. Radiological data including the initial brain and spinal MR images were reviewed independently by a neuroradiologist (I.O.K.). For intracranial GCTs, the pathological diagnosis is incomplete for many patients for 2 reasons. First, stereotactic or endoscopic biopsy was used in the majority of patients rather than resection of the entire tumor, because high response rates to adjuvant therapies make radical surgery less favorable. Second, patients with elevated tumor markers, such as AFP and β-HCG, can be diagnosed as presenting with intracranial GCTs without requiring a biopsy of tumor tissues. Therefore, we made clinical diagnoses based on serum/CSF tumor markers, as well as by pathological diagnoses. For example, if pathological examination of a small tissue biopsy revealed only teratomas or germinomas while the serum/CSF AFP levels were elevated above the normal limit of the institutions (20 ng/ml) or β-HCG levels were above the generally accepted maximum for germinomas (100 IU/ml), MGCTs were clinically diagnosed. All clinical diagnoses made at initial presentation and during the treatment of the patients were critically reviewed and revised accordingly.

A bifocal GCT was defined as a separate tumor involvement of both suprasellar and pineal areas on brain MR images taken at the time of diagnosis, regardless of the presence of other metastatic tumors in the ventricles (Fig. 1). The progression of disease was defined as the documentation of a new enhancing lesion or the growth of a preexisting tumor by more than 25% in 2D analyses during follow-up neuroimaging. The EFS was defined as the timespan from the day in which a clinical diagnosis was made to the date of the documentation of disease progression or the death of the patient from any cause, whichever came first. The OS was defined as the interval between the day of a clinical diagnosis and the date of death or March 10, 2011, whichever came first.

Statistical Analysis

We applied the chi-square test and the Fisher exact test to estimate the association of dichotomous variables. The Student t-test and ANOVA were used for the compar-
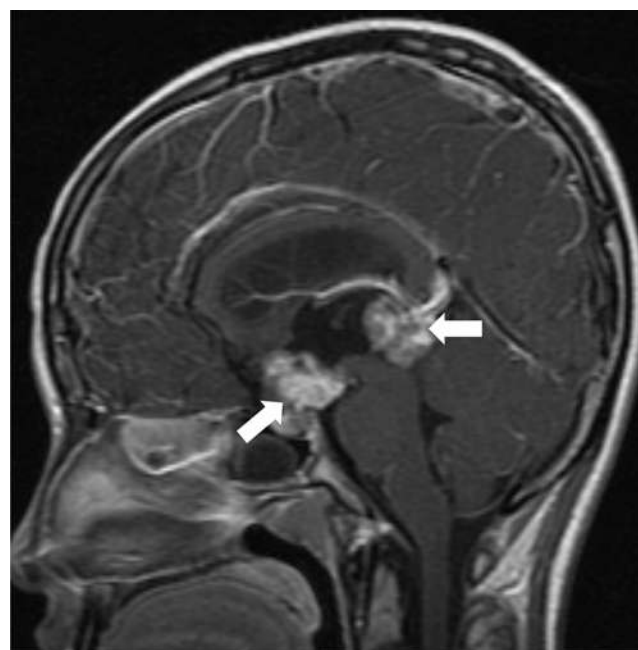

FIG. 1. Sagittal MR image obtained in a 14-year-old boy who presented with polyuria, polydipsia, and chronic fatigue. Two Gd-enhancing masses can be observed in the suprasellar and pineal regions (arrows).

ison of continuous variables. We calculated Kaplan-Meier survival curves for the EFS and OS of specific groups of patients. A log-rank test was applied for the comparison of the EFS and OS values between the groups. For verification of prognostic variables, we applied a Cox proportional hazards model for univariate and multivariate analyses. Basic clinical variables, such as sex and age at diagnosis, were included in the analyses, as well as other variables known or alleged to have prognostic values for germinomas, such as seeding at presentation, elevated levels of serum β-HCG, and radiation therapy limited to the involved fields.[8,15,20] Clinical variables with p < 0.15 in the univariate analyses were included in the multivariate models. All p values were 2-sided, and significance was set at p = 0.05. The SPSS software (version 17, SPSS, Inc.) was used in the statistical analyses.

Results

Epidemiology of the Patient Cohort

The patient cohort consisted of 181 consecutive patients. One hundred forty-five patients (80.1%) were male and 36 patients (19.9%) were female. The median age at diagnosis was 13.0 years (range 1 month–44 years). Five patients (2.8%) were infants, and 25 patients (13.8%) were older than 20 years. The mean age at diagnosis of female patients was significantly lower than that of male patients (11.4 ± 5.7 years vs 14.7 ± 7.1 years; p = 0.010, unpaired t-test). The pineal region (n = 81 [44.8%]) was the most common site for tumors, followed by the suprasellar region (n = 38 [21.0%]), basal ganglia (n = 29 [16.0%]), temporal lobe (n = 4 [2.2%]), and thalamus (n = 3 [1.7%]). Three tumors (1 tumor in each area) were located in the midbrain, cerebellopontine angle, and retrocerebellar area. Bifocal GCTs in both the suprasellar and pineal regions were observed in 23 patients (12.7%). One patient with a tumor in the basal ganglia also presented with double lesions in the suprasellar area, which were not considered as bifocal in this study.

Surgical biopsy or resection was performed in 167 patients (92.3%). Fourteen patients (7.7%) were diagnosed without biopsy as exhibiting MGCTs (n = 10), germinomas (n = 3), and yolk sac tumors (n = 1), based on the pattern of elevated levels of tumor markers. Serum AFP and β-HCG values were available for review in 175 and 173 patients, respectively. Cerebrospinal fluid AFP and β-HCG values were available for review in 131 and 129 patients, respectively. Levels of serum and CSF AFP that were elevated above the normal reference values were detected in 38 and 21 patients, respectively. Levels of serum and CSF β-HCG that were elevated above the normal reference values were detected in 48 and 60 patients, respectively. Clinical diagnoses of the patients were germinomas (n = 120 [66.3%]), MGCTs (n = 40 [22.1%]), immature teratomas (n = 11 [6.1%]), mature teratomas (n = 6 [3.3%]), yolk sac tumors (n = 2 [1.1%]), and choriocarcinomas (n = 2 [1.1%]).

Comparison of Suprasellar and Pineal Tumors

A significant difference was observed in the sex ratio between suprasellar and pineal GCTs. The male-to-female ratio for suprasellar GCTs was 0.58 (14:24), whereas the male-to-female ratio for pineal GCTs was 26.0 (78:3) (p < 0.001, chi-square test). The mean ages at diagnosis for suprasellar and pineal GCTs were 13.7 ± 6.7 and 14.3 ± 7.0 years, respectively. The difference between the groups was not significant (p = 0.679, unpaired t-test). The pineal region was characterized by the presence of NGGCTs. Except for MGCTs, which usually contain a germinoma component, the majority of NGGCTs, especially mature and immature teratomas, developed in the pineal region rather than in the suprasellar region (Table 1).

Bifocal GCTs

Of the 23 patients with dual lesions in both the suprasellar and pineal areas, 19 patients were male and 4 patients were female. The mean age of these patients was 16.4 ± 5.5 years. No differences were observed in the age distribution among patients with suprasellar, pineal, or bifocal GCTs (p = 0.290, ANOVA). Five patients were diagnosed with MGCTs based on elevated levels of tumor markers. The other 18 patients presented with germinomas. Bifocal GCTs exhibited an apparent similarity to suprasellar GCTs in the spectrum of clinical diagnosis in that no teratoma was detected. The clinical characteristics of the 5 patients with bifocal MGCTs are summarized in Table 2.

Assuming that bifocal GCTs originate from either the suprasellar or pineal area through metastasis from one site to the other, and that the metastatic potentials of the suprasellar and pineal GCTs are the same, in our study, the expected number of bifocal GCTs of suprasellar origin is

TABLE 1: Comparison of clinical characteristics of 142 suprasellar, bifocal, and pineal GCTs

Variable	Value*		
	Suprasellar (%)	Bifocal (%)	Pineal (%)
sex			
male	14 (36.8)	19 (82.6)	78 (96.3)
female	24 (63.2)	4 (17.4)	3 (3.7)
mean age at diagnosis (yrs)	13.7 ± 6.7	16.4 ± 5.5	14.3 ± 7.0
clinical diagnosis			
germinoma	28 (73.7)	18 (78.3)	49 (60.5)
MGCT	9 (23.7)	5 (21.7)	17 (21.0)
immature teratoma	1 (2.6)	0	9 (11.1)
mature teratoma	0	0	2 (2.5)
yolk sac tumor	0	0	2 (2.5)
choriocarcinoma	0	0	2 (2.5)
seeding			
total (gross + cytology)	5 (13.2)	11 (47.8)	9 (11.1)
gross ventricular seeding	4 (10.5)	10 (43.5)	7 (8.6)
gross spinal seeding	0	1 (4.3)	1 (1.2)
positive CSF cytology	1 (2.6)	0	1 (1.2)
total	38	23	81

* Values are the number of patients (%) except for age, which is presented as the mean ± SD.

TABLE 2: Clinical features of 5 patients with bifocal MGCTs*

Case No.	Age (yrs), Sex	Serum AFP (ng/ml)	CSF AFP (ng/ml)	Serum β-HCG (IU/ml)	CSF β-HCG (IU/ml)	Seeding	Surgery	Pathological Diagnosis
1	9, M	399	74	8	15	no	endoscopic Bx	mature teratoma
2	16, M	4	1	1092	5670	no	endoscopic Bx	germinoma
3	16, M	510	216	8	139	gross	stereotactic Bx	germinoma
4	18, M	<1	<1	192	308	no	endoscopic Bx	germinoma
5	29, M	580	31	NE	NE	no	none	none

* Bx = biopsy; NE = not evaluated.

7 (23 [the number of patients with bifocal GCTs] × 38 [the number of patients with suprasellar GCTs]/119 [the sum of the number of patients with either suprasellar or pineal GCTs]). Likewise, the expected number of bifocal GCTs of pineal origin can be calculated as 16 (23 × 81/119). If we apply the male proportion of suprasellar and pineal GCTs (0.37 and 0.96) to these hypothetical values, the expected number of male patients with bifocal GCT is 18 (7 × 0.37 + 16 × 0.96), and the expected number of female patients is 5 (7 × 0.63 + 16 × 0.04). These figures are similar to the observed numbers (19 male and 4 female patients with bifocal GCTs). No significant difference was determined between the observed and expected numbers based on our assumptions (p = 1.000, Fisher exact test).

In the 23 patients with bifocal GCTs, the pineal lesions were larger than the suprasellar lesions in 19 patients, and the reverse was true in 4 patients. The mean size of the pineal lesions was 298 ± 279 mm^2, and the mean size of the suprasellar lesions was 125 ± 158 mm^2 (p = 0.009, paired t-test). If we assume that the site of a larger tumor is more likely to be the tumor's site of origin and that the metastatic potentials of suprasellar and pineal GCTs are the same, then the expected ratio of a larger pineal tumor to a larger suprasellar tumor in bifocal GCTs is the same as the ratio of pineal to suprasellar tumors in our cohort (16:7 and 81:38). The observed numbers (19 pineal and 4 suprasellar larger tumors) are not significantly different from the expected numbers (16 pineal and 7 suprasellar larger tumors) (p = 0.491, Fisher exact test).

A Case of Documented Suprasellar GCT That Progressed to Bifocal GCTs

Only one patient had undergone prior brain MRI before the diagnosis of bifocal GCTs. This 29-year-old man presented with blurred vision. The MRI study obtained at that time was interpreted showing normal findings, but a retrospective review showed that the pituitary stalk was thickened to 4 mm (Fig. 2). Seven months later, the patient developed severe headaches. A brain MRI study indicated a large, well-enhancing mass in the suprasellar area and a smaller mass in the pineal region. The patient's serum AFP level was elevated to 580 ng/ml (reference value < 20 ng/ml). The patient was diagnosed with an MGCT without surgical biopsy.

Seeding and Tumor Location

Ventricular seeding of the primary tumor at the time of diagnosis was observed on brain MRI in 25 patients (13.8%). Intracranial extraventricular seeding was detected in 1 patient (0.6%). Spinal MRI studies were obtained at the time of diagnosis in 160 patients, and 2 patients (1.3%) exhibited seeding in the spinal compartment. Cerebrospinal fluid cytology was obtained at the time of diagnosis in 133 patients: 91 patients from spinal CSF via lumbar tapping and 42 patients from ventricular CSF. Two patients had a positive cytology from spinal CSF and 12 patients from ventricular CSF. Only positive cytology from spinal CSF was regarded as meaningful. Therefore, overall tumor seeding was observed in 29 patients (16.0%).

In 23 patients with bifocal GCTs, 11 (47.8%) displayed tumor seeding at presentation (the presence of gross seeding was detected by MRI in 11 patients), whereas tumor seeding was documented in 18 of 158 patients without bifocal GCTs (11.4%). Tumor seeding was significantly associated with bifocal tumors (p < 0.001, chi-square test).

Treatment and Outcome of Suprasellar, Pineal, and Bifocal Germinomas

The prognoses of intracranial GCTs can be stratified according to pathological subtypes. Because of the relatively low number of NGGCTs, including MGCTs, and their prognostic heterogeneity, we compared only the prognoses of 95 patients with germinomas of suprasellar, pineal, or bifocal origin. Eighty-two patients received chemotherapy before or after radiation therapy. Various chemotherapy regimens were applied to patients including an 8-drugs-in-a-day regimen[16] (6 patients), the Children's Cancer Group 9921 regimen[12] (6 patients), the Children's
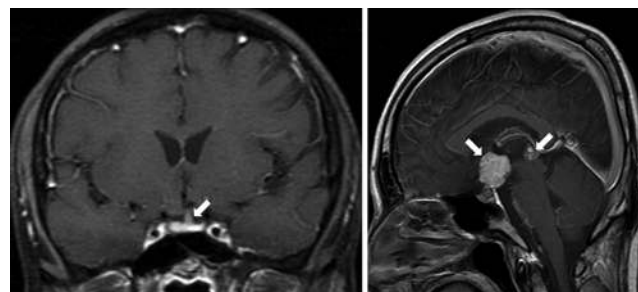

FIG. 2. Magnetic resonance images obtained in a 29-year-old man, showing seeding of suprasellar GCT to the pineal area. **Left:** Coronal image obtained at the initial presentation. A thickened pituitary stalk is observed *(arrow)*. **Right:** Seven months later, a sagittal image revealed a large suprasellar mass and a smaller pineal lesion *(arrows)*.

Bifocal germ cell tumors

Cancer Group 9931 regimen[1] (1 patient), the Korean Society for Pediatric Neuro-Oncology–G051 protocol[17] (29 patients), and a regimen consisting of bleomycin, etoposide, and carboplatin (39 patients). Information regarding the chemotherapy regimen was unavailable for one patient because the patient received chemotherapy at another institution. All patients except one who was lost to follow-up before the initiation of radiation therapy received radiation therapy. The coverage of the radiation therapy was limited to involved fields (17 patients), to the whole ventricle (28 patients), to the whole brain (3 patients), and to the whole craniospinal axis (38 patients). Information regarding the field and dose of radiation therapy was unavailable for 8 patients because they received radiation therapy at other institutions. The mean radiation doses to involved fields, to whole ventricles, to whole brains, and to whole craniospinal axis were 28.7 ± 11.2, 20.5 ± 5.0, 16.0 ± 9.5, and 24.4 ± 5.3 Gy, respectively. The chemotherapy regimens and radiation therapy protocols applied to the patients are summarized in Table 3, according to the site of tumor origin.

The 5-year EFS of patients with suprasellar and pineal germinomas was 91.9% and 88.4%, respectively. The 5-year EFS of patients with bifocal germinomas was 62.8%. The 5-year OS of patients with suprasellar, pineal, and bifocal germinomas was 91.9%, 94.4%, and 70.2%, respectively (Fig. 3). Significant differences were observed in EFS and in OS between patients with bifocal germinomas and those with single-location germinomas (suprasellar or pineal) ($p = 0.002$ and $p = 0.005$, respectively; log-rank test). The survival curves for both EFS and OS of patients with bifocal germinomas were below the survival curves of the patients with tumor seeding at presentation from any location (suprasellar, pineal, or bifocal), but the differences were not significant ($p = 0.111$ and $p = 0.267$, respectively; log-rank test).

The bifocal occurrence of germinomas was the only clinical variable that was significantly associated with shorter EFS and OS in univariate Cox proportional hazards models. Bifocal location was also associated with shorter EFS and OS in multivariate analyses (Table 4).

Discussion

Recently, epidemiological data from a large population-based tumor registry were published on the age-, sex-, and site-specific distributions of intracranial GCTs.[7,8,26] Our patient cohort exhibited similar patterns of distribution, including teenage onset, overall predominance of male sex, and germinoma pathology. One notable finding is that the sex predominance pattern for suprasellar and pineal GCTs was more pronounced than that of data from previous studies. In our study, the male-to-female ratios for suprasellar GCTs and for pineal GCTs were 0.58 and 26.0, respectively. In a study from the SEER-17 (Surveillance, Epidemiology, and End Results) registry in the US, one of the largest studies of GCTs to date, the male-to-female ratios for suprasellar GCTs and for pineal GCTs were 1.73 and 13.0, respectively.[7] Villano et al.[25] reported that the male-to-female ratios for pineal GCTs identified from 3 major tumor registries in the US, including the SEER database,

TABLE 3: Comparison of clinical characteristics of 95 suprasellar, pineal, and bifocal germinomas*

Variable	Value†		
	Suprasellar (%)	Bifocal (%)	Pineal (%)
sex			
male	9 (32.1)	14 (77.8)	47 (95.9)
female	19 (67.9)	4 (22.2)	2 (4.1)
mean age at diagnosis (yrs)	14.5 ± 7.4	16.1 ± 5.2	16.6 ± 6.8
elevated serum β-HCG	4 (14.3)	7 (38.9)	3 (6.1)
seeding			
total (gross + cytology)	4 (14.3)	10 (55.6)	8 (16.3)
gross ventricular seeding	3 (10.7)	9 (50.0)	6 (12.2)
gross spinal seeding	0	1 (5.6)	1 (2.0)
positive CSF cytology	1 (3.6)	0	1 (2.0)
chemotherapy			
BEP	9 (32.1)	5 (27.8)	25 (51.0)
KSPNO-G051	7 (25.0)	7 (38.9)	15 (30.6)
CCG9921	1 (3.6)	1 (5.6)	4 (8.2)
CCG9931	1 (3.6)	0	0
8-in-1	3 (10.7)	1 (5.6)	2 (4.1)
information unavailable	0	0	1 (2.0)
not applied	7 (25.0)	4 (22.2)	2 (4.1)
radiation therapy			
involved field	3 (10.7)	2 (11.1)	12 (24.5)
whole ventricle	9 (32.1)	1 (5.6)	18 (36.7)
whole brain	0	2 (11.1)	1 (2.0)
whole craniospinal axis	14 (50.0)	10 (55.6)	14 (28.6)
information unavailable	2 (7.1)	3 (16.7)	3 (6.1)
not applied	0	0	1 (2.0)
total	28	18	49

* BEP = bleomycin, etoposide, cisplatin; CCG = Children's Cancer Group; KSPNO = Korean Society for Pediatric Neuro-Oncology.
† Values are the number of patients (%) except for age, which is presented as the mean ± SD.

ranged from 14.3 to 21.4. This difference may be attributed to the limitations of studying a single institution's database or to the unique ethnic characteristic of Korean patients.

Since the first description of bifocal GCTs in 1974,[23] this phenomenon has continuously drawn clinical attention. However, most published studies on bifocal GCTs were based on only one patient or a small number of patients.[2–5,9,11,13,22] These small-scale studies could lead to inconclusive interpretations and uncertain conclusions regarding this phenomenon. Furthermore, previous large series on intracranial GCTs, including those based on nationwide cancer registries, paid little attention to bifocal GCTs. Most studies classified suprasellar and pineal GCTs without any explanation of how bifocal GCTs were classified. Previous studies have indicated that bifocal GCTs constitute about 6%–41% of intracranial GCTs.[10,11,22] Bifocal GCTs represented 12.8% of intracranial GCTs in our study. Considering the high proportion of bifocal GCTs, classification of GCTs of suprasellar or
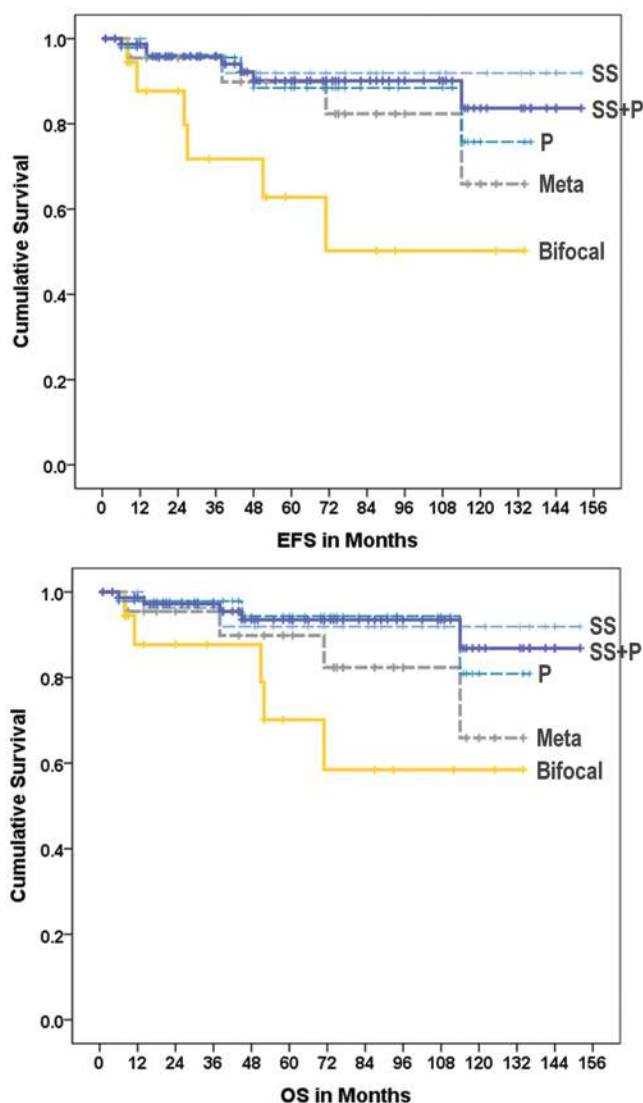
Fig. 3. Kaplan-Meier survival curves demonstrating EFS **(upper)** and OS **(lower)** for patients presenting with suprasellar (SS; n = 28), pineal (P; n = 49), suprasellar plus pineal (SS+P; n = 77), and bifocal (n = 18) germinomas. The survival curves for all patients who had tumor seeding at presentation from suprasellar, pineal, and bifocal germinomas (Meta; n = 22) are depicted simultaneously.

pineal origin without a description of bifocal GCTs may be misleading.

A limitation of our study is that not all patients underwent a tissue diagnosis. The majority of the patients received histological examinations of a small portion of the tumor via a stereotactic or endoscopic biopsy. The accurate diagnosis of GCTs remains a difficult task because of the presence of heterogeneous subtypes and the possibility of misdiagnosis by stereotactic or endoscopic biopsy.[21] Therefore, we performed a comprehensive review of surgical methods, histological diagnoses, and tumor markers to make the most plausible clinical diagnosis in each case. A clinical diagnosis based on these data may be the most reliable diagnosis for intracranial GCTs, because an initial radical resection is not routinely applied to intracranial GCTs.

To date, the majority of reported bifocal GCTs were germinomas. Therefore, some clinicians have suggested that the presence of double lesions in both the suprasellar and pineal areas is almost pathognomonic for germinomas and that biopsy of these lesions may not be mandatory.[11] Recently, a patient with an MGCT in both the suprasellar and pineal regions was reported for the first time.[5] In our study, we observed 5 patients with MGCTs in a total of 23 patients with bifocal lesions. Elevation of AFP and/or β-HCG levels was evident in the patients, making the clinical diagnosis of MGCTs indisputable. This finding challenges the previous notion of bifocal lesions as a specific feature of germinomas and alerts clinicians to the possibility that bifocal lesions may be MGCTs, which exhibit more aggressive biological behavior than do pure germinomas.[14]

The pathogenesis of bifocal GCTs has been debated, but no definite conclusion has been reached.[13] Many clinicians believed that bifocal GCTs were synchronous lesions because both locations are the most common sites of origin for GCTs. However, the metastatic spread of GCTs from one site to the other could not be excluded because GCTs readily seed in the ventricles. Lafay-Cousin et al.[11] suggested that bifocal germinomas are not a metastatic disease based on a positive outcome after limited-field radiation therapy for 6 patients. However, their study included only isolated bifocal germinomas, excluding patients with additional metastatic lesions. Germinomas with a single intraventricular metastasis may exhibit a good prognosis, only if the entire ventricle is included in the radiation field.

In our study, the male-to-female ratio for bifocal GCTs was 19:4. This value is between the male-to-female ratios obtained for suprasellar and pineal GCTs. If we assume that both suprasellar and pineal GCTs exhibit the same metastatic potential, then the observed male-to-female ratio of bifocal GCTs is similar to the expected figure based on the different incidences and sex predilections associated with suprasellar and pineal GCTs. The tumor size dominance of bifocal GCTs also supports this conjecture. If we suppose that the larger tumor is likely to be the origin of metastatic spread to the other site and that both sites exhibit the same metastatic potential, then the observed ratio for size dominance was similar to the expected ratio.

The most surprising finding in our study was that bifocal GCTs were significantly associated with multifocal, disseminated disease. Nearly half of the patients with bifocal lesions also presented with other instances of gross seeding or positive CSF cytology. This finding indicated that the bifocal manifestation of GCTs may be a feature of metastatic disease, not of synchronous tumor appearance. This finding is consistent with a previous report that, under direct endoscopic inspection, the seeding of germinomas to the third ventricular floor may be more frequent than expected.[19] The reason for the frequent occurrence of early metastasis occurs in the suprasellar or pineal region has not been elucidated. The infundibular recess and floor of the third ventricle are frequent sites of the metastatic spread of other intraventricular tumors, such as medulloblastomas.[18] The suprasellar and pineal

TABLE 4: Relative risks for shorter EFS and OS estimated with Cox proportional hazards models in 95 patients with suprasellar, pineal, and bifocal germinomas*

Clinical Factor	Univariate Analysis			Multivariate Analysis		
	p Value	RR	95% CI	p Value	RR	95% CI
EFS						
sex (male)†	0.642	1.359	0.373–4.952	0.806	0.833	0.193–3.592
age at diagnosis†	0.167	1.048	0.981–1.120	0.319	1.044	0.959–1.136
bifocal location	0.006	4.675	1.565–13.96	0.010	4.325	1.426–13.11
elevated serum β-HCG	0.448	1.679	0.441–6.397	NA	NA	NA
seeding at presentation‡	0.746	1.215	0.371–3.957	NA	NA	NA
RT to only involved fields	0.544	1.459	0.430–4.948	NA	NA	NA
OS						
sex (male)†	0.947	0.955	0.246–3.705	0.351	0.466	0.093–2.320
age at diagnosis†	0.138	1.056	0.983–1.135	0.137	1.072	0.978–1.175
bifocal location	0.011	5.025	1.449–17.43	0.013	4.942	1.393–17.53
elevated serum β-HCG	0.165	2.800	0.654–11.98	NA	NA	NA
seeding at presentation‡	0.340	1.854	0.522–6.586	NA	NA	NA
RT to only involved fields	0.696	0.727	0.146–3.611	NA	NA	NA

* NA = not applicable; RT = radiation therapy.
† Sex and age at diagnosis were included in the multivariate model as basic clinical variables.
‡ Seeding includes gross ventricular seeding and positive cytology from spinal CSF, excluding bifocal tumors without evidence of seeding.

regions may represent good soil for the seeding of GCTs because they are the most frequent site of origin for intracranial GCTs.

In contrast to a previous report in which a small number of patients with isolated bifocal germinomas had positive treatment outcomes after limited field radiotherapy,[11] in our study, patients with bifocal germinomas had significantly shorter EFS and OS than did patients with germinomas from single sites of origin. Seeding of a tumor at presentation is a poor prognostic factor for germinomas, and it requires more aggressive treatment, such as craniospinal axis irradiation.[20] Treatment toxicity may also be higher for this group of patients than for patients with germinomas in limited areas who usually receive radiotherapy to more limited fields. Reddy et al.[19] also emphasized the importance of the clinical staging of germinomas and demonstrated the visualization of germinoma seeding in the third ventricular floor by direct endoscopic exploration. These researchers considered these multicentric germinomas to be a disseminated disease and recommended craniospinal axis irradiation for the patients. One finding in our study is that the bifocal location of tumors affects the prognosis more strongly than seeding at presentation itself. In fact, seeding at presentation was not a significant prognostic variable. This finding could be attributed to the more aggressive treatment (that is, application of craniospinal axis irradiation) in patients with overt seeding at presentation per se than in patients presenting with bifocal lesions, which was not routinely considered as seeding. Seeding to a strategic location, such as a suprasellar area that governs the body's hormonal control may be more dangerous during long-term follow-up than the usual ventricular seeding because

endocrinopathy caused by the tumor's involvement or treatment may persist for a long time.

In summary, we hypothesize that bifocal GCTs may result from the metastatic spread of suprasellar or pineal GCTs, based on the similarity of the observed male-to-female ratio and tumor size dominance to the values predicted by our hypothetical model. The strong association of bifocal GCTs with tumor dissemination and the publication of a case of an overt metastatic spread from the suprasellar to the pineal region also support our hypothesis. Furthermore, bifocal germinomas showed a poorer prognosis than did germinomas from a single site of origin. The observed treatment outcome was similar to or even less than those of disseminated germinomas at presentation. Although all this evidence is indirect and cannot definitively tell whether bifocal GCTs arise synchronously or through dissemination, it is more likely that bifocal GCTs are a specific variant of disseminated disease with a relatively poor prognosis.

Conclusions

Bifocal GCTs are not restricted to germinomas, as had been previously suggested, but include NGGCTs, such as MGCTs. We hypothesize that bifocal GCTs could result from the metastatic spread of suprasellar or pineal GCTs. The bifocal presentation of germinomas can be a poor prognostic sign and may alert the clinician to the possibility of disseminated disease.

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