











# A pragmatic diagnostic approach to primary intracranial germ cell tumors and their treatment outcomes

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**Background:** Primary intracranial germ cell tumors (ICGCT) are often diagnosed with tumor markers and imaging, which may avoid the need for a biopsy. An intracranial germ cell tumor with mild elevation of markers is seldom stratified as a distinct entity. **Methods:** Fifty-nine patients were stratified into three groups: pure germinoma (PG), secreting germinoma (SG) and non-germinomatous germ cell tumors (NGGCTs). **Results:** At 5 years, progression-free survival and overall survival of the three groups (PG vs SG vs NGGCT) were 91% versus 81% versus 59%, and 100% versus 82% versus 68%, respectively. There was no statistically significant difference in outcome among histologically and clinically diagnosed germinomas. **Conclusion:** A criterion for clinical diagnosis when a biopsy is not feasible is elucidated, and comparable outcomes were demonstrated with histologically diagnosed germinomas.

**Lay abstract:** Intracranial germ cell tumors (ICGCTs) are rare brain tumors, which often require markers in blood or cerebrospinal fluid, imaging and a tissue biopsy to establish a diagnosis. However, when tissue sampling is not possible, tumor markers can sometimes be used to diagnose ICGCTs. The authors propose guidelines for a diagnosis and a novel subtype of ICGCT called secreting germinoma, which is also described. Fifty-nine patients were separated into three groups: pure germinoma (PG), secreting germinoma (SG) and non-germinomatous germ cell tumors (NGGCTs). At 5 years, progression-free survival and overall survival of the three groups (PG vs SG vs NGGCT) were 91% versus 81% versus 59%, and 100% versus 82% versus 68%, respectively. There was no significant difference in outcome among tumors diagnosed with markers in blood or cerebrospinal fluid and those diagnosed with a biopsy. The proposed guidelines for diagnosis need to be evaluated in future studies. SGs may not warrant aggressive treatment protocols as used in NGGCT, and their outcome as a distinct group needs to be explored in future studies.

**Tweetable abstract:** Central nervous system germinomas can often be diagnosed with tumor markers and imaging, and they may not always need a biopsy. A criterion for clinical diagnosis is elucidated in this retro study. Is secreting germinoma a new entity? #germinoma #cnsoncology #btism.

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Germ cell tumors (GCTs) comprise a heterogeneous group of tumors that are theorized to arise from totipotent primordial germ cells. They commonly occur in the gonads, followed by extragonadal sites such as the mediastinum and central nervous system (CNS). The incidence of intracranial germ cell tumors (ICGCTs) varies widely across

continents, ranging from 2 to 4% of pediatric brain tumors in North America to as high as 11 to 15% of brain tumors in children and adolescents in far eastern countries such as Japan and Korea [1–3]. Although two institutional-based Indian studies have reported that ICGCTs comprise 0.43 to 0.54% of all CNS tumors and 3.5% of pediatric brain tumors [4,5], the incidence of ICGCTs in India is difficult to ascertain, as robust population-based data are unavailable. Similar to their extracranial counterparts, ICGCTs are histologically classified as pure germinomatous (PG) and non-germinomatous germ cell tumors (NGGCTs).

The diagnosis of an ICGCT is often clinico-radiological along with serum and cerebrospinal fluid (CSF) tumor markers, such as alpha-fetoprotein ( $\alpha$ FP) and beta-human chorionic gonadotropin ( $\beta$ -HCG) and imaging findings, which may obviate the need for tissue diagnosis [6,7]. Pre-treatment levels of  $\beta$ -HCG and  $\alpha$ FP [8] in serum and CSF have not only been useful in distinguishing PG from NGGCT, but also for predicting the aggressiveness and prognosis of the disease. In PG, tumor markers are usually undetectable or within normal limits.  $\beta$ -HCG may be mildly elevated in the presence of syncytiotrophoblastic giant cells or immature teratoma/teratomas with malignant transformation [9] (Supplementary Table 1). These are often labeled as secreting germinoma (SG) or mixed germ cell tumors [10]. PGs are sensitive to chemotherapy and radiotherapy (RT) and have an excellent prognosis. NGGCTs demonstrate a relatively poor response to chemotherapy and RT, ultimately resulting in inferior local control rates. However, SGs are seldom stratified as a distinct entity, often grouped with NGGCTs [11]; hence, their disease outcomes and prognosis have not been investigated independently.

Various disparities in diagnostic approach, risk stratification and management protocols of ICGCTs have been observed globally in the literature. This retrospective study conducted on ICGCT patients treated in our tertiary care hospital in South India aims to evaluate the clinical characteristics, impact of histological diagnosis, analyze the outcome of SG as a discrete group and propose a diagnostic stratification based on tumor markers.

## Material & methods

### General considerations

Data of 59 patients diagnosed to have primary ICGCT and treated at the authors' institution from January 2006 to March 2018 were retrospectively collected after obtaining institutional review board approval (IRB Min No. 13013 [Retro]) and a waiver for informed consent. Data were collected from electronic medical records, including imaging and laboratory reports. Clinical information such as age, sex, tumor location, diagnosis, tumor marker levels in blood and CSF, treatment and follow-up data were retrieved.

### Diagnosis & staging

A diagnosis of ICGCT was made based on clinico-radiological, serum and/or CSF tumor marker levels and histological findings whenever available. Histology was reported according to the WHO classification, 2016 [12]. Immunohistochemistry markers such as placental-like alkaline phosphatase (PLAP),  $\alpha$ FP, cytokeratin, octamer-binding transcription factor (OCT 3/4), glypican 3 and  $\beta$ -HCG were performed as required to confirm the diagnosis. If the serum and/or CSF tumor markers ( $\alpha$ FP and  $\beta$ -HCG) were significantly elevated, substantiated by radiological features and/or histology suggestive of NGGCT subtype, a diagnosis of NGGCT was made. If the biopsy was either inconclusive or deferred, response to focal radiation therapy after 2 weeks of therapy was used to establish the diagnosis, especially if the markers were normal [13,14]. Staging investigations were done as listed in Table 1.

### Stratification

Patients were stratified into three groups per the authors' proposed diagnostic criteria for the final analysis (Group A: PG; Group B: SG; Group C: NGGCTs; Table 1). The biochemical levels were pragmatically incorporated from various published studies [15,16].

### Treatment

The treatment sequence and protocols (surgery, chemotherapy and RT) of ICGCTs have varied over the past two decades based on evolving evidence. The trends of the treatment protocol in this group of patients mirrored the timeline of evidence in the published literature. The overall diagnostic and treatment protocol is described in Figure 1. All patients who presented with features of diabetes insipidus were evaluated by an endocrinologist preceding any definitive intervention.

Table 1. Proposed diagnostic criteria.

Criteria	Group A Pure germinoma (PG) (All the parameters and histologically proven germinoma, when available)	Group B Secreting germ cell tumors (SGCTs) (Any parameter, not satisfying criteria for groups A and C)	Group C Non-germinomatous germ cell tumors (NGGCTs) (Any parameter and/or histologically proven NGGCT)
Serum $\beta$ -HCG (mIU/ml)	$\leq 20$	21–100	$> 100$
Serum $\alpha$ FP (IU/ml)	$\leq 5$	6–25	$> 25$
CSF $\beta$ -HCG (mIU/ml)	$\leq 20$	21–100	$> 100$
CSF $\alpha$ FP (IU/ml)	$\leq 5$	6–25	$> 25$
Histopathology	+ (preferred)	+/-	+/-
Additional tests for staging			
MRI brain and spine with contrast			
CSF cytology			
Metastatic workup (imaging of thorax and abdomen)			
CSF: Cerebrospinal fluid.			

Patients aged  $\leq 15$  years were treated according to the pediatric protocol wherein they received two cycles of carboplatin and etoposide alternating with two cycles of ifosfamide and etoposide (CarboPIE), per the SIOP GCT 96/SFOP 1999 protocol [16,17]. Patients aged  $> 15$  years were treated according to the adult protocol and received four cycles of chemotherapy with etoposide and cisplatin (EP) with or without bleomycin (BEP). Six patients (10%) did not receive or defaulted chemotherapy. All patients underwent serum tumor marker testing and imaging after chemotherapy to assess their response. Chemotherapy was preferred as the initial treatment in patients who had good performance status and did not have severe dyselectrolytemia secondary to diabetes insipidus.

RT was delivered at 1.5–1.8 Gy per fraction in the study population. Emergency RT was administered to 1 patient with symptomatic hydrocephalus not amenable to surgical intervention. Patients diagnosed with non-metastatic PG received whole-ventricular radiation (24–30 Gy equivalent) followed by focal boost (up to 40–50 Gy equivalent). Patients with germinomas with craniospinal dissemination were treated with craniospinal irradiation (30 Gy equivalent) followed by focal boost (up to 45–50 Gy equivalent) to the primary lesion in the brain and metastatic deposits along the craniospinal axis. All patients diagnosed with NGGCTs received craniospinal irradiation (30–36 Gy equivalent) followed by focal boost (up to 54 Gy equivalent) to the primary lesion in the brain and metastatic deposits (up to 45–50 Gy equivalent) along the craniospinal axis.

### Follow-up

The patients were followed up with serum tumor markers and MRI at the first follow-up (3 months from completion of RT/chemotherapy), and then yearly biochemical and imaging surveillance was performed. An endocrinology assessment was also performed at follow-up. Patients with less than 24 months of follow-up or not contactable at the time of the study were considered lost to follow-up and were censored in the survival analysis. Patients who developed disease progression/recurrence were stratified into local recurrence (at the primary site), locoregional recurrence (intracranial), spinal metastases and distant metastases. Interventions performed at recurrence and overall survival were recorded and reported.

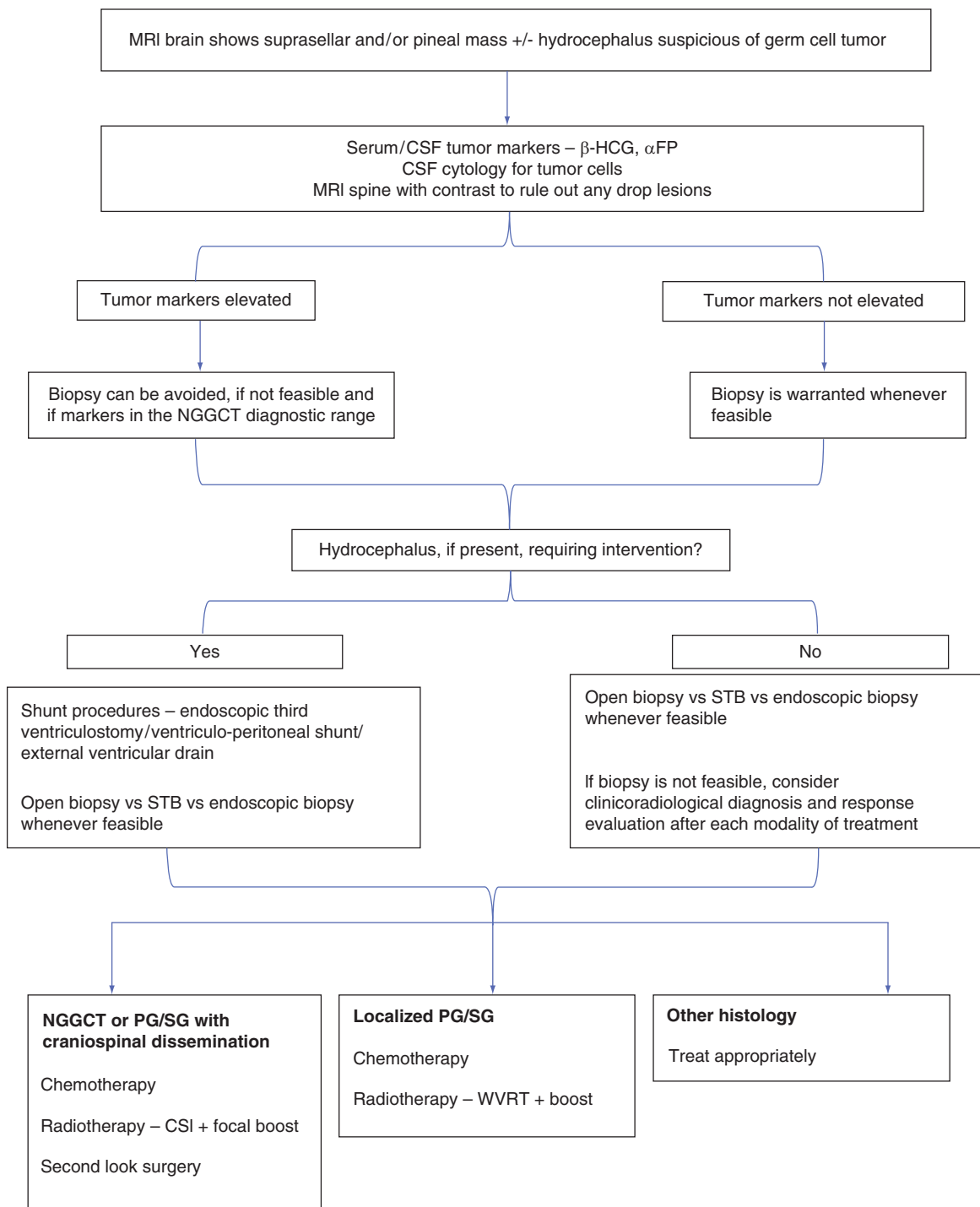
### Statistical analysis

Descriptive data are presented as mean or median values with ranges or absolute numbers with percentages and proportions, as appropriate. Kaplan–Meier methods were used to calculate the progression-free survival (PFS) and overall survival (OS) rates. Univariate analysis of prognostic variables was performed using a log-rank test, and Cox proportional hazards regression models were used to assess the predictors of PFS and OS on multivariate analysis. A two-sided p-value of less than 0.05 with 95% CI was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics® (version 25, NY, USA).

## Results

### Patient characteristics

The 59 patients included in the study accounted for 2% of all primary malignant brain tumors and 0.56% of all primary brain tumors diagnosed in the same period at the authors' institution. This was comprised of 41



**Figure 1. Algorithm for diagnosis and treatment of intracranial germ cell tumors.**

CSF: Cerebrospinal fluid; CSI: Craniospinal radiotherapy; NGGCT: Non-germinomatous germ cell tumor; PG: Pure germinoma; SG: Secreting germinoma; STB: Stereotactic biopsy; WVRT: Whole-ventricular radiotherapy.

(69%) male and 18 (31%) female patients, with a median age of 16 years (range: 3–38 years). Headache and vomiting were the most common presentations, followed by visual and neurological symptoms. The most common location of the tumor was in the pineal region in 31 (53%) patients, and these pineal lesions were commonly observed in male patients (Table 2). Twenty-one patients (34%), including all suprasellar ICGCTs, presented with endocrine abnormalities, and diabetes insipidus was the most common endocrine abnormality. Precocious puberty

Table 2. Patient characteristics.

Characteristics	Total n = 59	
	Frequency	%
Age (years)	≤15	49
	>15	51
	Range (in years)	3–38
Sex	Male	69
	Female	31
Endocrine abnormality at presentation	21	35
Hydrocephalus at presentation	43	73
Location of primary tumor	Pineal	53
	Suprasellar	22
	Thalamus/basal ganglia/internal capsule	12
	Bifocal (pineal and suprasellar)	8
	Multifocal	5
Meningeal/ependymal deposit	8	14
Spinal drop metastasis at diagnosis (CSF analysis or MRI spine)	4	6
Final diagnosis	Pure germinomas	45
	Secreting germ cell tumors	25
	NGGCTs	30

CSF: Cerebrospinal fluid; NGGCT: Non-germinomatous germ cell tumor.

was diagnosed in three patients with elevated  $\beta$ -HCG levels at presentation. Three patients with a primary lesion in the pineal region who had diabetes insipidus at presentation but no definitive lesions or tumor deposits in the sellar region on imaging were considered to have occult bifocal tumors.

### Histopathology & staging

Of the 59 patients, the diagnosis was established by histopathological confirmation and biochemical correlation in 25 patients (42%). In 34 patients (58%), the diagnosis was based on the clinico-radiological features and correlation of tumor markers (Table 3). Fifteen patients were stratified into the SG group; of these, three patients had biopsies suggestive of germinoma, but tumor markers were elevated within the range described in Table 1, and 12 patients without histopathological confirmation were stratified into this group based only on tumor markers and radiological features. Out of the five patients with NGGCT who were diagnosed with a biopsy, two were yolk sac tumor, one malignant teratoma, one mixed germ cell tumor with yolk sac and teratoma components and one germinoma with markers were elevated in the NGGCT range, likely a mixed germ cell tumor. The craniospinal axis was evaluated for dissemination with MRI spine in 45 patients (76%), CSF cytology in 43 patients (73%), or both in 36 patients (59%). Five patients (8%) had neither a CSF cytology study or MRI spine imaging.

### Sequencing of treatment

Various treatment sequences were observed wherein 40 (68%) patients underwent surgery (shunt/biopsy/excision) followed by chemotherapy and then RT, six (10%) underwent surgery followed by RT alone (no chemotherapy) and nine (16%) underwent surgery followed by RT and then chemotherapy. Among the patients who did not undergo any surgical intervention, two (3%) patients received radiation therapy followed by chemotherapy, and two (3%) patients received chemotherapy followed by RT.

### Surgical intervention

Hydrocephalus and increased intracranial pressure were found in 43 patients (73%) at presentation, and they required shunt surgery in the form of either endoscopic third ventriculostomy (16 patients), ventriculo-peritoneal (VP) shunt (22 patients), or external ventricular drainage (five patients). Excision surgery or biopsy alone was performed in 12 patients. None of the patients underwent a second-look surgery.

Table 3. Groupwise treatment and outcome details.

Factor		Group A PG (n = 26)	Group B SG (n = 15)	Group C NGGCTs (n = 18)
Diagnosis	HPE	17	3	5
	CR	9	12	13
Chemotherapy	Yes	21	15	17
	No	5	0	1
Sequencing of chemo	Before RT	16	11	12
	After RT	5	4	5
RT portals	WVRT + boost	23	10	9
	CSI + boost	3	4	9
RT dose	≤50.4 Gy	22	10	7
	>50.4 Gy	4	4	11
RT technique	Conventional Co 60	7	2	4
	Conventional LINAC	10	6	5
	Conformal (3DCRT/IMRT)	9	6	9
Survival	2-year PFS	91%	92%	79%
	5-year PFS	91%	81%	59%
	2-year OS	100%	93%	86%
	5-year OS	100%	82%	68%
Recurrence	Number in each group	3	2	5
	Primary location	Pineal – 3	Pineal – 1, bifocal – 1	Pineal – 4, suprasellar – 1
	Recurrence location	1 – EC 1 – L and SP 1 – IC (LMC)	1 – IC 1 – IC and SP	3 – L 1 – EC 1 – IC and SP

3DCRT: 3D conformal radiotherapy; Co 60: Cobalt 60; CR: Clinico-radiological; CSI: Craniospinal irradiation; EC: Extracranial metastases; HPE: Histopathological evidence; IC: Intracranial metastases; IMRT: Intensity Modulated Radiotherapy; L: Local recurrence; LINAC: Linear accelerator; LMC: Leptomeningeal carcinomatosis; NGGCT: Non-germinomatous germ cell tumor; OS: Overall survival; PFS: Progression-free survival; PG: Pure germinoma; RT: Radiotherapy; SG: Secreting germinoma; SP: Spinal; WVRT: Whole-ventricular radiotherapy.

### Chemotherapy

Among the 53 patients who received chemotherapy, the EP regimen was used most often in adults (28 patients, 52%), followed by BEP (three patients, 6%), and CarboPIE was used frequently in children (22 patients, 42%). Febrile neutropenia (n = 18) was the most common adverse effect of chemotherapy, followed by dyselectrolytemia (n = 11), thrombocytopenia (n = 4), peripheral neuropathy (n = 3) and pulmonary toxicity (n = 2). One patient developed abdominal visceral perforation and sepsis and subsequently died (grade 5 toxicity).

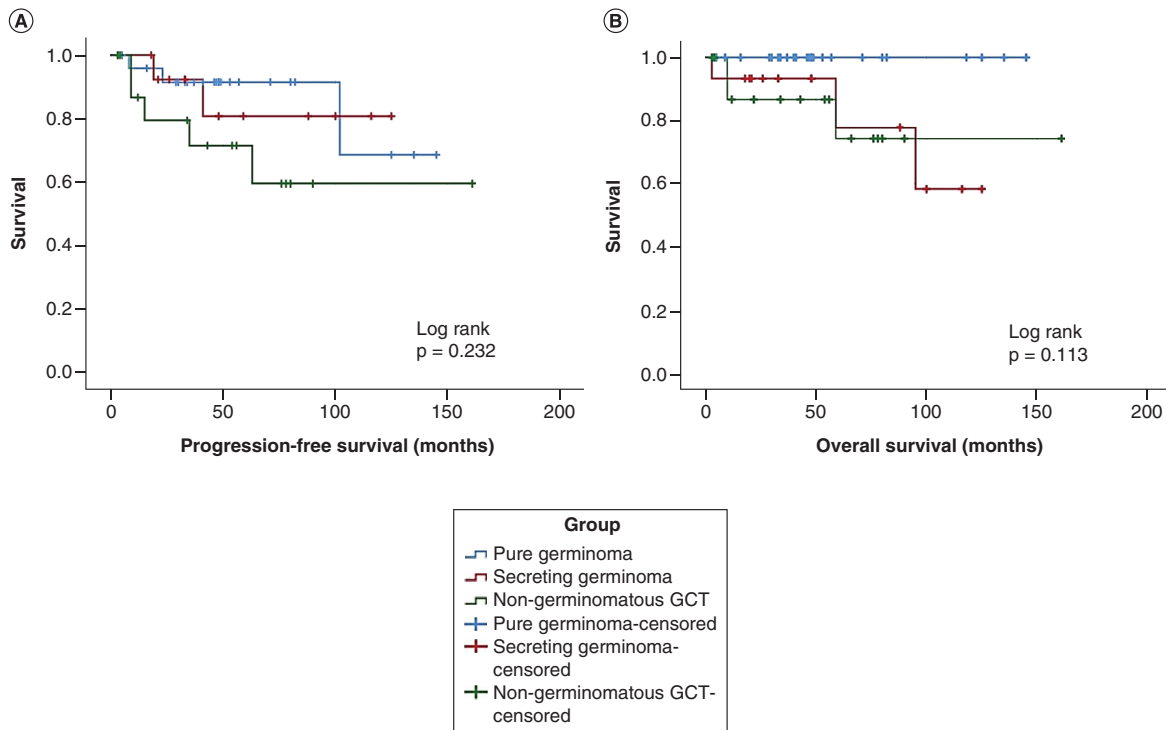
### Radiation therapy

The mean total dose of RT was 50.4 Gy (range: 30.6–55.8 Gy). One patient did not receive RT due to death from a post-chemotherapy complication. Among the remaining 58 patients, whole-ventricular radiation therapy (median dose: 30.6 Gy) followed by focal boost (median: 19.8 Gy) was delivered to 42 patients (72%) and craniospinal irradiation (median dose: 36 Gy) followed by focal boost (median dose: 18 Gy) to 16 patients (26%). Two patients with localized drop metastases detected on MRI received a focal boost dose of nine Gy following craniospinal irradiation. One patient defaulted RT after 30.6 Gy and one patient received RT alone, defaulted chemotherapy and was lost to follow-up.

All patients tolerated RT well, and no grade 3 or 4 acute toxicities were reported. The most common acute toxicity during RT was dermatitis. Neutropenia (more than grade 2) was seen among six patients undergoing craniospinal irradiation. The median overall treatment time of RT was 41 days (mean: 40.3 days; range: 21–70 days). Treatment and outcome details are described in Table 3.

### Survival

The median follow-up period was 48 months (range: 3–161 months). The OS and PFS of all patients are depicted in the Kaplan–Meier curves. Median PFS and OS were not reached in the study population. Eleven patients (18%) were lost to follow-up and were censored at their last date of follow-up on the survival analysis. The PFS of all patients at 2 years and 5 years was 88% and 83%, respectively. The OS of all patients at 2 years and 5 years was



**Figure 2. Kaplan-Meier survival curves of three groups. (A) Progression-free survival. (B) Overall survival.** GCT: Germ cell tumor.

90% and 85%, respectively. The 2-year PFS and OS in the three groups (PG vs SG vs NGGCT) were reported as 91% versus 92% versus 79%, and 100% versus 93% versus 86%, respectively (Figure 2A & B). At 5 years, the estimated PFS and OS of the three groups (PG vs SG vs NGGCT) were 91% versus 81% versus 59% ( $p = 0.232$ ), and 100% versus 82% versus 68% ( $p = 0.113$ ), respectively. Ten patients (17%) were diagnosed to have disease progression at follow-up, and eight patients died at the time of this study. Of the eight patients who died, six patients had disease-related death, one patient died due to post-chemotherapy complications, and one patient died in a road traffic accident.

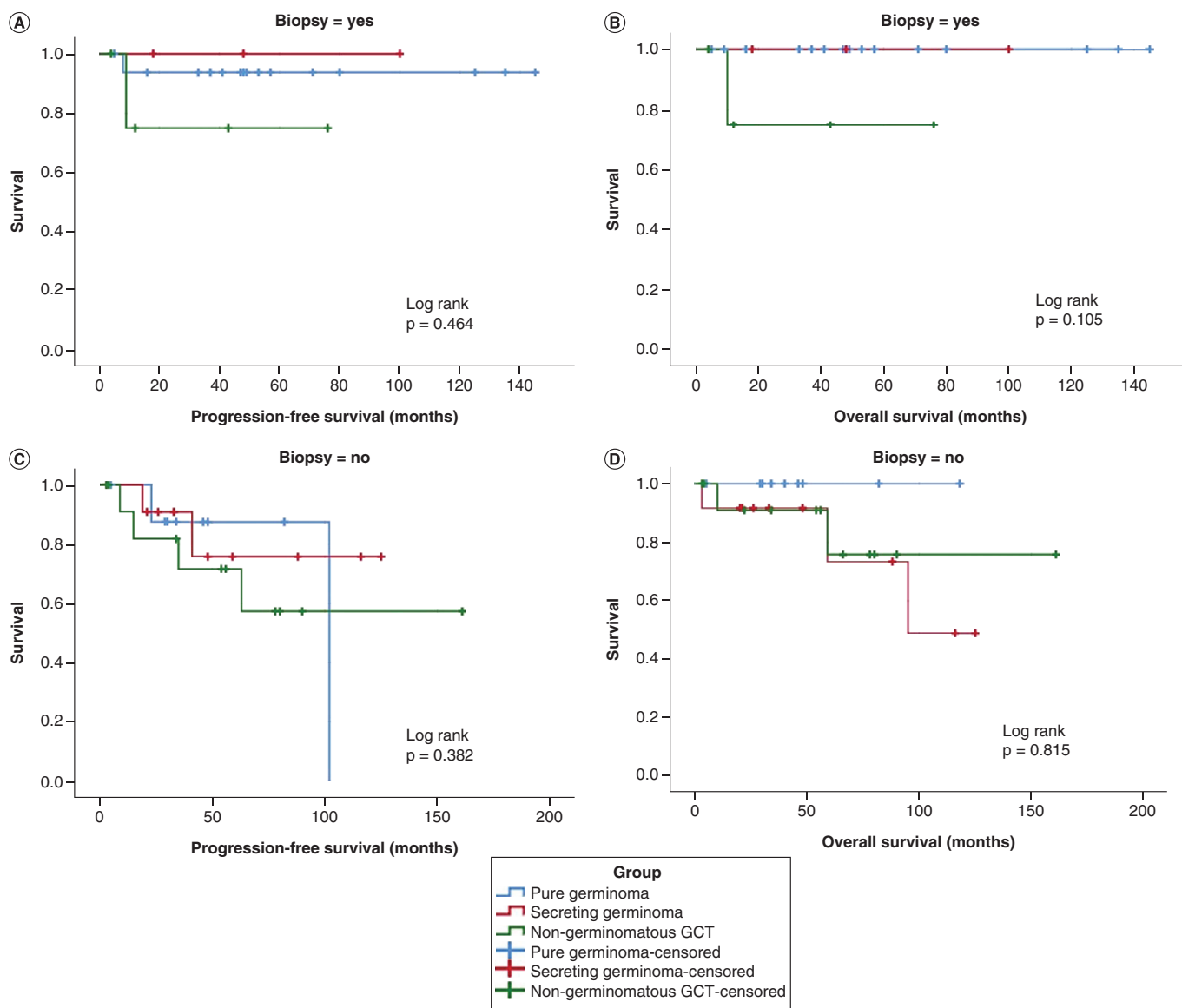
Among all groups, based on age at diagnosis, there was no significant difference in survival among younger patients (age  $\leq 15$  years) as compared with older patients (age  $> 15$  years). Patients with tumors in the pineal region had significantly worse PFS as compared with the non-pineal location of the tumor ( $p = 0.043$ ), although this difference was not observed with OS. The authors observed a trend toward better 5-year PFS (91% vs 77%) and OS (95% vs 74%) in patients with histological verification as opposed to those diagnosed with clinico-radiological features alone; however, these observations were not statistically significant ( $p = 0.140$  and  $0.109$ , respectively). Among the PG subgroup, histological verification did not have an impact on PFS (94% vs 88%;  $p = 0.68$ ) or OS (100% vs 100%) (Figure 3A–D). Outcome of PG and SG together was analyzed against NGGCT, which showed a numerically better 5-year PFS (87% vs 59%;  $p = 0.089$ ) and OS (89% vs 68%;  $p = 0.15$ ) but was statistically insignificant (Figure 4). Patients who received chemotherapy before RT had better OS than those who received chemotherapy after RT, with near statistical significance ( $p = 0.051$ ) but no significant difference in PFS. There was no difference in survival outcomes between the different techniques or doses of radiation (Supplementary Table 2).

### Disease progression & intervention at progression

Disease progression/recurrence was diagnosed in ten patients, and their characteristics are described in Supplementary Table 3. Interestingly, all five patients with NGGCT who had progressed had markedly elevated tumor marker levels, both at presentation and at progression. About a third of patients (nine out of 31) who had an initial tumor location in the pineal gland had disease progression.

All but two patients received second-line chemotherapy at progression; the remaining two patients were advised on best supportive care in view of poor general condition. Furthermore, two patients received reirradiation, and





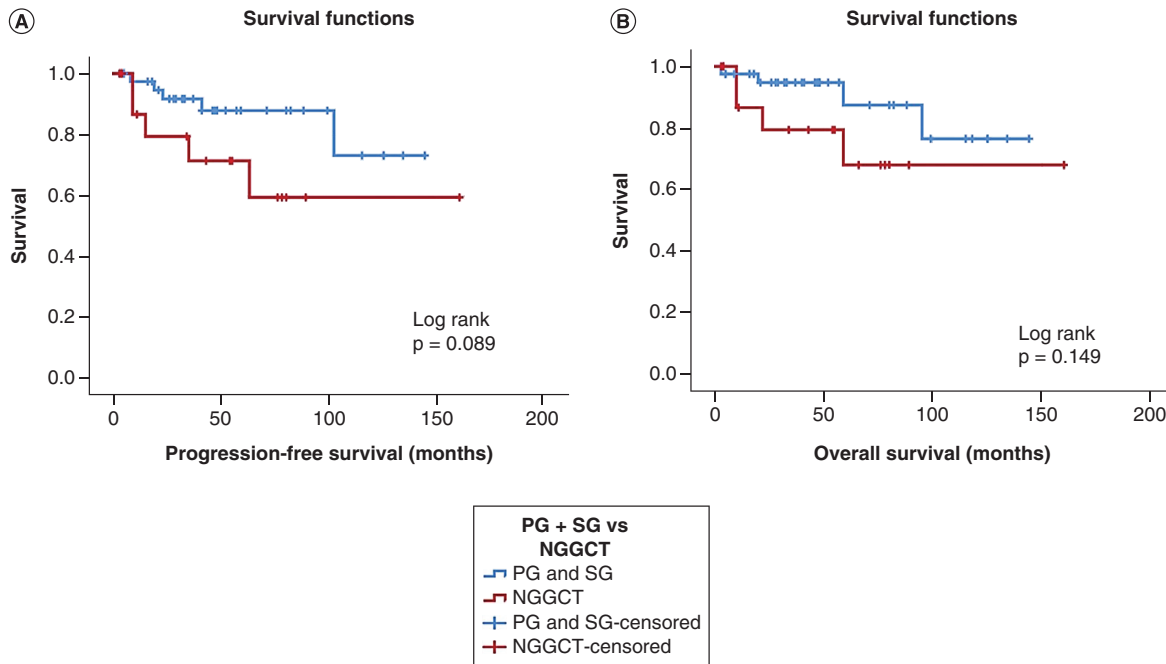
**Figure 3.** Kaplan–Meier curves for progression-free survival and overall survival (OS) of three groups with biopsy (A & B) and without biopsy (C & D), respectively. GCT: Germ cell tumor.

one patient underwent surgical excision of the liver metastases following chemotherapy. A substantial improvement in 2-year OS after disease progression was observed among patients who received local treatment after second-line chemotherapy (76% vs 60%;  $p = 0.176$ ); however, it was not statistically significant. No significant difference in response to salvage therapy was observed among the three groups.

### Discussion

Primary ICGCTs are rare CNS neoplasms commonly encountered in children and young adults. The incidence of ICGCTs reported in this study is similar to other multicentric reports from India [4,5]. Although the incidence is markedly higher in far east Asian countries than in Western countries, various study groups from both these populations have contributed to risk stratification and treatment protocols [18–22]. Established treatment protocols using radiation with or without chemotherapy have demonstrated excellent efficacy, with durable tumor control in 90% of germinomas. In contrast, NGGCTs have proven resistant to a wide array of multimodality treatments with chemotherapy and radiation protocols, resulting in a generally poor prognosis. However, a wide variation exists





**Figure 4.** Kaplan–Meier curves for progression-free survival and overall survival of PG + SG and NGGCT. (A) Progression-free survival; (B) Overall survival. NGGCT: Non-germinomatous germ cell tumor; PG: Pure germinoma; SG: Secreting germinoma.

globally in the diagnostic approach, chemotherapy schedules, RT portals, dose and intervention at progression [20]. Despite being a relatively small retrospective cohort, the authors undertook this study to analyze the clinico-radiological diagnostic criteria and outcomes of various tumor groups.

In this study, ICGCTs were most commonly seen in the pineal location (53%), followed by the suprasellar location (22%), in concordance with the published literature. A recent retrospective study [21] comparing patient characteristics in the North American (Mayo Clinic) and Japanese cohorts (NCC) reported significant differences in the tumor locations; specifically, the frequency of basal ganglia (8.4% vs 0%) and multifocal tumors (14.3% vs 3.8%) was higher in the Japanese database, and the frequency of bifocal location (18.8% vs 5.5%) was higher in the Mayo Clinic group. In this study, the proportion of multifocal tumors was comparable to that of the North American cohort, whereas that of the basal ganglia and bifocal tumors was similar to that in the Japanese cohort. Although the primary tumor site did not have a bearing on the survival of patients in their study, multiple other studies have shown that ICGCTs located in the pineal region fare better than those in non-pineal locations [4,23–26]. Surprisingly, in this study, patients with tumors in non-pineal locations had significantly better PFS ( $p = 0.043$ ) than those with pineal tumors, although no difference was observed in OS. This may be attributed to the frequent occurrence of the poor prognostic NGGCTs in the pineal location in this study's cohort, which reflects as an apparent decline in PFS.

It is essential to consider all available data, including radiological, biochemical and histological information, to establish the diagnosis. The risks of open biopsy were considered to outweigh the potential benefits due to the proximity of critical structures in the path of the expected surgical biopsy trajectory [26]. It is pertinent to histologically differentiate germ cell tumors from other tumors in the pineal region, such as pineocytoma, pinealoblastoma and midline dermoid, with regard to similar radiological features. Historically, operative risks associated with surgery for these lesions have led to the use of alternative diagnostic measures, such as therapeutic trials of irradiation [12,13,27]. In a study by Nakagawa *et al.*, if germinoma was highly suspected, 20 Gy was given with a local irradiation field and if tumor regression was marked, whole-brain or whole-CNS irradiation was subsequently performed. Despite being a historical study, it was important to recognize that there was no significant survival difference noted between the groups diagnosed with biopsy and with the trial of irradiation [12]. Interestingly, three studies [6,10,27] independently analyzed the outcomes of patients who were diagnosed without histopathological confirmation and showed no difference in survival. However, in the current endoscopic era, a drastic reduction in

complication rates has encouraged tissue sampling for an accurate diagnosis, especially in cases where no abnormal tumor marker elevation is detected. With the increasing use of endoscopic biopsies, intraventricular sampling safely yields an accurate diagnosis in over 90% of intraventricular tumors [26]. Additionally, biopsy allows for new avenues, such as genetic profiling, which have prognostic implications [28]. In this study, although there was a trend toward better survival among the patients who had a histopathological diagnosis, these observations were not statistically significant. Even in the subgroup of PG, where histopathological confirmation is considered paramount, there was no survival difference noted between patients diagnosed with or without a biopsy.

In addition to the histological classification by WHO [12] into germinoma and NGGCTs, two risk stratifications, European (SIOP GCT II) and Japanese (Matsutani), have been used widely for prognostication [20]. In the SIOP-CNS-GCT-96 trial [29], diagnosis of NGGCT was established without the need for biopsy confirmation if  $\alpha$ FP was  $>25$  ng/ml and/or  $\beta$ -HCG  $>50$  IU/l in at least one serum/CSF compartment, and it was recognized by the trial's authors that some HCG-secreting germinomas and  $\alpha$ FP-secreting teratomas might consequently have been included. Relatively better 5-year PFS and OS rates of 72% and 82%, respectively, were reported, which could have been considerably influenced by the secreting germ cell tumor population. Among 153 histologically verified ICGCTs in an analysis by Matsutani *et al.* [10], mixed germ cell tumors were categorized into three subgroups according to the tumor components they contained: mixed germinoma and teratoma, mixed tumors mainly consisting of predominant germinoma or teratoma combined with a small portion of pure malignant tumors and mixed tumors mainly consisting of pure malignant elements. Survival outcomes (3-year and 5-year OS) were significantly better in the first subgroup (94.1% and 84.7%, respectively) as compared with moderate outcomes in the second (70% and 52.5%, respectively) and extremely poor outcomes in the third (9.3% and 9.3%, respectively), establishing the ostensible heterogeneity among the group of mixed GCTs.

Secreting or mixed GCTs are rarely defined or stratified in published literature. In a retrospective series from Singapore, SG and mixed GCTs were defined and classified to prognostic groups but subsequently they were grouped with NGGCT for final analysis [11]. However, in this study, the authors incorporated pragmatic thresholds for  $\beta$ -HCG and  $\alpha$ FP levels into the authors' stratification to differentiate SG from PG and NGGCT, as well as to assess differences in outcomes. The authors observed that with similar treatment patterns, the outcome of the SG group was similar to that of the PG group. The authors suggest that a similar therapeutic approach as germinoma is likely to be adequate for SG to achieve comparable outcomes. Use of NGGCT treatment protocols may be overzealous in SG and should be avoided to reduce treatment-related morbidity and improve treatment outcomes.

The survival outcome of this study population was comparable to published outcomes of various study groups (Table 4) [4,6,11,15–17,22–25,29–32]. In this study, administration of chemotherapy prior to RT has been shown to translate into an OS benefit. Local recurrence was the most common pattern of recurrence, followed by intracranial and spinal dissemination, reiterating the importance of local therapy in ICGCTs. The most common intervention after recurrence in this group of patients was second-line chemotherapy (eight out of ten patients) followed by local therapy in three patients (Re-RT in two patients and metastatectomy surgery in one patient). Patients who received local therapy at progression had a significant prolongation of survival. Following recurrence, a study by Murray *et al.* [33] showed that in germinomas, reasonable outcomes can be achieved either with standard-dose chemotherapy with reirradiation or with high-dose chemotherapy with autologous stem cell rescue, but they eventually relapse. NGGCTs had significantly poorer outcomes despite salvage therapy. In contrast, no significant difference in response to salvage therapy was observed among the three groups in this study. This could be due to the relatively small number of patients who relapsed in the study.

## Conclusion

Intracranial GCTs are a rare and heterogeneous group of tumors, with various factors affecting treatment outcomes. This study elucidates criteria for clinico-radiological diagnosis when histopathological verification is not feasible and has demonstrated comparable outcomes with germinomas diagnosed with a biopsy; however, this criterion needs to be prospectively validated. Factors such as germinoma histology, non-pineal location of the tumor, initiation of chemotherapy prior to RT and local therapy at recurrence have conferred better survival in this cohort. As SGs fare better than NGGCTs, they may not warrant aggressive treatment protocols as used in NGGCT, and their outcome as a distinct group needs to be explored in future studies.

Table 4. Survival across different treatment groups.

Study/group	Population	5-year EFS/PFS (%)	5-year OS (%)	Ref.
SFOP 1999/2010	Germinoma	84.2	98.2	[15,17]
SIOP-GCT 96 2013	Germinoma (CSI alone)	97	95	[6]
	Germinoma (focal RT + chemo)	88	96	
SIOP-GCT 96 2017	Localized NGGCT	72	82	[29]
	Metastatic NGGCT	68	75	
COG ACNS0122	NGGCT	84	93	[31]
Spain	All groups	80	NR	[24]
	Germinoma	85.7	NR	
	NGGCT	60	NR	
Australia	Overall	81	85	[26]
	Germinoma	93	100	
	MGT/NGGCT	50	50	
Turkey	Overall	57.2	72	[32]
	Germinoma and immature teratoma	65	80	
	MGT/NGGCT	39.3	53.9	
Singapore	All groups	72.7	79.6	[11]
	Pure germinoma alone	85.2	89.2	
	SG/NGGCT	61.4	70.6	
	SG alone	90	100	
India	All groups	67.7	77.4	[4]
	Germinoma	84.8	84.8	
	NGGCT	40	56	
Canada	Germinoma (AYA alone)	86	93	[30]
	NGGCT (AYA alone)	70.8	85.9	
Japan	GCT with histological diagnosis (all groups)	78	93	[6]
	GCT without histological diagnosis (all groups)	79	94	
China	Overall (germinoma/MGT)	91.9	94.5	[25]
	GCT without biopsy	90.9	94.1	
	GCT with biopsy	95.3	95.7	
This study	All groups	83	85	
	Germinoma	91	100	
	Secreting GCT	81	82	
	NGGCT	59	68	

AYA: Adolescents and young adults; COG: Children's Oncology Group; CSI: Craniospinal irradiation; EFS: Event-free survival; GCT: Germ cell tumor; MGT: Mixed germ cell tumor; NGGCT: Non-germinomatous germ cell tumor; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; RT: Radiotherapy; SFOP: French Society of Paediatric Oncology; SG: Secreting germinoma; SIOP: International Society of Paediatric Oncology.

### Future perspective

Current research on germinomas has transitioned from achieving superior survival outcomes to the improvement of quality of life by reducing treatment-related toxicity, endocrine therapy and psychosocial rehabilitation. However, in NGGCTs, survival rates have plateaued, suggesting that conventional therapy has achieved its full potential. Unfortunately, novel therapeutic agents such as multiple tyrosine kinase inhibitors have been investigated in relapsed GCTs, which have yielded disappointing results, affirming the heterogeneity among these tumors [34].

### Limitations

This study, being a relatively small, single-institution, retrospective design, has several inherent limitations such as variations in patient selection, diagnostic methods and treatment schema. The diagnosis, treatment, and sequence of interventions have varied over the past two decades based on evolving evidence. These factors may have affected the outcome, making it difficult to interpret the results and draw broader conclusions that may be extrapolated to a larger group of patients.

### Summary points

- A biopsy is essential in the diagnosis of intracranial germ cell tumors, especially when the tumor markers are not elevated.
- However, in a scenario where biopsy is not feasible but radiological features are convincing, germ cell tumors can be diagnosed and stratified reasonably based on tumor marker levels and a criterion that has been proposed.
- Germinomas diagnosed without a biopsy have outcomes comparable with those diagnosed with a biopsy.
- Based on tumor marker levels, germ cell tumors with mild elevation of tumor marker levels can be classified as secreting germinomas.
- Despite elevated markers, secreting germinomas have distinct behavior and better outcome compared with non-germinomatous germ cell tumors.
- Hence, aggressive treatment protocols with non-germinomatous germ cell tumors may not be warranted for secreting germinomas.
- Factors such as germinoma histology, non-pineal location of the tumor, initiation of chemotherapy prior to RT and local therapy at recurrence conferred better survival in this cohort.

### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/suppl/10.2217/cns-2021-0012](http://www.futuremedicine.com/doi/suppl/10.2217/cns-2021-0012)

### Author contributions

J Venkatasai and R Balakrishnan are co-first authors contributing equally to the work. The study concepts and design were given by R Balakrishnan, S Backinathan, B Rajkrishna and P Sebastain, who also contributed in literature research. The data collection, data interpretation and data analysis were done by J Venkatasai and verified by R Balakrishnan, S Backinathan, P Sebastain and RR John. Manuscript writing and creation of tables and figures were done by J Venkatasai, R Balakrishnan, B Rajkrishna, S Backinathan and P Sebastain. Valuable intellectual input from across specialties was obtained from HA Vanjare, RR John, LG Mathew, K Prabhu and B Nair, which were incorporated into the final manuscript.

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### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval (IRB Min No. 13013 [Retro]) dated 24.06.2020 with a waiver of informed consent.

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