Takami and colleagues\(^1\) report on the clinical, histopathological, and molecular features of central nervous system (CNS) germ cell tumors (GCTs). They conducted a retrospective series of 190 cases classified as primary GCTs, based on a central review from the Intracranial Germ Cell Tumor (iGCT) Genome Analysis Consortium. Their goal was to address outstanding issues in the classification and clinical management of these tumors. The authors need to be commended on CNS GCT tissue collection and implementation of the iGCT Genome Analysis Consortium. However, the retrospective nature and the lack of homogeneously collected clinical data such as staging results and tumor marker and heterogeneous treatments limit some of their conclusions. In Europe and North America (the West), CNS GCTs account for 3% of all brain tumors, and their peak incidence is in the second decade of life, with a marked predilection for males. In contrast, in Japan and Far East Asia, these tumors make up 9–15% of all tumors, making them the second most commonly diagnosed brain tumor after gliomas. This marked geographical variation in incidence of GCTs and the different diagnostic approaches adopted in Japan ( spearheaded by neurosurgeons and upfront tumor resection) present opportunities for the West to gain greater insights into this “mixed bag” group of tumors. However, it is possible or even likely that GCTs from patients from the Far East are biologically distinct from tumors from their Western counterparts.

In the West, the diagnosis of intracranial germinomas is based on characteristic tumor location using imaging and tumor marker patterns. Germinomas do not secrete alpha-fetoprotein (AFP) and may secrete low levels of beta human chorionic gonadotropin (β-hCG) (<50–100 IU/L), detected in the serum and/or CSF. The exact β-hCG threshold, however, remains to be determined.\(^2\) Biopsy is required in marker-negative tumors.

Nongerminomatous germ cell tumors (NGGCTs) are a highly heterogeneous group of tumors, comprising yolk sac tumors (YSTs), embryonal carcinoma (EC), choriocarcinoma (ChC), immature teratoma with or without malignant components, and mixed malignant tumors in a variety of combinations, frequently with components of mature teratoma or germinoma. Classically, YSTs secrete only AFP, while ChC secretes only β-hCG, and EC may secrete both β-hCG and AFP.\(^3\) Based on these characteristics, in North America and Europe, AFP elevations >10–25 ng/mL and/or β-hCG elevations >50–100 IU/L in the serum and/or CSF are sufficient for a diagnosis of NGGCT, and no biopsy is required before starting treatment.\(^3\) Resection is reserved for residual tumors after completion of chemotherapy and prior to the start of radiotherapy, where the presence of residual tumor is associated with an inferior prognosis.\(^4\)

Takami and colleagues’ report highlights several important clinical and biological aspects:

Firstly, overall survival (OS) in germinoma with or without metastasis is excellent when treated with a combined chemoradiotherapy approach (Table 1). Of note, 8 patients with histopathologically confirmed germinoma demonstrated elevated tumor markers, above 25 ng/mL for AFP (\(n = 4\)) and/or above 50 IU/L for β-hCG (\(n = 5\)), respectively. This dismal progression-free survival (PFS) suggests that those patients were treated according to their histopathological diagnosis, and the authors underscore that tumor markers indeed need to be integrated into diagnosis and treatment. Sadly, this study was unable to identify a β-hCG threshold in serum or CSF to better distinguish germinoma with a syncytiotrophoblastic component from β-hCG producing NGGCTs, due to the lack of consistently collected serum/CSF marker at diagnosis. Thirty-four of 35 bifocal tumors were biopsy-proven germinomas and all
but 2 were tumor marker negative. The one exception was a bifocal yolk sac tumor with exceedingly high AFP levels. Hence, this patient’s treatment—even in the presence of a biopsy-proven germinoma—would have prompted appropriate NGGCT treatment. With this important finding in mind, the question now arises whether the risk of a biopsy in bifocal tumors is still appropriate in the presence of classical radiological and clinical features and in the absence of a biological prospective trial.

Secondly, compared with pure germinomas, NGGCTs have an inferior prognosis, as they are less radiosensitive (Table 2). One of the most notable findings was the presence of marker-positive germinomas (elevated AFP and/or moderately to severely elevated β-hCG) in 18.2% (8/44) of cases and 6.1% (2/33) of marker-negative NGGCT cases, highlighting that “not all that glitters is gold.” This issue exposes the challenges of designing and running clinical trials in such rare and heterogeneous tumors, as a small sample size involves and the inclusion of differing proportions of patients with biologically distinct tumors is also plausible.

Thirdly, in the absence of prospective trials and consistent with the recommendation from the Delphi consensus,2 if tissue is collected (upfront or after completion of chemotherapy) it is essential to homogeneously collect clinical data, to evaluate correlation between biology and outcome.

Finally, it is of note that novel drugs have not influenced treatment or the survival rates for GCT patients. For NGGCT patients, survival rates have plateaued, indicating that conventional therapy has achieved its full potential. Germinoma survivors still face lifelong treatment-related cognitive and endocrine side effects, due to the inability to dismiss radiation from treatment regimens. A previous report from the same group has revealed that germinomas and NGGCTs (including testicular GCTs) showed similar mutational profiles, suggesting a common molecular pathogenesis.6 To date, however, studies using imatinib or dasatinib as novel therapeutic agents in progressive or relapsed GCT patients with inhibition of the Kit/Ras/Raf/mitogen-activated protein kinase (MAPK) and/or the Akt1/phosphatidylinositol-3 kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway have yielded disappointing results.8 Using array-comparative genomic hybridization and either whole-exome or targeted sequencing, Takami and colleagues1 undertook molecular analyses on 123 and 74 of the 190 cases (74 were analyzed for both, respectively). These relatively limited

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### Table 1  Survival of CNS germinoma according to different treatment groups

| Treatment Group                        | 5-y EFS  | 5-y OS  |
|----------------------------------------|----------|---------|
| SIOP-GCT-96 results (n = 235)          | 97%±4% / 88%±4% | 95%±4% / 96%±4% |
| SFOP experience (n = 60)               | 84%      | 98%     |
| Japanese GCT study group (n = 228)     | 87%      | 98%     |
| CHLA experience (n = 19)               | 89%      | 100%    |
| Sick Kids experience (n = 24)          | 96%**    | 100%    |
| iGCT Consortium (n = 96)               | 87%      | 98.6%   |

*3-year event-free survival (EFS) and overall survival (OS).
**5-year progression free survival (PFS).
* For CSI alone.
5 For focal radiotherapy and chemotherapy.
CHLA, Children’s Hospital Los Angeles; NR, Not Reported; SFOP, French Society of Pediatric Oncology; SIOP, International Society of Pediatric Oncology.
^ Refers to a cohort of 123 patients, as described by the authors.

### Table 2  Survival and relapse pattern of CNS NGGCT according to different treatment groups

| Treatment Group                        | 5-y EFS  | 5-y OS  | Type of Relapse |
|----------------------------------------|----------|---------|----------------|
|                                      | Local    | Distant | Combined | Marker Alone |
| COG ACNS0122 (n = 102)                | 84 ± 4%  | 93 ± 3% | 9        | 4   | 0   | 2   |
| SIOP-GCT-96 (n = 116 localized (n = 33 metastatic) | 72 ± 4% / [68 ± 9%] | 82 ± 4% / [75 ± 8%] | 14[5] | 7[1] | 6[3] | 0   |
| iGCT Consortium (n = 40)               | 79.5 ± 20.6% | 76.1 ± 24.0% | NA       | NA | NA | NA |
| ACNS1123 (n = 66)                     | 87.8 ± 4.04%* | 92.4 ± 3.3%* | 0        | 6   | 2   | 0   |

EFS = event-free survival; SIOP = International Society of Pediatric Oncology.
*3-year progression free survival (PFS) and overall survival (OS).
**5-year PFS.
molecular analyses confirmed numerous chromosomal aberrations, some which were found to be independent markers of worse prognosis (2q, 8q gain, 5q, 9p/q, 13q, 15q loss). Additionally, a striking observation was that MAPK pathway mutations were seen in approximately half of males but only in 14% of females. Also, PI3K/mTOR pathway mutations were enriched in GCTs located in the basal ganglia. Together, these observations serve to demonstrate a much more complex underlying biology for these tumors. In contrast, in Western countries the genomic landscape of CNS GCT remains to be elucidated due to reliance on diagnostic tumor markers. The report by Takami and colleagues serves as a prompt for the East and West to consider novel strategies such as liquid biopsy and inclusion of microRNA analyses in lieu of tumor tissue on clinical trials to better inform patient stratification and un-

Ultimately, the application of molecular technology could drive improved outcomes for GCT patients through the development of tailored, patient-specific treatments. Without this, we are unlikely to make major advancements in treatment and will continue to conduct trials addressing only modifications in radiotherapy dose and/or volumes combined with conventional chemotherapy. The report by Takami and colleagues serves as a prompt for the East and West to consider novel strategies such as liquid biopsy and inclusion of microRNA analyses in lieu of tumor tissue on clinical trials to better inform patient stratification and unravel the biology of these heterogeneous tumors.

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