Comparison on epidemiology, tumor location, histology, and prognosis of intracranial germ cell tumors between Mayo Clinic and Japanese consortium cohorts

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OBJECTIVE Central nervous system (CNS) germ cell tumors (GCTs) are rare malignant neoplasms that arise predominantly in adolescents and young adults. CNS GCTs demonstrate characteristic trends in national associations, with implications for both tumor incidence and genetics. Although the incidence of CNS GCTs is markedly higher in East Asia than Western countries, direct comparative analyses between these CNS GCT populations are limited.

METHODS In Japan, to facilitate the genomic analyses of CNS GCTs, the Intracranial Germ Cell Tumor Genome Analysis Consortium was established in 2011, and more than 200 cases of GCTs are available for both tumor tissue and clinical data, which is organized by the National Cancer Center (NCC) Japan. At the Mayo Clinic, there have been 98 cases of intracranial GCTs treated by the Department of Neurologic Surgery since 1988. In this paper, the authors compared the epidemiology, clinical presentation including location and histology, and prognosis between cases treated in the US and Japan.

RESULTS There was no significant difference in age and sex distributions between the databases. However, there was a significant difference in the tumor locations; specifically, the frequency of basal ganglia was higher in the NCC database compared with the Mayo Clinic (8.4% vs 0%, $p = 0.008$), and bifocal location (neurohypophysis and pineal gland) was higher at the Mayo Clinic than at the NCC (18.8% vs 5.8%, $p = 0.002$). There was no difference in histological subdivisions between the databases. There was no difference in progression-free survival (PFS) and overall survival (OS) of germinoma cases and OS of nongerminomatous GCT (NGGCT) cases treated with chemotherapy and radiation therapy covering whole ventricles. However, PFS of NGGCTs differed significantly, and was better in the NCC cohorts ($p = 0.04$).

CONCLUSIONS There appears to be a differential distribution of GCTs by neuroanatomical location between major geographic and national groups. Further study is warranted to better characterize any underlying genomic, epigenetic, or environmental factors that may be driving the phenotypic differences.

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KEYWORDS germ cell tumor; international comparison; tumor location; prognosis; basal ganglia; bifocal; oncology

ABBREVIATIONS AFP = alpha-fetoprotein; BTRJ = Brain Tumor Registry Japan; CARE = carboplatin + etoposide; CNS = central nervous system; COG = Children's Oncology Group; GCT = germ cell tumor; HCG = human chorionic gonadotropin; ICE = ifosfamide + carboplatin + etoposide; iGCT Consortium = Intracranial Germ Cell Tumor Genome Analysis Consortium; NCC = National Cancer Center; NGGCT = nongerminomatous GCT; NOS = not otherwise specified; OS = overall survival; PE = cisplatin + etoposide; PFS = progression-free survival; PGC = primordial germ cell; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis; WB = whole brain; WV = whole ventricle.

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CENTRAL nervous system (CNS) germ cell tumors (GCTs) are rare neoplasms predominantly arising in adolescent and young-adult male patients. Standardized treatment protocols using chemoradiation have demonstrated excellent efficacy, with durable tumor control in 90% of germinomas.³⁴ By contrast, nongerminomatous GCTs (NGGCTs) have proven resistant to a wide array of chemotherapy, radiation, and combined protocols, resulting in a generally poor prognosis.³⁴

GCTs demonstrate characteristic racial-geographic distributions, with gonadal GCTs predominating in Western countries,⁵¹ whereas CNS GCTs arise more frequently in East Asian populations.^{24,33,43} Within the US, the frequency of intracranial GCTs was highest in Asian/Pacific islanders, followed by White and Black populations.⁴⁶ More specifically, while CNS GCTs account for only 5.2% of primary brain tumors in Western children younger than 14 years of age,⁴³ in a comparable Japanese cohort CNS GCTs account for 14.4%, a nearly 3-fold increase in incidence.³⁸ Although genetic or epigenetic factors driving this dramatic differential remain poorly understood, an important discovery was made by Wang et al. in 2015, who utilized whole-genome germline sequencing to identify a key association between a genetic variant of *JMJD1c* and Japanese CNS GCT, in whom it was 4.8-fold more prevalent, as compared to a matched Western cohort.⁶² *JMJD1c* is a Jumonji domain-containing protein, which encodes the histone H3K9 demethylating enzyme important for removing the trimethyl group on this histone lysine residue, which has been shown to maintain primordial germ cells (PGCs)—the GCT cells of origin—in a murine model.^{30,42} However, it is notable that the variant of this gene has not been proven to be involved in the pathogenesis of GCTs.

To better facilitate large-scale genomic investigations and the identification of targets for novel therapies in these rare and challenging tumors, the Intracranial Germ Cell Tumor Genome Analysis Consortium (iGCT Consortium) was established in 2011.^{12,13,19} At present, the iGCT Consortium has enrolled more than 200 cases including tumor specimens and clinical data, via the National Cancer Center (NCC) in Japan. In parallel, the Mayo Clinic in the US has prospectively registered, biobanked, and followed 98 cases of CNS GCT, including metastatic cases from other organs, that underwent neurosurgical management during the study period (1988–2017).

The goal of the present study was to perform a direct comparison between these large, prospective CNS GCT registries—with particular attention to characteristic differences in demographics, clinical presentation, and treatment response—in hopes of providing new avenues for focused translational inquiry. We report the first pan-Pacific comparison of registry-based CNS GCT cohorts, through which we identified a range of significant differences, including key variations in the distribution of intracranial tumor locations and responses to treatment, particularly among NGGCTs.

Methods

Data Source and Acquisition

Between 1988 and 2017, 80 cases of CNS GCT were neurosurgically managed at the Mayo Clinic. Cases were

treated with chemotherapy and radiation therapy by a multidisciplinary team according to the current Children's Oncology Group (COG) guidelines. Eighteen metastatic cases were excluded. Although referral origination data were not universally available, prior data on related samples have shown that approximately 80% of the patients would be expected to reside in Minnesota or one of the 5 surrounding states comprising the upper Midwest. All histopathological diagnoses were made at the Mayo Clinic, and all pertinent components of the present study were overseen and approved by the IRB.

From 2011 to 2017, 154 primary (e.g., nonmetastatic, nonrecurrent) CNS GCTs treated at 20 participating institutions were enrolled in the iGCT Consortium/NCC database and correspondingly included in this study. There is an overlap of the cases with the previous reports on genomic analyses: 95 of 154 cases were used previously, and the rest were newly employed in this study.^{12,13,19} Cases that were recurrent, metastatic, or diagnosed as non-GCT in the central histopathological review were excluded. According to the Brain Tumor Registry Japan (BTRJ),¹ the overall annual incidence of GCTs is estimated to be 2.14%. According to the latest results from Cancer Registry and Statistics by the Cancer Information Service, NCC Japan, the number of CNS tumors was 6228 in 2016, which roughly estimates the number of CNS GCTs to be approximately 130 cases per year. Although the proportion of cases captured by the iGCT Consortium cannot be precisely calculated from available data, we estimate that 15%–20% of all Japanese cases are included each year.

In contrast to the above Mayo Clinic cases, patients registered in the NCC database are considered ethnically Japanese people, given their highly homogeneous race background. All histopathological diagnoses were centrally reviewed and reclassified in accordance with the WHO classification of tumors of the CNS by a single expert neuropathologist (Dr. Nakazato). All pertinent aspects of the study were overseen and approved by the NCC Japan Ethics Committee and, as indicated, by each local IRB.

Systematic Literature Review

A retrospective literature search was conducted using PubMed to capture publications since 1990 reporting outcomes of intracranial GCTs in at least 10 cases per article. This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Fig. 1). PubMed was queried using the key MeSH search terms “neoplasms, germ cell and embryonal,” “germinoma,” and “central nervous system.” Non-MeSH terms were “intracranial” and “germ cell.” Citations were screened in all languages, using professional library translation services as needed. All abstracts were reviewed against prespecified criteria by the lead investigator (H.T.), and any candidate citations underwent full-text screening for possible study inclusion. Articles reporting only germinoma or NGGCT were excluded, given the significant association between histology and tumor location. If multiple candidate publications representing the same institutional cohort were identified, the article with the largest cohort was included. Articles not clearly identifying cases as specific to the basal ganglia (e.g., not combined with thalamic cases) were excluded.

FIG. 1. PRISMA protocol showing the final selection of articles. Figure is available in color online only.

Data abstraction was conducted to capture parallel outcomes to the multicenter series, as available.

Statistical Analysis

Categorical and continuous variables were analyzed using the Pearson chi-square test and Student t-test, respectively. Nonparametric values were compared using the Wilcoxon signed-rank and rank-sum tests, while time-to-event data were analyzed with the log-rank technique. All statistical analyses were performed using JMP (version 13, SAS Institute Inc.); statistical significance was defined by the type I error rate of $\alpha = 0.05$, and all tests were 2-tailed.

Results

Race, Age, Sex

Baseline clinical characteristic for all cases are summarized in Table 1. Demographics within the Mayo Clinic cohort included 69 Caucasians, 2 Asians, 1 Latino, 4 Arabs, 1 African American, and 3 unknown. In contrast, the NCC cohort is known to be almost exclusively composed of Japanese patients, a parameter that was not quantitatively verified on a case-by-case basis for this analysis.

Median ages in the Mayo Clinic and NCC databases were 17 and 15 years (ranges 0–56 and 0–60), respectively, a difference that was not significant ($p = 0.69$; Fig. 2A). Female patients comprised 12 (15.0%) of 80 patients in the Mayo Clinic database and 24 (15.6%) of 154 in the NCC database, which was not a significant difference ($p = 0.91$; Fig. 2B).

Tumor Histology and Markers

The distribution of histology of the Mayo Clinic database and the NCC database is outlined in Table 1. There were no significant differences in distribution of histologi-

cal subtypes across the databases, with the exception of GCTs not otherwise specified (NOS), which were more prevalent in the Mayo Clinic series; however, this most likely reflects a difference in pathologic practice, rather than underlying biology ($p < 0.001$; overall $p = 0.63$; Fig. 2C).

Serum and CSF tested for either human chorionic gonadotropin (HCG) or alpha-fetoprotein (AFP) were compared in germinoma cases between the Mayo Clinic database ($n = 36$) and NCC database ($n = 79$), and no statistically significant difference in tumor markers was observed (Fig. 3).

Tumor Location

Among Mayo Clinic cases, tumor locations were neurohypophyseal in 17 (21.3%), pineal in 40 (50.0%), bifocal neurohypophysis and pineal in 15 (18.8%), multiple in 3 (3.8%), and other in 5 (6.3%). In the NCC database, there were 20 neurohypophyseal (13.0%), 81 pineal (52.6%), 9 bifocal (5.8%), 13 basal ganglia (8.4%), 22 multiple (14.3%), including 7 bifocal plus other, and 9 other location (5.8%) cases. Significant differences in distribution by location included an increased prevalence of bifocal cases in the Mayo Clinic database, and a decreased prevalence of basal ganglia cases ($p = 0.002$ and $p = 0.008$; Fig. 4A). When multifocal cases that include bifocal neurohypophyseal and pineal tumors plus another third lesion (7 NCC cases) are counted as bifocal, the difference becomes smaller and nonsignificant (18.8% vs 10.4%, $p = 0.07$). The overall difference of locations between the two databases was statistically significant ($p = 0.0003$).

Systematic Literature Review of Basal Ganglia GCT Geographic Distribution

Fifty-one articles met criteria for analysis, resulting in

TABLE 1. Overview of characteristics of cases in the Mayo and NCC series and their comparison

Characteristic	Mayo Clinic (n = 80)	NCC (n = 154)	p Value
Race (White:others)	69:8	0:154	
F:M	12:68	24:130	0.91
F, %	15.0	15.6	
Age, yrs			
Range	0–56	0–60	0.69
Median	17	15	
Mean	17.6	16.9	
Histology, n %			
Germinoma	47 (58.8)	98 (63.6)	0.47
Mature teratoma	5 (6.3)	6 (3.9)	0.42
Immature teratoma	4 (5.0)	12 (7.8)	0.42
Teratoma w/ malignant transformation	0 (0)	1 (0.6)	0.47
Yolk sac tumor	1 (1.3)	6 (3.9)	0.26
Embryonal carcinoma	0 (0)	2 (1.3)	0.31
Choriocarcinoma	1 (1.3)	2 (1.3)	0.97
Mixed GCT w/ germinoma component	10 (12.5)	24 (15.6)	0.53
Mixed GCT w/o germinoma component	1 (1.3)	2 (1.3)	0.97
GCT NOS	11 (13.8)	1 (0.6)	<0.0001*
Location, %			
Neurohypophyseal	17 (21.3)	20 (13.0)	0.10
Pineal	40 (50.0)	81 (52.6)	0.71
Bifocal	15 (18.8)	9 (5.8)	0.002*
Basal ganglia	0 (0)	13 (8.4)	0.008*
Multiple	3 (3.8)	22 (14.3)	0.01*
Other	5 (6.3)	9 (5.8)	0.90

* p < 0.05.

2283 included cases (Supplementary Table 1).^{1–3,5–11,14,16–18, 20–23,25–29,31–34,36,37,39–41,44,45,47–50,52–55,57–59,63–68}

About half of the studies (n = 24) were from East Asia, as compared to 10 from Europe, 10 from North America, 3 from other Asian countries, and 4 from other regions. Among cohorts from Europe and North America, the prevalence of basal ganglia lesions was 0.0%–8.3% and 0.0%–7.7%, respectively, with more than half (15 of 20) reporting no basal ganglia cases. Similarly, among articles from Asian countries other than East Asia, or from other geographic regions, the rate of basal ganglia GCT ranged from 1.1% to 8.1% and from 0.0% to 4.5%, respectively. By contrast, the majority of reports published from East Asia documented basal ganglia lesions, and although the variance was wide at 0.0%–22.4%, 8 of 24 reports documented basal ganglia prevalence in excess of 10%, a significant difference, as compared to non–East Asian countries (p = 0.001; Fig. 4B). Total basal ganglia lesions counted by geographic region are detailed in Fig. 4C, ranging from a maximum of 10.5% in East Asia (105/1229) to a minimum of 5/322

in Europe and 8/377 in North America, a difference that was significant overall and in Bonferroni-corrected pairwise comparisons between East Asia and each of the other groups (p < 0.0001). In parallel, the overall prevalence of bifocal tumors was significantly higher in Europe (13.4%), as compared to each other region (p < 0.0001). The overall difference in location of the tumors among geographic regions was statistically significant (p < 0.0001).

Furthermore, the tumor location distribution varied significantly among countries within the Far East region. When cases from Japan (n = 685) were compared to those from all other countries in the Far East (including Korea, China, and Taiwan, n = 544), the overall difference in tumor location distribution was significant (p < 0.0001), as was the fraction of basal ganglia cases, which were significantly fewer in Japan (14.2 vs 6.1%, p < 0.0001).

Prognosis

Survival endpoints were compared between the 2 databases, selecting for treatments including both platinum-based chemotherapy and radiation therapy with ventricular coverage. Germinomas meeting criteria included 23 patients from the Mayo Clinic database and 64 from the NCC, while NGGCT (excluding mature teratoma) accounted for an additional 12 Mayo Clinic cases and 38 from the NCC. The median total follow-up duration at the Mayo Clinic was 2492 days (range 43–9274 days) versus 2090 days (range 3–9488 days) in the NCC database. Among germinomas, differences in both progression-free survival (PFS) and overall survival (OS) were nonsignificant. Mayo Clinic and NCC databases, respectively, demonstrated 10-year PFS rates of 100.0% and 86.9% (p = 0.08), and 10-year OS rates of 100% and 97.8% (p = 0.52; Fig. 5A and B).

By contrast, a significant difference was noted between the databases for PFS in NGGCT, but not OS. More specifically, the 1-, 3-, 5-, and 10-year PFS rates in the Mayo Clinic series were 81.8%, 40.9%, 40.9%, and 40.9%, versus 84.3%, 84.3%, 84.3%, and 75.9% in the NCC series, a difference that was statistically significant (p = 0.04). The 1-, 3-, 5-, and 10-year OS rates in the Mayo Clinic series were 100.0%, 81.8%, 81.8%, and 81.8%, which were not significantly different than the NCC results at the same time points (84.3%, 84.3%, 80.5%, and 80.5%, p = 0.92; Fig. 5C and D).

Discussion

We present a unique geographic analysis of intracranial GCT between a predominantly Caucasian cohort of patients treated at the Mayo Clinic and an almost completely Japanese cohort derived from the iGCT Consortium (NCC Japan database). Cumulatively, 234 cases were retrospectively reviewed, in an analysis that revealed no statistically significant differences in age, sex, tumor markers, histological variations, PFS/OS in germinomas, or OS in NGGCTs, with notable significant findings in both tumor location and PFS among NGGCTs. These findings were further supported by our systematic literature review, which similarly identified a significant difference in tumor location by geographic region—in particular, with respect to basal ganglia or bifocal GCTs.

FIG. 2. A: The distribution of cases depending on age in 2 cohorts is shown. Although there is a trend of older patient age in the Mayo Clinic cohort, the distribution was not statistically significant ($p = 0.69$, Student t-test). **B:** The ratio of females to males was not statistically significant between the 2 cohorts ($p = 0.91$, Pearson's chi-square test). **C:** The ratio of germinoma, mature teratoma, and NGGCTs between the 2 cohorts showed no statistically significant difference ($p = 0.63$, Pearson's chi-square test).

Systemic GCTs arise in the midline, with primary origination at the gonads (testis, ovary) or mediastinum.⁴² The GCT cell of origin is believed to be the PGC, which migrates from the base of the allantoic membrane of the yolk sac along the dorsal mesentery to the gonadal ridge during weeks 4–8 of gestation. Malignant transformation within these germ cell populations is thought to occur during the early differentiation phases of embryologic development. Of particular interest, mismigration of transformed PGCs into extragonadal organs, including the CNS, is considered to be the source of intracranial GCTs.⁶¹ Although it is considered that this mismigration of PGCs is the cause of the tumorigenesis, the reason for the predilection of the tumor occurrence for other midline sites within the CNS, including the neurohypophysis and pineal gland, remains poorly understood. Our novel observation that basal ganglia GCT incidence is variably distributed among geographic and national groups may reflect a key difference in tumor biology; we recently found that basal ganglia GCTs demonstrate a higher prevalence of mutations in the PI3K/mTOR pathway than GCTs in other locations.⁶⁰

Regarding lesion multiplicity, we noted that the difference was markedly decreased when bifocal cases were considered together with multifocal cases. This is most likely explained by variation in case distribution over time. More specifically, 42.5% of the pertinent Mayo Clinic cases occurred in 2000 or earlier, as compared to 23.4% of NCC database patients; correspondingly, differences in imaging technology may be responsible for a larger fraction of Mayo Clinic cases having been identified as bifocal, rather than multifocal.

We anticipate that the difference in tumor location will be better informed by future genomic investigations that

build on the comparison between these groups. Given the significantly increased prevalence of GCT in general and basal ganglia GCT within the East Asian population, we also emphasize the importance of continuing a focused evaluation into the mechanisms driving neoplastic transformation in this critical patient cohort.

Of further clinical interest is the trend we observed toward improved treatment response in germinoma cases treated at the Mayo Clinic, as compared to those captured by the NCC database, which included 8 cases of recurrence, 5 of which demonstrated multiple lesions. All of these cases received standard-of-care treatment with either PE (cisplatin + etoposide, $n = 6$), CARE (carboplatin + etoposide, $n = 1$), or ICE (ifosfamide + carboplatin + etoposide, $n = 1$). However, a notable difference in treatment was identified in the radiation strategy, with almost all Mayo Clinic cases receiving whole-brain (WB) radiotherapy, while 2 underwent whole-ventricle (WV) radiotherapy, following the COG protocol (currently ACNS1123); in contrast, the majority of NCC patients underwent WV radiotherapy only (49/64). Although this finding is of academic interest, we excluded it from the principal results for several reasons, including the nonsignificant differences in response rate, the failure of prior controlled trials to demonstrate a significant improvement in association with WB over WV radiotherapy, and the absence of location-specific detail regarding recurrences in the databases we studied. Correspondingly, our conclusion is that these nonsignificant differences simply reflect normal statistical variation between ostensibly heterogeneous cohorts.

The observation of a significant difference in PFS but not OS in NGGCT warrants some further consideration. In the NCC cohort, patients were overwhelmingly treated

FIG. 3. Serum and CSF HCG and AFP were compared in germinoma cases between the Mayo Clinic database (n = 36) and NCC database (n = 79). There was no statistically significant difference between the 2 cohorts.

with either CARE regimen chemotherapy followed by WV radiation with a local boost for tumors in the intermediate prognosis group (e.g., immature teratoma, or mixed GCTs predominantly consisting of teratoma or germinoma components), or the ICE regimen followed by craniospinal irradiation with a local boost in the poor prognosis

group (other NGGCTs except for mature teratoma).³⁴ In the companion Mayo Clinic cohort, patients were treated using either an institutional protocol of 4 cycles of cisplatin and etoposide, or COG ACNS 0122, a protocol alternating VP-16/carboplatin with VP-16/ifosfamide for 6 cycles, followed by craniospinal irradiation with a local

FIG. 4. A: The distribution of locations of tumors in each cohort is displayed. Whereas the Mayo Clinic cohort had a significantly higher rate of bifocal lesions ($p = 0.017$, Pearson's chi-square test), the NCC cohort had a significantly higher rate of basal ganglia lesions ($p = 0.03$) and multiple lesions ($p = 0.016$). **B:** In a systematic review of 51 reports on intracranial GCTs around the world, reports from countries in East Asia showed a significantly higher rate of GCTs in the basal ganglia compared with reports from other regions ($p = 0.001$, Wilcoxon rank-sum test). **C:** The distribution of tumor locations was displayed according to the geographic regions. Whereas the basal ganglia lesion rate in East Asia is 10.5%, those in other regions are statistically low, i.e., 1.6% in Europe, 2.1% in North America, 4.2% in other Asia, and 1.1% in other areas.

boost. The results we observed in both cohorts are largely in accordance with those of the major preceding large studies, including the data put forth by the BTRJ, which demonstrated a 76.1% 5-year PFS in mixed GCTs.⁵⁶ When

compared to the 84.3% we observed in the present study, this difference is quite modest, and likely accounted for by their exclusion of single-histology cases.⁵⁶ Comparable results were also observed in the recent SIOP (Société Inter-

FIG. 5. A: PFS of germinoma in 2 cohorts is shown. Despite a tendency of shorter PFS observed in the NCC cohort, there was no statistically significant difference ($p = 0.08$, log-rank test). Five-year PFS was 100% and 90.1% in the Mayo Clinic and NCC databases, respectively. **B:** OS of germinoma in the 2 cohorts shows similar results: 5-year OS was 100% and 97.2% in the Mayo Clinic and NCC databases, respectively. **C:** PFS in NGGCTs in the 2 cohorts is shown. Cases in the Mayo Clinic cohort showed significantly worse prognosis than those in the NCC cohort ($p = 0.04$): 5-year OS was 40.9% and 84.0% in the Mayo Clinic and NCC databases, respectively. **D:** OS in NGGCT in the 2 cohorts is shown. The difference between the cohorts was not statistically significant ($p = 0.92$): 5-year OS was 81.8% and 79.0% in the Mayo Clinic and NCC databases, respectively.

nationale d'Oncologie Pédiatrique) study in Europe, where the 5-year PFS rate of NGGCTs was 68%–72%,⁴ and in the COG in North America, which reported 84% 5-year PFS.¹⁵ The result was also examined from the perspective of extent of resection in the initial stage of the treatment (Mayo Clinic vs NCC; the biopsy rate was 18.2 vs 13.2%, $p = 0.65$, and the gross-total resection rate was 71.1% vs 63.6%, $p = 0.72$). Considering our results within these contexts, we note that the observed differences in PFS among NGGCTs between the 2 cohorts are unlikely to reflect inherent differences tied to the patients' racial backgrounds (and therefore genetic predispositions), but more likely to be a reflection of increased statistical variability in the small Mayo Clinic NGGCT cohort (12 cases). Previously

the prognosis of GCTs was shown to be similar between two databases in the US and Japan, although the study was limited by the insufficient details of the treatment regimens.³⁵

The present study is subject to several important limitations. As with any retrospective institutional analyses, selection, treatment, and referral biases may represent uncontrolled sources of confounding. Furthermore, although the reliance on large, prospective databases such as those maintained by the Mayo Clinic or the NCC enhances reliability within the dataset, they also restrict analysis to those endpoints included within the design of the registries. With specific respect to the NCC, case registration was predominantly motivated by genomic analyses,^{12,13,19}

and correspondingly enrollment is likely biased toward cases amenable to surgical intervention and therefore specimen acquisition was performed, to the exclusion of those cases that were radiographically or biochemically diagnosed and treated empirically. With regard to the neuroanatomical distribution of basal ganglia cases, there is a potential bias toward overestimation associated with our methodological decision to limit the inclusion criteria of the systematic review to those articles precisely specifying tumor locations. Finally, although the registries both captured extensive case details, and analyzed the prognosis of the cases that were treated similarly with platinum-based chemotherapy and radiation therapy, the multicenter study design resulted in at least moderate heterogeneity with respect to treatment protocols, a potential source of confounding that we have attempted to analyze and integrate into our assessment, but that cannot be fully delineated using the available data.

Conclusions

We report the first study to compare the characteristics of intracranial GCTs between large, prospectively followed cohorts diagnosed and treated in North America and Japan. Our results build on the preceding findings of distinct genetic signatures across these populations, by highlighting novel differences in overall disease prevalence, and distribution by location within the neuraxis. We anticipate that these findings will inform future investigations into the differential origination of GCTs in these key populations, as well as the development of population-specific paradigms for treatment optimization.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Daniels, Takami, Perry, Graffeo, Nishikawa. Acquisition of data: Takami, Giannini. Analysis and interpretation of data: Takami. Drafting the article: Takami. Critically revising the article: Daniels, Takami, Perry, Graffeo, Narita, Nakazato, Saito, Nishikawa, Matsutani, Ichimura. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Daniels. Statistical analysis: Takami. Administrative/technical/material support: Daniels, Perry, Graffeo. Study supervision: Daniels, Nishikawa, Matsutani, Ichimura.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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