Intracranial germ cell tumors (IGCTs) represent 3%-15% of pediatric brain tumors. According to the current WHO classification, IGCTs are classified as germinomas (50%-70%) and nongerminomatous germ cell tumors (NGGCTs). The subtypes of NGGCTs include embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, or a composite of multiple histological subtypes, and are characterized by raised β-human chorionic gonadotropin (β-HCG) and/or α-fetoprotein (AFP) in the serum and/or CSF. Common primary sites include the pineal (56%) and the neurohypophyseal regions (28%) and, less commonly, basal ganglia, thalamus, corpus callosum, cerebellum, and spinal cord. Germinomas are exquisitely radiosensitive, whereas nongerminomatous germ cell tumors may be cured without radiotherapy. Ongoing genomic studies reveal insights to attain an understanding of the biology of these tumors. New treatment strategies are needed to improve outcomes for IGCTs in this age group, particularly for germinomas.

The authors describe a series of 15 intracranial germ cell tumors (IGCTs) excluding mature teratomas; 3 cases in children younger than 3 years of age who were treated at 3 different international institutions over the course of 20 years, and 12 from a PubMed search. These tumors, with possible in utero origins, often occur in atypical locations. The clinical behavior differed significantly from these tumors’ counterparts in older children. In this young age group germinoma is highly aggressive, whereas nongerminomatous germ cell tumors may be cured without radiotherapy. New treatment strategies are needed to improve outcomes for IGCTs in this age group, particularly for germinomas.

**Key Words** • intracranial germ cell tumors • infants • oncology • excluding mature teratoma

**Abbreviations used in this paper:** AFP = α-fetoprotein; β-HCG = β-human chorionic gonadotropin; GTR = gross-total resection; IGCT = intracranial germ cell tumor; NGGCT = nongerminomatous germ cell tumor; PLAP = placental alkaline phosphatase; SEER = Surveillance, Epidemiology, and End Results; VP = ventriculoperitoneal.
A subset of infantile intracranial germ cell tumors

the 1st decade of life and in adolescence. The IGCTs found in infants and very young children are typically mature teratomas, which have excellent outcome after gross-total resection (GTR). In this young age group IGCTs, excluding mature teratomas, are extremely rare. We describe 3 rare cases that were treated at 3 different institutions in the course of 20 years, and 12 additional cases from a PubMed search. We used the PubMed database to identify patients from case reports, case series, and studies of infants and children younger than 3 years with IGCTs, excluding mature teratomas. A PubMed search of English language articles published between 1984 and 2012 was performed using a combination of key words, which included intracranial germ cell tumors, germ cell tumors, germinoma, nongerminomatous germ cell tumors, teratomas, not teratomas, embryonal carcinoma, yolk sac tumor, choriocarcinoma, brain tumor, intracranial tumor, congenital, infants, children, pediatric, and less than 3 years of age.

Case Reports

Patient 1

An 18-month-old girl presented with a history of macrocephaly, developmental regression, spastic left hemiparesis, facial weakness, and symptoms of raised intracranial pressure. Admission MRI studies revealed a large right cerebral hemispheric tumor that had multifocal solid components of diffusion restriction and hypointensity on T2-weighted images, mass effect, and obstructive hydrocephalus (Fig. 1A–C), without macroscopic spinal metastases but with positive tumor cells in the CSF. Tumor markers (AFP and β-HCG) were negative in both serum and CSF. The patient underwent near-total resection of the tumor and ventriculoperitoneal (VP) shunt insertion. Postoperative MRI studies revealed thin bands of residual tumor in the resection cavity and small tumor nodules in

![Image of MRI studies](image-url)

**Fig. 1.** Patient 1. Imaging characteristics of germinoma. A–C: Preoperative MRI studies demonstrating a large right cerebral hemispheric tumor, mass effect, and obstructive hydrocephalus. D–F: Postoperative MRI studies showing thin bands of residual tumor in the resection cavity and small tumor nodules in the right frontal and medial occipital lobes distant from the main tumor. G–I: Postoperative MRI studies obtained 3 weeks postsurgery, prior to initiation of chemotherapy, showing growth of disseminated intracranial tumor foci and development of extensive leptomeningeal disease within the cerebral hemispheres and cerebellum. Panels A, D, and G are axial views; B, E, and H are coronal views; and C, F, and I are sagittal views.
the right frontal and medial occipital lobes distant from
the main tumor (Fig. 1D–F). Histological findings were
consistent with a germinoma composed of pleomorphic,
frequently bi- and multinucleated tumor cells with promi-
nent nucleoli (Fig. 2A, arrow, and B; H & E) among small,
mature lymphocytes. Immunohistochemical staining was
positive for c-kit (CD117) (Fig. 2C), whereas β-HCG (Fig.
2D), placental alkaline phosphatase (PLAP), and cytokerat-
tin immunostains were negative (not shown).

Three weeks from surgery and prior to chemotherapy
her tumor progressed rapidly, with growth of disseminat-
ed foci and extensive leptomeningeal disease (Fig. 1G–I).

Fig. 2. Photomicrographs of germinoma and malignant NGGCT tissue sections obtained in Patients 1 and 3, respective-
ly. A–D: Patient 1. Germinoma tumor cells with pleomorphic nuclei and prominent nucleoli among small, mature lymphocytes. Frequent bi- and multinucleated tumor cells are present (arrow, A) (A and B, H & E). Tumor cells are immunoreactive for c-kit (CD117) (C) and are negative for β-HCG (D). E–I: Patient 3. Malignant NGGCT cells have large nuclei with prominent nucleoli (E and F, H & E). Tumor cells are diffusely immunoreactive for AFP (G) and β-HCG (H) and are negative for PLAP (I). Original magnifications: A and E, ×400; B–D and F–I, ×200.
A subset of infantile intracranial germ cell tumors

After 2 courses of chemotherapy (carboplatin and etoposide) administered 3 weeks apart, CSF analysis revealed a high concentration of clustered tumor cells. Despite clinical improvement, imaging revealed a mixed tumor response. She completed a third course of chemotherapy (cyclophosphamide and carboplatin) but deteriorated rapidly and died 1 week later, at 10 weeks from diagnosis.

**Patient 2**

A newborn baby girl presented antenatally at 36 weeks of gestation with an intracranial mass measuring 9.4 × 9.3 × 8.6 cm with intratumoral calcifications. She was delivered at 37 weeks in good condition, with macrocephaly. Computed tomography scans of the brain revealed a large multilobulated enhancing tumor involving the third and lateral ventricles with cysts, calcifications, and obstructive hydrocephalus (Fig. 3). A diagnosis of NGGCT was made based on significantly elevated AFP of 1,080,170 ng/ml in the CSF and 304,687 ng/ml in the serum, which is 7.3 times higher than what is expected of a term newborn infant (mean serum AFP in a term newborn: 41,687 ng/ml), and β-HCG of 21 mIU/ml in the CSF and 61 mIU/ml in the serum (range of serum β-HCG in a newborn: ≤ 50 mIU/ml).24 The patient underwent insertion of a palliative VP shunt and bilateral external ventricular drains without biopsy because her parents opted for palliative management. She died of disease progression at the age of 5 weeks.

**Patient 3**

A 6-week-old baby girl presented with lethargy and poor feeding. Admission MRI studies revealed a large suprasellar mass causing obstructive hydrocephalus (Fig. 4A–C). She underwent an endoscopic third ventriculostomy and biopsy. Serum and CSF AFP levels of 8669 ng/ml and 109 ng/ml, respectively, were suggestive of a diagnosis of yolk sac tumor (mean serum AFP at 29–45 days of life: 417 ng/ml).6 The β-HCG level was normal (< 2 mIU/ml in the serum and 3.7 mIU/ml in the CSF). Histological investigation revealed a malignant NGGCT (Fig. 2E and F, H & E) with diffuse immunopositivity for AFP (Fig. 2G) and β-HCG (Fig. 2H) and that was negative for PLAP (Fig. 2I), which is highly suggestive of a yolk sac tumor with a possible choriocarcinoma component. One week later she received a first course of chemotherapy (etoposide, carboplatin, and bleomycin), but developed progressive hydrocephalus (Fig. 4D–F) requiring VP shunt insertion. A second course of chemotherapy (etoposide, carboplatin, and bleomycin) was not completed due to clinical deterioration. Despite radiographic evidence of tumor response to chemotherapy with a reduction in size (Fig. 4G–I), without spinal metastases, the patient continued to deteriorate and died 6 weeks after diagnosis.

**Discussion**

The diagnosis and biological behavior of IGCTs (excluding mature teratomas) in children younger than 3 years of age are not well characterized. We describe the unique spectrum of tumors in this young age group (Fig. 5). These tumors are extremely rare; only 3 cases were identified in 3 large international tertiary institutions over a period of 20 years. A PubMed search of the English language literature identified 12 additional cases that included adequate clinical information and satisfactory follow-up of more than 18 months. In our analysis of all 15 cases (Table 1), we discovered that IGCTs (excluding mature teratomas) in this young age group often occur in atypical locations, including the cerebral hemispheres, lateral ventricles, cerebellum, and fourth ventricle (11 of 15), and only 4 cases occurred in the pineal and/or suprasellar regions, which are the predominant locations of germ cell tumors in children older than 3 years of age. It appears that lateral ventricles are frequently involved in infants younger than 1 year (Cases 1, 5, and 6), whereas cerebral hemispheres and cerebellum are commonly involved in children older than 1 year (as in Cases 8–12).1,19

The behavior and outcome of these tumors in this young age group clearly differ from that in older patients. In our review, germinomas in this young age group appear to be highly aggressive. Only 1 of the 4 patients with germinoma (Case 7) responded to chemotherapy, and all 4 patients, including Patient 1 from our series, died of their malignancy, with a median survival of 19.5 weeks (range 10–44 weeks). This dismal survival is in contrast

![Fig. 3. Patient 2. Imaging characteristics of NGGCT. Computed tomography scans of the brain showing a large multilobulated enhancing tumor involving the third and lateral ventricles with cysts, calcifications, and obstructive hydrocephalus. Panel A is an axial view, B is a coronal view, and C is a sagittal view.](image-url)
to that in older children with germinoma, which showed a greater than 90% response rate (complete and partial response) to chemotherapy\(^{17,19}\), and a 5-year survival rate exceeding 90%.\(^{2,19,22}\) In contrast to the uniformly fatal outcome of germinoma in this young age group, our review suggests that NGGCTs (excluding mature teratomas) among children younger than 3 years of age appear to have a relatively better outcome. Of 11 patients with NGGCT (excluding mature teratomas), 1 patient (Case 10) was a long-term survivor with surgery alone,\(^1\) and 5 additional patients (Cases 4, 5, and 13–15)\(^{8,9,11,26,27}\) survived for more than 72 weeks after chemotherapy (with or without radiation treatment). This survival rate (6 of 11; 55%) is comparable to the survival outcome in children older than 3 years of age who have NGGCTs.\(^{2,22}\) Collectively, children younger than 3 years who had NGGCTs (excluding mature teratomas) had a median survival of 92 weeks (range 5–232 weeks). It is intriguing that 4 (67%) of 6 NGGCT survivors (excluding those with mature teratomas) did not receive radiation treatment.

Whole-exome sequencing of germinoma (Case 1 [Patient 2]) revealed a distinct c-kit mutation (CC Lau, un-

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**Fig. 4.** Patient 3. Imaging characteristics of NGGCT: MRI showing a large suprasellar mass causing obstructive hydrocephalus (A–C), postchemotherapy development of progressive hydrocephalus (D–F), and radiographic evidence of tumor response to chemotherapy with a reduction of tumor size (G–I), without spinal metastases. Panels A, D, and G are axial views; B, E, and H are coronal views; and C, F, and I are sagittal views.

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**Fig. 5.** Venn diagram showing the estimated distribution of tumor types of IGCT in infants younger than 3 years of age (based on current evidence; not drawn to scale).
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, Sex</th>
<th>Histological Findings</th>
<th>Tumor Markers</th>
<th>Tumor Location</th>
<th>Treatment</th>
<th>Response to Treatment</th>
<th>OS (wks)</th>
<th>Outcome†</th>
<th>Source of Case Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>newborn, F</td>
<td>none</td>
<td>positive for β-HCG &amp; AFP (serum, CSF)</td>
<td>cerebral hemisphere, 3rd &amp; lat ventricles</td>
<td>none (palliative)</td>
<td>tumor progression</td>
<td>5</td>
<td>died</td>
<td>Patient 2, present study</td>
</tr>
<tr>
<td>2</td>
<td>6 wks, F</td>
<td>yolk sac tumor</td>
<td>positive for AFP (serum, CSF)</td>
<td>suprasellar</td>
<td>chemo (carboplatin, etoposide, bleomycin)</td>
<td>partial response 6</td>
<td>died</td>
<td>Patient 3, present study</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 mos, M</td>
<td>malignant teratoma</td>
<td>ND</td>
<td>4th ventricle</td>
<td>chemo (cisplatin, cyclophosphamide, bleomycin, vinblastine) + RT</td>
<td>local failure 20</td>
<td>died</td>
<td>Allen et al., 1987</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 mos, F</td>
<td>yolk sac tumor</td>
<td>positive for AFP (serum, CSF)</td>
<td>temporal, orbital</td>
<td>chemo (carboplatin, etoposide, cyclophosphamide)</td>
<td>complete response 228</td>
<td>alive</td>
<td>da Silva et al., 2010</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8 mos, F</td>
<td>embryonal carcinoma, teratoma</td>
<td>negative for β-HCG &amp; AFP (serum)</td>
<td>lat ventricle</td>
<td>STR + chemo (carboplatin, etoposide, ifosfamide)</td>
<td>complete response 124</td>
<td>alive</td>
<td>Goetz et al., 2002</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9 mos, M</td>
<td>germinoma</td>
<td>NA</td>
<td>pineal, lat ventricle</td>
<td>STR + CSI, salvage chemo (cisplatin, bleomycin, vinblastine)</td>
<td>stable tumor, extra-CNS dissemination 44</td>
<td>died</td>
<td>Howman-Giles et al., 1984</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>12 mos, M</td>
<td>germinoma</td>
<td>negative for β-HCG (serum, CSF)</td>
<td>pineal, suprasellar</td>
<td>NTR + chemo (cisplatin, etoposide, cyclophosphamide, bleomycin)</td>
<td>no evidence of disease, then metastatic recurrence 28</td>
<td>died</td>
<td>Kellie et al., 2004</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>16 mos, M</td>
<td>germinoma</td>
<td>NA</td>
<td>cerebellum</td>
<td>GTR</td>
<td>local failure 11</td>
<td>died</td>
<td>Ammar et al., 1991</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>18 mos, F</td>
<td>germinoma</td>
<td>negative for β-HCG &amp; AFP (serum, CSF)</td>
<td>cerebral hemisphere</td>
<td>NTR + chemo (carboplatin, etoposide, cyclophosphamide)</td>
<td>local failure 10</td>
<td>died</td>
<td>Patient 1, present study</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>24 mos, M</td>
<td>yolk sac tumor</td>
<td>NA</td>
<td>temporoparietal</td>
<td>GTR</td>
<td>complete response 144</td>
<td>alive</td>
<td>Al-Masri et al., 2011</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>24 mos, M</td>
<td>yolk sac tumor, embryonal carcinoma, germinoma</td>
<td>negative for β-HCG &amp; AFP (serum, CSF)</td>
<td>frontoparietal</td>
<td>GTR + CSI + chemo (cisplatin, etoposide, ifosfamide, bleomycin, vinblastine)</td>
<td>local failure 24</td>
<td>died</td>
<td>Calaminus et al., 2005</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>24 mos, M</td>
<td>yolk sac tumor</td>
<td>positive for AFP (serum)</td>
<td>cerebellar vermis</td>
<td>GTR + CSI + chemo (cisplatin, etoposide, ifosfamide)</td>
<td>local failure 92</td>
<td>died</td>
<td>Kawaguchi et al., 2011</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>24 mos, U</td>
<td>malignant teratoma</td>
<td>negative for β-HCG &amp; AFP</td>
<td>pineal</td>
<td>GTR + chemo (carboplatin, etoposide, bleomycin) + RT</td>
<td>complete response 232</td>
<td>alive</td>
<td>Smith et al., 2004</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>31 mos, M</td>
<td>yolk sac tumor</td>
<td>positive for AFP (serum, CSF)</td>
<td>cerebellar vermis</td>
<td>GTR + chemo (carboplatin, etoposide, intrathecal methotrexate/cytarabine + CSI)</td>
<td>local failure 72</td>
<td>alive</td>
<td>Tsukamoto et al., 1992</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>36 mos, M</td>
<td>yolk sac tumor</td>
<td>positive for AFP (serum)</td>
<td>cerebellum</td>
<td>GTR + chemo (carboplatin, etoposide, bleomycin)</td>
<td>complete response 192</td>
<td>alive</td>
<td>Cheon et al., 2006</td>
<td></td>
</tr>
</tbody>
</table>

* chemo = chemotherapy; CSI = craniospinal irradiation; NA = not available; ND = not done; NTR = near-total resection; OS = overall survival; RT = focal radiation therapy; STR = subtotal resection; U = unknown.
† Outcome or survival status at time of publication.

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published data). We have also successfully created an orthotopic intracranial mouse xenograft model of metastatic germinoma from one of the patients reported in this series (Patient 1), by using freshly resected tumor from this patient (XN Li, unpublished data). Genomic studies based on this established xenograft model will potentially reveal molecular insights underlying its aggressive biology.

Results from the analysis of Surveillance, Epidemiology, and End Results (SEER) data on infants with IGCTs reported a 3-year survival rate of approximately 60%; however, the histological findings in these tumors are not reported.5 Because most cases of infantile IGCTs are mature teratomas, which have excellent outcomes after GTR, the outcome data in the SEER database therefore cannot be used for comparison with our analysis. There is also no published series or reported incidence of IGCTs that excludes mature teratomas in children younger than 3 years of age. In 2 large series of brain tumors in infants younger than 1 year,21,25 of 1322 cases studied, there was not a single case of IGCT that was not a mature teratoma, which further reflects the rarity of this disease entity.

Conclusions

New treatment strategies are needed to improve outcome for IGCT in this age group, particularly for germinoma. The creation of the pediatric metastatic germinoma mouse model based on tumor tissue resected in Patient 1 in our series will facilitate preclinical drug testing in our search for effective chemotherapeutic and biological agents against this aggressive subset of tumors.

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Disclosure

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 to the study and manuscript preparation include the following. Conception and design: Teo, Su. Acquisition of data: all authors. Analysis and interpretation of data: Teo, Bollo, Mohila, Adesina, Su. Drafting the article: Teo, Bollo, Su. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Teo. Statistical analysis: Teo. Administrative/technical/material support: Teo. Study supervision: Teo.

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