

## Paediatric Extracranial Germ Cell Tumours: A Retrospective Review

L P N Lim,\*<sup>MBBS, MRCP (UK), M Med (Paed)</sup>, A M Tan,\*\*<sup>FAMS, MBBS, M Med (Paed)</sup>, M Y Chan,\*\*\*<sup>MBBS, MRCP (UK), M Med (Paed)</sup>,  
V Rajalingam,\*\*\*<sup>FAMS, MBBS, M Med (Paed)</sup>, J Lou,\*\*\*\*<sup>FAMS, M Med (Paed), FRACP</sup>, C L Tan,\*\*\*\*<sup>FAMS, FRACP, PPA</sup>

### Abstract

**Introduction:** Germ cell tumours (GCTs) are rare, constituting 3% of all childhood malignancies. The aim of this study was to analyse the epidemiology and outcome of these patients. **Materials and Methods:** A retrospective, cohort study was conducted on 38 paediatric patients presenting with extracranial GCTs, treated at the Singapore General Hospital, Tan Tock Seng Hospital and Kandang Kerbau Women's and Children's Hospital from 1 January 1989 to 30 June 1999. The median age at diagnosis was 1.7 years (0 to 13 years). **Results:** There was no sex or racial preponderance. Eighteen patients (47.3%) had teratomas, 16 (42.1%) had yolk sac tumours, 1 (2.6%) had dysgerminoma and 3 (7.9%) had mixed GCTs. Thirty-four patients (89.5%) had Stage I disease, 1 (2.6%) had Stage II disease, 1 (2.6%) had Stage III disease and 2 (5.3%) had metastatic disease. Complete tumour resection was achieved in 36 of the 38 patients (95%). Cisplatin-based combination chemotherapy was given to 11 patients (28.9%). None of the patients received radiotherapy. Complications from chemotherapy included anaemia requiring packed red cell transfusion ( $n = 3$ ), Port-a-cath<sup>®</sup> sepsis requiring removal ( $n = 1$ ), febrile neutropenia ( $n = 1$ ) and nephropathy ( $n = 1$ ). **Conclusion:** Using the Kaplan-Meier life tables, the overall and event-free survivals at 10 years for the patients with malignant GCTs were 96% and 88%, respectively, with a mean follow-up period of 5.1 years (0.7 to 10 years). The majority of the patients presented with early Stage I disease and this contributed to our high survival rate.

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**Key words:** Chemotherapy, Epidemiology, Morbidity, Survival

### Introduction

Germ cell tumours (GCTs) in children account for 2% to 3% of childhood malignancies.<sup>1,2</sup> They arise from primordial germ cells and constitute a heterogeneous group of tumours. The classification of GCT may seem complex and the nomenclature of the various histological subtypes can be confusing. In addition, the different histological subentities follow different clinical courses and vary in their susceptibility to different treatment modalities.

GCTs can be divided into 2 groups:

1. Tumours with cells remaining in the undifferentiated, pure germ cell state. These tumours are called "germinomas" in general. They do not secrete tumour markers like alpha-fetoprotein (AFP) or beta-human chorionic gonadotropin ( $\beta$ HCG). They are called "dysgerminomas" if they arise from the ovaries and "seminomas" if they arise from the testes.

2. Tumours with cells attempting to differentiate into embryonal or extra-embryonal cells. The former are called "teratomas" and they can be mature, immature or malignant. The latter are either yolk sac in origin (called "yolk sac tumours" or "endodermal sinus tumours"), placental in origin (called "choriocarcinomas") or mixed. AFP is raised in yolk sac tumours while  $\beta$ HCG is raised in choriocarcinomas.

During the embryonic stage of development, primordial germ cells migrate from the yolk sac, via the hind-gut mesentery to the gonadal ridge, and finally into the pelvis or the scrotal sac. These tumours are thus located along this migration path, that is, in the extra-gonadal sites like the brain (18%), mediastinum (4%), retroperitoneum (4%), sacrococcygeal region (24%) or the gonadal sites like the ovary (26%) or testis (18%).<sup>2</sup>

The treatment strategy for intracranial and extracranial

\* Registrar

\*\* Head and Senior Consultant

\*\*\* Consultant

\*\*\*\* Senior Consultant

Haematology/Oncology Service

Department of Paediatric Medicine

KK Women's & Children's Hospital

Address for Reprints: Dr Lillian Lim Peck Neo, Department of Paediatric Medicine, KK Women's & Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

E-mail: lillianl@kkh.com.sg

GCT differs. In the 1980s, as the operative mortality for intracranial tumours was as high as 60%,<sup>3</sup> empirical irradiation without histological confirmation was an acceptable treatment strategy.<sup>4</sup> In the 1990s, improved surgical techniques have led to gross total resection with adjuvant radiotherapy and chemotherapy becoming the treatment of choice.<sup>5</sup> In extracranial GCT, however, the role of chemotherapy is firmly established, such that upfront mutilating surgery in an attempt at total resection is not acceptable.<sup>6-9</sup>

## Patients and Methods

We conducted a retrospective, cohort study to evaluate the epidemiology and outcome of all patients under the age of 16 years with extracranial GCT treated at the Singapore General Hospital (SGH), Tan Tock Seng Hospital (TTSH) and Kangar Kerbau Women's and Children's Hospital (KKWCH) between 1 January 1989 and 30 June 1999. These patients were initially treated in SGH and TTSH. In 1997, the Paediatric Departments in these 2 hospitals merged to form the present unit in KKWCH.

The patients' particulars were collected from the Pathology Department from 1989 to 1996 and from the Childhood Cancer Registry since its establishment in 1997. Individual case records were reviewed and the relevant information collected.

TABLE I: CCG/POG STAGING SYSTEMS FOR EXTRACRANIAL GCT

|                      |                                                                                                                                                    |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Extragenital tumours |                                                                                                                                                    |
| Stage I              | Complete resection at any site; normal tumour margins                                                                                              |
| Stage II             | Microscopic residual disease; lymph nodes normal                                                                                                   |
| Stage III            | Gross residual disease; retroperitoneal lymph nodes either normal or showing evidence of malignancy                                                |
| Stage IV             | Distant metastases, including to the liver                                                                                                         |
| Ovarian tumours      |                                                                                                                                                    |
| Stage I              | Growth limited to ovaries; peritoneal washings negative for malignant cells                                                                        |
| Stage II             | Microscopic residual or positive lymph nodes (<2 cm); peritoneal washings negative for malignant cells                                             |
| Stage III            | Gross residual disease; lymph node with malignant nodule (>2cm); contiguous visceral involvement; peritoneal washings positive for malignant cells |
| Stage IV             | Distant metastases, including to the liver                                                                                                         |
| Testicular tumours   |                                                                                                                                                    |
| Stage I              | Limited to testis                                                                                                                                  |
| Stage II             | Microscopic disease in scrotum or high in spermatic cord (<5 cm from proximal end); retroperitoneal lymph node involvement (<2 cm)                 |
| Stage III            | Retroperitoneal lymph node involvement (>2 cm); no visceral or extra-abdominal involvement                                                         |
| Stage IV             | Distant metastases, including to the liver                                                                                                         |

CCG: Children's Cancer Group; GCT: germ cell tumour; POG: Pediatric Oncology Group

All patients were diagnostically evaluated with computed tomography (CT) or magnetic resonance imaging (MRI), and measurement of the tumour markers, AFP and  $\beta$ HCG. The tumour markers were measured at diagnosis, during therapy (usually weekly until normalisation was achieved) and at longer intervals thereafter. AFP was considered elevated when it is above the age-related normal values as determined by the normogram of Blohm et al.<sup>10</sup> Histological diagnosis was made via biopsy or resection of tumour.

The patients were staged according to the CCG (Children's Cancer Group) and POG (Pediatric Oncology Group) staging criteria, as shown in Table I. Chest X-rays, CT and bone scans were used for the screening of distant metastases. In all patients who received cisplatin, otoacoustic emission (OAE) test, glomerular filtration rate and liver enzyme measurements were obtained before, during and at the end of the chemotherapy. Pulmonary function tests were performed for patients receiving bleomycin.

Statistical analysis was performed using SPSS 10.0 for Windows. The overall and event-free survival rates were calculated using the Kaplan-Meier life tables. The event-free survival was defined as the time from diagnosis to the first relapse or death.

## Results

A total of 44 cases were diagnosed during the study period. Five patients were lost to follow-up while 1 did not have a histological diagnosis. The latter was a 4-year-old Chinese boy who presented with a large, well-circumscribed mediastinal mass with intralesional calcification on MRI suggestive of a teratoma. The patient's parents refused to give consent for surgery or biopsy.

Of the 38 cases analysed, 21 (55%) were males and 17 (45%) were females. There were 29 (76%) Chinese, 8 (21%) Malay and 1 (3%) Indian patients, which corresponds to our local racial distribution.<sup>11</sup> The median age at diagnosis was 1.7 years (range, 1 day to 13 years).

AFP was measured in all 38 patients and was elevated in all yolk sac tumours, mixed GCT and 75% of the malignant teratomas.  $\beta$ HCG was measured in 28 (74%) of the patients, at the discretion of the oncologists, and was normal in all cases measured.

Benign teratomas (36.8%) and yolk sac tumours (42.1%) were the most common histological subtypes (Table II). All the yolk sac tumours were localised in the testes. Seventy-nine per cent of the benign teratomas were localised in the testes or the ovaries while the remaining 21% were found in extra-gonadal regions. This is in contrast to malignant teratomas, where 75% were found in extra-gonadal sites and 25% in the gonads.

TABLE II: DISTRIBUTION OF PATIENTS ACCORDING TO HISTOLOGICAL TYPE AND TUMOUR SITE

| Histology          | Tumour site (No. of patients) |              |                |                 |             | Total (%)    |
|--------------------|-------------------------------|--------------|----------------|-----------------|-------------|--------------|
|                    | Testis                        | Ovary        | Sacrococcygeal | Intra-abdominal | Mediastinum |              |
| Benign teratoma    | 3                             | 8            | 1              | 1               | 1           | 14/38 (36.8) |
| Malignant teratoma | 0                             | 1            | 1              | 2               | 0           | 4/38 (10.5)  |
| Yoke sac tumour    | 16                            | 0            | 0              | 0               | 0           | 16/38 (42.1) |
| Dysgerminoma       | 0                             | 1            | 0              | 0               | 0           | 1/38 (2.6)   |
| Mixed GCT          | 1                             | 0            | 2              | 0               | 0           | 3/38 (7.9)   |
| Total (%)          | 20/38 (52.6)                  | 10/38 (26.3) | 4/38 (10.5)    | 3/38 (7.9)      | 1/38 (2.6)  | 38/38 (100)  |

GCT: germ cell tumour

TABLE III: STAGE OF ALL GCTS IN RELATION TO PRIMARY TUMOUR SITE

| Primary site    | Initial Stage |         |         |         | Total (%) |
|-----------------|---------------|---------|---------|---------|-----------|
|                 | I             | II      | III     | IV      |           |
| Testis          | 19            | 1       | 0       | 0       | 20 (52.6) |
| Ovary           | 10            | 0       | 0       | 0       | 10 (26.3) |
| Sacrococcyx     | 2             | 0       | 1       | 1       | 4 (10.5)  |
| Retroperitoneum | 1             | 0       | 0       | 1       | 2 (5.3)   |
| Adrenal gland   | 1             | 0       | 0       | 0       | 1 (2.6)   |
| Mediastinum     | 1             | 0       | 0       | 0       | 1 (2.6)   |
| Total (%)       | 34 (89)       | 1 (2.6) | 1 (2.6) | 2 (5.3) | 38 (100)  |

GCT: germ cell tumour

The sites and stages of the primary tumours are shown in Table III. Testicular tumours were the most common (52.6%), followed by ovarian tumours (26.3%). Sacrococcygeal tumours constituted 10.5% of the cohort, of which only 1 case was an antenatally diagnosed sacrococcygeal teratoma.

Fourteen patients (37%) had benign teratomas. All presented with Stage I disease and underwent complete tumour resection as the only mode of treatment. They remained disease-free on a mean follow-up period of 2.3 years (1 to 4.8 years). The stage at presentation of the other patients with malignant GCTs is shown in Table IV. Eighty-three per cent of the patients presented with Stage I disease. Of the malignant gonadal tumours, 18 out of 19

(95%) presented in Stage I while only 2 out of 5 (40%) of the malignant extra-gonadal tumours presented in Stage I.

Four patients presented with disease more advanced than Stage I. One patient with testicular mixed GCT presented with retroperitoneal lymph node enlargement, classified as Stage II disease. One presented at 2 years of age with presacral mixed GCT with gross residual tumour after surgery, invading the adjacent pelvic structures. One with retroperitoneal malignant teratoma presented with bone and liver metastases, while 1 with presacral mixed GCT presented with bone and lung metastases.

The clinical presentation depended on the primary site of the tumour. All 20 patients with testicular tumours presented with scrotal swelling noticed by the parents or diagnosed by primary health care physicians. Of the 12 patients with intra-abdominal tumours, 1 presented with an acute abdomen from torsion of the ovarian tumour, 3 presented with constipation and were found to have intra-abdominal masses on clinical examination, while the remaining 8 presented with non-specific abdominal distension.

None of the patients received radiotherapy. All 14 patients with benign teratomas received complete primary tumour resection as the only mode of treatment. Of the remaining 24 patients with malignant tumours, complete primary tumour resection was achieved in 21 patients (87.5%). Two patients had incomplete tumour resection, of whom 1 succumbed to metastatic disease while the other remained disease-free after 6 courses of chemotherapy. Only 1

TABLE IV: STAGE AND OUTCOME OF MALIGNANT GERM CELL TUMOURS IN RELATION TO PRIMARY TUMOUR SITE

| Primary site    | Initial Stage |         |         |         | Total (%) | Relapse | Death |
|-----------------|---------------|---------|---------|---------|-----------|---------|-------|
|                 | I             | II      | III     | IV      |           |         |       |
| Testis          | 16            | 1       | 0       | 0       | 17 (70.8) | 2       | 0     |
| Ovary           | 2             | 0       | 0       | 0       | 2 (8.3)   | 0       | 0     |
| Sacrococcyx     | 1             | 0       | 1       | 1       | 3 (12.5)  | 0       | 0     |
| Retroperitoneum | 0             | 0       | 0       | 1       | 1 (4.2)   | 0       | 1     |
| Adrenal gland   | 1             | 0       | 0       | 0       | 1 (4.2)   | 0       | 0     |
| Total (%)       | 20 (83.3)     | 1 (4.2) | 1 (4.2) | 2 (8.3) | 24 (100)  | 2       | 1     |

TABLE V: STANDARD DOSAGE OF CHEMOTHERAPY GIVEN IN 3-WEEK INTERVALS

|                    |                       |         |
|--------------------|-----------------------|---------|
| <b>PVB regimen</b> |                       |         |
| Cisplatin          | 20 mg/m <sup>2</sup>  | Day 1-5 |
| Vinblastin         | 0.15 mg/kg            | Day 1-2 |
| Bleomycin          | 15 mg/m <sup>2</sup>  | Day 1   |
| <b>BEP regimen</b> |                       |         |
| Bleomycin          | 15 mg/m <sup>2</sup>  | Day 1   |
| Etoposide          | 120 mg/m <sup>2</sup> | Day 1-3 |
| Cisplatin          | 100 mg/m <sup>2</sup> | Day 1   |

patient with presacral GCT had secondary surgery with complete tumour resection after 4 cycles of chemotherapy.

A total of 11 patients (28.9%) received cisplatin-based combination chemotherapy of either PVB or BEP (Tables V and VI). Patient no. 8 received 4 cycles of BEP before undergoing complete tumour resection. Patients nos. 3 and 11 received chemotherapy after biochemical and radiological evidence of retroperitoneal lymph node relapse. Patient no. 4 received chemotherapy when he presented with a secondary rise in AFP, while patient no. 9 received chemotherapy when his AFP remained elevated even after complete primary tumour resection. The remaining 6 patients received chemotherapy upfront within 2 weeks of primary surgery.

The side effects of chemotherapy were scored using the World Health Organisation grading criteria.<sup>12</sup> Three patients (nos. 1, 2 and 6) had Grade 3 anaemia requiring packed red blood cell transfusions. Patient no. 8 developed Grade 3 coagulase-negative *Staphylococcus* sepsis of the Port-a-cath® which necessitated its removal. Patient no. 10 presented with febrile Grade 4 neutropenia. He was treated empirically with intravenous ceftriaxone and gentamicin for one week. Patient no. 9 developed Grade 2 nephropathy, with a 23% decrease in glomerular filtration rate from 114 to 88 mL/kg/1.73m<sup>2</sup> and hypomagnesaemia requiring

intravenous replacement. The fifth cycle of his chemotherapy was delayed for 3 weeks. His glomerular filtration rate then normalised and he managed to complete 6 cycles of BEP. With the exception of patient no. 1 who presented with anaemia after 2 cycles of chemotherapy, the remaining patients developed complications after at least 4 cycles of chemotherapy.

None of our patients developed peripheral neuropathy, peripheral vascular disease or secondary malignancy as a consequence of chemotherapy.

There were 2 relapses in our study cohort. Both were diagnosed as Stage I testicular yolk sac tumours. They underwent complete primary tumour resection followed by normalisation of AFP levels. Both then presented with a secondary rise in AFP, with CT evidence of enlarged retroperitoneal lymph nodes, at 5 and 8 months after surgery. They received 6 courses of BEP, with AFP normalising after 4 courses, and have remained disease-free for 9 years and 16 months, respectively.

There was only 1 death in our study cohort. This was a 10-year-old girl with retroperitoneal malignant teratoma and metastases to the bone and liver at presentation. She underwent primary incomplete tumour resection followed by chemotherapy. Unfortunately, she relapsed after 5 cycles of BEP and succumbed 8 months after diagnosis from widespread metastatic disease.

Patients with benign teratomas did well with 100% survival over a mean follow-up period of 2.3 years (1 to 4.8 years). Using the Kaplan-Meier life tables, the 10-year overall and event-free survival rates for the malignant tumours were 96% and 88%, respectively, at a mean follow-up of 5.1 years (0.7 to 10 years).

## Discussion

Our unit manages about 70% of all childhood cancer cases in Singapore. Sacrococcygeal tumours constitute 10.5% of our cohort of extracranial GCT, with only 1

TABLE VI: PATIENTS WHO RECEIVED CHEMOTHERAPY

| No. | Histology          | Site            | Stage | Chemotherapy | No. of cycles | Complications       |
|-----|--------------------|-----------------|-------|--------------|---------------|---------------------|
| 1   | Dysgerminoma       | L ovary         | I     | BEP          | 4             | Anaemia             |
| 2   | Malignant teratoma | Sacroccyx       | I     | PVB          | 6             | Anaemia             |
| 3   | Yolk sac tumour    | R testis        | I     | BEP          | 6             | Nil                 |
| 4   | Yolk sac tumour    | R testis        | I     | BEP          | 4             | Nil                 |
| 5   | Malignant teratoma | R ovary         | I     | BEP          | 4             | Nil                 |
| 6   | Mixed GCT          | R testis        | II    | PVB          | 4             | Anaemia             |
| 7   | Malignant teratoma | Retroperitoneum | IV    | BEP          | 5             | Died                |
| 8   | Mixed GCT          | Presacral       | IV    | BEP          | 6             | Port-a-cath® sepsis |
| 9   | Yolk sac tumour    | R testis        | I     | BEP          | 6             | Nephropathy         |
| 10  | Mixed GCT          | Presacral       | III   | BEP          | 6             | Febrile neutropenia |
| 11  | Yolk sac tumour    | L testis        | I     | BEP          | 6             | Nil                 |

BEP: bleomycin, etoposide, cisplatin; GCT: germ cell tumour; PVB: cisplatin, vinblastin, bleomycin

patient (2.6%) diagnosed antenatally. This was significantly lower than the 17% to 31% of extracranial GCTs reported in other studies.<sup>2,6,7,9</sup> This may be due to the failure of notification from the surgical or neonatal units rather than a true low incidence.

With the establishment of the Childhood Cancer Registry as a centralised notification centre, we hope to overcome this problem. There is, thus, a predominance of testicular and ovarian tumours, which together constitute 79% of the cases. This is similar to other reported studies, citing testicular, ovarian and sacrococcygeal tumours as being most prevalent.<sup>2,7</sup>

We found serial monitoring of tumour markers valuable in assessing the response to treatment, especially in our cohort of patients, whereby the majority were managed with complete tumour resection alone. Persistently elevated AFP levels or a secondary rise in the levels were sensitive indicators of residual viable tumour or recurrence.

The different histological subtypes of GCTs follow different clinical courses. Unlike malignant teratomas, which tend to be found in extra-gonadal sites, benign teratomas in our study were more commonly localised in the gonads. The prognosis of these patients is very good after complete tumour resection and all of them were disease-free over a mean follow-up period of 2.3 years (1 to 4.8 years).

The remaining patients with malignant GCTs ( $n = 24$ ) were analysed separately. It was found that patients with gonadal tumours were more likely to present at Stage I than those with extra-gonadal tumours (95% versus 40%). Hence, complete resection was more likely to be achieved for the former (19 out of 19, 100%) than the latter (3 out of 5, 60%). This was also noted in other studies<sup>6,13</sup> and is probably the reason why the overall prognosis appears better in gonadal tumours.<sup>8,13-15</sup>

Primary tumour resection was the mainstay of treatment. Complete tumour resection is an important prognostic factor.<sup>2,6,8,13</sup> Completely resected teratomas have shown a relapse-free survival of 96% in comparison to a relapse-free survival of 56% in incompletely resected teratomas.<sup>9</sup> Complete resection was achieved in 87.5% of our patients with malignant GCTs and this has contributed to our high overall and event-free survival. In patients with bulky or invasive tumours, delayed tumour resection after 3 to 4 cycles of chemotherapy was the preferred mode of therapy.<sup>2,8</sup>

There were 2 patients with retroperitoneal lymph node relapse of Stage I testicular tumours, and 1 patient with Stage II testicular tumour. All were successfully treated with orchidectomy followed by chemotherapy. They had remained disease-free at 9 years, 16 months and 5 years of follow-up respectively. Our experience is similar to that of

other centres, whereby retroperitoneal lymph node dissection is no longer required in such patients.<sup>2,6,7,16</sup>

The improvement in chemotherapy has resulted in better prognosis with significantly less toxicity. Bleomycin and vinblastine were widely used in the 1970s.<sup>17,18</sup> Cisplatin was introduced in the 1980s and this proved to be a highly effective therapy for advanced disease and was the reason behind the dramatic improvement in survival for patients with GCTs.<sup>19</sup>

The combination of cisplatin, vinblastine and bleomycin was effective, but the weekly administration of bleomycin caused unacceptable pulmonary toxicity. When bleomycin therapy was reduced to a 3-weekly dose, the event-free survival was comparable (84%) and there were no significant pulmonary side effects.<sup>7</sup> Etoposide was then introduced in the late 1980s as an effective salvage agent with a superior side effect profile, other than the rare risk of second malignancies like acute myeloblastic leukaemia.<sup>20-22</sup>

Nine of our patients received BEP while 2 received PVB, at the discretion of the oncologists. Due to the small number of patients involved, we were unable to detect any significant differences in the efficacy or the side effects encountered in the 2 groups of patients. The overall chemotherapy side effect profile is, however, comparable to other published studies.<sup>2,7,8,9,16,19</sup> Bone marrow suppression was the most common complication. Most of the complications developed after at least 4 cycles of chemotherapy.

Bleomycin-induced pulmonary toxicity has been reported to range from 3% to 40%, with fatal toxicity in 1% to 15% of patients.<sup>23</sup> Of all our patients who received bleomycin, only 1 underwent lung function test prior to and upon completion of her chemotherapy. The remaining patients (8 were less than 6 years old while 2 were unable to co-operate with a lung function test) were followed up with detailed history-taking and clinical examination of the respiratory system. None of them presented with pulmonary signs or symptoms attributable to bleomycin, although this form of screening may not be sensitive enough to pick up early pulmonary disease. A modified treadmill test of these patients, to look for exercise-induced hypoxaemia, may be a more sensitive and objective screening method.

In conclusion, the 10-year overall and event-free survivals for patients with malignant GCTs were 96% and 88%, respectively, at a mean follow-up period of 5.1 years (0.7 to 10 years). This is contributed by the majority of patients (83%) presenting in early Stage I disease and by the high rate (87.5%) of complete tumour resection attained. Future challenges lie in reducing the treatment toxicity without compromising on efficacy, and in further improving the therapy for poor prognosis patients.

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