

# Clinical and epidemiological characteristics of children with germ cell tumors: A single center experience in a developing country

Sonay İncesoy-Özdemir<sup>1</sup>, Ulya Ertem<sup>2</sup>, Gürses Şahin<sup>2</sup>, Ceyhun Bozkurt<sup>2</sup>, Nazmiye Yüksek<sup>3</sup>, Ayşe Ceyda Ören<sup>2</sup>, Eda Balkaya<sup>2</sup>, Afra Alkan<sup>4</sup>

Departments of <sup>1</sup>Pediatric Oncology, and <sup>4</sup>Biostatistics, Yıldırım Beyazıt University, Ankara, Turkey; <sup>2</sup>Department of Pediatric Oncology, Dr. Sami Ulus Children's Hospital, Ankara, Turkey; <sup>3</sup>Department of Pediatric Oncology, Zonguldak Karaelmas University, Zonguldak, Turkey. E-mail: [sincesoy@yahoo.co.uk](mailto:sincesoy@yahoo.co.uk)

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**SUMMARY:** İncesoy-Özdemir S, Ertem U, Şahin G, Bozkurt C, Yüksek N, Ören AC, Balkaya E, Alkan A. Clinical and epidemiological characteristics of children with germ cell tumors: A single center experience in a developing country. *Turk J Pediatr* 2017; 59: 410-417.

Germ cell tumor (GCT) is a rare malignancy accounting for 2-3% of all pediatric tumors. The overall survival rate of children and adolescents with GCT is more than 80% after adopting combined therapy. The aim of this study is to review clinical presentation, management, and outcome in a single-center series with extracranial GCT. Clinical characteristics, pathologic presentations, and survival outcomes of 101 children with GCT, treated at our hospital from 1988 to 2011, were analyzed. Sixty-two of patients were female and 39 of them were male. Fifty-eight (57%) patients had gonadal tumor (24 testicular, 34 ovarian), 43 (43%) extragonadal. Histologically, teratomas were found most frequently (26 mature, 10 immature), followed by yolk sac tumors (n: 33), mixed malignant tumors (n: 13), embryonal carcinoma (n: 10), disgerminoma (n: 8) and seminoma (n: 1). Twenty-six patients were diagnosed as mature teratoma and we excluded them in the evaluation of staging and survival. Five-year overall and relaps-free survival were 80.3% (mean follow-up time: 215.8 months) and 73.4% (mean follow-up time: 176.2 months), respectively. Five-year survival rates were 93.2% and 90.2% in malign GCTs diagnosed after 1999.

*Key words:* germ cell tumor, treatment, survival, children.

Gonadal and extragonadal germ cell tumors (GCT) are infrequent in childhood, occurring at a rate of 2.4 cases per million children and representing approximately 1% of cancers diagnosed in persons younger than 15 years. Until recently, the myriad of histologic subtypes and sites of origin and the paucity of cases hindered the standardization of care for such children.<sup>1</sup> GCTs form an important group of gonadal neoplasms and are also found in a number of extragonadal sites like the mediastinum, pineal and sacrococcygeal regions and retroperitoneum. Although there are considerable differences between GCTs occurring in different anatomical locations they exhibit a remarkable homology, and are considered as a group.<sup>2,3</sup>

GCTs show numerous histologic subtypes. The histologic features of each subtype are independent of presenting clinical characteristics; tumor biology and clinical behavior vary with site of origin, state, and age of the patient.<sup>4</sup> The introduction of platinum-based chemotherapy resulted in cure rate in excess of 80%, even in advanced disease.

The aim of this study was to review our institutional experience with the clinical and epidemiological characteristics, management and outcome in extracranial GCTs over a period of 23 years.

## Materials and Methods

One hundred and one children with extracranial

GCT were admitted to our institution between 1988 and 2011. The cut-off date for analysis of these patients was February 2012. Their clinical characteristics, pathologic features, methods of treatment, relaps and survival outcomes were retrospectively evaluated. The tumors were classified according to the Dehner system.<sup>5</sup> Twenty-six patients were diagnosed as mature teratoma and we excluded them in the evaluation of staging and survival analyses. The Children's Oncology Group (COG) classification system for staging was used.<sup>1</sup>

The study was approved by the Ethics Committee of the Yildirim Beyazit University (Report number: 2017/08).

The quantitative variables were described using median and range; qualitative variables were described using frequency and percentages. We used chi-square test to examine the relationship between pairs of variables. Overall survival (OS) and relaps free survival (RFS) distributions were estimated by the method of Kaplan-Meier survival analyses. Using the Cox proportional hazards regression model, multivariate analyses were performed to determine the variables that were independently predictive of prognosis. A  $p < 0.05$  was used for statistical significance.

## Results

During the period of 23 years, 101 patients with extracranial GCTs were admitted to our clinic. Out of the 101 patients, 62 were female and 39 were male. Their median age was 72 months (0-192 months). The vast majority of patients presented with a combination of symptoms and signs; however, the most frequent primary symptoms and signs were abdominal pain and abdominal mass (n: 44 patients). Abdominal pain, either acute, cronic, or both was reported in 23 patients. The second most frequent symptom, abdominal distension by the abdominal or pelvic mass, was noted in 21 patients, associated with pain in all. The third important symptom was increase in testicular size with palpable mass. Other symptoms and signs included sacrococcygeal mass, constipation, nausea, vomiting, urinary symptoms and precocious puberty. One patient had acute abdominal condition. The duration of symptoms ranged from 1 day to 6 months, except for one patient who presented with a 2 years (since birth) history of sacrococcygeal

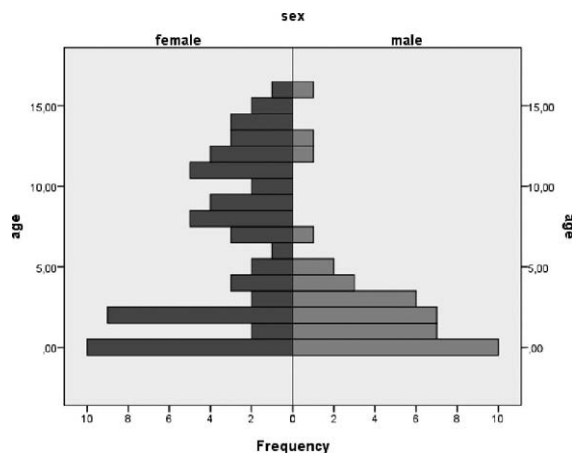


Fig. 1. Gender distribution according to age (years).

mass. The clinical presentation of these patients are summarized in Table I.

Figure 1 reveals the bimodal age distribution of GCTs. The first peak was observed during the first 2 years of life both in girls and boys. The second peak started at the age of 8 years in girls and at the age of 12 years in boys. The lowest incidence was found at the age of 5-6 years. Overall, GCTs were more common in girls than in boys (M:F, 1: 1.5). However, among children under 5 years of age, the tumors were more common in boys (M:F, 1.2:1). In the older age group, GCTs were more common in girls (34 females vs. 4 males) (M:F, 0.11:1,  $p < 0.001$ ). This striking female predominance relates to the high number of ovarian tumors (31 ovarian vs. 4 testicular) in older patients.

### Site of origin and diagnostic imaging

The site of the GCTs varied with genders and age. Fifty-eight (57%) patients had gonadal tumor (24 testicular, 34 ovarian), 43 (43%) extragonadal (29 sacrococcygeal, 13 retroperitoneum, 1 neck). Although bilaterality has been reported in gonadal GCTs, no contralateral tumours were identified in this series.

The ovarian tumors were most frequent in the age groups 5 to 10 years and over 10 years. The testis tumors were most frequent in the 1 to 5 years.

Sacrococcygeal and retroperitoneal regions were the most common extragonadal site of origin. Of the extragonadal GCTs, diagnosed during the first year of life, two-thirds (66%) occurred at the sacrococcygeal region.

**Table I.** Clinical and Laboratory Characteristics of Patients.

	n (%)
Gender	
Male	62 (61.3)
Female	39 (38.6)
Median age (month)	72 (0-192)
Presenting symptoms and signs	
Abdominal pain	23 (22.7)
Abdominal distension	21 (20.7)
Sacrococcygeal mass	15 (14.8)
Increase in testicle size	20 (19.8)
Other	22 (21.7)
Site	
Ovary	34 (33.6)
Testis	24 (32.6)
Extragonadal	43 (42.5)
Histopathology	
Mature teratoma	26 (25.7)
Immature teratoma	10 (9.9)
Yolk-sac	33 (32.6)
Mixed germ cell tumor	13 (12.8)
Embryonal carcinoma	10 (9.9)
Disgerminoma	8 (7.9)
Seminoma	1 (0.9)
Tumor markers	
AFP	43 (57.3)
B-HCG	4 (5.3)
AFP and B-HCG	4 (5.3)
Stage	
I	19 (25.3)
II	15 (20)
III	38 (50.6)
IV	3 (4)
Management	
Surgery	33 (32.6)
Surgery with chemotherapy	
BEP	51 (50.4)
VAC	17 (16.8)
Outcome	
Alive without disease	37 (49.3)
Lost to follow up in remission	13 (17.3)
Lost to follow up with disease	14 (18.6)
Exitus	11 (10.8)

AFP: alpha-feto-protein, beta-HCG: human beta chorionic gonadotropin, BEP: bleomycin, etoposide, and cisplatin, VAC: vincristine, actinomycin, cyclophosphamide

**Table II.** Number of Tumors According to Site, Histology and Age.

Site	Age (month)	Histology				Total
		Teratoma	Germinoma	Non-germinom / non-YST	YST	
Ovary	0-12	0	0	0	0	0
	13-60	0	1	2	0	3
	61-120	6	2	2	4	14
	>120	6	5	3	3	17
Testis	0-12	1	0	1	3	5
	13-60	3	0	3	9	15
	61-120	0	0	1	0	1
	>120	1	1	0	1	3
Extragonadal	0-12	14	0	2	3	19
	13-60	7	0	5	9	21
	61-120	0	0	0	2	2
	>120	0	1	0	0	1

YST: yolk sac tumor

Abdominal ultrasound was the most common investigation, performed in all patients. Computed tomography was performed for 24 patients. Magnetic resonance imaging was performed only in one patient.

**Tumor markers**

Alpha-feto-protein (AFP) and human beta chorionic gonadotropine (B-HCG) levels were normal (based on age) in all patients with mature teratomas (26 patients). We detected high AFP levels in 43 of 75 patients with malignant GCTs, high B-HCG levels in 4 of 75 patients. Both AFP and B-HCG levels were elevated in 4 patients. We found normal AFP

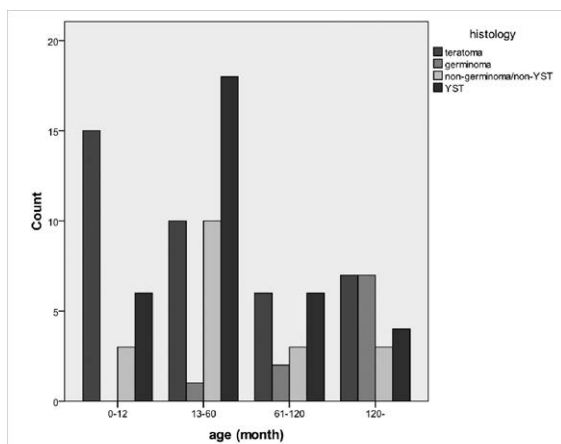
and B-HCG levels in 17 patients with malignant GCTs (six with immature teratomas, four with embryonal carcinoma, two with seminomas, two with yolk sac tumors, two with mixed malignant tumors and one with disgerminoma). Unfortunately, in two of them tumor markers were measured after surgery (one had stage I disease, another one had stage II disease). Seven patients were not studied for AFP and B-HCG because of socio economic difficulties.

**Histology and staging**

Histologically, teratomas were found most frequently (26 mature, 10 immature), followed by yolk sac tumors (n: 33), mixed malignant tumors (n: 13), embryonal carcinoma (n: 10), disgerminoma (n: 8) and seminoma (n: 1).

We observed that the GCT histology in children vary with sex and age groups (Figure 2 and Table II). Figure 2 shows that in infants, the vast majority of GCTs are teratomas. Malignant non-germinomatous GCT, the vast majority of which were yolk-sac tumors, were most common at the age of 13-60 months. Disgerminomas predominantly developed after the age of 5 years. Disgerminomas and teratomas constituted the most frequent histological subtype during adolescence.

Twenty-six patients were diagnosed as mature teratoma and they were excluded from the evaluation of staging and survival. Nineteen



**Fig. 2.** Age distribution according to histology. YSK: yolk sac tumor

out of 75 cases (25.3%) had stage I, 15 (20%) had stage II, 38 had (50.6%) stage III and 3 (4%) had stage IV disease. Additionally, 3 (4%) out of 38 patients with stage III disease and 3 (4%) patients with stage IV disease were only operated at other clinics and they admitted to our clinic with relapses.

### Treatment

For all patients with mature and immature teratomas treatment consisted of surgery alone. But, three patients with immature teratomas received chemotherapy because of local and systemic relaps. The first patient with immature teratoma was 29-day-old girl. She was admitted to the clinic with sacrococcygeal mass since birth. At laboratory examination, AFP (based on age) and B-HCG were normal. Complete surgical excision of tumor with coccygectomy was performed. She was close follow-up without any drug therapy every 3 weeks. Two months later, local relapse was identified. Tumor markers were normal. Adjuvant chemotherapy had been administered, consisting of 6 cycles of BEP (bleomycin, etoposide, and cisplatin). However, tumor recurred three months after the chemotherapy ends. AFP was never elevated in this patient. Re-resection was performed, because of local recurrence after systemic chemotherapy. Histologic examination showed that retroconversion of immature teratoma to mature teratoma. The patient had subsequently been lost to follow-up. The second patient, an 8-year-old girl, was referred to our clinic due to abdominal pain and distention for 2 months. CT scan revealed a complex cystic-solid mass, measuring 13x3x14 cm, on the right over and retroperitoneal region. AFP was 52 ng/ml (0-8), while B-HCG was normal. On exploratory laparotomy, a large right ovarian mass and liver metastasis were identified. Right salpingo-oophorectomy was performed and the resected ovarian tumor. Unfortunately, intraoperative rupture of the tumor occurred during operation. Adjuvant chemotherapy with BEP was administered. The patient completed 6 cycles of BEP. AFP level at the end of treatment was normal. She has maintained complete remission for over 10 years. The third patient, a 4-year-old girl, with a previous diagnosis of sacrococcygeal immature teratoma admitted to our clinic with new liver and pulmonary metastases after 18 months first diagnosis. Five

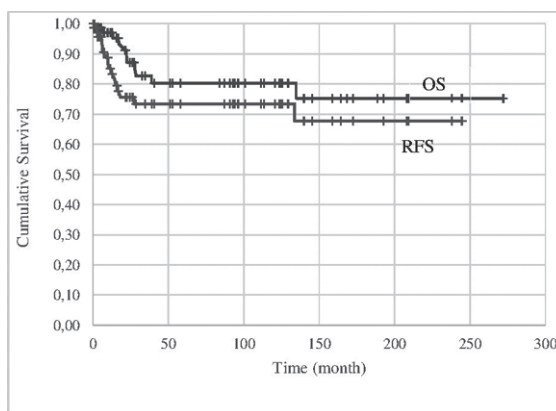


Fig. 3. Overall (OS) and relaps-free survival (RFS) in children with malignant extracranial germ cell tumors, 1988-2011.

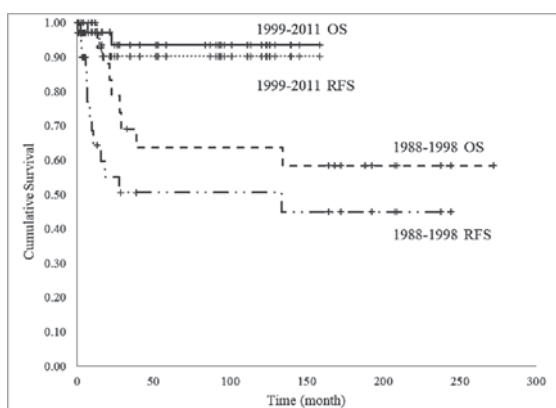


Fig. 4. Overall (OS) and relaps-free survival (RFS) in children with malignant extracranial germ cell tumors, 1988-1998 and 1999-2011.

cycles of chemotherapy were administered, but she was lost to follow-up.

Surgery was considered the sole treatment necessary in 33 (32.6%) patients, surgery + chemotherapy in 66 (65.3%) other patients, and surgery + chemotherapy + radiotherapy in 2 (1.9%) patients. Tumors were treated with VAC (vincristine, actinomycin, cyclophosphamide) protocol from 1988 to 1994. Cisplatin-based combination chemotherapy was used from 1994 onward. Fifty-one (50.4%) cases were treated with BEP protocol, 17 (16.8%) cases with VAC protocol. Only two patients received radiotherapy because of progressive disease.

### Outcome

Thirty-seven (49.3%) patients were disease-free at a median follow up of 215.8 months. Eleven patients (14.7%) had died from progressive disease ranging between 1 and 38 months

(median 21 months) after diagnosis. Fourteen patients were lost to follow up at a median follow up of 3 months (ranged, 1-15). Thirteen patients were lost without disease at a median follow up of 28 months (ranged, 12-139).

Sixteen (21.3%) patients had relapse in 3 to 18 months. The median time for tumor recurrence was 10 months. For the 16 relapses, 9 were locoregional recurrence and 7 were systemic metastases. Six out of them were referred to us for relaps treatment after primary was managed elsewhere. These patients were in the early 1990s, surgical centers are operated, stage 1 evaluated and followed without consultation of pediatric oncology clinic. (Table III).

The 5-year OS and RFS were 80.3% (mean follow-up time: 215.8; 95% CI: 186.0- 245.7 months) and 73.4% (mean follow-up time: 176.3; 95% CI: 147.45- 205.1 months), respectively (Figure 3).

We compared two time periods of 23 years (1988-1998 and 1999-2011). The 5-year OS and RFS improved from 63.7% and 50.5% in 1988-1998 to 93.2% and 90.2% in 1999-2011, respectively (p: 0.022; Fig. 4).

#### Prognostic Factors

We investigated prognostic factors by univariate and multivariate analysis. Age group, sex, site, histology, stage, tumor marker, and treatment were tested; they did not have a prognostic value. These methods identified patients treated between 1999 and 2011 as having decreased mortality in comparison with those treated in the earlier period (in the multivariate analysis, HR 0.16; 95% CI: 0.028-0.989; p: 0.049).

#### Discussion

Pediatric GCTs are rare tumors. Their overall incidence can be estimated as 0.9/100,000 children up to 15 years. They arise due to variation from normal differentiation of germ cells and include a heterogeneous group of neoplasms with remarkable variability concerning histology and site of presentation: Benign, malignant and immature GCTs can be observed in children and adolescents with different rates, also according to age.<sup>3</sup> We have confirmed that the GCT localization and histological subgroups in children vary among genders and age groups. The clinical characteristics found in this study are similar to other national and international studies related to the issue.<sup>6-12</sup>

Median age at diagnosis varied according to tumor site, histology, and sex. In a large population-based cohort study from Germany, including 1,442 cases up to 15 years of age, there was a bimodal age distribution. In this study, the first peak was observed during the first 2 years of life. The second rise of incidence started at the age of 7 years in girls and at the age of 10 years in boys. As the lowest incidence was found at the age of 5-6 years.<sup>8</sup> In another study from US, incidence peaks were observed before the age of 1 year and from ages 15 to 19 years in both boys and girls. In this study, the incidence of GCTs was similar in boys and girls in the age group of patients ages birth to 9 years, whereas the incidence was much higher in boys in the group ages 10 to 19 years.<sup>6</sup> In accordance with other studies, bimodal age distribution was observed in our patients. The first peak was observed during the first 2 years of life both in girls and boys.

**Table III.** Relapse Patterns and Results.

	n
Relapse site	
Local primary site	6
Local and intraabdominal	3
Systemic	
Lung	4
Liver	2
Lung and liver	1
Outcome of patients who experienced relapse	
Exitus	6
Lost to follow up	6
Alive without disease	4

The second peak started at the age of 8 years in girls and at the age of 12 years in boys. The lowest incidence was found at the age of 5-6 years. Among children under 5 years of age, the tumors were more common in boys (M:F, 1.2:1), while in the older patients, there was a striking female predominance (M:F, 0.11:1,  $p < 0.001$ ). This might be attributed to referral of male adolescent patients to adult centers in our country.

Tumor markers are important in the diagnosis, diagnosis of relapse and follow-up. High AFP and beta-HCG levels were detected in 63% and 11% of the studied patients, respectively.

Teratomas are the most common GCTs observed in most published series.<sup>6,7,9</sup> In our series, the most frequently recognized histological types were teratomas and yolk sac tumors. Teratomas constitute the vast majority of GCTs in neonate and that the incidence peak of YST follows approximately 1 year later.

Mature teratomas with normal tumor markers were kept in regular follow-up, but patients having malignant GCTs need follow-up regarding appropriate therapy and survival.

Immature teratomas, although not truly malignant, have been treated as malignant neoplasms in the past because of their potential to recur as malignant tumours. Either immature teratomas or immature teratomas with microscopic foci of yolk sac tumours have been included in the group of malignant GCTs in many series<sup>10,12</sup>; chemotherapy has been given to patients with grade II or III immature teratomas. In our series, three patients with immature teratomas received multi-agent chemotherapy because of relaps and elevated AFP and all remained free of disease at follow-up.

The prognosis in GCTs did not improve until the late 1970s, when the VAC regimen became the standart chemotherapy in GCTs. Since the introduction of platinum-based agents in pediatric chemotherapy regimens, the survival rates for children with malignant GCTs ranging from 75% to more than 90%.<sup>13-15</sup> With accurate staging, complete resection, and chemotherapy for malignant GCTs, patients are expected to have excellent survival rates. In a study from Turkey, Akyüz et al.<sup>11</sup> reported OS and EFS in ovarian tumors as 68% and 57%, respectively.

Feltbower et al.<sup>15</sup> reported the 5-year survival rates as 93-95% for gonadal GCT, and 70-75% for extragonadal GCT. Mann et al.<sup>14</sup> reported the 5-year survival rates as 90.9% and 87.8%. In another recent study from Finland, the overall 5-year survival was reported to be improved from 63.7% in 1969-1987 to 90.7% in 1988-2006.<sup>9</sup> In a more recent large population-based study from Germany, 5-year survival rate was reported as 92% for gonadal and extragonadal GCTs.<sup>10</sup>

In our series, OS rate (80.3%), which is lower than that of other series, could be partially explained by the high number of patients with advanced disease. Additionally, of 11 patients in our series, 10 died between 1988 and 1998. It was remarkable that within this period, six patients were operated in other surgical centers, followed-up without consulting pediatric oncology departments, and admitted to the clinic with advanced-stage relapse thereafter. Only two of the patients who were diagnosed after 1999 have relapsed so far. It was also considerable that except for one, all other cases had abandoned the treatment within this period. As clearly seen in our study group, survival rates increased from 1988-1998 to 1999-2011 and the number of patients who escaped from treatment decreased over the years.

For extracranial malignant GCTs, the tumour site, age and elevated AFP have been proven to be of importance as prognostic factors.<sup>13,16-18</sup> Gonadal GCTs have a significantly better prognosis compared to extragonadal tumours. We could not identify site, age and elevated AFP as a prognostic factor. In our study group, the prognosis of malign CCTs has improved over time through advances in treatment. In children with malignant GCTs, survival rates can be improved owing to factors such as advancement in diagnostic and therapeutic techniques, improved supportive care, and a multidisciplinary approach.

In conclusion, some significant differences in clinical features were documented. Among children under 5 years of age, the tumors were more common in boys (M:F, 1.2:1), while in the older patients, there was a striking female predominance (M:F, 0.11:1,  $p < 0.001$ ). This might be attributed to referral of male adolescent patients to adult centers in our

country. They were similar to patients in other large pediatric series with respect to sites of origin, age at presentation in relationship to primary site, histology and sex.

Our study has some limitations. This is a retrospective study from a single national institution. Our data has failed to demonstrate any correlation between tumor stage and survival. This can be explained by the very few numbers of patients with stage IV. Unfortunately, our infrastructure capacity to accurately determine stage at diagnosis was limited at that time.

However, this series confirms the good overall results that can be achieved in children with malignant GCTs. As parallel to the recent developments across the world, the rate of life expectancy has increased due to the elevation witnessed in general health services in Turkey. The advances in multidisciplinary approach to pediatric oncology care have led to dramatically improved survival for children with GCT in Turkey.

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