



# Extracranial Germ Cell Tumor in Children: A Three-year Experience of Pediatric Hematology/Oncology Center, Medical City

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## OBJECTIVE

The aim of this study was to describe the clinical, histological, and pathological characteristics in children with GCT and assess their outcome.

## METHODS

This was a retrospective study conducted for children with germ cell tumors who were treated at the Pediatric Hematology-Oncology Center/Medical City for 3 years from January 1<sup>st</sup>, 2016 to December 31<sup>st</sup>, 2018, and their follow-up till June 30<sup>th</sup>, 2021. Thirty-four cases were identified. The total information was collected by using data from the medical record at our oncology registry and from registered archives in outpatient records. Follow-up of patients over an average period of more than 3 years was carried out either in person at the outpatient clinic or by phone call. The Statistical Package for the Social Sciences version 23 was used for analysis.

## RESULTS

The initial age of presentation ranged from birth until 14 years. More than sixty percent presented below 4 years of age, and then after this, the age at diagnosis was near equally distributed in both 5–9 years and 10–14 years; 6 and 5 patients (17.6% and 14.7%, respectively). Females predominate in all age groups (76.5%) versus (23.5%) males with a male-to-female ratio of 1: 3.2. The main presenting symptom was fever in 13 (38.3%) patients. There were 11 (32.4%) patients who had testicular swelling, and 11 (32.4%) patients with abdominal distension. The duration of symptoms is more than 6 weeks in 19 (55.9%) cases. The common histological type is a yolk sac tumor in 18 (52.9%) patients. No patients presented with stage I, 9 patients with stage II, 6 (17.7%) patients with stage III, and 9 (26.5%) patients with stage IV. The duration of symptoms is more than 6 weeks in 19 (55.9%) cases. There were four benign cases.

## CONCLUSION

The delayed diagnosis is one of the main obstacles in the management of this group. Risk assessment and staging were not conclusive in some cases due to the gaps between surgeons and oncologists. The upstaging gives better outcome in the overall survival compared to other studies at the same place.

**Keywords:** Children; Iraq; teratoma; yolk sac tumor.

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## INTRODUCTION

Gonadal and extragonadal germ cell tumors (GCT) are very infrequent in childhood, occurring at a rate of 2.4 cases per million children and representing approximately 2–3% of cancers diagnosed in children and adolescents younger than 15 years. Germ cell tumors (GCT) are neoplasms that develop from primordial germ cells of the human embryo, which are normally destined to produce sperm or ova. It is a term used to point to a group of malignant germline cell tumors. They can be seen in the ovary, testes, sacrococcygeal region, mediastinum, or other extragonadal sites. They might be detected in the brain of children and adolescents.[1] From the epidemiological point of view, there are two overt peaks in incidence, the first in the young group (0–4 years) and the second one starts with puberty. They occur at a rate of 3 cases in every million children. They represent around 3% of all childhood cancers. The pubertal type represents 15% of malignancies diagnosed in adolescence.[2] The understanding of pathogenesis relies on the analysis of germline development. The adolescent type of GCT looks very similar to the adult type histologically. The childhood type is different, yet. This could put them under a distinct classification.[3] Two histologic classes of GCT are noted in the majority of affected children and infants; teratoma and yolk sac tumor. Yolk sac tumors are malignant. Teratoma is benign in the prepubertal testes but could be malignant in post pubertal age. Nearly most ovarian teratomas are of benign histology. Some are considered malignant if noted with immature components. Germinomas in the ovary are known as dysgerminomas and may occur in children and adults. Certain histologic variants of GCTs secrete the tumor markers alpha-fetoprotein and beta subunit of human chorionic gonadotropin. The production of these markers can be assessed by immunohistochemistry or measurement of blood levels, and has important diagnostic value and can be used to assess disease activity.[4] The treatment of GCTs tumors depends primarily on the site of origin, age of the patients, histopathological subtype, and staging system. The timing and evolving of surgical intervention in parallel with the development of effective chemotherapeutic agents improve the survival rate. The major treatment option of GCT is a cisplatin-based regimen, similar to the adult testicular GCT, which has proved to be a beneficial outcome event in advanced cases.[5] Studies of germ cell tumors are deficient in Iraq, and publications are rare. The aim of the current study was to describe the clinical characteristics, histological, and pathological types in patients with pediatrics GCT and assess their outcome.

## MATERIALS AND METHODS

This was a retrospective study for children with GCT who were treated at the Pediatric Hematology-Oncology Center, Medical City, for 3 years from January 1<sup>st</sup>, 2016 to December 31<sup>st</sup>, 2018, and their follow-up till June 30<sup>th</sup>, 2021. Thirty-four cases were identified; the information was collected from medical records of the hospital and registered archives in outpatient records. The demographic and clinical data, including age, gender, symptoms associated with the initial diagnosis, date of surgery, date of starting/finishing treatment, initial blood tests, and tumor markers all were recorded. The histopathological diagnosis was reviewed by two pathologists to confirm the diagnosis of GCT and its subtype. Clinical staging and the protocol used for treatment and the date of starting/finishing treatment and their outcome were recorded for all patients.[6] Bone marrow aspirate and biopsy were done for 19 patients; all of them are normal. A review of pathological specimen was done for 12 cases in the Department of Pathology, La Sapienza University, Rome. The postoperative adjuvant chemotherapy with four-six cycles of carboplatin–etoposide–bleomycin (JEB) or PEB (cisplatin-based strategy instead of carboplatin), if histology, was reported as malignant GCT. The staging system for GCT was based on tests of tumor markers done before surgery, physical examination, sonogram, computed tomography scans, and magnetic resonance imaging to identify the extent of the tumor and the state of the surrounding lymph node; after that, the staging was assigned based on information from the surgical note and the histopathology result for the tissue removed during surgery. The follow-up of patients over the period of this study was ranging from 3 to 5 years for survival by clinical examination, tumor marker estimation, and imaging studies. Archives of the outpatient clinic were used for follow-up registrations of patients and phone calls. Analysis of the data was done by the Statistical Package for the Social Sciences version 23. The Kaplan–Meier method was used to measure the overall survival and event-free survival rates.[7]

## RESULTS

The distributions of GCTs according to the age groups at the time of initial presentation and gender are shown in Table 1. Twenty-three (67.6%) patients were below 4 years of age; among them, 2 patients were diagnosed in utero and 5 at birth. Females predominate the disease

**Table 1** Demography and duration of symptoms

Data	n	%
Gender		
Male	12	23.5
Female	22	76.5
Age at presentation		
0–4 years	23	67.6
In utero	2	
At birth	5	
1–48 months	16	
5–9 years	6	17.6
10–14 years	5	14.7
Duration of symptoms		
< or =6 weeks	15	44.1
>6 weeks	19	55.9
Total	34	100

in all age groups (76.5% vs. 23.5%), with a male-to-female nearly ratio of 0.5:1. The duration of symptoms is more than 6 weeks in most of the cases 19 (55.9%).

Table 2 discusses the presentation of patients. The main presenting nonspecific symptoms were fever in 13 (38.3%) patients registered by medical history followed by constipation in 9 (26.5%) patients, and anemia in 6 (17.7%) patients. Testicular swelling was reported in 11 (32.4%) patients, 11 (32.4%) patients with abdominal distension, and/or abdominal mass represent the most common specific presentations of GCTs.

Table 3 explains the tumor characteristics. The ovary and testis were the most common sites for tumors detected in 10 patients for each (29.4% for each), followed by Sacrococcyx in 9 (26.5%) patients. Twenty-four cases were diagnosed by excisional biopsy (70.6%). Yolk sac tumor was the most common histopathology reported in 18 (52.9%) patients, followed by immature teratoma in 5 (14.7%) patients. The major location of yolk sac tumors was the testis in 10 patients, followed by the sacrococcygeal region in 5 patients. The immature teratoma was seen in the ovary in 3 patients, mediastinum in 1 patient, and intra-abdominal in 1 patient. All cases of dysgerminoma were in the ovary. Advanced stages were predominant with stage III and stage IV in 6 and 9, respectively (total 44.2%), and 9 cases (26.5%) with stage II with no patients treated as stage I. There were four benign cases. The lung as a metastatic site was noted in all stage IV cases, while liver metastasis was noted in 3 patients. One case was unclassified in regard to staging due to the family's refusal to remove the affected testis until after a few courses of chemotherapy. There were 5 cases labeled as stage III-X because com-

**Table 2** Different variable initial clinical presentation of germ cell tumor

Clinical presentation	n	%
Nonspecific		
Fever	13	38.3
Constipation	9	26.5
Anemia	6	17.7
Reduced urine	5	14.7
Loss of appetite	4	11.7
Vaginal bleeding	3	8.7
Precocious puberty	2	5.9
Specific		
Testicular swelling	11	32.4
Abdominal mass/swelling/pain	11	32.4
Lower back swelling	7	20.6
Gluteal swelling	5	14.7
Total	34	100

Some patients may present with more than one symptom

**Table 3** Tumor histopathology, staging, and location

Data	n	%
Tumor location		
Ovary	10	29.4
Testis	10	29.4
Sacrococcyx	9	26.5
Pelvic mass	2	5.9
Uterus	2	5.9
Mediastinum	1	2.9
Mode of diagnosis		
Excisional biopsy	24	70.6
Incisional biopsy	10	29.4
Histopathology		
Yolk sac tumor	18	52.9
Immature teratoma	5	14.7
Dysgerminoma	4	11.8
Mature teratoma	4	11.8
Mixed type	3	8.8
Stage*		
I	0	0
II	9	26.5
III	6	17.7
III-X	5	14.7
IV	9	26.5
Unclassified**	1	2.9

\*: 4 cases benign; \*\*: Family refused orchidectomy

plete resection was done without a peritoneal wash, and cytology was not taken during surgery.

Table 4 shows the strategies in the management of childhood GCT; they were different as they were relying

**Table 4** Treatment details and outcome of 34 patients with GCT

Data	n	%
Benign		
Surgery alone	3	75
Surgery and chemotherapy*	1	25
Malignant		
Died before treatment	1	3.3
Surgery and chemotherapy	29	96.7
Outcome		
Alive	31	91.1
Died	3	8.9
Total	34	100

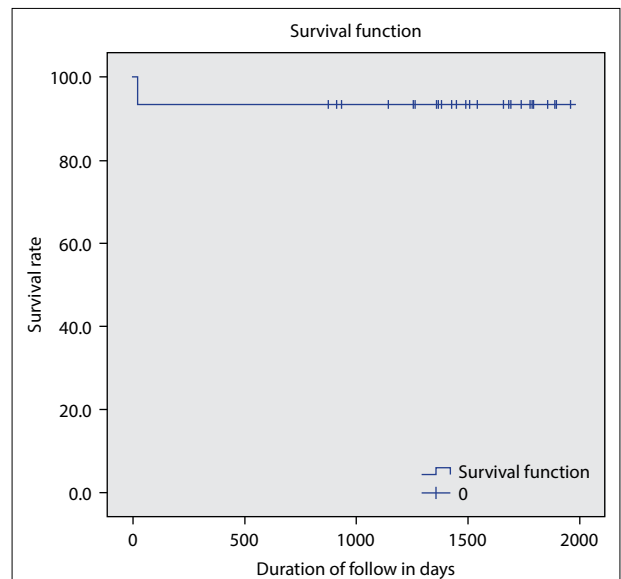
\*: Recurrent mature teratoma 4 months following surgery. GCT: Germ cell tumors

on histopathology results, tumor markers before and after surgery, and the mode of surgery. Out of the four benign cases, three were managed by surgery alone. In regard to malignant cases, 29 (96.6%) patients were treated with surgery and chemotherapy. The chemotherapy regimen was 4–6 cycles of JEB (carboplatin, etoposide, and bleomycin) or PEB (cisplatin, etoposide, and bleomycin). Out of the whole cohort, three patients passed away, one before treatment due to delayed referral and presented with metastasis (pulmonary, pleural effusion, and severe respiratory distress) and the other two – one with yolk sac tumor and the other with immature teratoma. The overall survival was 91.1% with a median follow-up of 1331 days (3.6 years) after treatment (Fig. 1).

## DISCUSSION

In the current study, the majority of cases were female. This finding is believed to be due to the limited number of germ cells in males, and the patterns are different by tumor location in males and females. This is in contrast to a Netherland study in Europe, which reported a low rate among girls.[8,9]

Testicular swelling, abdominal distension, and abdominal mass were the most common presenting symptoms which agree with other studies.[10,11] Abdominal pain is usually at the mid-abdomen, which is explained by the abdominal location of the ovary; while the bony structure of the pelvis formed a boundary for downward extensions, which permits only upward expansion of the tumor.[12] Precocious puberty was reported in 5.9%, a figure comparable in other studies.[13] The duration of symptoms is more than 6 weeks in most of the cases; this might be due to a low



**Fig. 1.** Survival rate for 34 patients with germ cell tumors.

index of suspicion for childhood cancers by a general pediatrician who represents the first line of physicians to examine the patients. Additional factors are a lack of urgent interventions, delayed appointments of imaging study and histopathology result after surgery, and the family acceptance of the disease diagnosis which poses an unintended burden to the disease. In the current study, one case of precocious puberty was treated as idiopathic precocious puberty for 5 years before referral.

The testes and ovaries were the major reported tumor sites, followed by the sacrococcyx. This was similar to similar studies in the same center.[14,15] The sacrococcygeal location was more frequent in infants and very young children. Other locations are the anterior mediastinum, the gonads, and other sites. It was also in agreement with other studies which reported that the tumor mainly arises in the gonads in more than 90%. [16] The explanations of this distribution may be related to improper migrations of primordial germ cells during development in embryonic life.

The yolk sac histopathology was the predominant type in this study, the same seen in other studies.[15] YST represents the most common type in children with GCT and is common at the sacrococcygeal and testicular locations in other studies also.[17] Difficulty in staging was mainly related to difficult communication with the surgeons who performed the surgery. The surgeon is usually seen first before the oncologist. Only one case in this cohort was referred by a gynecologist (dysgerminoma). Eskander et al.[18] have shown that most of the cases were referred by a gynecologist who

performs full surgical staging according to the Children's Oncology Group guidelines. This enlightens the emergent needs of oncologic surgeons and the multidisciplinary team. Lack of surgeon's notes like state of surrounding lymph nodes, retroperitoneal lymph nodes, lack of ascitic fluid cytology from peritoneal washing, and absence of the preoperative tumor markers in some patients are great hindrances to the exact staging; hence, upstaging was preferred by the oncologist.

Dramatic improvement in survival outcomes was represented by a 91.1% survival compared with previous studies in the same center (54.8% by Fatin and 59% by Al-Saeed). [14,15] In Smith et al.'s [19] study, the survival rate dramatically improves between 1975 and 2010 and decreased in mortality in more than fifty percent of cancer.

## CONCLUSION

The presentations of patients with GCT were similar to other studies. The issue of delayed diagnosis was one of the main obstacles in the management of this group. Risk assessment and staging were not conclusive in some cases due to the gaps in communication between surgeons and oncologists in addition to improper assessment of tumor markers related to the time of operation. No stage I was reported, and there was a tendency for upstaging due to a lack of preoperative data.

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**Ethics Committee Approval:** The study was approved by the Republic of Iraq Ministry of Health Medical City Welfare Teaching Hospital Ethics Committee (no: 1, date: 01/01/2021).

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