ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

# Clinical Characteristics and Treatment Outcomes of Patients with Malignant Extracranial Germ Cell Tumors: A 20-Year Single-Center Experience

## Ekstrakraniyal Malign Germ Hücreli Tümör Tanılı Hastaların Klinik Özellikleri ve Tedavi Sonuçları; 20 Yıllık Tek Merkez Deneyimi

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## Abstract

**Introduction:** Germ cell tumors account for 2–3% of all pediatric tumors. The aim of this study was to evaluate the clinical features and treatment outcomes of pediatric patients treated and followed up for extragonadal MGCTs in our center.

**Materials and Methods:** A total of 41 patients diagnosed with MGCTs in the pediatric oncology department of Akdeniz University between June 1999 and June 2019 were evaluated retrospectively.

**Results:** Twenty-nine (71%) of the patients were girls and female dominance ($p<0.001$). The median age was 3.22 (0–18) years. The most patients in the ≤ 5year age group ($p<0.001$). Nineteen (44%) of the tumors were gonadal and 22 (54%) were extragonadal. The most common histolology of MGCTs were yolk sac tumor (36%), mixed GCTs (29%), immature teratoma (20%), and dysgerminoma (15%). Twenty-five (61%) patients presented with advanced stage disease and 37 patients (90%) were treated with chemotherapy. The patients with stage I testicular and stage I ovarian germ cell tumors underwent complete tumor resection followed by a watch-and-wait approach with alpha fetoprotein monitoring without chemotherapy. Of six patients with relapse/refractory disease, two patients survived. Two patients who underwent autologous stem cell transplantation showed complete response but later died due to infection. The median follow-up period of the patients was 34.9 (4–190.6) months and the 10-year overall and disease-free survival rates were 77.1±6.8% 77.1±6.8%. Two relapsed refractory patients who underwent autologous transplantation survived at a mean of 33.21 months.

**Conclusions:** The clinical features and treatment outcomes of the patients in our study were consistent with the literature. The fact that most of our patients were symptomatic at presentation and had advanced stage disease when diagnosed highlights the importance of detailed evaluation and examination. Although good outcomes are achieved in patients with early stage disease, new treatment approaches are needed for patients with advanced and relapsing disease

**Keywords**
Extracranial, malignant, germ cell tumor, child

**Anahtar kelimeler**
Ekstrakranial, malign, germ hücreli tümör, çocuk

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## Öz

**Giriş:** Germ hücreli tümör tüm pediatrik tümörlerin %2-3'ünü oluşturur. Özellikle platin bazlı kemoterapi rejimlerinin uygulanmasından sonra sağ kalım oranları %85'lerden fazladır. Malign germ hücreli tümörler (MGHT) çocuklarda oldukça heterojen bir gruptur. Bu çalışma ile ekstrakraniyal MGHT tanılı hastalarımızın klinik özellikleri ve tedavi sonuçlarının değerlendirilmesi amaçlandı.

**Gereç ve Yöntem:** Akdeniz Üniversitesi Çocuk Onkoloji Kliniği'nde 1999 –2019 Haziran tarihleri arasında ekstrakraniyal MGHT tanısı alan 41 hasta geriye dönük olarak değerlendirildi.

**Bulgular:** Hastaların 29 (%71) `i kız olup K/E cinsiyet oranı: 1,75 olup anlamlı olarak kız cinsiyet hakimdi (p<0.001). Ortanca tanı yaşı 3,22 yıl (0-18 yaş) olup hastalar ağırlıklı olarak (%56 hasta) ≤ 5 yaş idi (p<0.001). Tümörlerin 19 (%44) `ü gonadal, 22 (%54) `ü ekstragonadal olup en sık ekstagonadal yerleşim yeri sakrokoksigeal bölge (%22) idi. Histolojik değerlendirmede sırasıyla yolk sak tümörü (%36), mikst GHT (%29), immatür teratom (%20) ve disgerminom (%15) saptandı.

Hastaların 25 (%61)`i ileri evre hastalık ile başvurmuştu. Hastaların 37 (%90)'ına kemoterapi verildi. Evre I testis ve evre I over GHT hastalarında tümörün cerrahi olarak tam çıkartılmasının ardından αFP değerleri takip edilerek "bekle ve izle" yaklaşımı ile kemoterapi verilmedi. Tanı sonrası relaps refrakter hastalık ile seyreden 6 hastanın ikisi progresif hastalıktan kaybedildi. Otolog kök hücre nakli yapılan iki hastada nakil sonrası kür sağlanmasına rağmen enfeksiyon nedeni ile kaybedildi. Hastaların ortanca izlem süresi 34.9 ay (4-190,6 ay), 5 ve 10 yıllık genel ve hastalıksız yaşam oranları 81.9±6.3%, 81.9±6.3% ve 77.1±6.8% 77.1±6.8 ve %77,1±6,8 olarak bulundu. Nakil yapılan iki hastanın sağkalım süresi ortalama 33.21 ay olarak hesaplandı.

**Sonuç:** Ekstrakraniyal MGHT`lerin tedavisinde, konservatif cerrahi, evre I hastalar için "bekle ve gör" yaklaşımı ve platin bazlı kemoterapi rejimleri ile başarılı sonuçlar alınmaktadır. İlk başvuruda hastaların yakınmalarının olmasına rağmen çoğu hastanın ileri evre hastalık ile başvurduğunun saptanması hekimlerin ayrıntılı değerlendirme ve muayenelerinin önemine dikkat çekmektedir. Erken evre hastalarda sonuçlar başarılı iken ileri evre ve relaps hastalarda yeni tedavi yaklaşımlarına ihtiyaç vardır.


## Introduction

Malignant germ cell tumors (MGCTs) constitute 3.5% of all childhood cancers occurring before the age of 15 years [1]. GCTs originate from primordial germ cells that migrate from the yolk sac to the gonads during embryogenesis [2]. The abnormal or interrupted migration of these primordial germ cells determines the location of the tumor. About 60% of pediatric GCTs are located in extragonadal sites [3]. Extragonadal GCTs are located on the midline in the pineal area (6%), mediastinum (7%), retroperitoneum (4%), and sacrococcygeal area (42%), while gonadal GCTs can occur in the ovary (24%) or testis (9%) [4, 5].

While 90% of GCTs in adults are gonadal, only 40% of GCTs in children are located in the gonads [3, 6]. GCTs are highly heterogeneous in terms of location, clinical signs, and histological type [6, 7]. The most common extragonadal site in children is the sacrococcygeal area. Patients' presenting symptoms and examination findings vary according to tumor location and histological type [8-10].

Alpha fetoprotein (αFP) and beta human chorionic gonadotropin (βHCG) are tumor markers used in diagnosis and follow-up. Yolk sac tumors produce αFP. All choriocarcinomas and some dysgerminomas, seminomas, and embryonal carcinomas produce βHCG. Tumor marker monitoring is important in diagnosis and the evaluation of recurrence [11].

Although surgical resection of the mass is the main treatment approach for most GCTs, chemotherapy should be added to treatment if the tumor cannot be completely resected or has malignant histology.

The treatment of MGCTs is among the major achievements in clinical oncology. Complete response to treatment was first achieved in 1970s with the use of combination chemotherapies such as vincristine, actinomycin D, and cyclophosphamide (VAC regimen). However, with the addition of cisplatin to combination chemotherapy (PVB regimen) the survival rates for children with MGCT's ranging from 75% to more than 90% [1, 7, 12]. The introduction of platinum drugs for the treatment of GCTs was a milestone, and every combination chemotherapy regimen successful in the treatment of MGCTs to date has included a platinum compound.

Objective: The aim of this study was to evaluate the clinical features and treatment outcomes of pediatric patients treated and followed up for extracranial MGCTs in our center.

## Materials and Methods

The clinical characteristics and treatment outcomes of patients diagnosed with extracranial MGCTs in

the pediatric hematology and oncology department of Akdeniz University between June 1999 and June 2019 were evaluated retrospectively. The patients' clinical follow-up information, radiological findings, and pathology and laboratory data were obtained from oncology follow-up charts, and hospital records. MGCT staging was done according to location using the Children's Oncology Group (COG) ovarian, testicular, and extragonadal staging systems [13]. After obtaining local ethics committee approval (KAEK-23.09.2020/732), the study was performed.

**Results**

Seventy-three patients were diagnosed and treated for GCT in our center between June 1999 and June 2019. Of these, 70 were extracranial. The 41 patients whose extracranial GCTs were diagnosed as malignant were included in the study. The patients' mean age was 6.41 (±6.16) years and the median age was 3.08 years (1 day to 18.1 years). Twenty-nine (71%) of the patients were girls (female/male ratio: 2.42), with statistically significant female dominance ($p<0.001$). The mean and median ages at diagnosis were 6.34 ± 5.74 years and 3.2 (0.1-16.5) years for girls and 6.58 ± 7.35 years and 2.27 (1-18.1) years for boys. Fifty-six percent (n=23) of the patients were aged 5 years or younger, 15% (n=6) were between 6 and <11 years of age, and 29% (n=12) were aged 11 years or older ($p<0.001$). The clinical and laboratory characteristics of the patients are presented in Table 1.

The most common presenting symptoms were abdominal pain and abdominal swelling, in 15 patients (37%). Other presenting symptoms included painless testis swelling in 6 patients (15%), hip pain in 7 (17%) patients, vaginal bleeding in 3 (7%), and painful urination and chest pain in 1 patient (2.4%). Masses were detected incidentally in 8 patients (20%) who were asymptomatic.

In terms of location, 54% (n=22) of the tumors were extragonadal and 44% (n=19) were gonadal. The most common extragonadal site were the sacrococcygeal region, in 9 patients (22%) and retroperitoneal region in 5 patients (12,2 %). There were also less common locations (3 mediastinum, 3 vaginal, 1 cervical,1 renal). Patients with mediastinal tumors did not have any syndromic features.

Twelve (29.3%) of the gonadal localized tumors were originated from the ovary and seven (17.1%) tumors from the testis. Bilateral gonadal GHT was not detected.

The ovarian tumors were most frequent in the ages groups over 5 years. The testis tumors were most frequent in the age groups < 5 years and over 10 years. The mean age of the 22 patients with extragonadal MGCT was 2.98 ± 4.39 years. Adolescents predominated among patients with gonadal tumors (n=10), while the majority of the children with extragonadal MGCT were aged 5 years or younger (n=14) ($p<0.001$). The mean and median ages at diagnosis were 14.95 ± 7.81 years, 10.48 (1.5-15) years for mediastinal tumors. Girls predominated in both groups.

In diagnostic evaluation, αFP and βHCG were measured in all patients and αFP value was high in 29 (70.7 %) patients whereas βHCG was high in 9 patients (22%). Eight patients had αFP and βHCG values within the normal range for their age. Four of these patients were mixed GCT, 2 were dysgerminoma, 1 patient was immature teratoma and yolk sac tumor.

Surgery was performed at time of diagnosis in 27 patients (66%), while 14 patients (34%) were diagnosed with biopsy. Unilateral salpingo-oopherectomy was performed in all patients with ovarian MGCTs (n:12) and radical orchiectomy was performed in all patients with testicular MGCTs(n:7). Five patients (41%) with ovarian GCT had stage I disease and the others were stage III or IV. Half of the patients who underwent radical orchiectomy were evaluated as stage I. Of the extragonadal GCTs, 59% (n=13) were removed by complete or near-complete surgical resection, and 76% (n=16) of the patients were staged postoperatively as having stage III-IV disease.

Distribution of MGCTs by stage is presented in Table 1. Twelve (29%) of the patients had stage I, 4 (10%) had stage II, 15 (37%) had stage III, and 10 (24%) had stage IV disease. The most common site of distant organ metastasis was the lung, in 5 patients (90%).

Histopathologic classification of the tumors was 15 (36%) yolk sac tumors, 12 (29%) mixed GCTs, 8 (20%) immature teratomas, and 6 (15%) dysgerminomas.

Patients with stage I testicular GCT and some patients with ovarian GCT underwent complete tumor resection followed by a watch-and-wait approach with tumor marker monitoring, and did not receive chemotherapy. Thirty-seven (90%) of the patients were given chemotherapy according to tumor location,

histopathologic type, and stage. One patient was treated with the EP (etoposide, cisplatin) regimen, while the BEP (bleomycin, etoposide, cisplatin) protocol was used in the other 36 patients. In stage I patients who received chemotherapy, the tumor was located in the ovary (n = 3), testis (n = 3), and extragonadal (n = 4). Histopathological diagnosis of these tumors were determined as mixed GCT (n = 4), 3 yolksac (n = 3), dysgerminoma (n = 3), and immature teratoma (n = 2).

Twelve of 16 patients with stage I-II disease received chemotherapy. The median number of cycles received by these patients was 4 (min:2-max:8), while that of the 25 patients with stage III-IV disease was 6 (min:1-max:10).

Four patients were found to have refractory disease after diagnosis, and another 2 patients relapsed at a mean of 24,92 (min:10.36-max:39.48) months after diagnosis. Relapse disease occurred at the primary tumor site. One patient died due to sepsis after chemotherapy. Two patients who underwent autologous stem cell transplantation achieved remission but later died due to lung infection and acute respiratory distress syndrome. Two relapsed refractory patients who underwent autologous transplantation survived at a mean of 33.21 months.The characteristics of patients with refractory and relapsing disease are shown in Table 2.

The median follow-up time was 34.9 (4-190.6) months and the 5- and 10-year overall and disease-free survival rates were 81.9±6.3%, 81.9±6.3% and 77.1±6.8% 77.1±6.8% (respectively) (Graphic 1). Analyses of survival rates revealed no statistically significant relationships with sex, tumor location, disease stage, or tumor histology (Table 3).

Table 1. Patient characteristics and staging and treatment information according to tumor location

| | | Gonadal Location | Extragonadal Location | Total N (%) |
|---|---|---|---|---|
| Patient number, n (%) | | 19 (46,4%) | 22 (53.6 %) | 41 (100%) |
| **Age group, n (%)** | | | | |
| | ≤ 5 | 4 (9.6%) | 14 (34.4%) | 18 (44%) |
| | >5-< 11 | 5 (12.2%) | 1 (2.4%) | 6 (26.7%) |
| | ≥ 11-18 | 10 (24,4 %) | 2(4.8%) | 12 (29.3%) |
| **Sex** | | | | |
| | Female | 12 (29.3%) | 17 (41.4%) | 29 (70.7%) |
| | Male | 7 (17.1%) | 5 (12.2 %) | 12 (29.3%) |
| **Histology** | | | | |
| | Immature Teratoma | 2 (4.8%) | 6 (14.8 %) | 8 (19.6%) |
| | Yolk Sac | 5 (12.2%) | 10 (24.3%) | 15 (36.5%) |
| | Dysgerminoma | 5 (12.2%) | 1 (2.4%) | 6 (14.6%) |
| | Mixed GCT | 7 (17.1%) | 5 (12.2%) | 12 (29.3%) |
| **Surgery procedure** | | | | |
| | Biopsy | 1 (2.4%) | 13 (31.7%) | 13 (31.7%) |
| | Subtotal resection | | 1 (2.4%) | 2 (4.8%) |
| | Total resection* | 18 (33.2 %) | 8 (19.6%) | 22 (52.8%) |
| **Stage** | | | | |
| | I | 8(19.7%) | 4 (9.6%) | 12 (29.3%) |
| | II | 2 (4.8%) | 2 (4.8%) | 4 (9.6%) |
| | III | 5(13%) | 10 (24%) | 15 (37%) |
| | IV | 4 (9.4 %) | 6 (14.6%) | 10 (24%) |
| **Relapse** | | | | |
| | Yes | - | 6 (14.6%) | 6 (14.6%) |
| | No | 19(46.2%) | 16 (39.4%) | 35 (85.6%) |

*Salpingo-oophorectomy / Radical orchiectomy / Total resection

## Discussion

Pediatric GCT's are rare tumors. Its incidence and histologic features vary depending on the primary tumor site and the patient's gender and age [8-10]. In a retrospective study by Islam Nasir et al. evaluating 207 pediatric patients with GCT, malignant tumors were more common than benign tumors and 80% were gonadal [14]. Lin et al. reported that 75% of 127

Table 2. Characteristics of patients with refractory and relapsing disease

| Patient | Sex | Age (years) | Diagnosis | Location | Primary CT | Time from Diagnosis to Relapse | Relapse Treatment | Final outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 0.9 | Stage 3 Yolk sac | Retroperitoneal | 4 BEP | First relapse: 13 months Second relapse: 27 months | 3 ICE + autologous SCT | Death (Disease-free) |
| 2 | M | 0.1 | Stage 2 Immature teratoma | Intraabdominal | 2 BEP | Refractory disease | 1 ICE | Death (Progressive disease) |
| 3 | F | 2.9 | Stage 3 Yolk sac | Sacrococcygeal | 3 BEP | Refractory disease | 7 ICE | Surviving disease-free |
| 4 | F | 1.4 | Stage 2 Mixed GCT (IT+YS) | Retroperitoneal | 4 BEP | Refractory disease | 2 ICE + Surgery + RT | Death (Progressive disease) |
| 5 | F | 3.1 | Stage 4 Yolk sac | Bladder | 4 BEP | Refractory disease | 6 BEP + Surgery + Autologous SCT | Death (Disease-free) |
| 6 | F | 2.5 | Stage 4 Mixed GCT (embryonal carcinoma + YS) | Retroperitoneal | 6 BEP + Surgery | First relapse: 11 months | 2 BEP + Surgery + RT | Surviving disease-free |

CT: Chemotherapy, F: Female, M: Male, Mixed GCT: Mixed germ cell tumor, BEP: Bleomycin, etoposide, cisplatin, ICE: Ifosfamide, carboplatin, etoposide, SCT: Stem cell transplantation, IT: Immature teratoma, YS: Yolk sac, RT: Radiotherapy

Table 3. Analysis for Overall Survival And Dissease Free Survival in Pediatric Patient With Extracranial Germ Cell Tumors

| Characteristic | | OS rate (%) | | p-value | DFS rate(%) | | p-value |
|---|---|---|---|---|---|---|---|
| | | 5 year | 10 year | | 5 year | 10 year | |
| Sex | Male | 83.3 ± 10.8 | 83.3 ± 10.8 | .896 | 83.3±10.8 | 83.3±10.8 | .553 |
| | Female | 80.7 ± 8.0 | 80.7 ± 8.0 | | 73.8 ± 8.6 | 73.8 ± 8.6 | |
| **Histology** | Immature teratoma | 62.5 ± 17.1 | 62.5 ± 17.1 | | 62.5 ± 7.1 | 62.5 ± 7.1 | |
| | Yolk sac tumor | 70.6 ± 12.6 | 70.6 ± 12.6 | .067 | 72 ± 12 | 72 ± 12 | .282 |
| | Dysgerminoma | 100 | 100 | | 100 | 100 | |
| | Mixed GCT | 100 | 100 | | 81.9±11.6 | 81.9±11.6 | |
| Age at diagnosis, year | ≤ 5 | 71.5 ± 10.1 | 71.5 ± 10.1 | .213 | 62.2 ± 10.8 | 62.2 ± 10.8 | .073 |
| | 5-10 | 100 | 100 | | 100 | 100 | |
| | ≥11 | 91.7 ± 8 | 91.7 ± 8 | | 91.7 ± 8 | 91.7 ± 8 | |
| Stage of tumors | Stage I-II | 93.8 ± 6.1 | 93.8 ± 6.1 | .138 | 87.1 ± 8.6 | 87.1 ± 8.6 | .238 |
| | Stage III-IV | 73.7 ± 9.5 | 73.7 ± 9.5 | | 70.5 ± 8.7 | 70.5 ± 8.7 | |
| Location | Gonadal | 89.5 ± 7 | 89.5 ± 7 | .292 | 89.5 ± 7 | 89.5 ± 7 | .092 |
| | Extragonadal | 74.8 ± 10 | 74.8 ±10 | | 65 ±10.9 | 65 ±10.9 | |

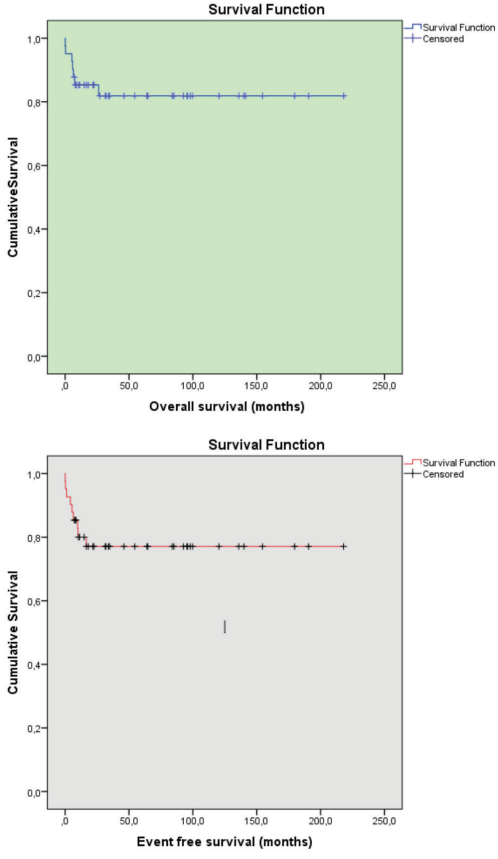
Mixed GCT: Mixed germ cell tumor

pediatric patients with GCT's had malignant gonadal GCT [15]. We treated 73 GCT patients in our center in a period of 20 years, but our study only included the 41 (56%) patients with MGCT.

The reason for the high rate of malignancy among these patients may be that patients with GCTs that completely resected and found to be benign were not referred to pediatric oncology centres.

In the Children's Cancer and Leukemia Group (CCLG; United Kingdom) study involving extracranial GHTs; It was reported that the most common yolk sac tumor (49%) and mixed MGHT (35%) were observed [16]. Mixed GHT was reported as the most common MGCT in another study [17]. Islam et al. also showed that yolk sac tumor (44%), mixed GCT (20%), and dysgerminoma (16%) were most common in children under 18 years of age [14]. The most common GCT was yolk sac tumor (36%) and second was mixed GCT (29%) in our series.

Germ cell tumors have two peak incidence, before 3 years of age and adolescence, but most of the patients




**Graphic 1.** Overall – event free survival and

are younger than 3 years. The median age at diagnosis varied between 3 months and 14 years months in the reported series [15, 18, 19]. The age distribution in our series is similar to that reported in the literature and 44 % of patients were younger than 5 years and 29 % older than 11 years.

Ovarian GCTs are more common in adolescents and young adults and mostly unilateral [6, 14, 20]. In our series, ovarian tumors were seen more frequently over the age of 11 (58%) and dysgerminoma was the most common histopathologic type as reported in the literature [1, 7, 11]. The incidence of testicular GCTs peaks before the age of 3 years and again in early adolescence [7, 21]. While the most common testicular MGCT under the age of three is a yolk sac tumor, mixed MGHT or seminoma is seen after adolescence [18, 22]. However, of the 7 testicular tumors in our series, yolk sac and mixed GCT were most common, and the patients were all younger than 5 or older than 15 years of age.

Extragonadal GCTs are most frequently located in the sacrococcygeal region in early childhood, while the mediastinum is the most common site in adolescents and young adults [17]. Sacrococcygeal teratomas account for 78% of extragonadal GCTs. No teratomas were included in this study, but the sacrococcygeal region was still the most common extragonadal location (41%). All patients with these tumors were aged 3 years or younger and the female/male ratio was 3.5. In our study, the most common tumor location in early childhood was consistent with the literature, whereas gonadal location was most common in the adolescent period. As in our study, Drozynska et al. reported that the sacrococcygeal location was most common in early childhood and gonadal location was most common in adolescence [17].

Acute abdomen is common sign of ovarian tumors, with up to 10% of ovarian tumors causing acute abdomen due to ovarian torsion, rupture, or hemorrhage [23, 24]. In children with ovarian torsion, the masses are generally solid and the incidence of malignancy is lower [25]. Our series included 2 patients who presented with and were operated for acute abdomen. For ovarian masses that do not present with acute abdomen, preoperative αFP and βHCG assessment and radiological evaluation to determine tumor size and solid/cystic structure are helpful in determining the surgical approach.

Eighty percent of the patients had mass-related symptoms and only 10% were diagnosed at stage I while 61% of the patients presented with advanced stage. As this study was based on a retrospective data analysis, we could not obtain information about the time from symptom onset to diagnosis from the patients' files. However, the high rate of diagnosis at later disease stages suggests that patients' complaints require more careful consideration by both families and physicians and that detailed examination by physicians would facilitate detection at earlier stages. Physicians can get help from ultrasonography which is a cheap, accessible, and effective method for the initial evaluation of a mass.

The tumor markers αFP and βHCG are useful in diagnosis, in the early detection of relapse and follow-up. High αFP and βHCG levels were detected in 70.7 % and 22% of patients in this study, respectively. Especially in low-risk patients followed up without chemotherapy after surgical resection, monitoring serum αFP levels for recurrence is part of treatment management and patient follow-up [15, 26]. COG AGCT0132 study demonstrated the correlation between tumor marker (aFP) not decreasing at the expected rate and poor prognosis (31).

GCTs can be treated successfully with complete surgical resection, accurate histopathologic diagnosis, and appropriate chemotherapy. Testicle-sparing surgery has no place and radical orchiectomy is performed with testiculer MGCT patients [18]. In patients with stage I testicular tumors, treatment is considered complete with complete tumor resection, inguinal orchiectomy with high cord ligation, and normalization of tumor markers [27, 28].

In patients with stage I ovarian tumors, treatment is considered completed with unilateral salpingo-oophorectomy. Only salpingo-oophorectomy was performed in 10 patients whose operation was planned, and chemotherapy was not given.

In surgical staging, 4 patients were evaluated as stage III and 3 patients were evaluated as stage IV due to peritoneal lavage or retroperitoneal lymph node positivity or involvement of adjacent structures. Among our patients who underwent complete mass removal, there was only one (stage I patient) recurrence.

Immature teratomas are graded according to their immature neuroepithelial tissue content, and the histological grade and malignant tissue content of the tumor are more important determinants of biological behavior than tumor stage. Surgical treatment is sufficient for immature teratomas that are not malignant. However, there are also studies showing that grade 2-3 (high grade) immature teratomas respond to the chemotherapy regimens used for MGCTs [23, 29]. Among our patients, chemotherapy was given to 2 patients with high-grade immature teratomas because αFP value did not return to within the normal range after surgical treatment.

Platinum-based chemotherapy regimens are highly effective in children with extracranial MGCT, especially those with early-stage disease. Different study groups have reported overall and event-free survival rates in the 95% range for stage I-II patients, while overall and disease-free survival rates of 70-85% have been reported for stage III-IV patients [7, 16, 19, 30, 31]. Our 5-year overall and disease-free survival rates were 86.5 ± 6.4% and 80.7 ± 7.1%, respectively. Considering 67% of our patients had advanced stage disease, our results are consistent with the literature.

In our center, 18F-fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (PET / CT) is not routinely performed for pediatric patients with germ cell tumors. The use of 18F-FDG PET / CT scanning in adult GCT management is useful for evaluating large (> 3 cm) residual mass after chemotherapy for pure seminoma and may be considered in some patients with elevated tumor markers without evidence of disease on conventional imaging [32]. 18F-FDG PET / CT is not helpful in staging or evaluating mature teratoma or residual non-seminomatous lesions, therefore PET is not indicated for post-chemotherapy evaluation of non-seminomatous advanced testicular germ cell tumors [33]. Both teratoma and necrosis lack FDG avidity on PET scaning and therefore, a negative PET does not eliminate the need for surgical resection. Their biological behavior may differ between adult and pediatric germ cell tumors. Previous pediatric GCT studies describing the benefit of 18F-FDG PET / CT have evaluated a limited number of patients [34-36]. In the pediatric GCT study, which has the largest series in the literature (n: 9 patients), PET has shown lesions that were not detected on CT, causing a change in treatment management in 33% of patients [36]. However, studies in this field include very limited patient numbers, and

since it is a rare tumor, multi-center studies and larger cohorts are needed to be evaluated.

Children with recurrent/progressive extragonadal GCT are characterized by a poor prognosis. For recurrent pediatric GHTs, high-dose chemotherapy (HDC) and hematopoietic stem cell transplantation (HSCT) can be considered salvage therapy [13].

In one European series, to better characterise the role of HDC with HCST as salvage therapy for children with extragonadal GCT, the large database of the patients registered with the European Group for Blood and Marrow Transplantation (EBMT) was reviewed. Ten of 23 children with relapsed/recurrent extragonadal GHTs achieved long-term disease-free survival (median follow-up, 66 months) after receiving HD chemotherapy with stem cell support [37]. HDC with HCST has been shown to provide impressive long-term remission as salvage therapy in children with extragonadal extracranial GHTs.

Pediatric oncology groups have adapted their experience in the treatment of adults to the pediatric age group. Using a risk-based approach to treatment, COG developed a "functional" classification based on tumor location, histological type, and stage, and determined 3 risk groups [30].

The Malignant Germ Cell Tumor International Collaborative evaluated 25 years of experience encompassing 591 patients in order to determine prognostic factors in pediatric and adolescent patients [19]. When they evaluated the effects of age, disease stage, disease site, αFP reduction, histology, and the presence of gonadal dysgenesis on prognosis, it was determined that stage IV disease ($p=0.001$), age ≥ 11 years ($p<0.001$), and ovarian location ($p<0.001$) were prognostic factors associated with lower survival. In this study, when the factors that may affect the prognosis such as the histological type, location, disease stage, gender, and age of the tumor were evaluated, no statistically significant difference was found in terms of survival. This may be because MGHT is a very heterogeneous group and the number of our patients is limited. Extracranial germ cell tumors are a rare pediatric malignancy. This cohort has a relatively small number of patients as it studies a rare tumor group of a single center. Although we showed differences in the relationship between age, stage, tumor location, and survival in our study, we could not show statistical significance due to the small size of the study group.

## Conclusion

In the treatment of MGCTs, conservative surgery, a watch-and-wait approach for stage I patients, and platinum-based chemotherapy regimens yield favorable outcomes. The clinical features and treatment outcomes of the patients in our series were consistent with the literature. The fact that most of our patients were symptomatic at presentation and had advanced stage disease when diagnosed highlights the importance of detailed evaluation and examination. Although patients with early stage disease have very good outcomes with current treatment, new treatment approaches are needed for patients with advanced and relapsing disease.

*Ethics*

**Conflict of Interest:** No conflict of interest was declared by the authors.

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