

Primary ovarian tumors in children: a single center experience of 124 patients

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ABSTRACT

Background. Primary ovarian tumors are rare in the pediatric age group. We reviewed our 40-year experience with ovarian tumors to evaluate the clinical features and treatment results in a single institution.

Methods. Between January 1975 and October 2015, 124 girls with primary ovarian tumor were diagnosed and treated in our center. Tumors were identified with biopsy or total resection and/or serum markers. Seventy four children were included in the treatment analysis.

Results. Median age for 124 children was 11.0 years (0.73-17.63). The main complaint was abdominal pain in 85 patients (68.5%). One hundred and five patients (84.6%) had total one-sided salpingo-oophorectomy and five patients had bilateral salpingo-oophorectomy. Amongst 124 cases, 29 patients had mature teratoma, which was the most common tumor in this study. Dysgerminoma (n=21) was the most common malignant histopathologic type. Stage I disease was diagnosed in 57.2% and stage IV in 6.6% of the patients. Five year overall survival (OS) and event-free survival (EFS) for 124 children were 82.5% and 76.3% respectively. For 74 children who received treatment, 5-year OS and EFS were 75.2% and 67.1%, respectively. Age (p <0.017), histopathological subgroup (p <0.001), stage (p =0.003) and chemotherapy protocols (p =0.049) were significant prognostic factors for OS.

Conclusions. The survival rates in children with ovarian tumors were comparable with studies in the literature. Although patients treated with platin based regimens had better survival rates, prognosis was still poor for the patients in advanced stages. This should be the focus for further studies and improvements.

Key words: childhood cancer, ovarian tumors, germ cell tumors.

Ovarian tumors are rare in the pediatric population and comprise approximately 1-2% of all childhood malignancies.¹⁻³ Limited information is available regarding the relative frequency of benign and malignant ovarian tumors in this age group. Ovarian tumors in childhood and adolescence include germ

cell tumors (mature-immature teratoma, dysgerminoma, endodermal sinus tumor, embryonal carcinoma, choriocarcinoma, gonadoblastoma and mixed germ cell tumor), surface epithelial tumors (serous or mucinous cystadenoma, adenocarcinoma), sex cord-stromal tumors (Sertoli-Leydig cell tumors, granulosa cell tumors and gynandroblastoma) and miscellaneous tumors (malignant lymphoma and leukemia, small cell carcinoma, and soft-tissue tumors.⁴ The most common types are germ cell tumors, both in benign and malignant groups.⁵ Previous studies have predominantly focused on histopathologic subtypes and treatment protocols with small numbers of patients, most of these studies

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included germ cell tumors from other sites, apart from those of ovarian origin.⁶⁻⁸ Although patients were treated with many regimens, an improvement in survival rate was accomplished only with the introduction of platin-based regimens.^{6,8-10}

In this study, we report our experience with ovarian tumors in pediatric patients diagnosed at our institution between the years 1975 and 2015. We provide additional data regarding frequency, histological subtypes, clinical presentations and treatment results.

Material and Methods

Primary ovarian tumor was diagnosed in 124 patients between January 1975 and October 2015. All data used in this study were collected from institutional records. Initial symptoms, physical findings, surgical treatment, tumor histopathology, and staging was evaluated with The International Federation of Gynecology and Obstetrics (FIGO) and Children's Oncology Group (COG) treatment protocols and survival analyses were retrospectively evaluated.

Surgical methods included exploratory laparotomy and excision of the tumor with the ovary when possible. Surgeons also inspected the other ovary, abdominal organs, omentum, and lymph nodes and collected ascites or peritoneal washings for cytology when necessary.

Tumor staging was carried out according to the guidelines of FIGO and COG, as follows: COG, stage I was defined as a disease limited to ovaries; stage II as the tumor extended to the pelvis, stage III if intraperitoneal dissemination was noted, and stage IV if distant metastase was shown.^{11,12} The FIGO staging system was revised in 2014.¹³ We also evaluated the use of two different staging systems in pediatric ovarian tumors.

All surgical specimens were examined by the pathologist at the pediatric pathology

department. Ovarian tumors were classified histologically according to the World Health Organization criteria.¹⁴

Serum alpha-feto protein (α -FP) and β -human chorionic gonadotropin (β -hCG) levels were measured and used as tumor markers in most of the patients. α -FP and β -hCG were not noted in files of patients diagnosed before 1984.

Patients with mature teratoma, who were treated in other centers or with stage I and II disease treated with surgery alone were excluded from the treatment analysis. Seventy-four children were analysed and all of them had been treated with chemotherapy regimens such as vincristine, adriamycin, cyclophosphamide (VAC), cisplatin, vinblastine and bleomycin (PVB) and bleomycin, etoposide and cisplatin (BEP) protocols. The VAC regimen was used from the years 1975 to 1986. Platin-based regimens such as PVB were used from the years 1986 to 1989 while BEP was used from 1989 onwards. Thus, three distinct time periods and treatment regimens were available for analysis. BEP regimen included bleomycin 15 units/m²/day, IV, day 2; etoposide 100 mg/m²/day, IV, days 1-3; cisplatin 100 mg/m²/day, IV, day 1, every three weeks; PVB regimen consisted of cisplatin 120 mg/m²/day, IV, day 1; vinblastine 0.15 mg/kg/day, IV, days 1-2 and bleomycin 10 mg/m²/day, IV, days 2, 9, 16; VAC regimen had an induction of vincristine 2 mg/m²/day, max 2 mg, IV, weekly for 12 weeks; dactinomycin 15 μ /kg/day, IV, days 1-5; and cyclophosphamide 10 mg/kg/day, IV, days 1-3 and 20 mg/kg/day at weeks 3,6,9.; and maintenance for every 4 weeks, vincristine 2 mg/m²/day, max 2 mg, IV, days 1-5; dactinomycin 15 μ /kg/day, IV, days 1-5; and cyclophosphamide 10 mg/kg/day, IV, days 1-3, every 4 weeks. AVAC had adriamycin 30 mg/m²/day, days 1-2, IV, instead of dactinomycin in the VAC regimen. The patients were evaluated after three cycles of therapy, and fourteen with residual disease underwent surgery. Those with malignant disease in resected specimen received at least three or more additional cycles of their assigned regimen.

Radiotherapy was administered to 24 patients. Five patients received radiotherapy as the first line of treatment after surgery before the year 1980 (three with dysgerminoma, one with embryonal carcinoma and one with malignant teratoma). After the year 2000, radiotherapy was used only in two patients, one with mixed germ cell tumor and the other with immature teratoma with disseminated and recurrent disease respectively.

Mean and median values were used for analysing demographic characteristics. Events and survival estimates were obtained using the Kaplan-Meier method. Differences in survival curves were tested using the log-rank test.¹⁵

The study was approved by Hacettepe University Ethical Board (number: 2020/13-07).

Results

Clinical characteristics

One hundred and twenty four patients with a primary ovarian tumor between the years 1975 and 2015 were analyzed. The median age of patients at the time of diagnosis was 11.0 years (range 0.73-17.63) with only one patient being younger than 12 months. Most ovarian tumors were seen in the age group of 10 to 14 years (58 patients, 46.7%). However, in the whole group, malignant ovarian tumors were seen more frequently in children under five years of age. The presenting symptoms (Table I) were predominantly abdominal pain (85 patients, 68.5%), 60 patients (48.5%) had both abdominal pain and distension. Three patients had no symptoms at all; of these, two were diagnosed during routine clinical checkup and follow-up for mixed gonadal dysgenesis and spinal muscular atrophy type 3, respectively. One patient had an ovarian tumor without symptoms and was incidentally diagnosed. In the eight girls, acute abdominal pain was noted, 4 of whom underwent emergency surgery for the presumed diagnosis of ovarian torsion. An abdominal mass was found in 87 patients (70.2%) during physical examination.

Table I. Symptoms at diagnosis of 124 pediatric patients with ovarian tumors.

	N	%
Abdominal pain	85	68.5
Abdominal swelling	60	48.5
Abdominal pain and swelling	27	21.7
Nausea and vomiting	13	10.4
Anorexia and weakness	8	6.4
Menstrual irregularities	8	6.4
Fever	4	3.2
Urinary complaint	4	3.2
Constipation	3	2.4
Puberte precox	3	2.4
Dyspnea	3	2.4
No symptoms*	3	2.4
Other**	1	0.8

* One patient had mixed gonadal dysgenesis, one had spinal muscular atrophy, the other patient was diagnosed during a check-up.

** A patient had growth delay, and developmental intellectual disability.

Lag time is defined as the duration between the onset of symptoms and establishment of a definitive diagnosis. Thirty two patients were diagnosed on the first day of onset of symptoms while the longest lag time was one year for a patient with intermittent abdominal pain. The median lag time was 20.5 days (1-365 days). The patients (n=29) with mature teratoma had a median lag time of ten days (1-150 days). The lag time for patients (n=21) with dysgerminoma was 15 days (1-180 days).

Disease location

Sixty-six patients (53.2 %) had right, 51 (41.2%) had left ovarian involvement and 6 (4.8%) had bilateral involvement. Laterality could not be identified in one patient.

Surgical details

Of the 124 patients, 105 had unilateral and 5 had bilateral salpingoopherectomy. Eleven underwent tru-cut biopsy at admission, while one was diagnosed by inguinal lymph node biopsy. Two patients were diagnosed with tumor markers alone and did not undergo surgery.

Table II. Distribution of COG and FIGO staging system in 124 children with ovarian tumors.

FIGO staging	COG staging				Total
	Stage I	Stage II	Stage III	Stage IV	
Stage I	69	1	0	0	70
Stage II	2	11	5	0	18
Stage III	0	1	27	1	29
Stage IV	0	0	0	7	7
Total	71	13	32	8	124

COG: Children's Oncology Group, FIGO: International Federation of Gynecology and Obstetrics

A unilateral salpingo-oophorectomy was performed in 105 patients. Seventy nine patients had neither macroscopic nor microscopic disease; fourteen patients had microscopic disease. Twelve patients had partial resection with gross residual disease. Five patients underwent surgery for bilateral salpingo-oophorectomy (3 of whom had no microscopic disease). Eleven patients had biopsy only; five of them were diagnosed with laparotomy (either tru-cut or laparotomy). Fourteen patients had a second look surgery.

Staging

The staging was performed according to the FIGO system and resulted in the following distribution: Stage I disease was found in 56.5% of the patients; stage II in 14.5%, stage III in 23.4%, and stage IV in 5.6% patients. Stage distribution according to the COG staging system, identified stage I disease in 57.2% of the patients, stage II in 10.4%, stage III in 25.8%, and stage IV in 6.6% of the patients. There were only ten patients who had different stages according to both staging systems (Table II).

Histopathologic Findings

Of the 124 ovarian tumor specimens examined, 29 (23.4%) were mature teratoma and this was the most common tumor type in our study. Histopathological distribution is shown in Table III. Dysgerminoma was the most common malignant histopathologic type (n=21, 16.9%) followed by the mixed germ cell tumor, which accounted for 13.7% (n=17). Other tumor types identified included unclassified germ

cell tumors (n=4), granulosa cell tumors (n=4), adenocarcinoma (n=1), and gonadoblastoma (n=2). We also had one patient with a cystadenoma, two patients with Sertoli-Leydig cell tumors and one patient with a borderline mucinous tumor. *DICER1* mutation was not investigated in Sertoli-Leydig cell tumors.

Tumor Markers

Tumor markers α -FP and β -hCG were unavailable and not measured in patients diagnosed before the year 1984. We found high α -FP levels in 46 patients and high β -hCG

Table III. Histopathological distribution of 124 pediatric patients with ovarian tumors.

Histopathological distribution	N	%
Germ cell tumors		
Mature teratoma	29	23.4
Dysgerminoma	21	16.9
Mixed germ cell tumor	17	13.8
Endodermal sinus tumor	14	11.3
Embryonal carcinoma	13	10.5
Immature teratoma	12	9.7
Teratocarcinoma	2	1.6
Malignant teratoma	1	0.8
Unclassified germ cell tumor	4	3.2
Epithelial tumors		
Adenocarcinoma	1	0.8
Mucinous tumor	1	0.8
Serous cystadenoma	1	0.8
Sex cord stromal tumors		
Granulosa cell tumor	4	3.2
Gonadoblastoma	2	1.6
Sertoli-Leydig cell tumor	2	1.6
Total	124	100

levels in 25 patients. The highest β -hCG level (285.500 mIU/ml) was found in a patient with unclassified germ cell tumor and this patient had an α -FP level of 1300 ng/ml. She did not undergo surgery or a biopsy but was instead diagnosed based on tumor marker levels. Additionally, there was another patient who was diagnosed only based on tumor marker levels without a biopsy or surgery. High serum α -FP level at diagnosis was not a significant factor for 5-year overall survival (OS) and event-free survival (EFS) (patients with normal vs high level of α -FP; OS 79.3% vs 72.4%, $p=0.84$; EFS 75.9% vs 61.2%, $p=0.26$).

Chemotherapeutic regimens

Several chemotherapeutic regimens were used in our center during the study years based on the year of diagnosis. Seventy-four patients were treated with chemotherapy in this study. Patients who received chemotherapy at other centers before referral were excluded from the analyses. Forty-eight cases (64.9%) were treated with the BEP (bleomycin, etoposide, cisplatin) regimen, 14 (18.9%) with PVB regimen, 12 (16.2%) with VAC and AVAC (only one patient with adriamycin plus VAC).

Radiotherapy

Twenty-four patients received radiotherapy for disease progression, disseminated abdominal diseases and recurrence. Five patients received radiotherapy as the first line treatment after surgery before the year 1980, three had dysgerminoma, one with embryonal carcinoma and one with malignant teratoma.

Survival analysis

We performed survival analysis using data from 74 patients who received chemotherapy. The OS at five years in all 74 patients was 75.2% while the EFS rate was 67.1% (Fig. 1). The OS was significantly different among different age groups ($p=0.017$) (Fig. 2). Patients treated with the BEP protocol had the best survival rates. The OS and EFS rates for the VAC regimen

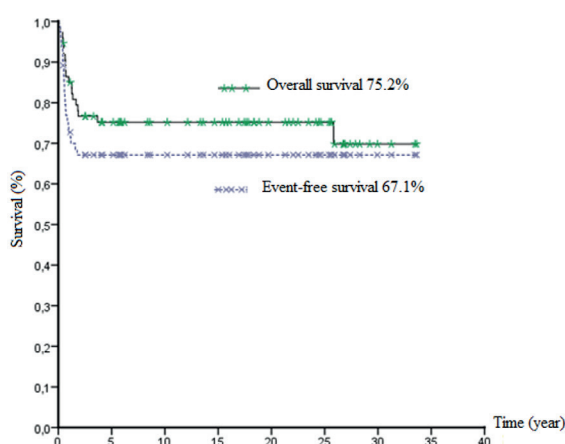


Fig. 1. Overall and event-free survival of 74 patients with malignant ovarian tumors (The numbers show the five year survival rates).

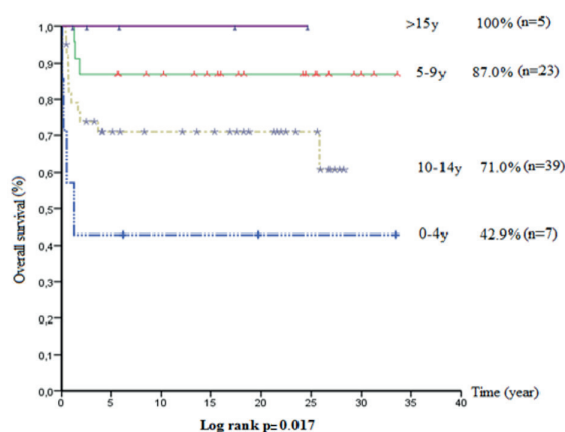


Fig. 2. Overall survival of children with malignant ovarian tumors according to age groups (The numbers show the five year survival rates).

at five years were 66.7% and 50%, 57.1% and 42.9% for PVB, and 82.5% and 78.5% for BEP, respectively (Fig. 3 and 4). Survival rates according to the chemotherapy regimens were significantly different ($p=0.049$). Other factors that were significantly associated with overall survival were age ($p<0.017$), histopathological subgroup ($p<0.001$), FIGO stage ($p=0.019$) and COG stage ($p=0.003$) (Table IV). Since the germ cell tumors were the major group of ovarian tumors in this study, we conducted a detailed survival analysis for 113 germ cell tumors. The overall and event-free five-year survival rates of 113 patients diagnosed with germ cell tumors were 82.9% and 76.2% respectively.

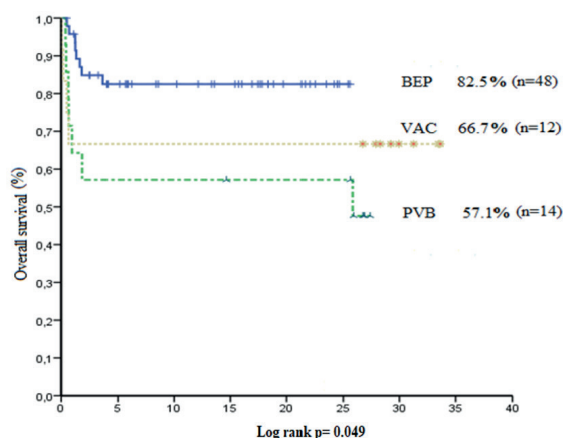


Fig. 3. Overall survival according to treatment regimens for malignant ovarian tumors of children (The numbers show the five year survival rates).

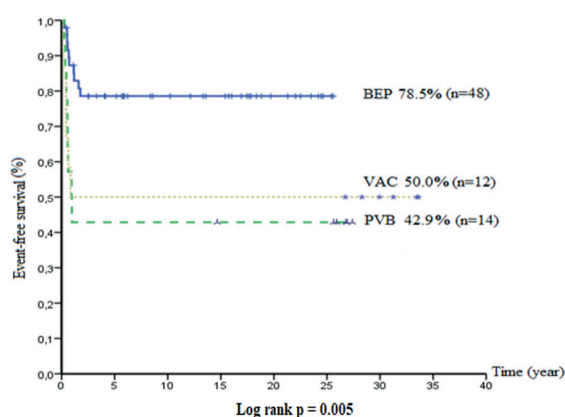


Fig. 4. Event-free survival according to treatment regimens for malignant ovarian tumors of children (The numbers show the five year survival rates).

Table IV. Overall and EFS rates according to the histopathological types and stages in 74 patients receiving chemotherapy regimens.

	N	%	Survival rates	
			for five years (%)	
			OS	EFS
Histopathological subgroups				
Dysgerminoma	18	24.3	83.3	77.8
Mixed germ cell tumor	17	22.9	75.3	63.0
Endodermal sinus tumor	13	17.5	67.1	67.1
Embryonal carcinoma	12	16.2	75.0	50.0
Immature teratoma	7	9.5	71.4	71.4
Teratocarcinoma	2	2.7	50.0	50.0
Malignant teratoma	1	1.4	-	-
Unclassified germ cell tumor	4	5.4	100	100
COG				
Stage I	25	33.7	95.8	91.8
Stage II	13	17.6	84.6	69.2
Stage III	29	39.1	58.6	48.3
Stage IV	7	9.6	45.7	45
FIGO				
Stage I	24	32.4	95.7	95.7
Stage II	18	24.3	72.2	55.6
Stage III	26	35.1	65.4	53.8
Stage IV	6	8.1	31.3	31.3

OS rates for COG staging p= 0.003, EFS rates for COG staging p= 0.008, OS rates for FIGO staging p= 0.019, EFS rates for FIGO staging p= 0.005, OS rates for histopathological subgroup p< 0.001, EFS rates for histopathological subgroup p< 0.001

COG: Children’s Oncology Group, EFS: event-free survival, FIGO: International Federation of Gynecology and Obstetrics, OS: overall survival

Five-year OS and EFS were 100 % & 100% for mature teratoma, 85.7% and 81% for dysgerminoma, 75.3% and 63% for mixed germ cell tumors, 69.6% and 70.1% for endodermal sinus tumors, 76.9% and 53.8% for embryonal carcinomas, and 81.8% and 71.4% for immature teratomas.

Discussion

This retrospective study aimed to analyse the different ovarian tumors, regarding the clinical features, parameters affecting prognosis, assess the long-term follow-up of children with malignant ovarian tumors and compare data with other published studies in the literature. There are several studies on the ovarian tumor in children in the literature.^{5,8,16-25}

124 cases with ovarian tumors were represented in this series, in which 91.1% were germ cell tumors, 2.4% were epithelial tumors and 4.8% were sex-cord stromal tumors. Seventy-five percent of all ovarian tumors and 74.3% of germ cell tumors were malignant in our study. Bhattacharyya et al. published a series of 151 girls with ovarian tumors aged 0-20 years, in which 38% of the patients had germ cell tumors.²² In the same study, 66% of germ cell tumors were malignant and dysgerminomas were the most common malignant tumor. Breen et al. reported that 35% of all ovarian neoplasms in children and adolescents were malignant.³ The rate of malignant ovarian tumors in our study was higher than others because most patients were referred to our hospital after a malignant disease diagnosis had been obtained.^{19,26-29}

In our study, the most common ovarian tumor was the mature teratoma (23.4%) and the most common malignant germ cell tumor was dysgerminoma. Similar results have been previously reported.³⁰⁻³³ The proper distinction of malignant and benign cases are critically important for the management of ovarian tumors. The main presenting complaints were abdominal pain followed by distention.

Presentation with acute abdomen was a frequent occurrence and was noted in 6.4% of the patients. Baranzelli et al. stated that 11% of the girls with ovarian tumor had acute abdominal pain.³⁴ Sixty-six patients (53.2%) had a tumor on the right ovary and 51 (41.1%) had a tumor on the left ovary and 6 (4.8%) had bilateral involvement. One patient's primary tumor could not be detected by radiologic scanning. The frequencies of dysgerminoma, mixed germ cell tumor, immature teratoma, and endodermal sinus tumor were similar to that reported in the literature.³⁰⁻³⁵

In our study, the OS and EFS were significantly different among the various histopathologic subgroups ($p < 0.001$). Patients with dysgerminoma, immature teratoma, and endodermal sinus tumor survived longer compared with other tumor types. Ablin et al. reported that histopathologic subgroups among malignant germ cell tumors was not associated with the outcome.²⁰ Other studies were not able to definitively address this subject.³⁶⁻³⁸ This needs to be investigated in prospective studies.

Secretion of α -FP and less commonly β -hCG can be important for diagnosis, assessing treatment response and post-treatment surveillance.³⁹ In our study, the primary tumor was not detected in one patient and she was instead diagnosed based on tumor markers. Other patients who had high α -FP levels during the follow-up period had relapses. Thus, we suggest to evaluate tumor markers in all ovarian germ cell tumors for diagnosis and during follow up and relapse. The Children's Cancer and Leukaemia Group, the French Society of Pediatric Oncology and the COG have previously identified serum α -FP as a prognostic factor.^{23,40} Murugaesu et al. mentioned that pre-treatment tumor markers levels are valuable for predicting recurrence and OS.⁴¹ Tangjitgamol et al.⁴² stated that only perioperative tumor markers significantly affects the progression-free survival. The survival rates were lower in patients with high α -FP levels but not statistically significant in our study.

Standard management of ovarian tumors is surgical removal which allows a definitive histopathological diagnosis and subsequent chemotherapy.⁴³⁻⁴⁵ The tumor should be removed as much as possible.⁴⁶ In our study, a total resection without microscopic residue was performed in ninety three patients (75.1%) at diagnosis. We think that second-look surgery should only be performed in patients who had any residual masses after three or four courses of chemotherapy. Eight patients had no active tumor at second-look surgery, but one of them relapsed during follow-up period. There are no conclusive reports in the literature to recommend the need for second-look surgery; most of the studies had a small sample size.⁴³⁻⁴⁵

Although all ovarian masses in girls most commonly occur between the ages of 15 and 19 years, ovarian cancer is rarely seen under the age of ten.^{16,47,48} In our study, 58 (46.8%) of 124 patients were diagnosed in the ages between 10-14 years and 40 (32.3%) were in the ages of 5-9 years. The median age was 11.0 years (0.73-17.63). We even had a patient under the age of one in this series. 74 patients who received chemotherapy regimens were analysed for survival rates according to the age groups. The OS rate of patients over the age of 15 years was 100%, while that of patients in the 0-4 year group was 42.9%. We also found a relationship between age and disease progression in our study ($p=0.017$). Poorer prognosis was found in younger patients. While, contrarily earlier studies reported that age did not have a significant influence on survival, last studies showed that age is an important risk factor for progression and survival.^{49,50} This should be investigated in further studies.

FIGO and COG were used for staging in this study. We suggested that COG staging is more useful for the retrospective studies because FIGO staging system requires detailed information of the operation and cytopathological evaluation. Both systems are effective for staging in pediatric tumors. For practical reasons, the COG system is easy to learn and implement in centers which do not have a high patient volume.

Survival in patients with lower stages have better survival rates. For treatment analysis of 74 patients, the best survival was found in patients who had stage I tumors according to both systems of classification as expected. Overall survival rates of stage I disease for COG and FIGO was 95.8% and 95.7%, respectively ($p=0.003$ / $p=0.019$). Survival results of COG were 84.6%, 58.6%, 45.7% for stage II, III and IV, respectively. According to FIGO systems, survival rates were 72.2%, 65.4%, 31.3% for stage II, III and IV, respectively. Ablin et al. mentioned that metastases of the germ cell tumors did not affect the prognosis.²⁰ But we observed that advanced disease with metastasis had poorer prognosis in our study. Wollner et al. reported that 32 patients diagnosed with germ cell tumors had EFS rates of 100% for stage I, 80% for stage III, and 67% for stage IV.³⁶ Lockley et al.'s review of ovarian cancer in adolescence and young adults suggested that the patients diagnosed with an ovarian germ cell tumor had better survival rates (<90%) than other epithelial ovarian tumors.⁵¹ Marina et al. also showed that patients with low-grade ovarian tumors had a better survival rate than advanced stage diseases and that 5 year EFS rates for 137 patients were 84.8% in those with stage III disease and 78% in those with stage IV tumors.³⁷ In the study by Billmire et al., the patients ($n=25$) underwent initial surgery for stage I malignant germ cell tumors and 5 year OS rate was 96% after three cycles of BEP with an EFS rate of 52%.²⁴ The SFOP (Societe Francaise d'Oncologie Pediatrique) study from France which included 12 girls with stage I ovarian tumors there were six relapses; five of them received successful salvage chemotherapy and one patient died due to non-responsiveness.³⁴ Rogers et al. showed that patients below 21 years of age with stage I and stage II ovarian malignant germ cell tumors had 6 year OS rates of 95% and 93.8%, respectively.⁷ In the CCSG (Children's Cancer Study Group) study from the United Kingdom which included nine girls with stage I ovarian tumors who were treated with surgery only, three cases had relapse and all of them underwent successful salvage chemotherapy.⁴⁰

The COG/CCG group presented 124 cases with ovarian germ cell tumors and compared survival rates after three vs four cycles of BEP regimen. The EFS rates were 88% vs 92%, respectively.⁵² In our study, survival rates in the early stages of the disease are similar to the published results but survival rates in the advanced stages are lower based on the different time periods of our center. The survival rates need to be improved in these cases.

Three different chemotherapy regimens were used in our center during the years 1975-2015. The best results were seen with the BEP protocols. Overall survival rate for five years in BEP regimen was 82.5%. The patients who received PVB and VAC had OS rates for five years as 57.1% and 66.7% respectively ($p = 0.049$). For five years, EFS rates were 78.5%, 42.9% ve 50.0% for BEP, PVB and VAC regimens, respectively ($p = 0.005$). Kapoor et al. reported OS after five years to be 83% with the BEP protocol in patients with germ cell tumors.⁵³ In a review, Gershenson suggested that the BEP protocol is superior to VAC and PVB protocols in the management of the ovarian tumor.⁴⁶ Ghosn et al. recommended high dose cisplatin, ifosfamide and etoposid in refractory germ cell tumors, but the response rate was relatively low and the regimen had high toxicity rates.⁵⁴ The COG pilot study regarding escalating doses of cyclophosphamide did not have better responses than standard BEP regimens.⁵⁵ The COG/CCG group study showed that the frequency of treatment-related toxicity increased in children with testicular and ovarian tumors receiving BEP regimen with high-dose cisplatin (40 mg/m²/day, 1-5 day) versus low dose cisplatin (20mg/m²/day, 1-5 days).⁶ Survival rates for BEP regimen is similar to the literature and we suggest that the BEP regimen is an appropriate and effective regimen for pediatric ovarian tumors.

Currently the main treatment is surgery and chemotherapy but, in the past, the standard of care also included adjuvant abdominal

radiotherapy. It's known that germ cell tumors especially, dysgerminoma and embryonal carcinoma are very radiosensitive.⁵⁶ However, radiotherapy is no longer standard practice in children, largely due to high toxicity rates and the effectiveness of platinum-based chemotherapy for ovarian tumors.

In conclusion, the BEP regimen remains the best option while high risk patients should be treated with more intensive treatment strategies.

The level of care in pediatric oncology in Türkiye is getting better. As an upper middle income country, we have to focus to improve survival rates in advanced cases. Professional awareness, structured referral systems and investment in strengthening the health system will help to improve survival rates to the level of high income countries.

Ethical approval

The study has been approved by Hacettepe University Ethical Board (number: 2020/13-07).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MC, TK, AV; data collection: MC, TK; analysis and interpretation of results: MC, TK, AV; draft manuscript preparation: MC, TK, AV, BY, BA, NK, CA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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