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Outcomes of pediatric and adolescent girls with malignant ovarian germ cell tumors

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HIGHLIGHTS

- Oncologic and reproductive outcomes were evaluated in 42 pediatric and young adolescent girls with malignant ovarian germ cell tumor.
- All patients received uniform treatment consisting of fertility-sparing, complete cytoreductive surgery with or without BEP chemotherapy.
- Survival outcomes were excellent and reproductive outcomes were favorable, regardless of histologic type or FIGO stage.

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ABSTRACT

Objective. To analyze the oncologic and reproductive outcomes of pediatric and young adolescents with malignant ovarian germ cell tumors (MOGCTs).

Methods. Pediatric or young adolescent girls aged 16 years or under with MOGCT were eligible for this study.

Results. Forty-two pediatric or adolescent girls with MOGCT met the inclusion criteria. The median age was 12 years (range, 6–16 years) and 29 patients were premenarchal. The most common histologic type was immature teratoma, and 30 patients (54.3%) had stage I MOGCT. All patients underwent fertility-sparing surgery, which was defined as the preservation of at least one adnexa and the uterus. No patient had residual disease after surgery. Thirteen patients had tumor spillage, two patients had a positive peritoneal cytology, and two patients had lymph node metastasis. After surgery, 31 patients received adjuvant chemotherapy with bleomyocin, etoposide, and cisplatin (BEP) (median, 4 cycles; range, 1–6 cycles). After a median follow-up time of 93 months (range, 22–217 months), six patients had a recurrence of the disease, and one patient died. The 5-year disease-free and overall survival rates were 85% and 97%, respectively. Among the surviving 41 patients, seven were premenarchal, 30 had regular menstruation, and three had irregular menstruation. No patient had premature ovarian failure.

Conclusion. All patients received uniform treatment consisting of fertility-sparing complete cytoreductive surgery followed by BEP chemotherapy. Regardless of histologic type and FIGO stage, the oncologic outcomes were excellent and the reproductive outcomes were favorable.

1. Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare malignant tumors that account for about 5% of all ovarian malignancies [1–3], and they usually occur in young females with a peak of incidence between 16 and 20 years of age [4]. MOGCTs consist of several different histologic types, but all are derived from primordial germ cells of the ovary. The most common histologic type is dysgerminoma followed by immature teratoma and yolk sac tumor, which together comprise over 90% of all MOGCTs [5]. Choriocarcinoma, embryonal carcinoma, and polyembryoma comprise the remaining 5–10% of MGOCTs [6]. Sometimes, a mixed type MOGCT is diagnosed, with dysterminoma and yolk sac tumor being the most common combination [7].

Because MOGCT is a relatively rare malignancy, few clinical trials have been done to guide standard treatment. Its incidence is only about one-tenth of that of malignant testicular germ cell tumor. Treatment modalities for MOGCT are mostly based on those of testicular cancer. The survival outcome of MOGCT was dramatically improved when platinum-based chemotherapy for testicular cancer was applied to treat patients with MOGCT [8,9]. Treatment outcomes are usually reported only for older adolescent and young adult patients, because

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MOGCTs are rare in children and young adolescents. MOGCTs account for less than 1% of all childhood malignant tumors and only about 20% of MOGCTs are diagnosed in premenarchal girls [10].

The aim of this study was to analyze the oncologic and reproductive outcomes of children and young adolescents with MOGCT.

2. Materials and methods

After obtaining the approval of the Institutional Review Board of Asan Medical Center (AMC, Seoul, Korea), we searched for patients who met the following inclusion criteria: 1) age ≤ 16 years, 2) histologically proven MOGCT, 3) patients who were treated and followed-up at AMC between 1996 and 2011. Demographic data were gathered from the patients' medical records, including age, menarche, co-morbid medical disease, and history of surgery; clinicopathologic data including presenting symptoms, tumor markers, surgery, adjuvant therapies, complications, histologic types, and grade and stage of tumor; and follow-up data including recurrence, the pattern of recurrence, treatment at recurrence, death, menstruation, menopause, and pregnancy. A telephone interview was also performed to ascertain the reproductive outcomes of patients. Histologic types of MOGCT were classified according to the World Health Organization (WHO) classification and the stage was determined according to the revised version (2014) of the International Federation of Gynecology and Obstetrics (FIGO) staging system [11–13]. The histologic grade of immature teratoma was determined according to the Norris classification [14]. Disease-free survival time was calculated as the time interval in months from the date of diagnosis to the date of recurrence or censoring. Overall survival time was calculated as the time interval in months from the date of diagnosis to the date of death from the disease or the last follow-up. Survival curves were calculated using the Kaplan–Meier method and the differences in survival rate were compared using log-rank test in SPSS software (version 21.0; IBM, Armonk, NY). $P < 0.05$ was regarded as a statistically significant difference.

3. Results

Between 1996 and 2011, 42 pediatric or adolescent girls with MOGCTs met the inclusion criteria for this study. The demographic and clinicopathologic characteristics of patients are listed in Table 1. The median age at diagnosis was 12 years (range, 6–16 years) and 29 patients were premenarchal. Thirty nine patients presented with a palpable abdominal mass with or without abdominal pain, two patients presented with torsion of the ovarian mass, and one patient presented with rupture of the ovarian mass. The most common histologic type was immature teratoma followed by mixed MOGCT, dysgerminoma, and yolk sac tumor. Most patients had FIGO stage I MOGCT. Thirty nine patients had at least one tumor marker test before surgery; 16 patients had an elevated serum cancer antigen 125 level, 20 patients had an elevated serum alpha fetoprotein level, and five patients had an elevated serum beta-human chorionic gonadotropin level.

All patients underwent surgical management. No one received neoadjuvant chemotherapy before surgery. Table 2 lists the surgical procedures that were performed on 42 patients. Surgery was performed through laparotomy in 38 patients and through laparoscopy in four patients. All patients underwent fertility-sparing surgery, defined as the preservation of at least one adnexa and the uterus. Comprehensive surgical staging, involving peritoneal exploration, cytology, and biopsies and omentectomy, was performed on 25 patients. Pelvic and para-aortic lymph node dissection was performed on 15 and 11 patients, respectively. Bowel resection and reanastomosis was performed on three patients as a part of debulking surgery. Complete cytoreduction was performed on all patients. Intraoperative or preoperative spillage of tumor was observed in 13 patients. Of the 26 patients who underwent peritoneal cytology, two patients had a positive cytology. Two patients had lymph node metastasis.

Table 1
Demographic and clinicopathologic characteristics of patients (n = 42).

Characteristics		N	%
Age	Median (range), years	12 (6–16)	
	≤10 years	13	31
	>10 years	29	69
Histology	Dysgerminoma	9	21.4
	Immature teratoma	19	45.3
	Grade 1	5	
	Grade 2	9	
	Grade 3	5	
	Yolk sac tumor	3	7.1
	Mixed	11	26.2
FIGO stage	IA	21	50
	IB	1	2.4
	IC	8	19
	IIC	3	7.1
	IIIA	3	7.1
	IIIB	2	4.8
	IIIC	3	7.1
	IV	1	2.4
CA 125[a]	Median (range), U/mL	49.7 (6.2–1700)	
	Not elevated	10	23.8
	Elevated	16	38.1
	Not checked	16	38.1
AFP[b]	Median (range), ng/mL	10.6 (0.63–616,000)	
	Not elevated	19	45.3
	Elevated	20	47.6
	Not checked	3	7.1
b-hCG[c]	Median (range), mIU/mL	1.0 (0.1–12,000)	
	Not elevated	24	57.1
	Elevated	5	11.9
	Not checked	13	31

FIGO, the International Federation of Obstetrics and Gynecology; CA 125, cancer antigen 125; AFP, alpha fetoprotein; b-hCG, beta-human chorionic gonadotropin.
[a] Reference range: 0–35 U/mL.
[b] Reference range: 0–20 ng/mL.
[c] Reference range: 0–3 mIU/mL.

After surgery, 31 patients received adjuvant chemotherapy with bleomyocin, etoposide, and cisplatin (BEP). The median number of chemotherapy cycles was four (range, 1–6). In general, all patients excluding stage IA MOGCT received adjuvant chemotherapy. One patient with stage IV MGOCT due to malignant pleural effusion also underwnent cytoreductive surgery followed by adjuvant chemotherapy. After a median follow-up time of 93 months (range, 22–217 months), six patients had disease recurrence. All patients with recurrent disease received BEP chemotherapy with or without secondary surgery. Four patients showed complete response, one patient showed partial response, and one patient died of disease due to disease progression. Table 3 shows the characteristics of patients with recurrent disease. Of the 30 patients who had FIGO stage I MOGCT, three patients experienced disease recurrence. One patient had FIGO stage IA disease and did not receive adjuvant chemotherapy, while the other two patients had FIGO stage IB

Table 2
Surgical management of malignant ovarian germ cell tumors (n = 42).

Surgical procedures	N	%
Unilateral ovarian cystectomy	1	2.4
Unilateral oophorectomy	2	4.8
Unilateral salpingo-oophorectomy	31	73.8
Unilateral salpingo-oophorectomy and contralateral ovarian cystectomy	8	19
Pelvic lymphadenectomy	15	35.7
Para-aortic lymphadenectomy	11	26.2
Omentectomy	25	59.5
Appendectomy	9	21.4
Small bowel resection and reanastomosis	2	4.8
Large bowel resection and reanastomosis	1	2.4