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Analysis of outcomes and prognostic factors after fertility-sparing surgery in malignant ovarian germ cell tumors

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HIGHLIGHTS

- Fertility-sparing surgery has excellent survival outcomes in early and advanced stage MOGCT.
- The pregnancy rate was 75%, and live birth rate was 65% after fertility-sparing surgery.
- Yolk sac tumor, incomplete surgical staging, and residual tumor were independent risk factors for recurrence.
- Yolk sac tumor and residual tumor were independent risk factors for death.

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ABSTRACT

Objective. To evaluate the oncologic and reproductive outcomes and to analyze prognostic factors after fertility-sparing surgery in patients with early and advanced malignant ovarian germ cell tumors (MOGCTs).

Methods. This study included 171 patients who underwent fertility-sparing surgery. Data were gathered from patients' medical records. Survival analysis was performed using the log-rank test and Cox's proportional hazards model. Reproductive outcomes were analyzed.

Results. Twenty-five patients (14.6%) had recurrent disease, and five patients (2.9%) died of disease during the median follow-up time of 86 months (range, 9–294 months). The 5-year disease-free survival (DFS) was 86%, and the 5-year overall survival (OS) was 97%. The 5-year DFS was 84% for stage I and 89% for stage II–IV. The 5-year OS was 99% for stage I and 91% for stage II–IV. In multivariate analysis, yolk sac tumor, incomplete staging surgery, and residual tumor were independent risk factors for reduced DFS, and yolk sac tumor and residual tumor were independent risk factors for reduced OS. Reproductive and obstetric outcomes were evaluable in 124 patients, and 106 patients (85.5%) had regular menstruation, 12 patients (9.7%) had irregular menstruation, and six patients (4.8%) had premature menopause. Twenty patients tried to conceive, 15 patients (75%) succeeded in achieving 21 pregnancies, and 13 of the patients (65%) gave birth to 20 healthy babies.

Conclusion. Fertility-sparing surgery has excellent survival outcomes in young women with MOGCTs, even in advanced stages. Reproductive and obstetric outcomes were promising. Yolk sac tumor, incomplete surgical staging, and residual tumor were independent prognostic factors.

1. Introduction

Malignant ovarian germ cell tumor (MOGCT) is a rare ovarian malignancy, which originates from primordial germ cells. It accounts for approximately 5–7% of all ovarian malignancies [1,2]. The incidence of MOGCT has not changed over the past several decades [3,4]. Several histologic types are observed, including dysgerminoma, immature teratoma, yolk sac tumor, choriocarcinoma, polyembryoma, and mixed MOGCT [5]. The survival outcomes and cure rates are excellent because of the high chemosensitivity of MOGCTs, even in advanced stage disease [3,4].

MOGCTs usually affect children, adolescent girls, and young women who wish to preserve gonadal and reproductive function. The peak incidence is at 15–19 years of age, and MOGCTs represent approximately 70% of malignant ovarian tumors in this age group [5,6]. Therefore, fertility preservation is one of the most important quality of life issues in young patients with MOGCTs. The current treatment guideline suggests the use of fertility-sparing surgery, which is defined as the preservation of the contralateral adnexa and the uterus in early stage MOGCTs that are confined to one ovary [7]. Because of the highly chemosensitive nature of MOGCTs, fertility-sparing surgery is also performed with

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cytoreductive surgery in young patients with advanced MOGCTs. However, only a few studies have evaluated the oncologic and reproductive outcomes after fertility-sparing surgery in early and advanced stage MOGCTs. In addition, the prognostic factors after fertility-sparing surgery have been rarely reported. The aim of this study was to evaluate the oncologic and reproductive outcomes and to analyze the prognostic factors after fertility-sparing surgery, in patients with early and advanced MOGCTs.

2. Materials and methods

This was a retrospective study, performed in a single center after the approval of the Institutional Review Board of Asan Medical Center, Seoul, Korea. All consecutive patients with MOGCTs who underwent fertility-sparing surgery at Asan Medical Center, Seoul, Korea, between 1992 and 2015, were included in this study. Patient demographics, clinicopathologic findings, follow-up information, and reproductive outcome data were gathered from the patients' medical records. Fertility-sparing surgery was defined as the preservation of the uterus and at least one adnexa. Complete staging surgery was defined as peritoneal staging and lymph node evaluation. Peritoneal staging included peritoneal exploration, cytology, biopsy, and omentectomy or omental biopsy. Lymph node evaluation involved one of the following: 1) lymph node dissection, 2) lymph node sampling, or 3) palpation and removal of enlarged lymph nodes. Residual tumor was defined as residual MOGCTs of any size after surgery. The strategy for adjuvant chemotherapy for MOGCTs in our center is to recommend three to six cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy in all patients, except those with stage IA dysgerminomas and stage IA grade 1 immature teratomas. All patients were evaluated at follow-up every 3 months during first 2 years after treatment, every 6 months during the next 3 years, and then once a year. The follow-up included history taking, physical examination, tumor markers, and/or imaging, including ultrasonography, magnetic resonance imaging, or computed tomography.

The association between survival outcomes and demographic and clinicopathologic factors was analyzed. Reproductive and obstetric outcomes including menstruation, premature menopause, pregnancy, and delivery were also analyzed. Disease-free survival (DFS) was calculated as the time interval, in months, between the date of surgery and the date of recurrence or censored. Overall survival (OS) was calculated as the time interval, in months, between the date of surgery and the date of death or censored. The survival curve was calculated using the Kaplan-Meier method. The difference in survival between groups was compared using the log-rank test or Cox's proportional hazards model in the univariate analysis. Multivariate survival analysis was performed using Cox's proportional hazards model, including prognostic factors that were statistically significant in the univariate analysis. Pregnancy rate was calculated by dividing the number of patients who succeeded in achieving pregnancy by the number of patients who tried to conceive. Live birth rate was calculated by dividing the number of patients who gave birth to a healthy baby by the number of patients who tried to conceive. *P*-values <0.05 in a two-sided test were regarded as statistically significant. All statistical analyses were performed using SPSS software, version 21.0 (IBM Corporation, Armonk, NY, USA).

3. Results

During the study period, 199 patients with MOGCTs underwent surgery at Asan Medical Center, and 171 of these patients who underwent fertility-sparing surgery were eligible for this study. The characteristics of the 171 patients with MOGCTs are listed in Table 1. The mean age (±SD) of patients was 22 years (±8.8 years), and 154 patients (90.1%) were nulliparous women. Immature teratoma was the most common histologic type, followed by dysgerminoma, mixed MOGCT, yolk sac tumor, choriocarcinoma, and embryonal carcinoma. A total of 125 patients (73.1%) had International Federation of Obstetrics and Gynecology (FIGO) stage I disease. None of the patients received neoadjuvant chemotherapy. The surgery mode was open surgery in 151 patients (88.3%), and the type of adnexal surgery performed was a unilateral salpingo-oophorectomy or an oophorectomy in 162 patients (94.7%). Complete staging surgery was performed in 119 patients (69.6%), and residual tumor was present in five patients (2.9%). Of five patients with residual tumor, two patients had stage IIIC dysgerminoma and each one patient had stage IIIC yolk sac tumor, stage IIIC embryonal carcinoma, and stage IV mixed MOGCT (yolk sac tumor and immature teratoma). Ascites was present in 92 patients (53.8%), and tumor rupture was reported in 52 patients (30.4%). The pathology report revealed positive peritoneal cytology in 12 patients (7%), ovarian surface

Table 1
Characteristics of patients ($n = 171$).

Characteristics		
Age, years	Mean ± SD	22 ± 8.8
	≤22 years, *n* (%)	90 (52.6)
	>22 years, *n* (%)	81 (47.4)
Parity, *n* (%)	Nulliparous	154 (90.1)
	Parous	17 (9.9)
Previous history of surgery, *n* (%)	No	128 (74.9)
	Yes	43 (25.1)
Preoperative serum α-FP level[a], *n* (%)	Not elevated	63 (36.8)
	Elevated	70 (40.9)
	Not checked	38 (22.2)
Preoperative serum β-hCG level[b], *n* (%)	Not elevated	79 (46.2)
	Elevated	23 (13.5)
	Not checked	69 (40.4)
Preoperative serum CA 125 level[c], *n* (%)	Not elevated	27 (15.8)
	Elevated	113 (66.1)
	Not checked	31 (18.1)
Histologic type, *n* (%)	Immature teratoma	54 (31.6)
	Dysgerminoma	53 (31)
	Mixed	34 (19.9)
	Yolk sac tumor	25 (14.6)
	Choriocarcinoma	4 (2.3)
	Embryonal carcinoma	1 (6)
FIGO stage, *n* (%)	I	125 (73.1)
	II	18 (10.5)
	III	26 (15.2)
	IV	2 (1.2)
Tumor size, *n* (%)	Mean ± SD, cm	14.8 ± 5.8
	≤15 cm	89 (52)
	>15 cm	82 (48)
Ascites, *n* (%)	No	79 (46.2)
	Yes	92 (53.8)
Peritoneal cytology, *n* (%)	Negative	126 (73.7)
	Positive	12 (7)
	Not done	33 (19.3)
Tumor rupture, *n* (%)	No	119 (69.6)
	Yes	52 (30.4)
Ovarian surface invasion, *n* (%)	No	141 (82.5)
	Yes	30 (17.5)
Lymph node metastasis, *n* (%)	No	69 (40.4)
	Yes	10 (5.8)
	Not sampled	92 (53.8)
Surgery mode, *n* (%)	Open	151 (88.3)
	Laparoscopy	20 (11.7)
Adnexal surgery, *n* (%)	USO or UO	122 (71.3)
	USO or UO + UOC	40 (23.4)
	UOC	5 (2.9)
	BOC	4 (2.3)
Staging surgery, *n* (%)	Complete	119 (69.6)
	Incomplete	52 (30.4)
Residual tumor, *n* (%)	No	166 (97.1)
	Yes	5 (2.9)

CA 125, cancer antigen 125; α-FP, alpha-fetoprotein; β-hCG, beta-human chorionic gonadotropin; FIGO, the International Federation of Obstetrics and Gynecology; USO, unilateral salpingo-oophorectomy; UO, unilateral oophorectomy; UOC, unilateral ovarian cystectomy; BOC, bilateral ovarian cystectomy.
[a] Reference range: 0–20 ng/mL.
[b] Reference range: 0–3 mIU/mL.
[c] Reference range: 0–35 U/mL.