

Oncologic and reproductive outcomes after fertility-sparing surgery in young women with malignant ovarian germ cell tumors

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Objective: This study evaluated the oncologic and obstetric outcomes after fertility-sparing surgery (FSS) in young patients with malignant ovarian germ cell tumors (MOGCTs). **Methods:** The medical records of women aged ≤ 40 years who underwent FSS for MOGCTs at our institution between July 2002 and December 2018 were retrospectively reviewed. FSS was defined as the preservation of the uterus and at least one adnexa. **Results:** Forty-four patients were included in this study. The median age of the patients was 22 years (range, 7–39 years). FIGO stage I (81.8%) was the most common, and stage II (6.8%), III (9.1%) and IV (2.3%) was also present. Twenty-nine patients (65.9%) received adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (BEP) after a surgery. During a median follow-up period of 62 months (range, 7–185), four patients (9.1%) had a recurrence. Of these four patients, two with dysgerminoma had recurrences at para-aortic lymph nodes and two with immature teratomas had recurrences at the remaining ovary. Thirty-seven patients (88.1%) had regular menstruation. Of fourteen women desiring pregnancy, twelve achieved the term delivery of twelve singleton pregnancies. The pregnancy and live birth rates were 85.7% and 100%, respectively. **Conclusions:** FSS with or without following BEP chemotherapy is an appropriate option for young women with MOGCTs who wish to preserve their fertility.

Keywords

Malignant ovarian germ cell tumor; Fertility-sparing surgery; Oncologic outcome; Obstetric outcome

1. Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare accounting for approximately 5% of ovarian malignancies [1–3]. Based on histopathology, MOGCTs consist of dysgerminoma, immature teratoma, yolk sac tumor, embryonal carcinoma, non-gestational choriocarcinoma, and mixed MOGCT, but all are derived from ovarian primordial germ cells [4]. They usually occur in young women with a peak incidence between 15 and 20 years of age and represent approximately 70% of ovarian malignancies in this age group [4–6]. The most important issue is the preservation of fertility and ovarian function in the quality of life of young women with MOGCTs. Accordingly, fertility-sparing surgery (FSS),

which is defined as the preservation of the uterus and at least one adnexa, with or without adjuvant chemotherapy is accepted as the standard treatment for young patients with MOGCTs [7]. Because of the high chemosensitivity of MOGCTs, the treatment and survival outcomes are excellent, even in advanced disease [1, 2, 8]. This study evaluated the oncologic and obstetric outcomes after FSS in young patients with MOGCTs.

2. Materials and methods

This study was retrospectively performed in a single center after approval by the Institutional Review Board of Chonnam National University Hospital (CNUH), Gwangju, Korea. We investigated for patients who met the following inclusion criteria: (1) age ≤ 40 years, (2) histologically proven MOGCT, and (3) patients who were treated and followed at CNUH between July 2002 and December 2018. Of 53 patients who met the criteria, 44 who underwent FSS were finally included in the study.

Patient demographics, clinicopathologic findings, and follow-up information were obtained from medical records including age, menarche, preoperative tumor markers, initial surgery, adjuvant therapies, follow-up time, recurrence, time interval to recurrence, treatment for recurrence, patient status at the last follow-up, histology and grade of the tumor, the International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size and rupture, ascites, peritoneal cytology, lymph node (LN) status, and residual tumor. We used the original pathology reports of initial surgical specimens from a pathologist specialized in gynecologic oncology without repetition of the histopathological review of pathologic slides. The histologic subtypes of MOGCT were classified according to the World Health Organization (WHO) classification and the stage was confirmed according to the revised 2014 FIGO staging system [9, 10]. The histologic grade of an immature teratoma was determined according to the Norris classification [11]. Residual tumor was defined as any sized residual MOGCT after surgery.

Preoperatively, all patients underwent laboratory testing including tumor markers and imaging studies consisting of abdominopelvic magnetic resonance imaging (MRI) and whole body positron emission tomography computed tomography (PET-CT). FSS was defined as the preservation of the uterus and at least one adnexa. Pelvic and/or para-aortic lymphadenectomy was performed when LN enlargement of >5 mm was present in the preoperative images or LN enlargement was palpated during surgery. Our center recommended three to six cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy for all patients except patients with stage I any-grade dysgerminomas and stage I grade-1 immature teratomas. After initial treatments, all patients were examined every three months during the first two years, every six months during the next three years, and yearly thereafter. Posttreatment surveillance included history-taking, physical examination, tumor markers, and/or imaging studies, including intravaginal and/or abdominal sonography and abdominopelvic CT or MRI. CT or MRI was routinely performed every six months during the first two years, and then once a year. Patient symptoms such as abdominal pain, elevated tumor markers and abnormal sonographic findings led to CT or MRI evaluation. PET-CT was also used to check for recurrence when follow-up images showed newly developed tumors.

The obstetric outcomes in the patients' medical records including menstruation, pregnancy, and delivery were analyzed. A telephone interview was performed to confirm these outcomes. The pregnancy rate was calculated by dividing the number of patients who had successful conceptions by the number of patients who tried to conceive. The live birth rate was calculated by dividing the number of patients who delivered healthy babies by the number of patients who tried to conceive.

3. Results

3.1 Clinicopathological characteristics

The clinical characteristics of a total of 44 patients are shown in Table 1. All patients underwent unilateral salpingo-oophorectomy (USO) with or without staging procedures. Ovarian cystectomy was added in six women with contralateral ovarian tumors. After primary surgery, 29 patients (65.9%) received adjuvant chemotherapy. The median number of chemotherapy cycles was four (range, 1–6). During the median follow-up time of 62 months (range, 7–185 months), four patients (9.1%) had a recurrence, but no patient died of disease progression. The only fatality was a 9-year-old girl diagnosed with mixed MOGCT (dysgerminoma, immature teratoma and yolk sac tumor) staged IC1. She died due to chemotoxicity after the first cycle of adjuvant chemotherapy.

Table 2 shows the characteristics of the tumor pathology after FSS. Immature teratoma was the most common histologic subtype, followed by dysgerminoma, yolk sac tumor, mixed MOGCT, non-gestational choriocarcinoma, and embryonal carcinoma. In six patients who received contralateral

Table 1. Clinical characteristics of patients who underwent fertility-sparing surgery (FSS) with malignant ovarian germ cell tumors (MOGCTs) (n = 44).

Characteristics		n (%)
	Median, range (years)	22, 7–39
	<10	3 (6.8)
Age	10–19	13 (29.6)
	20–29	20 (36.3)
	30–39	8 (19.2)
	No	3 (6.8)
Menarche	Yes	41 (93.2)
	Median, range (U/mL)	42, 9–1,245
CA 125 ^a	Not elevated	16 (36.4)
	Elevated	21 (47.7)
	Not checked	7 (15.9)
	Median, range (IU/mL)	16, 0–42,696
AFP ^b	Not elevated	21 (47.7)
	Elevated	21 (47.7)
	Not checked	2 (4.6)
	Median, range (mIU/mL)	3, 1–2,354
b-hCG ^c	Not elevated	8 (18.7)
	Elevated	7 (15.9)
	Not checked	29 (65.9)
	Median, range (IU/mL)	416, 107–4,981
LDH ^d	Not elevated	23 (52.3)
	Elevated	19 (43.2)
	Not checked	2 (4.5)
	Surgical approach	Laparotomy
Laparoscopy		9 (20.5)
USO		38 (86.4)
USO + contralateral ovarian cystectomy		6 (13.6)
Surgical procedure	PLND	15 (34.1)
	PALND	7 (15.9)
	Peritoneal biopsy	15 (34.1)
	Omentectomy	11 (25.0)
	Appendectomy	25 (56.8)
	No	15 (34.1)
Adjuvant chemotherapy (BEP)	Yes	29 (65.9)
	Median, range (months)	62, 7–185
Follow-up time	No	40 (90.9)
	Yes	4 (9.1)
Recurrence	Median, range (months)	41, 27–136

CA 125, cancer antigen 125; AFP, alpha-fetoprotein; b-hCG, beta-human chorionic gonadotropin; LDH, lactate dehydrogenase; BEP, bleomycin + etoposide + cisplatin; USO, unilateral salpingo-oophorectomy; PLND, pelvic lymph node dissection; PALND, para-aortic lymph node dissection.

^a Reference range: 0–35 U/mL; ^b Reference range: 0–7 IU/mL; ^c Reference range: 0–5 mIU/mL; ^d Reference range: 218–472 IU/mL.

ovarian cystectomy, the rate of tumor in the opposite ovary was 16.7% (1/6 cases). In these six patients, one of two with dysgerminoma had dysgerminoma in the opposite ovary and the other had corpus luteal cyst. Three patients with immature teratoma and one with yolk sac tumor had mature cystic teratoma in the opposite ovary. Over 80% of the patients

Table 2. Pathological characteristics of patients who underwent fertility-sparing surgery (FSS) with malignant ovarian germ cell tumors (MOGCTs) (n = 44).

Characteristics	n (%)		
Histology	Dysgerminoma	13 (29.5)	
	Grade 1	7 (15.9)	
	Immature teratoma	Grade 2	8 (18.2)
		Grade 3	5 (11.4)
	Yolk sac tumor	6 (13.5)	
	Non-gestational choriocarcinoma	1 (2.3)	
	Embryonal carcinoma	1 (2.3)	
	Mixed	3 (6.8)	
	FIGO stage	IA	24 (54.5)
		IB	1 (2.3)
IC1		6 (13.6)	
IC2		4 (9.1)	
IC3		1 (2.3)	
IIB		3 (6.8)	
IIIA1		3 (6.8)	
IIIA2		1 (2.3)	
IVB		1 (2.3)	
Tumor size		Median, range (cm)	14, 4–27
Tumor rupture	No	38 (86.4)	
	Yes	6 (13.6)	
	No	10 (22.7)	
Ascites	Yes	30 (68.2)	
	N.A.	4 (9.1)	
	Negative	35 (79.5)	
Peritoneal cytology	Positive	4 (9.1)	
	N.A.	5 (11.4)	
	Negative—imaging	29 (65.9)	
Lymph node metastasis	Negative—pathology	11 (25.0)	
	Positive (all; para-aortic)	4 (9.1)	
Residue	No	42 (95.5)	
	Yes	2 (4.5)	

FIGO, the International Federation of Obstetrics and Gynecology.

were diagnosed with stage I disease. Para-aortic LN metastasis was pathologically confirmed in four patients (9.1%).

3.2 Oncologic outcomes

The oncologic outcomes according to histologic type, surgical stage, and adjuvant chemotherapy are listed in Table 3. In two patients who underwent USO for dysgerminoma, the recurrence sites were para-aortic LNs. The two patients diagnosed with immature teratomas had a recurrence in the remaining ovary despite receiving adjuvant chemotherapy. No patient diagnosed with other histologic subtypes had recurrences. The details of the patients with recurrences are shown in Table 4. Among four patients with a recurrence, three patients underwent secondary surgical procedures and received BEP chemotherapy. These three patients showed complete remission and were alive without secondary relapse by the end of the last follow-up. The remaining one received further treatment at another hospital, and no further information on the patient was available.

3.3 Obstetric outcomes

Information on the reproductive and obstetric outcomes was obtained on 42 patients, except for one who died and one with an unknown outcome (Fig. 1). The median age of 42 patients was 26.5 years (range, 11–39 years). Thirty-seven women (88.1%) had regular menstruation, four (9.5%) had irregular menstruation, and one (2.4%) had premenarchal status. Of 14 patients who attempted to conceive, 12 (85.7%) succeeded in achieving 12 singleton pregnancies. Of 12 patients who successfully conceived, eight had received prior BEP chemotherapy. The mean interval between primary surgery and conception was 40.8 months (range, 7–93 months). Of 12 pregnancies, 11 were spontaneous pregnancies and one got pregnant with the help of assisted reproductive technology. Twelve women with successful conception delivered healthy babies after term pregnancies. There were no abortions, preterm deliveries, or congenital anomalies. Of three patients with recurrence, two relapsed in the remaining ovary before attempting to conceive and lost fertility by removal of the remaining ovary. The remaining one had regular menstruation after treatment for recurrent disease, but she had not attempted pregnancy since the initial treatment.

4. Discussion

The results of this study highlight important factors in young women with MOGCT. The first point concerns the good oncologic outcomes and the safety of FSS. In this study of young women under the age of 40, over 80% had stage I MOGCT and this led to favorable oncologic outcomes after FSS. However, the results demonstrated that the treatment and survival outcomes of FSS were good even in patients with advanced disease. A recent large population-based study presented the safety of FSS for all stages of MOGCTs [3]. Park *et al.* [12] reported that FSS could be performed safely in young patients with advanced MOGCT, who wish their fertility preservation. In the current study, of the total 44 young patients, only four had a recurrence, including one of eight with stage II–IV disease. FSS with or without adjuvant chemotherapy can be an acceptable treatment for young patients with any stages MOGCT, who desire the preservation of fertility.

The second point concerns the prognostic factors for recurrence. Previous studies presented that yolk sac tumor was an independent poor prognostic factor [3, 12]. In this study, however, there were no recurrences in six women with yolk sac tumors. Two of 13 patients with dysgerminomas (15.4%) and two of 20 with immature teratomas (10.0%) had recurrences. Notably, both patients with stage I dysgerminoma had recurrences in para-aortic LNs and both patients with immature teratoma, even after receiving adjuvant chemotherapy, had a recurrence in the remaining ovary. In general, systemic pelvic and para-aortic lymphadenectomy might be omitted in women with early MOGCTs [13]. However, in cases of dysgerminoma, it might be necessary to consider the pathological evaluation of para-aortic LN metastasis

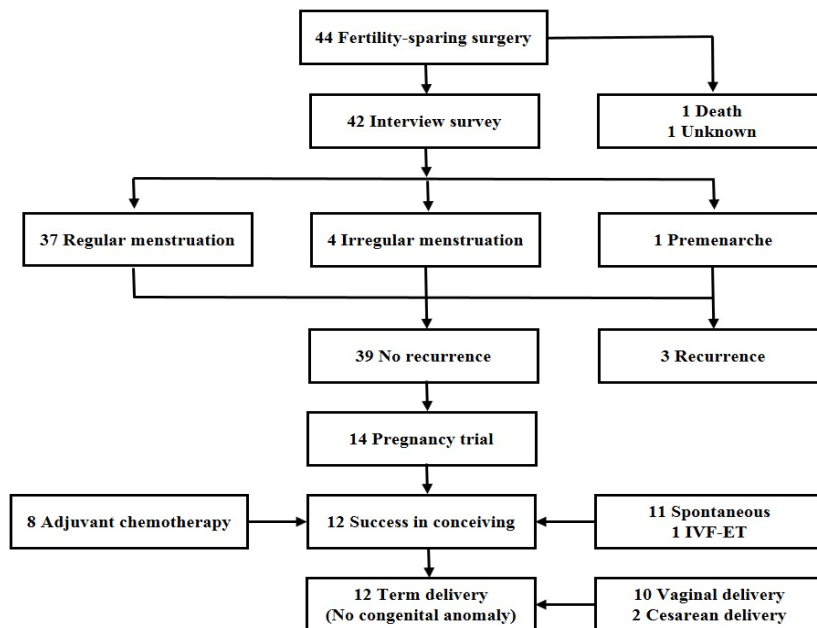


Fig. 1. Flowchart representing the reproductive outcomes of the patients who underwent fertility-sparing surgery (FSS) for malignant ovarian germ cell tumors (MOGCTs). IVF-ET, *in vitro* fertilization embryo transfer.

at the time of primary surgical procedures and imaging examinations are required to evaluate the recurrence of para-aortic LN since the initial treatments. The issue of complete surgery (removal of the remained ovary and uterus) when family planning is not needed remains controversial in young women with MOGCTs. No standard treatment policy has been accepted. The majority of recurrent tumors could be salvaged by combined treatments. Nevertheless, the removal of the remained ovary when family planning has been completed might be considered in cases of immature teratomas, and adequate evaluation of the remaining ovary since the initial treatment is also needed.

The third important point concerns the obstetric outcomes for young women after FSS with or without adjuvant chemotherapy. In the current series, the obstetric outcomes were very good in young women who underwent FSS with or without BEP chemotherapy for MOGCTs [14–16]. Most women had normal menstruations and well-preservation of gonadal function after treatment [14–16]. In a study reporting the outcomes of pediatric and adolescent girls with MOGCT receiving uniform treatment consisting of FSS and BEP chemotherapy, all had regular or irregular menstruation without experiencing premature ovarian failure [17]. In this study, most women had normal menstruation after initial managements. Among 14 women who tried to conceive, 12 (85.7%) had successful pregnancies and healthy babies. Among these 12 women, eight (66.7%) received previous adjuvant BEP chemotherapy. The obstetric outcomes after FSS are good, even in women with BEP chemotherapy. These findings suggest that this treatment is safe and realistic management for young women with MOGCTs regardless of

the tumor histology or the disease stage. In a recent study, serum anti-Mullerian hormone (AMH) level was used to assess gonadal function in young women (median age, 30 years; range, 18–39 years) with MOGCTs after FSS and platinum-based chemotherapy [16]. The results of the current study support the safety of FSS with adjuvant BEP chemotherapy in young women with MOGCTs from the viewpoint of the preservation of gonadal function [16].

Nevertheless, BEP chemotherapy can cause acute and/or chronic complications, which can be life-threatening. During BEP chemotherapy, grade 3–4 neutropenia and febrile neutropenia were reported to occur in 25% and 10% of the patients, respectively [18]. Bleomycin-induced pulmonary complications, which can be fatal, occur in 10% [19]. Cisplatin-induced renal dysfunction, which is associated to the cumulative dose of cisplatin, can occur in 11% to 26% after BEP chemotherapy [20]. Recent large-scale studies presented an increased risk of secondary malignancies after BEP chemotherapy [21]. Furthermore, the incidence of reproductive impairment may be increased. In this respect, delaying chemotherapy until recurrence might be a choice for young patients without remnant tumor after the initial surgery. Only-surgery followed by surveillance strategy has been commonly investigated in children and young adolescents with stage I MOGCTs. Marina *et al.* [22] presented the safety of this strategy in 73 children with extracranial immature teratomas. Of the 73 children, 44 had stage I ovarian immature teratomas and the 3-year disease-free survival rate was 97.8% after complete surgical excision alone [22]. Cushing *et al.* [23] reported the safety of this strategy in 44 children and adolescents with stage I immature teratomas with or with-

Table 3. Recurrence according to histology, FIGO stage and adjuvant chemotherapy (n = 44).

Histology	FIGO stage	Total n	Observation, n		Adjuvant chemotherapy, n	
			Recurrence		Recurrence	
Dysgerminoma	IA	6	6	1 (PALN)	-	
	IB	1	-		1	0
	IC1	1	1	1 (PALN)	-	
	IC3	1	1	0	-	
	IIIA1	3	-		3	0
	IIIA2	1	-		1	0
Immature teratoma	Grade 1	IA	7	-	0	
	Grade 2	IA	4	-	4	1 (contralateral ovary)
		IC1	3	-	3	0
Yolk sac tumor	Grade 3	IIB	1	-	1	1 (contralateral ovary)
		IA	5	-	5	0
	IC1	1	-	1	0	
Non-gestational choriocarcinoma	IC2	IC2	4	-	4	0
		IIB	1	-	1	0
	IVB	1	-	1	0	
Embryonal carcinoma	IA	IA	1	-	1	0
		IA	1	-	1	0
Mixed	IC1	IC1	1	-	1	0
		IIB	1	-	1	0

FIGO, the International Federation of Obstetrics and Gynecology; PALN, para-aortic lymph node.

Table 4. Clinicopathological details of patients with recurrences.

Age (years)	Histology	FIGO stage	Surgery	Adjuvant chemotherapy	Time interval to recurrence (months)	Site	Treatment at recurrence	F/U time	Outcome	
1	23	Dysgerminoma	IA	LSO, PALND, appendectomy	No	27	PALN	Treatment at another hospital	-	-
2	39	Dysgerminoma	IC1	Laparoscopic RSO	No	41	PALN	Op + BEP × 4	90	NED
3	20	Immature teratoma, G2	IIB	LSO, peritoneal biopsy, appendectomy	BEP × 4	41	Right ovary	Op + BEP × 4	98	NED
4	21	Immature teratoma, G2	IA	RSO	BEP × 3	136	Left ovary	Op + BEP × 4	185	NED

FIGO, the International Federation of Obstetrics and Gynecology; LSO, left salpingo-oophorectomy; PALND, para-aortic lymph node dissection; PALN, para-aortic lymph node; RSO, right salpingo-oophorectomy; Op, operation; BEP, bleomycin + etoposide + cisplatin; NED, no evidence of disease.

out yolk sac tumors. Only one had a recurrence after only surgery and was salvaged successfully [23]. In a report on the only-surgery strategy evaluated in 25 children and young adolescents with stage I MGOCTs, after a 42 months of median follow-up time, 12 had recurrences, 11 of which were successfully salvaged by chemotherapy, and the 4-year overall survival rate was 96% [24]. Application of the only-surgery strategy did not impair the overall oncologic outcomes and resulted in 50% of the patients avoiding the need for following chemotherapy [24, 25]. Further studies are required to confirm the safety of the only-surgery strategy in young women with more advanced disease after optimal surgery without chemotherapy.

The current study was limited by the small number of patients and its retrospective nature. These limitations are common to previous studies on MGOCTs because of the rarity of diseases. The strengths of this study were that all patients underwent FSS and the follow-up time was sufficient to evaluate the oncologic and obstetric outcomes of young women with MGOCTs.

5. Conclusions

Our results confirmed that FSS with or without adjuvant BEP chemotherapy was a safe and appropriate option for young women with MGOCTs who wished the preservation of fertility, regardless of histologic subtype or FIGO stage. The obstetric outcomes were also favorable. Recurrent tumors can be successfully salvaged by secondary surgical procedures and adjuvant chemotherapy.

Author contributions

UCJ, WDK and SMK designed the research study. UCJ and WDK performed the research and analyzed the data. SMK provided help and advice on the data analyzation. UCJ and WDK wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol was approved by the Institutional Review Board of CNUHH (approval number: CNUHH-2020-246).

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Conflict of interest

The authors declare that there are no conflicts of interest.

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