RESEARCH ARTICLE

Outcomes of Malignant Ovarian Germ-Cell Tumors Treated in Chiang Mai University Hospital over a Nine Year Period

Vithida Neeyalavira, Prapaporn Suprasert*

Abstract

Malignant ovarian germ cell tumors (MOGCT) are rare neoplasms that most frequently occur in women at a young reproductive age. There have been limited data regarding this disease from Southeast Asian countries. We therefore conducted a retrospective study to analyze the clinical characteristics and the treatment outcomes of MOGCT treated at our institute between January, 2003 and December, 2012. Seventy-six patients were recruited from this period with the mean age of 21.6 years and 11.8% were pre-puberty. The two most common symptoms were pelvic mass and pelvic pain. Two-thirds of the studied patients presented at an early stage. The most common histology was immature teratoma (34.2%) followed by endodermal sinus tumor (28.9%), dysgerminoma (25%), mixed type (10.5%) and choriocarcinoma (1.3%). Over 80% of these patients received fertility sparing surgery and about 70% received adjuvant chemotherapy with the complete response rate at 73.3% and partial response at 11.1%. The most frequent chemotherapy was BEP regimen (bleomycin, etoposide, cisplatin). With the mean follow up time at 56.0 months, 12 patients (15.8%) developed recurrence and only an advanced stage was the independent prognostic factor. The ten year progression free survival (PFS) and overall survival rate of our study were 81.9% and 86.2%, respectively. In conclusion, MOGCT often occurs at a young age. Treatment with fertility sparing operations and adjuvant chemotherapy with a BEP regimen showed a good outcome. An advanced stage is a significant prognostic factor for recurrence.

Keywords: Malignant ovarian germ cell tumor - outcomes - chemotherapy

Asian Pac J Cancer Prev, **15 (12)**, 4909-4913

Introduction

Malignant ovarian germ cell tumors (MOGCT) are rare tumors that occur in 2-6% of all ovarian cancers and develop mostly in young women (Bhurgri et al., 2011; Matei et al., 2013). The most common histology is dysgerminoma followed by immature teratoma and endodermal sinus tumor (EST) (Bilici et al., 2013; Vazquez and Rustin, 2013). Moreover, MOGCT is often found in a mixed type with the most common combination of dysgerminoma and EST (Parkinson et al., 2011). The typical tumor markers of these MOGCT cases were lactate dehydrogenase (LDH), alfa-fetoprotein (AFP), and beta-hCG that are typically elevated in dysgerminoma, EST, and choriocarcinoma, respectively (Parkinson et al., 2011). Due to the high incidence in young age women and good response to chemotherapy with BEP (bleomycin, etoposide,cisplatin) regimen, the standard treatment of MOGCT is fertility-sparing surgery followed by adjuvant chemotherapy except in patients with stage IA dysgerminoma or grade I immature tereatoma in which adjuvant chemotherapy is unnecessary after surgery (Gershenson 2012). With this treatment strategy, the 5-year overall survival rate was 100% in the early stage and over 70% in the advanced stage (Parkinson et al., 2011). However, most data regarding MOGCT originated from Western countries while Asian MOGCT data is still limited.

In our institute, that is the tertiary care of the Northern region of Thailand, we found MOGCT in 10% of all ovarian cancer which was a slightly higher incidence than the literature reports. However, we did not have our own data for the outcomes of MOGCT patients. Thus, we conducted this retrospective study to analyze the clinical characteristics and the treatment outcomes of MOGCT treated at our institute. These results might enhance the knowledge of this rare disease in Southeast Asian countries.

Materials and Methods

After the protocol was approved from the local ethics committee, the medical records of patients who presented with MOGCT between January, 2003 and December, 2012 were reviewed. The basic clinical data, histology, staging, type of surgery, chemotherapy regimen and the outcomes were identified. All pathologic specimens were examined by gynecologic pathologists in our institute. The decision

*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology. Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand *For correspondence: psuprase@gmail.com*

of treatment depended on the preference of the physicians.

The types of the surgery used in this study were defined as the following: *i*) Complete surgical staging which included hysterectomy, bilateral salpingooophorectomy (SO), retroperitoneal node sampling, partial omentectomy, peritoneal washing; *ii*) Incomplete surgical staging included hysterectomy with at least unilateral SO; *iii*) Conservative surgical staging that included unilateral SO, retroperitoneal node sampling, partial omentectomy, peritoneal washing; *iv*) Conservative incomplete surgical staging with only unilateral SO.

The response of chemotherapy was evaluated by using WHO criteria. The serum tumor markers for germ cell tumors were regular checked preoperatively and prior to the start of chemotherapy in each course and also at the follow up time. The surveillance schedule after complete treatment was every three months in the first year, every four months in the second year, and every six months in the third to fifth year, then annually. At that time, all of the patients were examined by gynecologic oncologists. Pelvic ultrasonography was done at each visit for unmarried patients. Other imaging such as CT-scan was utilized when indicated by clinical data or with a rising of tumor markers.

The progression free survival (PFS) was defined as the time between the month of the initial treatment and the month of tumor progression detection or last contact whereas the overall (OS) was defined as the similar starting time of PFS to the month of patient death or last contact.

Statistical analysis of the data was carried out using the SPSS for Window program (Version 17.0, Chicago, IL, USA). Descriptive data of all studied patients were presented as means with range and discrete data were reported as number and percentages. The Chi-square test, the Fisher Exact test and logistic regression multivariate analysis were used to evaluate the statistical significance of the prognostic factors for recurrence. The overall survival was estimated by the Kaplan-Meier method. The statistical significance was noted when a P-value was less than 0.05.

Results

There were 76 patients who met the inclusion criteria. The mean age was 21.6 with a range from 4 to 50 years old. The most common presenting symptom was pelvic mass and pelvic pain which were found equally in each group as 34%. About sixty percent of the patients were unmarried and 10% of the patients were in pre-pubertal status. Nearly 70% of the patients were in Stage I and the most common histology was immature teratoma (34.2%) followed by EST (28.9%), dysgerminoma (25.0%), mixed cell type (10.5%) and choriocarcinoma (1.4%). Two patients revealed gonadoblastoma with abnormal chromosome. Forty-two percent of the patients underwent surgery at our institute while the rest were referred to our institute postoperatively from the provincial hospitals. However, only 47.4% of the studied patients received their operation by gynecologic oncologists.

About the type of surgery. Sixty-one (80.3%) patients underwent conservative surgery with 39.4 percent of them

Table 1. The Clinical Characteristics of Patients who Received Non-Fertility Sparing Surgery

No	Age (year)	status	Parity	Presenting symptom	Place of surgery	Type	Histology	stage	Treatment &outcome	Note
1	19	Single	0	Pelvic pain	CMUH	CSS	M[1]	IIC	BEP x 3,loss	Chromosome XY, primary amenorrhea
2	25	Single	0	Pelvic mass	Other	CSS	IT	IC	BEP x 1,loss	-
3	33	Married	0	Pelvic pain	CMUH	CSS	EST	IC	BEP x 6,CR,loss	Patient demanded
4	32	Married	2	Pelvic pain	CMUH	CSS	EST	IIIA	BEP x 6,CR	PFS 30 mo→ ascites R/O recurrence→loss
5	25	Married	1	Pelvic mass/ hyper-menorrhea	Other	CSS	D	IIIC	BEP x 4 ,loss	-
6	35	Single	0	Pelvic pain	CMUH	TAH& Rt SO &BPND	IT	IA	FU	Adhesion uterus and Rt ovarian tumor, PFS= 17 mo
7	30	Married	1	-	Other	TAH&BSO	D	-	Cyclophosphamide x 6	PFS 17mo→PV: vaginal stump mass→Re-op→BEP x 4→CR→loss
9	22	Single	0	Pelvic mass/pain/ primary amenorrhea	Other	TAH&BSO& omentectomy	D	IIB	BEPx6→PR	PFS 91 mo, abn.chromosome 45X0,46XY
10	16	Single	0	Primary amenorrhea	CMUH	Bilateral SO	M[2]	IA	FU	PFS 95 mo Chromosome 46,XY
11	50	Married	2	Pelvic pain	CMUH	TAH&BSO& omentectomy	M[3]	IIIA	BEPX5→ICE x 5→PT x 1→taxol x 2	Progression
12	25	Married	1	Pelvic mass	CMUH	TAH&BSO& debulking tumor	EST	IIIC	BEPx6	CR, PFS 37 mo
13	26	Married	1	Pelvic pain	Other	TAH&BSO& omentectomy	IT	IC	BEP x 7	PFS 43 mo
14	30	Married	1	Pelvic mass	Other	TAH&LtSO& omentectomy	D	IC	BEPx6	PR, PFS 30 mo
15	37	Single	0	Pelvic mass	CMUH	S/P LtSO → TAH&RtSO	IT	IC	FU	Patient demanded,PFS 19 mo

M[1]: dysgerminoa; EST: immature teratoma, gonadoblastoma; M[2]: gonadoblastoma; dysgerminoma, M[3]: EST, immature teratoma; CMUH=Chiang Mai University Hospital; IT=Immature teratoma; EST=Endodermal sinus tumor; D=Dysgerminoma; CSS=Complete surgical staging; BEP=Bleomycin etoposide cisplatin; PT=carboplatin paclitaxel; ICE=ifosfamide cisplatin etoposide; FU=follow up; TAH=Trans abdominal hysterectomy; Rt SO=right salpingo-oophorectomy; BSO=bilateral salpingo-oophorectomy; BPND=bilateral pelvic node dissection; S/P=status post
PFS=progression free survival; CR=complete response; PV=per vaginal examination; Re-op=Re=operation

Table 2. The Clinical Data of Patients with Recurrence (N=12)

SN	Age	Stage	Histology	Surgery	Chemotherapy	PFI (months)	Symptom	P.E	Management	Outcome
1	25	IA	EST	Conservative incomplete SSx	Cisplatin + cyclophosphamide x 6	14	Distension	Abdominal mass	Sx + BEP	CR
2	30	IC	Dysgerminoma	Incomplete SSX	Cyclophosphamide x 6	17	Abdominal mass	Abdominal mass	Sx + BEP	CR
3	26	IA	IT (G1)	Conservative incomplete SSx	None	77	Abdominal pain	Abdominal mass	BEP	Loss
4	26	IC	Mixed	Conservative incomplete SSx	None	1	Abdominal pain	Abdominal mass	Sx+BEP	Loss
5	15	IIIC	EST	Conservative incomplete SSx	BEP x 6	8	Distension	Abdominal mass	Sx+BEP	Dead
6	16	IV	EST	Conservative incomplete SSx	BEP x 11	12	None	Cervical LN enlargement	Ifosfamide	Dead
7	50	IIIA	Mixed	Incomplete SSX	BEP x 5	7	None	Vaginal mass	Ifosfamide+carboplatin+etoposide	Dead
8	18	IC	Mixed	Conservative incomplete SSx	BEP x 2	3	None	None	Carbopatin + paclitaxel	CR
9	18	IA	IT(G1)	Conservative complete SSX	None	21	Dyspnea	Pleural effusion	Sx+carboplatin+paclitaxel+RT	Dead
10	32	IV	EST	Conservative incomplete SSx	None	3	Abdominal distension	Ascites	Sx+BEP	CR
11	17	IV	chorioCA	Conservative complete SSX	EMA-CO x 6	5	None	None	Sx+cisplatin&ifosfamide	Dead
12	13	IV	EST	Conservative incomplete SSx	Carboplatin + EP x6	5	None	None	EP	Dead

EST=endodermal sinus tumor; IT=immature teratoma; Chorio=choriocarcinoma; SSX=surgical staging; BEP=bleomycin etoposide cisplatin; EMA-CO=etoposide methotrexate actinomycin D,cyclophosphamide vincristine; EP=etoposide cisplatin; Sx=surgery; RT=radiation; CR=complete response

Figure 1. Progression Free Survival (PFS). Mean follow up time=58.43 months (1-131 months) 5 year PFS=85.2 %, 10 year PFS=81.9%

Figure 2. Overall Survival. Mean follow up time = 66.63 months (9-197 months) 5 year overall survival 86.2%, 10 year 86.2% Death=9 cases

receiving conservative surgical staging. Only 14 cases underwent non-fertility sparing surgery with six cases who received complete surgical staging. The details of these patients were noted in Table 1. The reason for operation with this technique were as follows: advanced stage in four cases, over 50 years old in one case, abnormal sex chromosome in three cases, patients' demand in two cases while the rest did not mention the reason. Fourteen patients (18.4%) did not return postoperatively.

Fifty-four patients received adjuvant chemotherapy. The most common regimen was a three day BEP regimen. However, nine patients did not complete their course of treatment due to loss of follow up in eight cases and one patient could not tolerate the toxicity. For 45 patients who received complete chemotherapy administration, 73.3% achieved complete response while 11.1% showed partial response and 15.6% revealed progress. Furthermore, with the median follow up time at 56.0 months, 12 patients developed recurrence and the ten year PFS and overall survival was 81.9% and 86.2%, respectively as shown in Figure 1.

The details of patients with recurrence were noted in Table 2. About half of them showed an initial early stage. The most common histology was EST. Four patients never received any adjuvant chemotherapy due to Stage IA immature teratoma Grade 1 in 2 patients and failure to follow up postoperatively in the rest. Most of them revealed positive findings and were treated with reoperation followed by chemotherapy. However, three patients were diagnosed with a recurrence by the rising of their tumor marker alone. Univariate and multivariate regression analysis were performed to evaluate the prognostic factors for recurrence which is reported in Table 3. Only advanced stage was the independent poor prognostic factor for recurrence.

Table 3. Prognostic Factors for Recurrence

Factors		Recurrence rate (%)	Univariate (P)	Multivariate (P)
Age (years)	Less than or equal 20	6 (17.1)	0.765	0.769
	More than 20	6 (14.6)		
Place of surgery	CMUH	3 (9.7)	0.187	0.231
	Other	9 (20.0)		
Stage	I&II	6 (10.5)	0.029	0.029
	III&IV	6 (31.6)		
Histology	Dysgerminoma	1 (5.3)	0.136	0.15
	Non-dysgerminoma	11 (19.3)		
Surgeon	Gyne-oncology	3 (8.6)	0.099	0.114
	General	9 (22.0)		
Chemotherapy	None	4 (18.2)	0.479	0.719
	Receive	9 (14.8)		
Type of surgery	Non-fertility	2 (13.3)	0.564	0.775
	Fertility sparing	10 (16.4)		

Discussion

The peak incidence of MOGCT is at age 15 to 19 years (Parkinson et al., 2011) which was closely to the present study that revealed the mean age of the studied patients at 21 years. However, we found one case age 50 years that presented with stage IIIA, mixed type consisted of EST and immature teratoma. MOGCT in the fifth decade is quite rare (Low et al., 2012). Solheim et al (Solheim et al., 2013) reviewed 351 Norwegian patients with MOGCT and found that patients over 50 years old had a significantly poorer prognosis than younger patients consistent with this case in our study that showed an uneventful outcome even though she received many chemotherapy regimens.

The most common presenting symptoms in the present study were pelvic mass and pelvic pain that corresponded to a previous report which found over eighty percent of the MOGCT patients with these symptoms (Bilici et al., 2013; Matei et al., 2013). Although, dysgerminoma represented the most common type of MOGCT in the literature review (Bhurgri et al., 2011., Low et al., 2012), we found dysgerminoa was the third ranking histology in our study while the first ranking was immature teratoma and the second ranking was EST. This finding resembled the Weinberg et al publication (Weinberg et al., 2011). The authors showed the most common histology of MOGCT in their series was also immature teratoma and the second common was dysgerminoma. However, EST in their study was only 10% while in the present study was nearly 30%. This difference might be from non-similar ethnic backgrounds.

As MOGCT often occurs at a young reproductive age and the nature of chemosensitive tumor, the conservative surgical approach including unilateral adnexectomy, omentectomy, peritoneal washing, peritoneal biopsies and retroperitoneal lymphadenectomy followed by adjuvant chemotherapy excepted in dysgerminoma and Grade 1 immature teratomy was recommended with a good outcome in Stage I MOGCT (Low et al., 2012; Matei et al., 2013). However, Mahdi et al, (2011) analyzed 493 MOGCT patients who underwent lymphadenectomy compared to 590 MOGCT patients who did not receive this procedure and found that neither lymphadenectomy nor lymph node metastasis was an independent prognostic factor for survival. Furthermore, even in the advanced stage a conservative study also yielded good outcomes (Vazquez and Rustin, 2013; Billmire et al., 2004). In the present study, about 80% of the patients were received fertility sparing surgery and most of them were young adults. The outcomes of our study also found that the type of surgery was not an independent prognostic factor.

All MOGCT patients were recommended to receive adjuvant chemotherapy except Stage IA dysgerminoma and immature teraotma Grade 1 due to the very low incidence of recurrence in both histology (Parkinson et al., 2011). However, the recent study suggested that there may be no need to give adjuvant chemotherapy in stage IA non-dysgerminoma because only one-third of the patients experienced relapse and over 90% of them were successfully treated with chemotherapy (Patterson et al., 2008). In the present study, chemotherapy was commonly given in all MOGCT patients except in Stage IA dysgerminoma and immature teratoma Grade 1. However, some cases did not receive adjuvant chemotherapy due to being lost to follow up after their operation or dependent on physician preference. We found recurrence rate in our study at 15.8%. Of these patients, four patients were not given adjuvant chemotherapy. Two cases were Stage IA immature teratoma Grade 1 and the other two were Stage IC mixed type and Stage IV EST. The treatment after recurrence of MOGCT with salvage chemotherapy produced an unsatisfactory outcome with patients being lost to treatment because they were unable to tolerate chemotherapeutic toxicity in two cases and one patient who died of her disease although heavily treated with multiple chemotherapy regimens. Thus, from our data, the adjuvant chemotherapy in the early stage of non-dysgerminoma might be still needed.

The standard chemotherapy of MOGCT is a BEP regimen that consisted of bleomycin plus etoposide plus cisplatin with a recent report from an Italian study that showed a five year overall survival rate in 123 MOGCT patients to be 88.8% (Mangili et al., 2011) similar to our study that revealed a five year overall survival rate as 86.2%. The authors mentioned that the advanced stage and EST histology were the independent prognostic factors while in the present study we found that only advanced stage was the independent prognostic factor. This inconsistent result might be from the low number of patients in our study.

The strength of our study was the research in a single institute that might decrease the variation of surgical technique and the types of chemotherapy regimens. However, one limitation was observed from a limited number of patients due the rare disease and some of the studied patients were lost to follow up.

In conclusion, MOGCT often occurs in the young reproductive age with successful treatment of conservative surgery and adjuvant chemotherapy. Advanced stage was the only independent prognostic factor to the recurrence rate.

Acknowledgements

We wish to thank the National Research University Project under Thailand's Office of Higher Education

Commission and Chiang Mai University for the financial support in this project.

References

Bilici A1, Inanc M, Ulas A, et al (2013). Clinical and pathologic features of patients with rare ovarian tumors: multi-center review of 167 patients by the Anatolian Society of Medical Oncology. *Asian Pac J Cancer Prev*, **14**, 6439-9.

Bhurgri Y1, Shaheen Y, Kayani N, et al (2011). Incidence, trends and morphology of ovarian cancer in Karachi (1995-2002). *Asian Pac J Cancer Prev*, **12**, 1567-71.

Billmire D, Vinocur C, Rescorla F, et al (2004). Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. *J Pediatr Surg*, **39**, 424-9.

Gershensom DM (2012). Treatment of ovarian cancer in young women. *Clin Obstet Gynecol*, **55**, 65-74.

Low JJ, IIancheran A, Ng JS (2012). Malignant ovarian germ-cell tumours. *Best Pract Res Clin Obstet Gynaecol*, **26**, 347-55.

Matei D, Brown J, Frazier L (2013) . Updates in the management of ovarian germ cell tumors. *Am Soc Clin Oncol Educ Book*, 210-6.

Mahdi H, Swensen RE, Hanna R, et al (2011). Prognostic impact of lymphadenectomy in clinically early stage malignant germ cell tumour of the ovary. *Br J Cancer*, **105**, 493-7.

Mangili G, Sigismondi C, Gadducci A, et al (2011). Outcome and risk factors for recurrence in malignant ovarian germ cell tumors: a MITO-9 retrospective study. *Int J Gynecol Cancer*, **21**, 1414-21.

Parkinson CA, Hatcher HM, Ajithkumar TV (2011). Management of malignant ovarian germ cell tumors. *Obstet Gynecol Surv*, **66**, 507-14.

Patterson DM, Murugaesu N, Holden L, et al (2008). A review of the close surveillance policy for stage I female germ cell tumors of the ovary and other sites. *Int J Gynecol Cancer*, **18**, 43-50.

Solheim O, Kærn J, Tropé CG, et al (2013). Malignant ovarian germ cell tumors: presentation, survival and second cancer in a population based Norwegian cohort (1953-2009). *Gynecol Oncol*, **131**, 330-5.

Vazquer I, Rustin GJ (2013). Current controversies in the management of germ cell ovarian tumours. *Curr Opin Oncol*, **25**, 539-45.

Weinberg LE, Lurain JR, Singh DK, et al (2011). Survival and reproductive outcomes in women treated for malignant ovarian germ cell tumors. *Gynecol Oncol*, **121**, 285-9.