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Original Article

Cytoreductive surgery in advanced stage malignant ovarian germ cell tumors

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ABSTRACT

Introduction: To evaluate the survival effect of cytoreductive surgery in advanced stage malignant ovarian germ cell tumors (MOGCT).
Material and Methods: Clinicopathological data of patients with MOGCT that were treated between 1991 and 2014. Maximal debulking was defined as no gross residual tumor after primary or recurrence surgery; optimal and suboptimal debulking were used for patients with residual tumors of ≤1cm and >1cm, respectively.
Results: In total, 31 patients with advanced stage MOGCT were analyzed. The median age at diagnosis was 21 (14-57) years. The median follow-up duration was 64.1 months. Of these 31 patients; 7 patients underwent sub-optimal debulking, 5 patients had optimal surgery and 18 had maximal debulking. Five-year DFS according to surgical resection rates were 29% in suboptimal debulking group, 75% in optimal debulking group and 93% in maximal cytoreduction group ($p < 0.001$). Three of seven patients who underwent sub-optimal debulking were died of disease, however no deaths were seen in patients with optimal and maximal debulking. Five-year OS was 32% in suboptimal debulking group, and 100% in optimal and maximal debulking groups (p=0.001).
Discussion: The benefit of cytoreductive surgery is less well-established in MOGCT of ovary compared to ovarian tumors of epithelial origin due to rareness of this histological subtype. Patients with MOGCT are usually younger and preservation of fertility is an important issue which may lead to suboptimal procedures, sometimes in exchange for diminished survival. Our data demonstrated that maximal cytoreduction should be aimed in patients with advanced stage MOGCT, as it is significantly associated with improved overall survival.

Introduction

Malignant ovarian germ cell tumors (MOGCT) originating from primordial germ cells constitute 2–3% of ovarian malignancies [1]. Symptoms such as abdominal pain and distention appear at early period of disease due to rapid growth pattern of these tumors and MOGCTs are often identified at early stages unlike epithelial ovarian cancers [2]. However, 20–30% of the cases present advanced stage at the time of diagnosis [3]. The stage of the disease, presence of residual tumor after surgery and histological type are the most important prognostic factors [3].

Treatment options for MOGCTs include fertility preservation methods because it usually affects adolescents and young women. However, data on fertility-preserving surgery for advanced stage MOGCT is scarce and there is no consensus on extent of the surgical management [4].

Platinum-based adjuvant chemotherapy is the standard treatment approach for all patients with MOGCT except patients with stage I dysgerminoma or immature teratoma [5]. Patients with early disease MOGCT have excellent oncologic outcomes, whereas response rates decrease with advanced stage disease [1].

The present study aimed to determine the factors associated with recurrence and survival in advanced stage (International Federation of Gynecology and Obstetrics [FIGO] stage III and IV) MOGCTs. Our secondary objective was to evaluate the role of the

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cytoreductive surgery and fertility-preserving surgery on survival on oncological outcomes in patients.

Material- method

Data of 100 patients who were treated with a diagnosis of MOGCT between July 1991 and December 2014 in our institution were obtained from the electronic database of gynecological oncology clinic. Patients' files were reviewed retrospectively. Thirty-one patients with FIGO stage III&IV disease were included in the study.

The management of the MOGCT is detailed as follows. Peritoneal cytology was obtained from ascites or with peritoneal lavage in the absence of ascites. Ovarian mass was removed via oophorectomy or cystectomy and was sent for intraoperative frozen section consultation. Surgical exploration was performed via palpation of the peritoneal surfaces, retroperitoneal area and solid organs. Patients that underwent cystectomy had completion oophorectomy when frozen section confirmed the presence of MOGCT. Lymphadenectomy and omentectomy were added at surgeon`s discretion. Cytoreductive surgery were performed when needed. In case of equivocal frozen section results, the final pathology report was taken into consideration for patient management. The decision to restage the patients was made due to patient age, fertility desire and extension of the disease. Gynecologic oncology surgeons performed the procedures. Maximal debulking was defined as no visible tumor after surgery. Optimal and suboptimal debulking were used for patients with residual tumor $\leq$1 cm and >1 cm, respectively. Preservation of uterus and at least one ovary was defined as a conservative surgery. Hysterectomy and bilateral salpingo-oophorectomy was defined as definitive surgery. Desire to preserve fertility and patient age were the factors that lead to conservative approach. Adjuvant treatment options were discussed in multidisciplinary tumor board.

Patient demographics, intraoperative findings, postoperative pathologic features and oncologic outcomes (recurrence and survival), were collected. Recurrence time, localization of recurrence and the cause of death are noted. Patients before 2014 were re-staged according to the 2014 FIGO criteria.

Patients who had complete clinical response after initial treatment were followed up quarterly in the first 2 years, semi-annually up to 5 years and annually later on with pelvic examination, abdominal-pelvic ultrasonography, complete blood count, blood chemistry and tumor markers. Chest X-ray was utilized yearly. Thoracic and/or abdominal computerized tomography was used when needed.

Statistical analysis

Progressive disease is defined as 20% or greater increase in the sum of the largest diameter of target lesion or the appearance of one or more new lesions, or progression of any non-target lesion according to the assessment made in the first month after treatment [6]. Disease that recurred during follow-up of patients whose routine evaluations showed absence of the disease at first month after initial treatment was accepted as a recurrence. Period from initial surgery to recurrence/progression or last visit was defined as disease-free survival (DFS), and period from surgery to death because of the disease or last visit was defined as disease-specific survival (DSS). SPSS (SPSS Inc, Chicago IL, USA) version 17.0 was used for statistical analysis. Categorical variables were compared by using Chi-Square. The Kaplan-Meier method was used for the assessment of DFS and DSS. Survival curves were compared by using the log-rank test. The cut-off for statistical significance was set at p value <0.05.

Results

Median age of the entire cohort was 21 years (range; 14–57) and main symptom was abdominal distention (64.5%). The tumor was located at right and left ovary in 13(41.9%) and 17(54.8%) patients, respectively. The tumor involved bilateral ovaries in 1 patient (3.2%). All but one of the patients had stage III disease. The most common tumor type was dysgerminoma (54.8%). The data related with clinical, surgical and pathological factors are presented in Table 1.

Ascites was present in 15 (48.4%) patients and the median ascites volume was 500 cc (range; 50–4000). Eight (30.8%) patients had positive cytology. Twenty-one (67.7%) patients underwent lymphadenectomy. The median number of removed lymph nodes was 25 (range; 10–74) in total, 10 (range; 5–37) for the pelvic region and 11 (range; 1–44) for the para-aortic region. Lymph node metastasis was detected in 18 (85.7%) of 21 patients who underwent lymphadenectomy. Of these, 2 (11.1%) patients had pelvic lymph node metastasis, 10 (55.6%) patients had para-aortic nodal metastasis, and 6 (33.3%) patients had both pelvic and para-aortic nodal spread. The other involved organs were omentum in

Table 1
Characteristics of overall patients.

Characteristics	median	range
Age	21	14-57
Preoperative β-hCG (mIU/mL)	49	0.1-6019
Preoperative α-fetoprotein (ng/ml)	475	1-19489
Preoperative Ca125(IU/ml)	79	21-1050
Tumor Size (mm)	200	50-300
	n	%
Main symptom		
Abdominal pain	9	29
Abdominal distension	20	64.5
Menstrual disorder	1	3.2
Routine control	1	3.2
Tumor type		
Dysgerminoma	17	54.8
Non-Dysgerminoma	14	45.2
Yolk sac	7	22.6
Immature teratoma	2	6.5
Mixed	3	9.7
Yolk sac + disgerminoma	2	6.5
Yolk sac + immature teratoma	1	3.2
Choriocarcinoma	1	3.2
Embryonal carcinoma	1	3.2
Ascites		
Yes	15	48.4
No	16	51.6
Lymphadenectomy		
Performed	21	67.7
Not performed	10	32.3
Surgical outcome		
Maximal cytoreduction	18	58.1
Optimal cytoreduction	5	16.1
Sub-optimal cytoreduction	7	22.6
Unknown	1	3.2
Adjuvant therapy		
Chemotherapy	28	90.3
Radiotherapy	3	9.7
FIGO stage (2014)		
3A1	13	41.9
3B	3	9.7
3C	14	45.2
4B	1	3.2
Recurrence or progression		
Negative	24	77.4
Progression	2	6.5
Recurrence	5	16.1
Follow-up time (months)	64.1	6-240

Sub-optimal cytoreduction: Residue tumor >1 cm; Optimal cytoreduction: Residue tumor <1 cm; Maximal cytoreduction: No visible tumor.

11 patients, appendix in 2 patients, spleen in 1 patient and small bowel in 1 patient.

Conservative and definitive surgery were performed to 18 patients (58.1%) and 13 (41.9%), respectively. Surgical outcomes were maximal debulking in 18 (58.1%) patients, optimal debulking in 5 (16.1%) patients and sub-optimal debulking in 7 (22.6%) patients. The data of surgical outcome for 1 patient was not reached. One patient had peritonectomy, 2 patients had colon resection, 1 patient had tumor excision from colon serosa, 1 patient had splenectomy in and 1 patient had liver metastasectomy to achieve maximal cytoreduction.

All patients received adjuvant therapy. 28 (90.4%) patients had multimodal chemotherapy. Chemotherapy regimens were given as BEP (Bleomycin + Etoposide + Cisplatin) in 22(70.9%) patients, VAC (Vincristine + Actinomycin D + Cyclophosphamide) in 3(9.6%) patients and VBP (Vinblastine + Bleomycin + Cisplatin) in 3(9.6%) patients. Adjuvant therapy was given as a pelvic radiotherapy in 3 (9.6%) patients with dysgerminoma.

Survival analysis

Median follow-up time was 64.1 months (range, 6–243). Recurrence developed in 5 (16.1%) patients and progression was observed in 2 (6.5%) patients during the follow up (Table 2). Patients with progressive disease had suboptimal cytoreduction at initial surgery. Median recurrence time was 12 months (range; 6–31). Recurrence sites were pelvis in 1 patient, para-aortic lymph nodes in 1 patient, liver parenchyma in 1 patient and at upper abdomen in 2 patients. In patients with recurrence, tumor type was dysgerminoma in 3 patients (*patient #3, patient #4 and patient #5*) and immature teratoma in 2 patients (*patient #1 and patient #2*) (Table 2).

Two patients with recurrence had conservative surgery. The surgical outcome of patients with recurrence was maximal in 1 patient, optimal in 1 patient and sub-optimal cytoreduction in 3 patients. Five (71.4%) of 7 patients who had sub-optimal cytoreduction at initial surgery experienced disease failure as a progressive disease in 2 (28.5%) patients and as a recurrence in 3 (42.9) patients during the follow-up. The recurrence time of these 3 patients, who had complete clinical response to adjuvant therapy following surgery was 7, 11 and 12 months (*patient #2, patient #5 and patient #3, respectively*) (Table 2). One patient who had optimal cytoreduction and another patient who had maximal cytoreduction recurred 24 months and 31 months after surgery, respectively (Table 2). Totally 3 (9.7%) patients including 2 patients who had progressive disease and 1 (*patient #3*) of 5 patients with recurrence died due to the disease.

The 5-year DFS and DSS in whole study group were 79.8% and 87.6%, respectively. Initial surgical outcome was significantly associated with both DFS and DSS. 5-year DFS was 29% in sub-optimal cytoreduction group, 75% in optimal cytoreduction group and 93% in maximal cytoreduction group ($p < 0.001$) (Fig. 1). These rates for the 5-year DSS were 32%, 100% and 100%, respectively ($p = 0.001$) (Fig. 2, Table 3).

Age at diagnosis (≤21 years vs. > 21 years), tumor size (≤200 mm vs. > 200 mm), performance of lymphadenectomy, median number of removed lymph nodes (≤24 vs. > 24), tumor histology (dysgerminoma vs. non-dysgerminoma), presence of ascites, peritoneal cytology and type of surgery (conservative vs. definitive) was not significantly associated with both DFS and DSS (Table 3).

The 5-year DFS and 5-year DSS were 74% and 83% for patients who underwent conservative surgery, and 84% and 92% for patients who underwent definitive surgery ($p > 0.05$). The percentage of patients that had maximal/optimal cytoreduction surgery were similar conservative and definitive surgery cohorts (%78 *vs.* %75, respectively; $p = 0.605$). The sub-group analysis limited to patients who underwent maximal or optimal cytoreduction showed no statistically significance in 5 year DFS (89% and 90%, respectively; p = 0.907). All patients in this sub-group were alive at the time of analysis.

2 patients with dysgerminoma and 1 patient with yolk sac tumor experienced pregnancy after conservative surgery with a total of 4 deliveries.

Table 2
Clinical, Surgical and Pathologic Characteristics of Patients with Recurrence or Progression.

Characteristics	Patient with recurrence					Patient with progression	
	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Age at diagnosis	20	22	21	31	25	57	21
Stage FIGO 2014	3C	3C	3C	3A1	3A1	4B	3C
Surgical outcome	Optimal	Sub-optimal	Sub-optimal	Maximal	Sub-optimal	Sub-optimal	Sub-optimal
Adjuvant therapy	BEP (4 cycles)	BEP (4 cycles)	VAC (6 cycles)	BEP (4 cycles)	BEP (4 cycles)	BEP (4 cycles)	BEP (4 cycles)
Tumor type	Immature teratoma grade 3	Immature teratoma grade 3	Dysgerminoma	Dysgerminoma	Dysgerminoma	Choriocarcinoma	Dysgerminoma
Tumor size (mm)	60	75	300	80	95	100	300
Ascites (cc)	80	No	100	No	No	No	2000
Lymphadenectomy	Not performed	Not performed	Performed	Performed	Performed	Not performed	Performed
Conservative surgery	Not performed	Not performed	Not performed	Performed	Performed	Not performed	Not performed
Recurrence site	Liver	Upper abdomen	Upper abdomen	Pelvic	Para-aortic lymph node	Liver	Para-aortic lymph node
Surgery after recurrence	Performed	Not performed	Not performed	Performed	Not performed	Not performed	Not performed
Salvage chemotherapy at recurrence	EP	BEP (4 cycles)	Not received	EP	Not received	VIP	Platin-based
Recurrence time (months)	24	7	12	31	11	–	–
Follow-up time (months)	30	13	14	51	15	11	13
Exitus	AWOD	AWOD	DOD	AWOD	AWD	DOD	DOD

AWOD: Alive without disease.
AWD: Alive with disease.
DOD; Death of disease.
BEP: Bleomisin + Etoposide + Cisplatin.
EP: Etoposide + Cisplatin.
VAC: Vincristine + Actinomycin D + Cyclophosphamide.
VIP:Etoposide + Ifosfamide + Cisplatin.

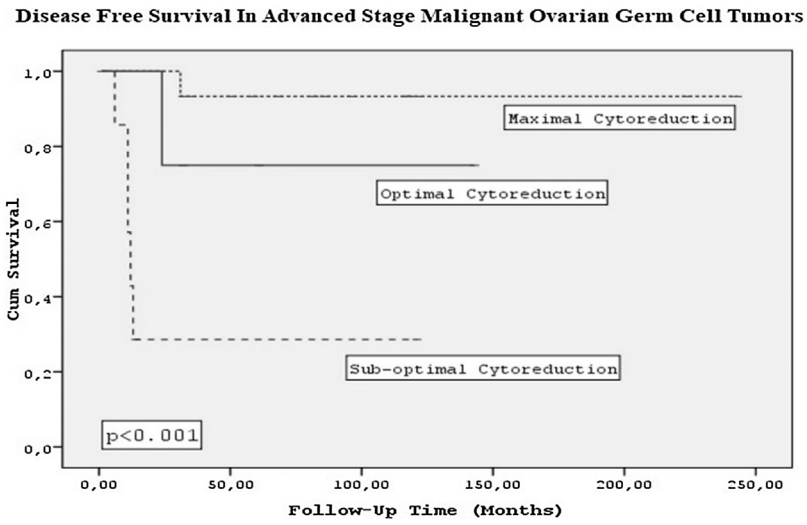

Fig. 1. Disease Free Survival in Advanced Stage Malignant Ovarian Germ Cell Tumors.

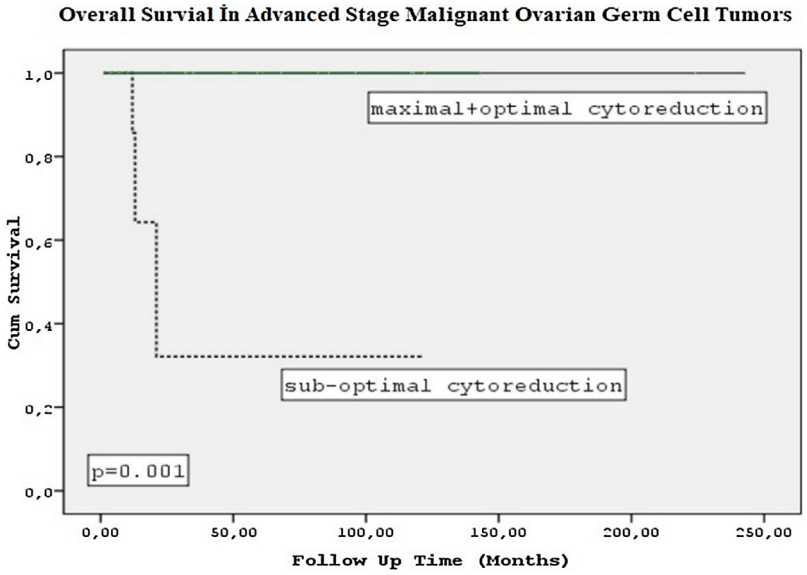

Fig. 2. Overall Survival in Advanced Stage Malignant Ovarian Germ Cell Tumors.

Discussion

MOGCT constitutes 2–3% of all ovarian cancers and is usually diagnosed at early stages due to tumor biology [1,7]. However, 20–30% of patients present with advanced stage [3]. The incidence of advanced stage MOGCT was 31% in our clinic. Because of the rapidly growing behavior, symptoms of MOGCT are mostly distention (35%) and pain (%55–80) [3]. Abdominal distention and abdominal pain constituted approximately 95% of presentation symptoms in our study similar to published literature.

Completeness of cytoreduction was the only predicting factor for disease recurrence and overall survival in our study. Maximal cytoreduction was achieved in 58% of our patient cohort and optimal cytoreduction was the outcome in 16% of our patients. The residual tumor was over 1 cm in 22% of the patients. 5-year DFS was significantly higher in patients with maximal and optimal cytoreduction than patients who had suboptimal cytoreduction (93%, 75% and 29% respectively). In addition, progressive disease was observed only in sub-optimal cytoreduction group. Whereas no deaths were observed within 5 years in maximal/optimal cytoreduction group, only 32% of the patients survived in the sub-optimal group ($p = 0.001$). There was no statistically significant differences in DFS and DSS between patients who had maximal cytoreduction and optimal cytoreduction.

The effect of the cytoreductive surgery on the oncologic outcomes is unclear due to the limited number of patients with advanced MOGCT. Bafna et al., evaluated oncological outcomes in 19 patients with MOGCT. They showed that persistent disease and recurrence developed in 13% of patients whose postoperative residual tumor was less than 2 cm, whereas this rate was 75% in patients with more than 2 cm residual tumor [8]. Slayton et al. defined the size of the residual tumor for optimal cytoreduction as 3 cm and determined that treatment failure rate for suboptimal surgical group was 68% whereas it was 28% for other group when all patients received VAC as adjuvant treatment. [9]. Park et al. showed that the residual tumor size is an independent prognostic factor for recurrence and survival in stage I–IV MOGCT [7]. Williams et al. evaluated the outcomes in patients undergoing suboptimal surgery followed by adjuvant chemotherapy as a PVB (cisplatin + vinblastine + bleomycin), VAC or BEP. 4.4% with

Table 3
The Factors Predicting Disease-Free Survival and Disease-Specific Survival.

Prognostic Factors		5-year disease-free survival		5-year disease-specific survival	
		%	*p* value	%	*p* value
Age[a]	≤ 21 years	89	0.433	100	0.257
	< 21 years	74		85	
Tumor size (mm)[a]	≤ 200	80	0.836	91	0.294
	< 200	88		75	
Lymphadenectomy	Not performed	59	0.156	80	0.716
	Performed	88		89	
Lymph node count[a]	≤ 24	78	0.662	76	0.218
	< 24	83		100	
Tumor type	Dysgerminoma	80	0.950	87	0.810
	Non-dysgerminoma	80		89	
Chemotherapy protocol	BEP	83	0.142	94	0.188
	Others	60		80	
Chemotherapy protocol	BEP	78	0.429	88	0.129
	VBP	100		100	
	VAC	50		50	
Surgical outcome	Sub-optimal cytoreduction	29	<0.001	32	0.001
	Optimal cytoreduction	75		100	
	Maximal cytoreduction	93		100	
Type of surgery	Conservative surgery	74	0.470	83	0.432
	Definitive surgery	84		92	
Ascites	No	78	0.708	91	0.499
	Yes	83		83	
Peritoneal cytology	Negative	78	0.831	86	0.801
	Positive	86		86	

BEP: Bleomycin + Etoposide + Cisplatin.
Others: VAC (*Vincristine + Actinomycin-D + Cyclophosphamide*), VBP (*Vinblastine + Bleomycin + Cisplatin*).
Sub-optimal cytoreduction: Residue tumor >1 cm.
Optimal cytoreduction: Residue tumor <1 cm.
Maximal cytoreduction:No visible tumor.
[a] Median value.

complete debulking and 9.7% of patients with incomplete debulking were found to have disease on their second look surgery [10].

The association between surgical radicality and survival outcomes was also studied in patients that underwent salvage surgery for recurrent MOGCT [11,12]. Lai et al. reported no disease related deaths within 5 years in patients with residual tumor less than 1 cm after salvage surgery [11]. Similarly, Lee et al. found that 5-year DFS could not be achieved in patients who had residual tumor above 1 cm after salvage cytoreduction ($p = 0.0014$) [12]. Adjuvant chemotherapy should be given without delay after surgery because of MOGCTs short doubling time and high chemo-sensitivity [13]. It is asserted that performing an aggressive surgery might cause delays in the adjuvant treatment which will reflect to the survival [14].

In our study, it was observed that factors other than surgical radicality such as age, ascites, chemotherapy protocol, tumor size, tumor type, peritoneal cytology, performance of lymphadenectomy or fertility preserving approach were not associated with recurrence and survival. 5-year DFS and DSS for conservative surgery and definitive surgery in the whole study cohort were 74% *vs.* 84% ($p = 0.470$) and 83% *vs.* 92% ($p = 0.432$), respectively. There were no disease related deaths in maximal/optimal cytoreduction cohort and 5-year DFS was 90% in patients who had conservative surgery and was 89% in those who had definitive surgery (p = 0.907).

Platinum-based chemotherapy following surgery is the standard treatment approach for MOGCT except stage 1A dysgerminoma and stage 1 immature teratoma [5]. The prognosis of MOGCT was very poor before 1970s when disease was managed with surgical resection only [15]. MOGCT turned into a curable disease after the discovery of its chemosensitivity [3]. VAC chemotherapy was one of the first regimens used for MOGCT. Gershenson et al., reported that progression or recurrence developed in 22(30%) of 66 patients with non-dysgerminoma MOGCT who were treated with VAC protocol [16]. Cisplatin-based protocols (VBP, BEP) gained wide acceptance due to high treatment success after their first introduction. BEP protocol with its 90% treatment success in all stage MOGCT becomes the standard chemotherapy approach [13,17]. We failed to find any difference in oncological outcomes of the patient regarding the adjuvant chemotherapy regimen. However only 28 patients were available for analysis. 5-year DFS and DSS obtained with the BEP protocol was 78% and 88%, respectively.

Successful results have been reported with adjuvant radiotherapy in patients with advanced stage MOGCTs, particularly with dysgerminomas. De polo et al. obtained 61.4% recurrence-free survival and 89.5% overall survival with adjuvant radiotherapy in 12 patients who had stage III dysgerminoma after 67 months median follow-up [18]. In our study, no progression or recurrence was observed in 3 patients with stage III dysgerminomas who underwent radiotherapy.

MOGCT is mostly encountered in late adolescence or in young adult women. Therefore, presentation of a fertility-sparing approach to these age groups has become a standard of care. In a previous study from our center we showed that conservative surgery is feasible in stage I and II MOGCT and should be the standard approach. 5-year DFS was 95% in the conservative surgery group, whereas it was 92% in the definitive surgery group ($p = 0.758$) [19]. A similar result was suggested in a study by Peccatori et al. in which 128 patients with stage I–IV MOGCT was evaluated [20]. They reported a 5-year overall survival of 96% for patients (n: 108) treated with a fertility sparing approach [20]. In the present study, there was no difference in terms of recurrence and survival between conservative surgery and definitive surgery groups. There are very limited number of studies about fertility sparing approach in advanced stage MOGCT and most of these studies have small sample size [21–26]. Park et al. reported that the

fertility sparing approach can be performed in advanced stages of MOGCT according to their study (n: 171) including 28 patients with stage III & IV. In that study, presence of residual tumor, yolk sac histopathology and incomplete staging were defined as independent prognostic factors for recurrence and survival [7]. In the absence of randomized clinical trial data, clinicians should rely on well documented series from large tertiary centers when counselling advanced stage MOGCT patients about preserving their fertility.

The association between histological subtype of MOGCT and survival outcomes is not clear in MOGCT. While several studies has showed the non-dysgerminoma tumor type is related with poor prognosis compared to dysgerminoma in MOGCTs [5,7,11,26,27], others failed to find any association between tumor type and prognosis [25,28]. Lai et al., evaluated 93 patients with stage I-IV MOGCT and reported that 5-year OS was 80.3% and 100% for non-dysgerminoma and dysgerminoma tumor type, respectively ($p = 0.0004$) [11]. Tumor type was not found to have a prognostic effect on recurrence and survival in our study. 5-year DSS was 89% and 87% for non-dysgerminoma and dysgerminoma, respectively.

There is limited data on the use of neoadjuvant chemotherapy (NACT) in patients with MOGCT. In a recent study by Zhang et al, patients were offered 1 or 2 cycles of NACT before cytoreductive surgery. Investigators concluded that NACT improved survival rates and increased the chance for fertility-sparing surgery in advanced yolk-sac tumors [29]. None of our patients received NACT in the present study. We believe that further studies are needed to change the current standard approach in patients with advanced MOGCT.

The present study is one of the largest series in the published literature which includes only stage III&IV MOGCT and specifically evaluates the outcomes of the fertility-sparing approach. The other strength of our study is the long median follow-up time. The limited numbers in chemotherapy arms prevented us to make a sub-group analysis for chemotherapy protocols. Our study also carries the inherent limitations unique to retrospective design.

Conclusion

Completeness of cytoreduction is the only factor determining the efficacy of adjuvant therapy, recurrence and survival in stage III&IV MOGCT. The option to preserve the fertility can be offered to patients who had maximal or optimal cytoreduction without jeopardizing the oncological outcomes. However, multi-centered prospective studies are needed to clarify the results.

References

[1] Brown J, Friedlander M, Backes FJ, Harter P, O'Connor DM, de la Motte Rouge T, et al. Gynecologic Cancer Intergroup (GCIG) consensus review for ovarian germ cell tumors. Int J Gynecol Cancer 2014;24(Suppl. 9):S48–54.
[2] Kumar S, Shah JP, Bryant CS, Imudia AN, Cote ML, Ali-Fehmi R, et al. The prevalence and prognostic impact of lymph node metastasis in malignant germ cell tumors of the ovary. Gynecol Oncol 2008;110(2):125–32.
[3] Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. Cancer Treat Rev 2008;34(5):427–41.
[4] Ertas IE, Taskin S, Goklu R, Bilgin M, Goc G, Yildirim Y, et al. Long-term oncological and reproductive outcomes of fertility-sparing cytoreductive surgery in females aged 25 years and younger with malignant ovarian germ cell tumors. J Obstet Gynaecol Res 2014;40(3):797–805.
[5] Mangili G, Sigismondi C, Gadducci A, Cormio G, Scollo P, Tateo S, et al. Outcome and risk factors for recurrence in malignant ovarian germ cell tumors: a MITO-9 retrospective study. Int J Gynecol Cancer 2011;21(8):1414–21.
[6] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[7] Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Analysis of outcomes and prognostic factors after fertility-sparing surgery in malignant ovarian germ cell tumors. Gynecol Oncol 2017;145(3):513–8.
[8] Bafna UD, Umadevi K, Kumaran C, Nagarathna DS, Shashikala P, Tanseem R. Germ cell tumors of the ovary: is there a role for aggressive cytoreductive surgery for nondysgerminomatous tumors? Int J Gynecol Cancer 2001;11 (4):300–4.
[9] Slayton RE, Park RC, Silverberg SG, Shingleton H, Creasman WT, Blessing JA. Vincristine, dactinomycin, and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary. A Gynecologic Oncology Group Study (a final report). Cancer 1985;56(2):243–8.
[10] Williams SD, Blessing JA, DiSaia PJ, Major FJ, Ball 3rd HG, Liao SY. Second-look laparotomy in ovarian germ cell tumors: the gynecologic oncology group experience. Gynecol Oncol 1994;52(3):287–91.
[11] Lai CH, Chang TC, Hsueh S, Wu TI, Chao A, Chou HH, et al. Outcome and prognostic factors in ovarian germ cell malignancies. Gynecol Oncol 2005;96 (3):784–91.
[12] Lee CW, Song MJ, Park ST, Ki EY, Lee SJ, Lee KH, et al. Residual tumor after the salvage surgery is the major risk factors for primary treatment failure in malignant ovarian germ cell tumors: a retrospective study of single institution. World J Surg Oncol 2011;9:123.
[13] Gershenson DM. Management of ovarian germ cell tumors. J Clin Oncol 2007;25(20):2938–43.
[14] Billmire D, Vinocur C, Rescorla F, Cushing B, London W, Schlatter M, et al. Children's Oncology Group (COG), Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 2004;39(3):424–9.
[15] Tewari K, Cappuccini F, Disaia PJ, Berman ML, Manetta A, Kohler MF. Malignant germ cell tumors of the ovary. Obstet Gynecol 2000;95(1):128–33.
[16] Gershenson DM, Copeland LJ, Kavanagh JJ, Cangir A, Del Junco G, Saul PB, et al. Treatment of malignant nondysgerminomatous germ cell tumors of the ovary with vincristine, dactinomycin, and cyclophosphamide. Cancer 1985;56 (12):2756–61.
[17] Chen CA, Lin H, Weng CS, Wen KC, Lu CH, Chou HH, et al. Outcome of 3-day bleomycin, etoposide and cisplatin chemotherapeutic regimen for patients with malignant ovarian germ cell tumours: a Taiwanese Gynecologic Oncology Group study. Eur J Cancer 2014;50(18):3161–7.
[18] De Palo G, Pilotti S, Kenda R, Ratti E, Musumeci R, Mangioni C, et al. Natural history of dysgerminoma. Am J Obstet Gynecol 1982;143(7):799–807.
[19] Turkmen O, Karalok A, Basaran D, Comert GK, Tasci T, Ureyen I, et al. Fertility sparing surgery should be the standard treatment in patients with malignant ovarian germ cell tumors. J Adolesc Young Adult Oncol 2017;6(2):270–6.
[20] Peccatori F, Bonazzi C, Chiari S, Landoni F, Colombo N, Mangioni C. Surgical management of malignant ovarian germ-cell tumors: 10 years' experience of 129 patients. Obstet Gynecol 1995;86(3):367–72.
[21] Tangir J, Zelterman D, Ma W, Schwartz PE. Reproductive function after conservative surgery and chemotherapy for malignant germ cell tumors of the ovary. Obstet Gynecol 2003;101(2):251–7.
[22] Perrin LC, Low J, Nicklin JL, Ward BG, Crandon AJ. Fertility and ovarian function after conservative surgery for germ cell tumours of the ovary. Aust N Z J Obstet Gynaecol 1999;39(2):243–5.
[23] Boran N, Tulunay G, Caliskan E, Köse MF, Haberal A. Pregnancy outcomes and menstrual function after fertility sparing surgery for pure ovarian dysgerminomas. Arch Gynecol Obstet 2005;271(2):104–8.
[24] Nishio S, Ushijima K, Fukui A, Fujiyoshi N, Kawano K, Komai K, et al. Fertility-preserving treatment for patients with malignant germ cell tumors of the ovary. J Obstet Gynaecol Res 2006;32(4):416–21.
[25] Lee KH, Lee IH, Kim BG, Nam JH, Kim WK, Kang SB, et al. Korean Gynecologic Oncology Group, Clinicopathologic characteristics of malignant germ cell tumors in the ovaries of Korean women: a Korean Gynecologic Oncology Group Study. Int J Gynecol Cancer 2009;19(1):84–7.
[26] Chan JK, Tewari KS, Waller S, Cheung MK, Shin JY, Osann K, et al. The influence of conservative surgical practices for malignant ovarian germ cell tumors. J Surg Oncol 2008;98(2):111–6.
[27] Topuz S, Iyibozkurt AC, Akhan SE, Keskin N, Yavuz E, Salihoglu Y, et al. Malignant germ cell tumors of the ovary: a review of 41 cases and risk factors for recurrence. Eur J Gynaecol Oncol 2008;29(6):635–7.
[28] Zhao T, Zhang H, Liu Y, Jiang H, Wang X, Lu Y. The role of staging surgery in the treatment of apparent early-stage malignant ovarian germ cell tumours. Aust N Z J Obstet Gynaecol 2016;56(4):398–402.
[29] Zhang GY, Zhang R, Wu LY, Li B, Li SM. Neoadjuvant bleomycin, etoposide, and cisplatin (BEP) chemotherapy in the treatment of extensively advanced yolk sac tumors: a single center experience. Int J Gynecol Cancer 2018;28(4):713–20.