Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2023;48(1):54-63
DOI: 10.17826/cumj.1176706

RESEARCH

The effect of clinicopathological features on prognosis in malignant ovarian germ cell tumors

Malign over germ hücreli tümörlerde klinikopatolojik özelliklerin prognoza etkisi

Yegana Sadigova[1], Sevtap Seyfettinoğlu[2], Ümran Küçükgöz Güleç[1], Ghanim Khatib[1], Ahmet Barış Güzel[1], Derya Gümürdülü[3], Semra Paydaş[4], Mehmet Ali Vardar[1]

[1]Cukurova University, Faculty of Medicine, Gynecologic Oncology Department, [3]Pathology Department, [4]Medical Oncology Department, Adana, Turkey
[2]Adana City Training and Research Hospital. Gynecologic Oncology Department, Turkey

Abstract

Purpose: Malignant ovarian germ cell tumors cause 5% of ovarian cancers. Studies examining prognosis and survival rates are significant due to malignant ovarian germ cell tumors' rarity. We aimed to investigate outcome and prognostic factors in these patients.

Materials and Methods: The study includes clinicopathological records of malignant ovarian germ cell tumor patients in our clinic between April 1992 and November 2017. Demographic and clinical characteristics, pathological observations, adjuvant treatment modalities, and follow-up details were analyzed, and their survival effects were investigated.

Results: One hundred fifteen patients with malignant ovarian germ cell tumors were analyzed. Most patients were reproductive-age nulliparous. The patients' mean age was 27.5+14.3, and the mean follow-up was 71.04 months. The research includes 42 dysgerminomas, 37 immature teratomas, 17 mixed germ-cell tumors, 16 endodermal sinus tumors, and three embryonic carcinomas. The disease stage was 1, 2, 3, and 4 in 53%, 16.5%, 25.2%, and 5.2% of patients, respectively.

Fertility-sparing surgery was conducted in 55 of 79 patients, and 34.5% received pregnancy. Five-year overall survival was 74%. Localization of tumors, non-optimal cytoreduction, advanced-stage disease, poor differentiation, metastasis, and mixed cell histology were determined as poor prognostic factors. In multivariate analyzes, factors affecting disease-free survival are the FIGO stage, mixed germ cell histology, and suboptimal cytoreduction.

Conclusion: The prognosis of malignant ovarian germ cell tumors is excellent, especially in young, early-stage, and adequately operated patients. FIGO Stage, mixed germ cell

Öz

Amaç: Malign over germ hücreli tümörleri, yumurtalık kanserlerinin %5'ine neden olur. Malign over germ hücreli tümörlerin nadir görülmesi nedeniyle prognoz ve sağkalım oranlarını inceleyen çalışmalar önemlidir. Çalışmamızda bu hastalarda sonuç ve prognostik faktörleri araştırmayı amaçladık.

Gereç ve Yöntem: Çalışma, Nisan 1992 ile Kasım 2017 tarihleri arasında kliniğimizde tedavi olmuş malign over germ hücreli tümör hastalarının klinikopatolojik kayıtlarını içermektedir. Demografik ve klinik özellikler, patolojik gözlemler, adjuvan tedavi modaliteleri ve takip detayları analiz edilerek sağkalıma etkileri araştırılmıştır.

Bulgular: Malign over germ hücreli tümörleri olan yüz onbeş hasta çalışmaya dahil edildi. Hastaların çoğu üreme çağındaki nullipar kadınlardı. Hastaların yaş ortalaması 27.5+14.3, ortalama takip süresi 71.04 ay idi. Araştırma 42 disgerminom, 37 immatür teratom, 17 miks germ hücreli tümör, 16 endodermal sinüs tümörü ve üç embriyonik karsinom olgusu içermektedir. Hastalık evresi sırasıyla hastaların %53'ünde %16.5, %25.2'sinde ve %5.2'sinde Evre 1, 2, 3 ve 4 idi.

Yetmişdokuz hastanın 55'ine fertilite koruyucu cerrahi uygulandı ve hastaların %34.5'inde gebelik elde edildi. Beş yıllık genel sağkalım %74 idi. Tümörlerin lokalizasyonu, optimal olmayan sitoredüksiyon, ileri evre hastalık, kötü farklılaşma, metastaz, mikst hücre histolojisi kötü prognostik faktörler olarak belirlendi. Çok değişkenli analizlerde hastalıksız sağkalımı etkileyen faktörler FIGO evresi, mikst germ hücre histolojisi ve suboptimal sitoredüksiyon olarak saptandı.

Sonuç: Malign over germ hücreli tümörlerin prognozu, özellikle genç, erken evre ve uygun şekilde ameliyat edilmiş hastalarda mükemmeldir. FIGO Evresi, mikst germ hücre

Address for Correspondence: Sevtap Seyfettinoglu, Adana City Training and Research Hospital. Department of Gynecologic Oncology, Adana, Turkey E-mail: sevtaponcul@gmail.com
Received: 21.09.2022 Accepted: 03.01.2023

histopathology and complete cytoreduction affect the prognosis of MOGCT. Treatment at reproductive age does not significantly affect pregnancy outcomes. Therefore, the fertility sparring approach should be considered a good option, especially in young patients.
Keywords: Malignant germ cell tumor, ovarian cancer, fertility-sparing surgery, prognosis

histopatolojisi ve tam sitoredüksiyon, MOGCT'nin prognozunu etkileyen faktörlerdir. Üreme çağındaki tedavi gebelik sonuçlarını önemli ölçüde etkilemez. Bu nedenle, özellikle genç hastalarda koruyucu yaklaşım da iyi bir seçenek olarak düşünülmelidir.
Anahtar kelimeler: Malign germ hücreli tümör, over kanseri, doğurganlığı koruyucu cerrahi, prognoz

INTRODUCTION

Ovarian germ cell tumors (OGCTs) are rare neoplasms. Although 20-25% of all malignant and benign ovarian neoplasms are germ-cell-derived, only 3% of these tumors are malignant[1]. Malignant ovarian germ cell tumors (MOGCTs) are diagnosed early with large masses and abdominal pain[2].

Germ cell tumors mainly affect young reproductive patients. Therefore, fertility-sparing surgery is the preferred treatment in these patients[3]. The early-stage disease has an excellent prognosis, while the advanced and recurrent disease remains a problem in the reproductive ages. However, data on surgery-sparing fertility for advanced-stage MOGCT are few, and there is no consensus on the scope of surgical treatment. Essential surgery principles for MOGCTs prescribe that fertility preservation is sufficient even with a broad metastatic illness[4]. Postoperative adjuvant chemotherapy with platinum and etoposide-based regimens was accepted as standard treatment, except for those with stage IA dysgerminoma and stage IA grade I immature teratoma[5]. Following fertility-sparing surgery and chemotherapy, several studies have demonstrated normal reproductive function without compromising survival[6].

The ability to perform fertility-sparing surgeries and avoid adjuvant chemotherapy in reproductive patients depends on an accrual definition of the prognostic factors. Comprehensive studies on the prognostic factors of these tumors are lacking in the literature due to their rarity. However, the stage of the disease, presence of residual tumor after surgery, and histological type are defined as the most important prognostic factors in these patients[6]. Tumor size is also a significant prognostic factor in primary and relapsed cases [7].

This study aimed to investigate the effect of demographic and clinicopathological features on the prognosis of patients with germ cell tumors. It is also aimed to present the rates of fertility-sparing surgery and its effects on prognosis. We hypothesized that even when combined with adjuvant chemotherapy, fertility-sparing surgery is a safe and effective treatment that leads to a high fertility rate.

MATERIALS AND METHODS

Data collection

The present retrospective study was conducted in the Gynecologic Oncology Department of Çukurova University Balcalı Hospital between January 1992 and December 2017. Approval for this study was obtained from the Research Ethics Committee at University (10/11/2017, No: 90). All patients were operated on by experienced gynecological oncologists and pathologically analyzed by expert gynecological pathologists at the same hospital. The patient's electronic and archival data were reviewed retrospectively. Patients with malignant ovarian germ cell tumor histology were the subject of this study; therefore, all other histologies were excluded, and the remaining 115 cases were recruited for this study.

Informed consent form, demographic and clinical features (age, marital status, parity, tumor markers, surgery type, complaints of admission, additional systemic diseases, family history, fertility desire), pathological findings, operational data, adjuvant treatment modalities, and follow-up information were reviewed, and their effects on survival were investigated. The reproductive status of the patients was grouped as prepubertal, adolescent, reproductive period, perimenopausal and postmenopausal. In patients who relapsed, recurrence time and localization of recurrence were noted.

The World Health Organization 2014 ovarian histology classification criteria were used as the pathological diagnosis. The tumor stage was determined according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 classification. Patients who were staged before 2014 were restaged according to the 2014 FIGO criteria.

Surgery, adjuvant treatment, and follow up

Surgical treatment was divided into four groups; fertility-sparing surgery, total hysterectomy with salpingo-oophorectomy (TH-BSO), comprehensive staging surgery (TH-BSO, omentectomy, retroperitoneal lymphadenectomy, peritoneal biopsies), and restaging group. Fertility-sparing surgery was defined as preserving the uterus and at least part of the contralateral ovary.

Adjuvant treatment options were discussed in the multidisciplinary tumor board. Patients were followed up quarterly in the first two years, semiannually for up to 5 years, and then annually.

Statistical analysis

Statistical Package for Social Sciences 20 (IBM SPSS Inc. Chicago, IL) was used. The distribution normality of the data was evaluated with the Kolmogorov-Smirnov test. Data fitting the normal distribution were expressed with mean ± standard deviation, while data do not provide the normal distribution were shown with a median. Categorical data were analyzed using the Chi-square test or Ficher's exact test, and variables were expressed as percentages (%).

The disease-free survival (DFS) was defined as the period in months from initial surgery to recurrence. The overall survival (OS) was calculated in months from initial surgery to death. Survival analyzes were realized with the Kaplan-Meier test and compared with the log-rank test. Cox regression analysis was utilized for the multivariate analysis. Independent factors in predicting survival (such as age, bilaterality, stage, grade, fertility-preserving surgery status, tumor diameter, histology, and cytoreduction) were analyzed for both OS and DFS using the backward selection method using Cox regression analysis. Although age was insignificant, it was retained in the model as a biological correction factor. P value was considered significant at the level < 0.05.

RESULTS

The median patients' age was 27.5 ±14,3. The clinical and demographic characteristics of the study population are shown in Table 1. The majority of patients were nulliparous and at reproductive age. The most common complaint was abdominal pain.

Table 1. Clinical and demographic features of the study population

	Number (n)	Percentage (%)
Parity		
Nulliparous	70	60.9
Multiparous	45	39.1
Symptoms		
Abdominal pain	54	47.0
Abdominal mass	27	23.5
Abnormal vaginal bleeding	8	7.0
İncidental	8	7.0
Other	18	15.5
Additional systemic disease		
Absent	84	73.0
Present	31	27.0
Reproductive Status		
Prepubertal	3	2.6
Adolescent	28	24.3
Reproductive Ages	69	60.0
Perimenopausal	5	4.3
Postmenopausal	10	8.7

Surgical-pathological features of the patients are shown in Table 2. The present study contains 42 (34.8%) dysgerminoma (DG), 37 immature teratoma (IT), 16 (13.9%) yolk sac tumors (YST), 3 (2.6%) embryonal carcinoma (EC), and 17 (14.8%) mixed germ cell tumor (mGCT). Mixed germ cell tumor was detected in 62% (n:8) of patients in the postmenopausal period. Tumor markers were within normal limits in the majority of patients. The tumor was bilateral in 15 (13%) cases.

Stage of the disease was 1, 2, 3, and 4 in 53%, 16.5%, 25.2%, and 5.2% of the patients, respectively. A frozen section was performed in 76 patients. Frozen accuracy was %88. Only nine patients who were diagnosed with mature teratoma by frozen section exam were finally diagnosed with immature teratoma.

Fertility-sparing surgery was performed in 55 of 79 patients who desired to preserve their fertility. Pregnancy was obtained in 34.5% of them during the follow-up period. Lymphadenectomy was performed in 80 (69.5%) patients. During the follow-up period, 20 patients (17.3%) experienced recurrence. Most of them were in the pelvic region.

The mean follow-up period of the patients is 71.04 months. Univariate analyses of OS and DFS are shown in Table 3

Table 2. Characteristic features of MOGCT patients

	N	%
Tumor marker level		
Normal range	57	49.6
High AFP	20	17.4
High LDH	8	7.0
High β-hCG	4	3.5
High Ca.125	19	16.5
High AFP and β-hCG	1	0.9
High AFP + Ca 125	4	3.5
High β-hCG + Ca 125	2	1.7
Localization		
Right ovary	52	45.2
Left ovary	48	41.7
Bilateral	15	13.0
Tumor Histological Grade		
Unknown	27	23.5
Grade 1	48	41.7
Grade 2	12	10.4
Grade 3	28	24.3
Fertility Request		
No	36	31.3
Yes	79	68.7
Surgery		
Fertility sparing surgery (USO±BPPALND±Omentectomy)	55	47.8
Hysterectomy and bilateral salphingo-oophorectomy (TH-BSO)	5	4.3
Comprehensive surgery (TH+BSO with Omentectomy and retroperitoneal lymphadenectomy)	33	28.7
Restaging	22	19.2
Lymphadenectomy		
Not	35	30.4
Pelvic	9	7.8
Pelvic and paraaortic	71	61.7
Metastasis		
None	69	60.0
Lymph node metastasis	15	13.0
Distant organ metastasis	1	0.9
Peritoneal Metastasis	9	7.8
Lymph node, distant organ and peritoneal metastasis	5	4.3
Lymph node and peritoneal metastasis	16	13.9
Frozen section and final pathology	Frozen	Final Pathology
Dysgerminoma	29	29
İmmature teratoma	19	28
Mixed Germ cell tumor	8	8
Embryonal Carcinoma	2	2
Endodermal sinus tumor	9	9
Intraoperative complications		
None	88	76.5
Bleeding	22	19.1
Urinary tract injury	0	0.0
Gastrointestinal Complications	0	0.0
Other	5	4.4

AFP: alpha-fetoprotein, LDH: Lactate dehydrogenase, β-Hcg: Beta-human chorionic gonadotrophin, USO: unilateral salpingo-oophorectomy, BPPALND: bilateral pelvic para-aortic lymphadenectomy, TH: total hysterectomy, BSO: bilateral salpingo-oophorectomy

Table 3. Univariate analysis of OS and DFS.

Risk Factor	Dead /Alive	Alive percent	OS			DFS		
			Mean (month)	Median (month)	p*	Mean (month)	Median (month)	p*
Parity								
Nulliparous	19/51	72.50%	172.70	270.00		131.07	270.00	
Multiparous	19/26	57.80%	184.84	181.00	0.083	98.40	63.00	0.046
Additional systemic disease								
-	17/67	77.10%	196.34	270.00		167.86	270.00	
+	19/12	38.70%	99.04	63.00	<0.001	86.09	49.00	0.005
Family cancer history								
(-)	25/66	72.50%	182.90	270.00		160.48	270.00	
(+)	13/11	43.50%	117.51	72.00	0.037	93.51	49.00	0.058
Localization								
Right ovary	13/38	74.50%	178.54			148.90		
Left ovary	16/33	66.70%	178.33	207.00		145.54	154.00	
Bilateral	9/6	40.00%	75.11	28.00	0.012	74.52	28.00	0.188
Grade								
Unknown	6/20	76.90%	158.68	207.00		145.19	154.00	
Grade 1	8/40	83.30%	224.67	270.00		192.60	270.00	
Grade 2	4/9	66.70%	67.66			44.41	28.00	
Grade 3	20/8	28.60%	59.58	18.00	<0.001	46.85	13.00	<0.001
Lymphadenectomy								
None	4/31	88.60%	239.62	270.00		209.793	270.00	
Pelvic Lymphadenectomy	3/6	66.70%	175.50	152.00		144.77		
Pelvic and paraaortic lymphadenectomy	32/39	55.70%	122.33	125.00	0.003	98.81	59.00	0.006
Cytoreduction								
Non-optimal surgery	17/6	22.70%	50.46	16.00		25.88	8.00	
Optimal surgery	21/71	77.20%	195.56	270.00	<0.001	171.66	207.00	<0.001
Stage of Disease								
Stage 1	4/57	93.40%	253.30	270.00		223.52	270.00	
Stage 2	6/12	63.20%	137.20	207.00		118.41	207.00	
Stage 3	8/22	21.40%	66.77	25.00		38.17	12.00	
Stage 4	5/1	16.70%	45.79	16.00	<0.001	38.70	13.00	<0.001
Histopathology								
Dysgerminoma	12/28	70.00%	190.99	270.00		171.18	270.00	
Immature Teratoma	4/33	89.20%	183.36			161.85		
Endodermal Sinus Tumor	7/8	53.30%	103.18	172.00		63.61	24.00	
Mixed Germ Cell Tumor	13/4	23.50%	58.64	11.00	<0.001	50.44	9.00	<0.001
Recurrence								
No	10/85	89.47%	228.17	270.00		228.17	270.00	
Yes	15/5	33.33%	79.93	36.00	<0.001	22.43	12.00	<0.001
TOTAL	38/77	67.00%	167.23	181.00		143.58	142.00	
*p: Log Rank Test								

OS: Overall survive, DFS: Disease Free Survive

When the OS of the patients is evaluated with the histological subspecies, The OS duration of patients with mixed germ cell tumors was significantly lower than other histologies. (mixed: 50.44 ± 21.38, endodermal sinus tumor: 103.18 ± 22.18, dysgerminoma: 190.93 ± 20.13, Immature teratoma: 183.36 ± 12.51; p <0.001).

The OS duration of patients with tumor diameter greater than or equal to 10 cm was significantly lower than those below 10 cm (98.04 ± 16.81 vs183.00 ±

15.00, respectively, p <0.001). Conversely, there was no significant difference regarding DFS between tumor diameter subgroups.

OS and DFS were significantly lower in the lymphadenectomy group (OS: p: 0.003; DFS: p: 0.006). The mean of OS and DFS were 122.3 and 98.8 months in the systematic lymphadenectomy group versus 239.6 and 209.7 in the non-lymphadenectomy group. OS and DFS of patients with advanced-stage, non-optimal surgery, or mixed germ cell tumors were significantly lower than their counterparts.

When the mean OS of patients who received BEP as a chemotherapy regimen and those treated with other chemotherapeutic agents were evaluated, the OS of patients who received BEP (170.11 ± 15.93) were significantly longer than other patients (80.28 ± 26.86) (p=0.008).

DFS durations are evaluated according to fertility-sparing surgery or other surgical procedures; The disease-free survival of patients undergoing fertility-sparing surgery is statistically significantly longer than the disease-free survival time of patients undergoing other surgical procedures. (FSS (+): 227.30 months ± 15.59, FSS (-): 93.62 months ± 14.25; p: 0.00).

Table 4. Multivariate analyzes of independent factors predicting OS

Factors	HR*	(%95 CI)**		P value
		Min	Max	
Age	0.973	.941	1.005	0.097
Additional systemic disease	3.318	1.122	9.809	0.030
Bilaterality	2.389	.991	5.760	0.052
Stage	3.845	1.519	9.732	0.004
Dysgerminoma (reference)	-	-	-	0.009
Immature Teratoma	0.624	.189	2.058	0.438
Endodermal Sinus Tumor	1.463	.519	4.125	0.472
Mixed Germ Cell Tumor	3.406	1.439	8.061	0.005
FSS	-2.907	-7.468	-1.131	-0.027
Cytoreduction	3.487	1.467	8.289	0.005

* HR: Hazard Ratio; ** 95% Confidence Interval; FSS: Fertility-Sparing Surgery

Table 5. Multivariate analyzes of independent factors predicting DFS

Factors	HR*	(%95 CI)**		p-value
		Min	Max	
Age	0.986	.955	1.017	0.376
Additional systemic disease	2.011	.748	5.406	0.166
Bilaterality	1.611	.671	3.866	0.286
Stage	3.855	1.560	9.529	0.003
Dysgerminoma (reference)				
Immature Teratoma	1.066	.388	2.930	0.901
Endodermal Sinus Tumor	2.013	.776	5.221	0.150
Mixed Germ Cell Tumor	3.745	1.507	9.309	0.004
FSS	-0.973	-0.414	-2.289	-0.950
Cytoreduction	2.879	1.238	6.700	0.014

* HR: Hazard Ratio; ** 95% Confidence Interval; FSS: Fertility-Sparing Surgery

Prognostic factors in predicting survival (age, bilaterality, stage, grade, Fertility-sparing surgical condition, tumor diameter, histology, cytoreduction) were analyzed with multivariate analysis. Multivariate analyzes of factors predicting OS and DFS are shown in Table 4 and Table 5.

In our study, the presence of other systemic diseases, advanced-stage disease, mixed germ cell tumor histology, not performing FSS, and non-optimal surgery were independent prognostic factors for OS. Whereas advanced-stage disease, mixed germ cell tumor histology, and non-optimal surgery were the independent prognostic factors for DFS.

While the mean OS values of these patients were 167.23 months, the average DFS duration was 143. The mean follow-up period was 71.04 months

DISCUSSION

MOGCT accounts for 2-3% of all ovarian cancers and is usually diagnosed in the early stage[8]. It is especially common in young girls and women of reproductive age. The scope of fertility-sparing surgery, prognostic factors, and the necessity of staging surgery are questioned in recent studies. In this study, the clinical and pathological features of MOGCT and the factors affecting prognosis were investigated retrospectively.

Although the literature on MOGCT mainly covers the young population, the number of postmenopausal patients is undeniable. There are also review studies in the literature focusing on specific subgroups such as postmenopausal ages[9]. In our study, increased mixed malignant germ cell tumor frequency in postmenopausal women has also been shown in the postmenopausal population.

Acute abdominal pain is the most common symptom. This is followed by chronic abdominal pain, asymptomatic mass, abnormal vaginal bleeding, and abdominal distension[10]. Therefore, MOGCT should be considered in the differential diagnosis of young patients presenting with these complaints. In our study population, the most common symptom was abdominal pain, in accordance with the literature.

Germ cell tumors are primarily classified as dysgerminoma and non-dysgerminoma in many studies. In the SEER study, approximately 1/3 of 2541 patients were diagnosed with dysgerminoma (n: 815)[11]. Tangjitgamol et al.[12] reported that 37.7% of the patients were diagnosed with dysgerminoma, and 34 patients were diagnosed with endodermal sinus tumor (27.4%); in a study conducted in our country, the frequency of dysgerminoma was reported as 54,8%[13]. There are also studies in which most of the cases were non-dysgerminoma[14]. In another study, in contrast to other reports, Endodermal sinus tumor was the most frequent type which was followed by IT[15].

Rare occurrences of MOGCT make studies for determining prognostic factors interesting. However, in the light of extensive data-based studies, histological species, FIGO stage, presence of residual disease after surgery, and increased tumor markers were determined as prognostic parameters[16]. While poor prognosis was attributed to the mixed histology of germ cell tumors (mGCT) in some studies, it was attributed to the immature teratoma histology in others[15]. Hu et al. reported that the 5-year OS ratio of mGCT patients was lower than the DG, EC, and IT patients. They noted that a large proportion of the ESS components might cause the poor prognosis of malignant mixed germ cell tumors[17]. In our report, the duration of both OS and DFS was lower in mixed germ cell cases compared to other histopathological forms. The limited number of mixed germ cell cases, however, limits the accuracy of our data.

The relationship between tumor size and survival in ovarian malignancies has been questioned in many studies. Cicin et al.[18] reported that tumor size greater than or less than 10 cm had no prognostic significance in their study of 70 patients of MOGCT. In our analysis, OS time was shorter in patients with tumors larger than 10 cm. However, we did not find a significant difference in DFS durations. This difference may be significantly affected by tumor histopathology and the larger study population than the mentioned study.

Treatment management of MOGCT is based on clinical practice guidelines for ovarian epithelial malignancies. Currently, the National Comprehensive Cancer Network (NCCN) clinical practice guideline recommends conservative surgery regardless of the cancer stage as the standard treatment for MOGCT when fertility protection is desired. Otherwise, completion surgery with extensive staging is recommended[19,20]. The effects of surgical management on prognosis have been investigated in retrospective designed studies. Liu et al. demonstrated that comprehensive staging surgery does not improve patient prognosis but has a higher complication rate and more operative blood loss[14]. In another study, authors reported that conservative surgery was feasible in stage I and II MOGCT with 95% 5-year DFS and 92% in the definitive surgery group without significant difference ($p = 0.758$)[3]. In addition, the exact center in a recent study demonstrated that maximal cytoreduction should be aimed at patients with advanced-stage MOGCT, as it was significantly associated with improved overall survival. At the same time, factors out of surgical radicalities such as age, ascites, chemotherapy protocol, tumor size, tumor type, peritoneal cytology, the performance of lymphadenectomy, or the fertility-sparing approach were not associated with recurrence or survival[13]. The majority of the patients

in our study population were diagnosed at an early stage. Most of the patients had optimal cytoreduction. OS and DFS were significantly shorter in those who underwent lymphadenectomy, and this was attributed to the advanced stage of these patients.

Routine lymphadenectomy is the most controversial procedure for complete staging surgery of malignant germ cell tumors[21]. There is no consensus about the role of systematic lymphadenectomy, but the omission of staging peritoneal procedures seems to increase the rate of recurrence without impacting overall survival[19]. Qin et al. reported in their recent study of 245 clinically early-stage MOGCT patients that lymphadenectomy did not contribute to prognosis[22]. Lymphadenectomy was performed in 119 patients, and the lymph node metastasis rate was 0.8% in this study. The low metastasis rate indicates that lymphadenectomy may have a minimal role in evaluating metastasis and may be ignored after careful intra-operative examination for diagnostic purposes.

Numerous trials have shown that fertility-sparing surgery is safe and efficient in MOGCT management[23]. In the current research, there was no statistically significant difference between DFS, OS, and mortality rates among women undergoing radical and fertility-sparing surgery[14]. In our study, DFS and OS durations were longer in patients undergoing fertility-sparing surgery.

Literature data indicate reasonable pregnancy rates after fertility-sparing surgery. In their study, Low et al.[24] analyzed 74 MOGCT patients treated with conservative surgery, and they reported that 14 patients had a live birth without congenital anomaly. Tangir et al.[25] have published a series of 106 pregnancies after 64 fertility-sparing procedures for MOGCT. In a recent study, Chan et al. reported a pregnancy rate of 73% and decided that FSS was the best approach in MGCT patients[26]. In our study, pregnancy occurred in %34.5 (n: 19) of the FSS group. This ratio was attributed to the fact that some patients with fertility desire gave up planning pregnancy.

Recurrence was detected in 17.3% of our patients. This rate is slightly higher than the rates given in the literature[12,27]. In our study, the 5-year survival rate was 74%; OS and DFS periods were 167.23 and 143.58 months, respectively. The 5-years survival rates of studies in the literature range from 87 to 97%. This result can be attributed to the proportion of advanced-stage cases in our study.

In our study, factors affecting OS were systemic disease, advanced stage, mixed germ cell tumor histology, no FSS, and absence of optimal surgery in cytoreduction. The factors affecting DFS were an advanced stage, mixed germ cell tumor histology, and the absence of optimal surgery in cytoreduction.

The high number of patients with malignant germ ovarian tumors and long-term follow-up is the main strong aspects of this study. On the other hand, the main negative aspect of our study was the retrospective design. However, despite the limitations of the retrospective analysis, 115 patients with uncommon ovarian tumors were treated at a single referral gyneco-oncology facility with an oncology team comprised of a gyneco-oncologist, expert gynecologic pathologists, expert gynecologic radiologist, and medical oncologist. In addition, the department of reproductive and infertility at our center controls patients' reproductive outcomes. Multicenter studies with more case numbers are needed to clarify prognostic factors in germ cell tumors.

In conclusion, FIGO Stage, mixed germ cell histopathology, and complete cytoreduction were independent prognostic factors for DFS and OS in MOGCTs. MOGCT's conservative surgical treatment at reproductive ages does not significantly affect future pregnancy outcomes. The present study has shown that fertility-sparing approaches should be considered first in all conditions in these patients. However, prospective studies are required on this subject.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ÜKG, MAV, YS, GK, ABG; Veri toplama: YS, SP, DG; Veri analizi ve yorumlama: ÜKG, GK, ABG; Yazı taslağı: YS, SS; İçeriğin eleştirel incelenmesi: MAV, GK, ÜKG, DG, SP; Son onay ve sorumluluk: YS, SS, ÜKG, GK, ABG, DG, SP, MAV; Teknik ve malzeme desteği: YS, SS, GK, DG; Süpervizyon: ÜKG, MAV, SP; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Çukurova Üniversitesi Tıp Fakültesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulundan 10.11.2017 tarih ve 70/16 sayılı kararı ile etik onay alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : ÜKG, MAV, YS, GK, ABG; Data acquisition: YS, SP, DG; Data analysis and interpretation: ÜKG, GK, ABG; Drafting manuscript: YS, SS; Critical revision of manuscript: MAV, GK, ÜKG, DG, SP; Final approval and accountability: YS, SS, ÜKG, GK, ABG, DG, SP, MAV; Technical or material support: YS, SS, GK, DG; Supervision: ÜKG, MAV, SP; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained for this study from the Ethics Committee of Non-Interventional Clinical Trials of the Faculty of Medicine of Çukurova University with the decision dated 10.11.2017 and numbered 70/16.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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;24:48-54.
2. Low JJ, Ilancheran A, Ng JS. Malignant ovarian germ-cell tumours. Best Pract Res Clin Obstet Gynaecol. 2012;26:347-55.
3. Turkmen O, Karalok A, Basaran D, Kimyon GC, 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;6:270-76.
4. Di Tucci C, Casorelli A, Morrocchi E, Palaia I, Muzii L, Panici PB. Fertility management for malignant ovarian germ cell tumors patients. Crit Rev Oncol Hematol. 2017;120:34-42.
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;21:1414-21.
6. Vasta FM, Dellino M, Bergamini A, Gargano G, Paradiso A, Loizzi V et al. Reproductive outcomes and fertility preservation strategies in women with malignant ovarian germ cell tumors after fertility sparing surgery. Biomedicines. 2020;30:554.
7. Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. Cancer Treat Rev. 2008;34:427-41.
8. 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;40:797-805.
9. Boussios S, Attygalle A, Hazell S, Moschetta M, McLachlan J, Okines A et al. malignant ovarian germ cell tumors in postmenopausal patients: The royal marsden experience and literature review. Anticancer Res. 2015;35:6713-22.
10. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. Int J Gynaecol Obstet. 2021;155:61-85.
11. Solheim O, Gershenson DM, Tropé CG, Rokkones E, Sun CC, Weedon-Fekjaer H et al. Prognostic factors in malignant ovarian germ cell tumours (The surveillance, epidemiology and end results experience 1978-2010). Eur J Cancer. 2014;50:1942-50.
12. Tangjitgamol S, Hanprasertpong J, Manusirivithaya S, Wootipoom V, Thavaramara T, Buhachat R. Malignant ovarian germ cell tumors: clinico-pathological presentation and survival outcomes. Acta Obstet Gynecol Scand. 2010;89:182-9.
13. Karalok A, Comert GK, Kilic C, Turkmen O, Kilic F, Basaran D et al. Cytoreductive surgery in advanced stage malignant ovarian germ cell tumors. J Gynecol Obstet Hum Reprod. 2019;48:461-66.
14. Liu Q, Ding X, Yang J, Cao D, Shen K, Lang J et al. The significance of comprehensive staging surgery in malignant ovarian germ cell tumors. Gynecol Oncol. 2013;131:551-4.
15. 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;96:784-91.
16. Murugaesu N, Schmid P, Dancey G, Agarwal R, Holden L, McNeish I et al. Malignant ovarian germ cell tumors: identification of novel prognostic markers and long-term outcome after multimodality treatment. J Clin Oncol. 2006;24:4862-6.
17. Hu T, Fang Y, Sun Q, Zhao H, Ma D, Zhu T et al. Clinical management of malignant ovarian germ cell tumors: A 26-year experience in a tertiary care institution. Surg Oncol. 2019;31:8-13.
18. Cicin I, Eralp Y, Saip P, Ayan I, Kebudi R, Iyibozkurt C et al. Malignant ovarian germ cell tumors: a single-institution experience. Am J Clin Oncol. 2009;32:191-6.
19. 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;39:424-9.
20. Gershenson DM. Management of ovarian germ cell tumors. J Clin Oncol. 2007;25:2938-43.
21. Chen J, Li Y, Wu J, Liu Y, Kang S. Whole-exome sequencing reveals potential germline and somatic mutations in 60 malignant ovarian germ cell tumors†. Biol Reprod. 2021;105:164-78.
22. Qin B, Xu W, Li Y. The impact of lymphadenectomy on prognosis and survival of clinically apparent early-stage malignant ovarian germ cell tumors. Jpn J Clin Oncol. 2020;50:282-87.
23. Lee KH, Lee IH, Kim BG, Nam JH, Kim WK, Kang SB et al. Clinicopathologic characteristics of malignant germ cell tumors in the ovaries of Korean women: a Korean Gynecologic Oncology Group Study. Int J Gynecol Cancer. 2009;19:84-7.
24. Low JJ, Perrin LC, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumors. A review of 74 cases. Cancer. 2000 ;89:391-8.
25. 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 ;101:251-7.
26. Zamani N, Rezaei PM, Ghasemian DS, Alizadeh S, Modares GM. Fertility sparing surgery in malignant ovarian Germ cell tumor (MOGCT): 15 years experiences. BMC Womens Health. 2021;21:282.

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;29:635-7.