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Clinical management of malignant ovarian germ cell tumors: A 26-year experience in a tertiary care institution

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ABSTRACT

Background: The standard prognostic system for malignant ovarian germ cell tumors (MOGCT) has not yet been established and the scope of surgery was also controversial. Mixed ovarian malignant germ cell tumor (mGCT) is a rare histological type of MOGCT with higher malignant degree than other types. The aim of the present study was to investigate the clinical features and prognosis of mGCT, and prognostic factors for MOGCT to provide guidance for future treatment.

Methods: Retrospective analysis was carried out on 137 patients, who were admitted from 1991 to 2014. Survival curves were constructed using Kaplan–Meier method and were compared with the log-rank test across various pathological types and different stages. Multivariate survival analysis was performed using Cox's proportional hazards model.

Results: There were 29 dysgerminomas (DG), 3 embryonal carcinomas (EC), 43 immature teratomas (IT), 48 yolk sac tumors (YST) and 14 mixed germ cell tumors (mGCT). The most common type of mGCT is YST (85.7%), followed by IT (64.3%), EC (28.6%), and DG (21.4%). The respective 5-year OS rates were 100% in DG, 100% in EC, 92.5% in IT, 54.5% in YST and 66.7% in mGCT, while the corresponding 5-year PFS rate were 89.7% in DG, 100% in EC, 85.1% in IT, 55.9% in YST and 60% in mGCT. FIGO stage III-IV, certain pathological types (Yolk sac tumors and mGCT) and the number of postoperative chemotherapy courses were independently unfavorable prognostic in a multivariate model that included age, Admission decade, fertility-sparing surgery, and comprehensive staging surgery.

Conclusions: Fertility-sparing surgery and incomplete surgical staging did not affect the prognosis. It might be safe to preserve fertility and shrink the scope of the surgical procedures in MOGCT patients regardless of stage or pathology. However, prospective randomized controlled trials were needed for further evaluation.

1. Introduction

Malignant ovarian germ cell tumors (MOGCT) is a collective group of various histopathological malignant tumors originating from primordial germ cells in the embryonic gonad, including dysgerminoma (DG), embryonal carcinoma (EC), immature teratoma (IT), yolk sac tumor (YST), non-gestational choriocarcinoma (CC) and mixed ovarian malignant germ cell tumor (mGCT), accounting for 2–5% of all ovarian malignancies [1]. These tumors are characterized by their rapid growth and high malignancy, but highly chemosensitive. Due to the low incidence, no prospective randomized trials have been conducted yet and the current management protocols have been mostly adopted from practices of managing male germ cell tumors. Since the introduction of cisplatin drug by Einhorn and Donohue in 1977 for germ cell tumor treatments (testicular cancer), the regimens for patients with MOGCT have made a great advances in improving outcomes [2–6].

Currently, according to the National Comprehensive Cancer Network (NCCN) clinical practice guideline, the standard treatment for MOGCT when fertility preservation is desired remains conservative surgery regardless of cancer stage. Otherwise, completion surgery with comprehensive staging is recommended. Comprehensive surgical staging should also be performed in adult women but may be omitted for

Abbreviations: MOGCT, malignant ovarian germ cell tumors; mGCT, Mixed ovarian malignant germ cell tumor; DG, dysgerminoma; EC, embryonal carcinoma; IT, immature teratoma; YST, yolk sac tumor

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children or adolescents presenting with early-stage MOGCT [7].

However, in spite of the high remission rate of MOGCT, more attention needs to be paid in lessening acute morbidity and long-term effects associated with treatment [8]. MOGCT generally appear in teenage girls or young women, and predominately unilaterally. Therefore, it is important to reduce the scope of surgery by aiming for high cure rate. Comprehensive surgical staging has raised much controversy in recent years [9]. There have been some reports where comparable clinical outcome were obtained between patients treated by comprehensive surgical staging and incompletely-staged patients [10]. The most divisive component remains bilateral pelvic and para-aortic lymphadenectomy, which may result in lymphatic cyst [10,11]. Moreover, it has also been reported that omentectomy in early-stage MOGCT may not improve patient's prognosis and therefore might not be required [12].

Mixed ovarian malignant germ cell tumor (mGCT) is a rare histological type of MOGCT with higher malignant degree than other types, which contains two or more malignant germ cell components. In certain literature, mGCT comprised of about 10% of all MOGCT [9,13]. So far, a majority of publications on mGCT have been case reports [14–16]. Because of the low incidence of mGCT, there are not many studies which focused on the prognosis and clinical features of the disease.

The standard prognostic system for MOGCT has not yet been established because of the low incidence rate, and reports concerning prognostic indicators are also scarce. The aim of the present study was to investigate the clinical features and prognosis of mGCT, and prognostic factors for MOGCT to provide guidance for future treatment.

2. Material and methods

2.1. Data collection

137 MOGCTs patients were admitted in the Department of Obstetrics and Gynecology (n = 136) and Department of Pediatric Surgery (n = 1) from January 1991 to January 2014 and were taken into account for analysis. This study was reviewed by the Ethics Committee of Huazhong University of Science and Technology, and informed consent was obtained from each patient. All the clinical records were carefully reviewed and the pathological diagnoses verified. The World Health Organization 2003 edition of ovarian histology classification criteria was used as the pathological diagnosis standard [17]. International Federation of gynecology and Obstetrics (FIGO) staging system was referred for clinical staging [18]. Our study was confined to original MOGCTs, so we excluded some applicable patients such as primary retroperitoneal YST (n = 1), vaginal YST (n = 1), sacral YST (n = 1), accompanied by ovarian serous adenocarcinoma (n = 1), and concurrent sigmoid colon adenocarcinoma (n = 1). The former 3 patients' pathology did not originate from ovaries, and the latter 2 were discarded because combined with adenocarcinoma the prognosis is seriously poor which would overwhelm the essential characteristics of MOGCTs.

The data collected in this research included general information (name, age at diagnosis, gestational and parturition history prior to diagnosis), clinical symptoms, ultrasound results, date of surgery, surgical approaches, pathological diagnosis, clinical staging, initial chemotherapy regimens and processes, salvage surgery and chemotherapy if provided, as well as prognosis (follow-up period, adverse events and intervals, survival status). Patients providing insufficient information mentioned above were excluded. The time periods collected in our research were presented in months except for age at diagnosis which was denoted in years.

2.2. Surgery

All the enrolled patients had undergone surgical management. There were several surgical approaches examined in present study. In our hospital, in general, patients with MOGCT who wish to preserve fertility were treated with fertility-sparing surgery regardless of stage. Fertility-sparing operation was defined as preserving uterus and at least part of the contralateral ovary, with or without comprehensive surgical staging (omentectomy, peritoneal biopsies, peritoneal cytology, and para-aortic and pelvic lymphadenectomy). Patients presenting with lesions outside the ovaries also underwent tumor reductive surgery. Before 2000, surgical approach was usually performed via open laparotomy. Afterwards, with the advent of laparoscopic instruments and improvement of laparoscopic surgical skills, most surgeries are gradually being performed via laparoscopy. Before the surgery, there must be preliminary examinations assessing the extent of the lesions through B-ultrasound, computed tomography or magnetic resonance imaging. If the tumor diameter exceeded 10 cm, laparoscopy was impossible and an open laparotomy had to be adopted. In order to minimize the burden from the tumor, resection of the bladder or colons were sometimes required.

2.3. Chemotherapy

After comprehensive typing and staging of MOGCTs were confirmed, postoperative chemotherapy was administered. Since the beginning of our research, the first line chemotherapy regiment for MOGCTs was BEP (bleomycin, etoposide and cisplatin). In general, except for stage Ia DG and stage Ia grade 1 IT patients, other MOGCTs patients should receive postoperative chemotherapy. The amount of chemotherapy courses often range from 4 to 8. If there were visible tumors and abnormal levels of tumor markers, more courses or other chemotherapy regimens should be considered. The dosage of BEP was calculated as follows: bleomycin hydrochloride 10 $mg/m^2/d*3d$, etoposide 100 $mg/m^2/d*5d$, cisplatin 20 $mg/m^2/d*5d$. Indomethacin 25–50 mg was taken orally before injection of bleomycin to prevent high fever side effect. Usually hydration regimen should be given for the prevention of cisplatin's nephrotoxicity. Attention should also be paid such that the lifetime dose of bleomycin has been exceeded to prevent irreversible pulmonary fibrosis. For preadolescent young girls, we preferred VAC (vincristine, dactinomycin, cyclophosphamide) as the first line chemotherapy. It has equivalent efficacy with BEP but lesser impediment on body development. Alternative regimens and courses were also adopted for different reasons. Some patients had primary respiratory diseases so bleomycin-containing regiment should be avoided. For mGCTs, the chemotherapy strategies were always directed against the principal pathological component or the component with the worst prognosis. Besides, some patients abandoned subsequent treatments for personal reasons.

2.4. Follow-up

The 137 MOGCT patients were followed up periodically mainly during consult at the outpatient department or through telephone. We had adequate communications with every patient about their treatment and prognosis. Most of them could be seen at the outpatient department regularly, and the rest were inconvenienced by face-to-face interview agreed to be reached by phone calls. The deadline for the follow-up period was October 1, 2018. The progression-free survival (PFS) was defined as the period from initial surgery to recurrence, or the last follow-up. The overall survival (OS) was calculated in months from initial surgery to death, or the last follow-up.

2.5. Statistics

Median survival time was calculated using the reverse Kaplan-Meier method [19]. Survival curves were constructed using Kaplan–Meier method and were compared with the log-rank test across various pathological types and different stages. Multivariate survival analysis was performed using Cox's proportional hazards model, in which all

covariates were included in the final model, with no stepwise variable selection performed [20]. Covariates of the Cox model included age, FIGO stage, pathological types, fertility-sparing surgery, comprehensive staging surgery, and courses of postoperative chemotherapy. Age was treated as a continuous variable and allowed a spline fit for nonlinear partial effects, for which restricted cubic splines with 3-knot transformation was used [21]. Courses of postoperative chemotherapy was modeled as continuous variable, besides, the other covariates were treated as discrete and converted to categorical data. Admission decade was also included in the model as a stratification variable to account for possible treatment variation. Since the EC group had only three patients, the EC pathology joined with DG group for the Cox analysis, because of their similar long-term survival rates. Interaction terms between pathological types and FIGO stage were also investigated in Cox analysis. The predictive accuracy of Cox models was described by the Harrell's C-index, which was corrected for optimism using 10-fold cross validation [22]. P values less than 0.05 was considered as statistical significance. All analyses were performed in R version 3.6 (http://www.r-project.org/).

3. Results

3.1. Clinical features

The present study contains 29 (21.2%) dysgerminoma (DG), 3 (2.2%) embryonal carcinoma (EC), 43 (31.4%) immature teratoma (IT), 48 (35.0%) yolk sac tumor (YST), 14 (10.2%) mixed germ cell tumor (mGCT). The ages at diagnosis ranged from 2.8 to 60 with a median of 23 years old. 86 (62.8%) patients had no history of pregnancy, 49 (35.8%) had histories ranging from 1 to 12 times with a median of 3, and 2 patients were unknown. Among the gravid patients, 44 had 1-4 parity histories. The clinical stages distributions were 79 (57.7%) stage I, 15 (10.9%) stage II, 30 (21.9%) stage III, and 13 (9.5%) stage IV. In each pathological type, the detailed information of clinical stage distribution, age, surgery modality and chemotherapy regimen were presented in Table 1.

Most of the 137 patients enrolled were admitted in our hospital following onset of various symptoms. Only a small part of them were diagnosed in an early period during routine health examinations. Among all the recorded clinical manifestations, pelvic or abdominal mass was the most common symptom, which was expressed by 126 (92.0%) patients. In our study, the mass sizes ranged from 3 to 40 cm with a median of 10.5 cm. Most of tumors were unilateral: 59 (43.1%) were located in the left ovary and 73 (53.3%) lied in the right and the remaining 5 (3.6%) masses were bilateral. The second common associated symptom was abdominal pain (67 patients, 48.9%). The other common manifestations included abdominal distension (31 patients, 22.6%), ascites (13 patients, 9.5%), various menstrual abnormalities such as abnormal vaginal bleeding (8 patients, 5.8%), and fever (4 patients, 2.9%).

3.2. Pathological types and clinical stages of mGCTs

In our study, there were 14 patients who identified with mGCTs. The diagnosis involves specifically detecting different components from specimen sections by visual inspection. 12 (85.7%) patients of mGCTs reported 2 components, 2 (14.3%) patients expressed 3 components. With respect to the proportion of combined histological components, the most common type is YST (12 patients, 85.7%), followed by IT (9 patients, 64.3%), EC (4 patients, 28.6%), and DG (3 patients, 21.4%). Non-gestational choriocarcinoma (CC) had the lowest proportion, merely accounting for 7.1% (1 patient) of mGCT components. The most common histologic combination of mGCTs was IT + YST, which accounted for 50% mGCT patients. In mGCTs, there were 8 stage I (57.1%), 2 stage II (14.3%), 3 stage III (21.4%) and 1 stage IV (7.1%) patients. The detailed pathology and clinical stages of mGCTs are shown in Table 2.

3.3. Treatment

96 (70.1%) patients consented to fertility sparing surgery, while 41 (29.9%) patients underwent cytoreductive surgery. Of the 137 postoperative patients, 131 (95.6%) underwent chemotherapy, and the other 6 patients rejected chemotherapy due to undisclosed reasons. The BEP regimen (bleomycin, etoposide and cisplatin) were carried out in 115 patients (87.8%). 16 patients (12.2%) received other chemotherapy strategies, including TP (paclitaxel and cisplatin, 5 patients), VAC (vincristine, dactinomycin and cyclophosphamide, 2 patients), PVB (bleomycin, vincristine and cisplatin, 2 patients), PVC (vincristine, cisplatin and cyclophosphamide, 1 case), VEP (vincristine, cisplatin and etoposide, 1 case), PAC (cisplatin, doxorubicin and cyclophosphamide, 1case) and EMA-EP (etoposide, methotrexate, actinomycin, and cisplatin, 1 case). The courses of chemotherapy ranged from 1 to 11 with a median of 4.

3.4. Prognosis

The median follow-up period for the 137 patients was 73 months (range from 10 to 276 months; 95% CI, 66–81 months). Overall, patients had a 5-year OS rate of 79.9%, and a 5-year PFS rate of 74.7%. The 5-year OS rate was 89% for stage I-II patients and 61% for stage III-IV patients. The 5-year PFS rate of stage I-II patients was 85.1%, but 52.5% in stage III-IV patients. It supported that both of the 5-year OS and PFS rate of stage I-II patients was obviously higher than those of stage III-IV patients ($p < 0.001$, Table 3).

In each type of MOGCTs, the respective 5-year OS rates were 100% in DG, 100% in EC, 92.5% in IT, 54.5% in YST and 66.7% in mGCT, while the corresponding 5-year PFS rate were 89.7% in DG, 100% in

Table 1
Patient characteristics of 137 malignant ovarian germ cell tumors.

Pathology	Number of cases (percent)	Age (year)		Stage (FIGO)				Surgery		Chemotherapy	
		Range	Median	I	II	III	IV	Type A[a]	Type B[a]	BEP	non-BEP[b]
IT	43 (31.4%)	15–45	23	28	3	11	1	12	35	41	2
DG	29 (21.1%)	5–42	21	23	1	4	1	9	26	21	8
YST	48 (35.0%)	2.8–52	23	19	8	11	10	15	42	44	4
EC	3 (2.2%)	17–60	19	1	1	1	0	1	2	3	0
mGCT	14 (10.2%)	11–54	26.5	8	2	3	1	4	11	10	4
Total	137 (100%)	2.8–60	22	79	15	30	13	41	116	119	18

DG, dysgerminoma; EC, embryonal carcinoma; mGCT, mixed germ cell tumor; IT, immature teratoma; YST, yolk sac tumor.

[a] Surgery type A: fertility preservation surgery; type B: comprehensive surgical staging surgery.

[b] Non-BEP includes TP (paclitaxel and cisplatin), VAC (vincristine, dactinomycin and cyclophosphamide), PVB (bleomycin, vincristine and cisplatin), PVC (vincristine, cisplatin and cyclophosphamide), VEP (vincristine, cisplatin and etoposide), PAC (cisplatin, doxorubicin and cyclophosphamide) and EMA-EP (etoposide, methotrexate, actinomycin and cisplatin) regimens.

Table 2
Clinical profiles of mixed germ cell tumors (mGCTs) in present study.

No.	Mixed MOGCT components	Age (years)	Follow-up period (months)	Status	Relapse	Relapse interval (months)	Stage (FIGO)	Fertility sparing surgery[a]	Radical staging surgery	Side	Chemotherapy regimen	Cycles of chemotherapy
1	IT + CC	21	60	Alive	No	–	IV	F	Yes	Left	EMA-EP	4
2	IT + DG + EC	11	35	Dead	Yes	20	I	F	Yes	Left	BEP	5
3	YST + DG	26	276	Alive	No	–	I	F	No	Right	VAC	8
4	YST + DG	28	171	Alive	No	–	III	F	Yes	Left	BEP	8
5	YST + IT + EC	33	166	Alive	No	–	II	C	Yes	Right	BEP	8
6	YST + EC	15	30	Dead	Yes	16	I	F	Yes	Right	BEP	4
7	YST + EC	54	17	Dead	Yes	8	III	C	Yes	Left	TP	7
8	YST + IT	27	10	Alive	No	–	I	F	Yes	Right	BEP	2
9	YST + IT	33	93	Alive	Yes	19	I	F	No	Right	BEP	2
10	YST + IT	25	12	Alive	No	–	II	C	Yes	Right	BEP	3
11	YST + IT	40	14	Dead	Yes	6	III	C	Yes	Left	PAC	3
12	YST + IT	32	144	Alive	No	–	I	F	No	Right	BEP	4
13	YST + IT	13	123	Alive	No	–	I	F	Yes	Left	BEP	6
14	YST + IT	14	129	Alive	No	–	I	F	Yes	Left	BEP	6

BEP, bleomycin, etoposide and cisplatin; CC, choriocarcinoma; DG, dysgerminoma; EC, embryonal carcinoma; EMA-EP, etoposide, methotrexate, actinomycin, and cisplatin; IT, immature teratoma; PAC, cisplatin, doxorubicin and cyclophosphamide; TP, paclitaxel and cisplatin; VAC, vincristine, dactinomycin and cyclophosphamide; YST, yolk sac tumor.

[a] F: preserving uterus and at least part of the contralateral ovary with or without comprehensive surgical staging, C: completion surgery (hysterectomy and bilateral salpingo-oophorectomy) with or without comprehensive surgical staging.

EC, 85.1% in IT, 55.9% in YST and 60% in mGCT (Fig. 1A and B). The 5-year OS rate of patients with YST was significantly lower than patients with IT and DG except for EC ($P < 0.05$). The 5-year OS rate of patients with mGCT was lower than DG, EC and IT patients but there was no significant difference. When divided into two groups (stage I-II and stage III-IV), the 5-year OS and PFS rate of patients with YST and mGCT were also lower than others types but only the difference in 5-year OS rate between YST and DG was significant ($P < 0.05$). The detailed information is shown in Table 3.

Cox's regression analysis of risk factors for overall survival analysis, which is shown in Table 4, revealed that FIGO stage III-IV, certain pathological types (Yolk sac tumors and mGCT) and the number of postoperative chemotherapy courses had independent unfavorable prognostic roles. However, fertility sparing surgery and extensive surgical staging (peritoneal staging) did not correlate with the overall survival. Interactions between stage and pathology was calculated and the global test of additivity has $P = 0.958$, so we ignore the interactions in the final model. We did 10-fold cross validation of the model, the corrected c-index of which was 0.80, which exhibited good validation.

4. Discussion

MOGCT is a rare type of ovarian tumor, accounting for 2–5% of all ovarian malignancies. In contrast to other reports, YST was the most frequent type in our study, which was followed by IT [23–25].

Since the introduction of VAC and cisplatin-based chemotherapy regimen to MOGCT, the survival rate has radically improved in the past 30 years. However, owing to the low incidence of MOGCT, no standard prognostic system has been established yet and many management protocols have been adapted from practices aimed at managing male germ cell tumors. Only a handful of reports regarding prognostic factors of MOGCT have been published. Park et al. reported that, after fertility-sparing surgery for early and advanced MOGCTs, patients with endodermal sinus tumor or incomplete staging or larger residual tumor size were more likely to replapse, and endodermal sinus tumor and residual tumor size were independent risk factors for death [26]. Another report from 144 patients with stage I MOGCTs stated that the presence of endodermal sinus component was an independent risk factor, while postoperative chemotherapy, stage IC, fertility-sparing surgery and peritoneal staging were not significantly associated with patients' outcome [9].

MOGCTs are displaying an increasing trend in young girls and young women. In present study, the patients' median age was 22 years old. This means that the preservation of fertility and survival have the same essential significance for such patients. Regardless of stage and pathological types, fertility preserving surgery can always be considered for young patients who have reproductive objectives. Therefore, a better quality of life is also needed. Only a small number of cases regarding the safety of fertility-sparing surgery have been reported. However, the fertility-sparing surgery is widely performed worldwide for young patients with early-stage MOGCT as a reasonable treatment option. The present study has demonstrated that fertility-sparing operation was not a risk factor for prognosis in MOGCT patients after adjusting for stage, age, histology and other risk factors. So it might be safe to preserve fertility in MOGCT patients regardless of stage or pathology. However, prospective randomized controlled trials were

Table 3
The 5-year overall (OS) and disease-free (DFS) survival rates of various MOGCT types in stage I-II and III-IV patients.

Pathological types	Number of patients		Stage I-II			Stage III-IV			*P value*	
	Number	Percent (%)	Number	5-year DFS (%)	5-year OS (%)	Number	5-year DFS (%)	5-year OS (%)	5-year DFS	5-year OS
DG	29	21.2	24	95.8	100	5	60.0	100	0.014	0.046
IT	43	31.4	31	92.9	95.8	12	65.6	83.3	0.025	0.128
YST	48	35.0	27	68.6	70.7	21	40.8	35.6	0.02	0.011
EC	3	2.2	2	100	100	1	100	100	[a]	[a]
mGCT	14	10.2	10	62.5	75	4	50	50	0.393	0.263
Total	137	100	94	85.1	89	43	52.5	61	< 0.001	< 0.001

DG, dysgerminoma; EC, embryonal carcinoma; IT, immature teratoma; mGCT, mixed germ cell tumor; YST, yolk sac tumor.

[a] Because of the limited number of patients, p value cannot be calculated.

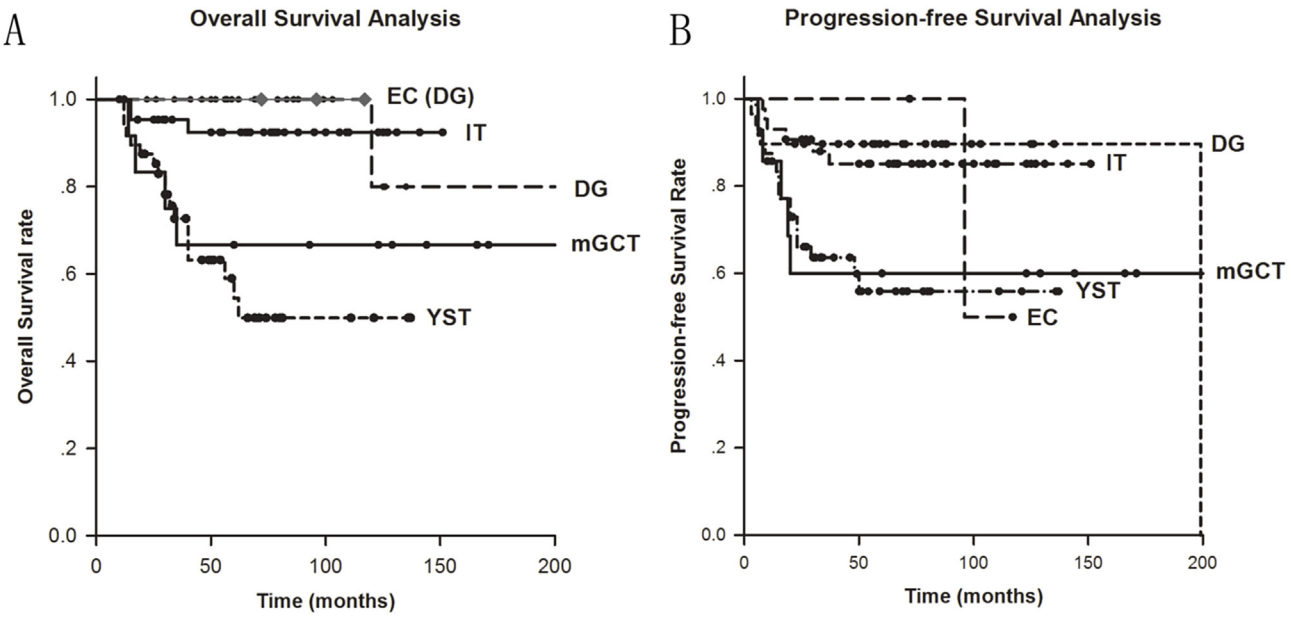

Fig. 1. A–B: Comparison of overall survival (OS) and disease-free survival (DFS) rate between EC, DG, YST, EC and mGCT patients. Abbreviations: IT, immature teratoma; DG, dysgerminoma; YST, yolk sac tumor; EC, embryonal carcinoma; mGCT, mixed germ cell tumor.

Table 4
Cox's regression analysis of risk factors for overall survival.

	Beta Coefficient	*P value*	Hazard ratio	95% confidence interval
Age				
Age'	−0.15	0.007		
Age″	0.17	0.022		
FIGO stage				
I-II	Reference			
III-IV	2.12	< 0.001	8.31	2.95–23.43
Pathological types				
EC + DG	Reference			
IT	1.11	0.35	3.05	0.29–32.24
mGCT	3.84	0.002	46.30	3.97–540.38
YST	3.45	0.003	31.55	3.35–296.81
Fertility-sparing surgery				
Yes	0.28	0.67	1.32	0.36–4.78
No	Reference			
Comprehensive staging surgery				
Yes	−0.75	0.20	0.47	0.15–1.48
No	Reference			
Postoperative chemotherapy				
Number of courses	−0.21	0.026	0.81	0.67–0.98

mGCT, mixed germ cell tumor. Age was modeled using restricted cubic spline function with three knots, containing two independent coefficients: age', and age″.

needed to confirm the safety of fertility-sparing surgery in MOGCT patients.

Furthermore, the incidence of MOGCT is significantly lower than ovarian epithelial carcinoma. Many surgical approaches are based on clinical practice guidelines for ovarian epithelial malignancies. Comprehensive staging surgery, which is standard practice for women with ovarian epithelial carcinoma, is now also routinely applied irrespective of fertility-sparing surgery for the treatment of MOGCT among gynecologic oncology community. However, criticisms have recently been raised about the role of comprehensive staging surgery in MOGCT, particularly in the absence of visible disease. MOGCT is much more chemosensitive than epithelial ovarian cancer. Routine lymphadenectomy often lead to late morbidity of lymphedema and may affect the reproductive ability. Lately, Wu et al. questioned the need to perform omentectomy in three common subtypes of MOGCT (YST, DG, and IT) in a retrospective review. They found that there were no significant difference in 10-year overall survival between patients with and without omentectomy at stage I and II disease [12]. Besides, some investigators suggested equivalent clinical outcomes between comprehensive surgical staging and patients who are not [9,10,27–29].

On the other hand, a large retrospective study from the Surveillance, Epidemiology, and End Results Program (SEER) has reported that the prevalence of lymph node metastasis in MOGCT was 18.1%, and cox's regression analysis revealed that lymph node involvement was an independent risk factor for prognosis after matching for age, race, stage, grade and histology [11]. It also revealed that lymph node metastasis was not rare. The validity of comprehensive staging surgery is the most debatable issue at present [8–10,12,24,30,31]. In the multivariate analysis of our study, comprehensive surgical staging appears not to be a favorable prognostic factor in MOGCT patients.

Cisplatin-based chemotherapy regimen plays important roles in treatment of MOGCT. In NCCN clinical practice guidelines for ovarian cancer, 4-cycle BEP regimen is recommended as the standard procedure. However, there is still no supportive evidence on the use of chemotherapy, especially the number of chemotherapy cycles required. In our study, a number of patients with advanced disease received more than four cycles of chemotherapy, and the multivariate analysis conveyed that the number of chemotherapy courses was an independent prognostic factor for MOGCT. 115 patients (87.8%) in our study received BEP regimen while 16 patients (12.2%) received other chemotherapy strategies. Since there was no auxiliary research on the number of the adequate cycles of chemotherapy, another issue about whether more cycles could be suggested in MOGCT patients with advanced stage was raised.

In literature, the most frequent combination of malignant mGCTs is DG and YST [23,32,33]. In our study, the most frequent combination was YST and IT, which accounted for 50%, and the proportion of the combination of YST and DG was 14.3% (2/14). However, the disparity might be caused by the small number of cases. Furthermore, we also found that YST was the most common component of mGCT in our study (85.7%), and patients with malignant mGCTs had equivalent 5-year overall survival rate (66.7%) compared with those with YST (54.5%) in present study. YST is the second most common subtype of MOGCTs and

has been described as an independent unfavorable prognostic factor [34–36]. The Cox analysis of the present study also indicated the unfavorable prognostic role of YST and malignant mixed germ cell tumors. Therefore, we theorized that high proportion of YST component in our study might be a reason behind poor prognosis of malignant mixed germ cell tumors in our study.

In summary, this present study showed that FIGO stage III-IV, certain pathological types (Yolk sac tumors and mGCT) and limited number of postoperative chemotherapy courses were independent unfavorable prognostic factors in MOGCT. Comprehensive surgical staging may be not favorable for prognosis in MOGCT patients, thus prospective clinical trials are needed to confirming the validity of comprehensive surgical staging especially in children or adolescents. Due to the rarity and diversity of this disease, there is a need for establishing a standard prognostic system of each histological type to devise individualized treatment approach. Large-scale, retrospective reviews or prospective trials are required to identify more effective individualized therapeutic strategies in the future.

Authorship statement

All authors have approved this manuscript and meet the requirements of authorship.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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