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Original Article

Clinical characteristics of malignant ovarian germ cell tumors

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Abstract: This study was aimed to investigate the clinical characteristics, treatment and prognosis effect of malignant ovarian germ cell tumors (MOGCTs). A total of 39 patients with MOGCTs treated at Gynecology Obstetrics in Tianjin Central Hospital were enrolled from January 1999 to November 2009 in this study. All the patients underwent pathological examination and diagnosis was confirmed. We used univariate and multivariate logistic regression analysis to evaluate influencing factors, and Kaplan-Meier survival analysis and cox promotional hazard regression analysis were used to evaluate the survival rate. All of patients were followed up until November 30, 2014. Eight cases (20.5%) were dead. Six months were the shortest survival time and this patient with IV stage yolk sac tumor was ill-controlled after operation, progressing to death rapidly. In respect of surgical procedures, 5 cases in pregnant group underwent laparotomy and 3 cases underwent laparoscope; In unpregnancy group, 3 cases underwent laparotomy and 3 cases underwent laparoscope. There were no significant differences between two groups (P=1.000). Seven cases in pregnant group received chemotherapy and one didn't. In unpregnancy group, all the 6 cases received chemotherapy. The chemotherapy regimen was BEP (bleomycin, etoposide and cisplatine) and 4 courses were used. There were no significant differences between two groups (P=1.000). Kaplan-Meier survival analysis showed no significant differences in the impact of Federation of Gynecology and Obstetrics (FIGO) I-II staging on survival prognosis (P > 0.05), however, manifesting significant differences were found when compared to stage IV respectively (I vs IV, X^2=27.072, P < 0.001; II vs IV, X^2=6.983, P=0.008; III vs IV, X^2=10.671, P=0.001) and between stage I and stage III (X^2=4.965, P=0.026). The result of Cox regression identified only MOGCT histological type as a predictor of overall survival (OS, Wald=6.240, P=0.012). For pregnancy analysis, univariate logistic regression analysis showed that no significant difference was found between pregnancy group and non-pregnancy (Wald=2.410, P=0.121). A multivariate logistic regression analysis also showed no statistical differences between two groups. FIGO staging and MOGCT histological type are critical factors affecting the prognosis of the patients with MOGCTs. The pregnant outcome of the patients receiving chemotherapy is desirable, and there are no significant effects of age, surgical-pathological staging, MOGCT histological type, surgical procedures and tumor size on the pregnancy outcome.

Keywords: Malignant ovarian germ cell tumors, clinical characteristics, treatment, prognosis

Introduction

Malignant ovarian germ cell tumors (MOGCTs) originate from embryonic primordial germ cells, and a higher incidence is found in adolescent and young adult women [1-3]. MOGCTs should be highlighted by the clinicians because of their high growth rate and relatively poor prognosis [4-6]. Patients with MOGCTs have no specific clinical manifestations, and the common symptoms include stomachache, vaginal bleeding, abdominal distension or pelvic masses, etc. [7-9]. The late symptoms are mostly emaciation or weak, etc. Because MOGCTs have high grade of malignancy and fast growth rate, their tumor capsules are more easily ruptured, and more than half of the patients complicated by fever [10]. Even in late stage of the MOGCT patients, the uterus and contralateral ovary are little affected. Pedicle torsion happens easily due to the shift of barycenter of teratoma. In this study, the clinical data of 39 cases of patients with malignant ovarian germ cell tumors were retrospectively analyzed. Their pathological feature, major factors and the impact of receiving surgery with function of preserving fertility and pregnancy were studied.

Table 1. The age and MOGCT histological type of the patients

Histological type/Age range	Yolk-sac tumor	Embryonic carcinoma	Dysgerminoma	Immature teratoma	Mixed type	N (%)
< 20	1	1	3	4	1	10 (25.6)
20-29	4	-	7	5	2	18 (46.2)
30-39	2	-	4	1	1	8 (20.5)
> 40	2	-	-	-	1	3 (7.69)
Total	9 (23.1)	1 (2.6)	14 (35.9)	10 (25.6)	5 (12.8)	39 (100)

Table 2. MOGCT histological type and clinical manifestation of the patients

Histological type	N (cases)	Clinical manifestation [cases (%)]				
		Abdominal mass	Abdominal distension	Stomachache	Vaginal bleeding	None
Yolk-sac tumor	9	5 (55.6%)	2 (22.2%)	1 (11.1%)	1 (11.1%)	0
Embryonic carcinoma	1	1 (100.0%)	0	0	0	0
Dysgerminoma	14	8 (57.2%)	2 (14.3%)	2 (14.3%)	1 (17.1%)	1 (17.1%)
Immature teratoma	10	6 (60.0%)	2 (20.0%)	2 (20.0%)	0	0
Mixed type	5	1 (20.0%)	2 (40.0%)	0	1 (20.0%)	1 (20.0%)
Total (cases)	39	21 (53.8%)	8 (20.5%)	5 (12.8%)	3 (7.7%)	2 (5.2%)

Table 3. Histological type and operation-pathologic stage of the patients

Histological type	N (cases)	FIGO staging [cases (%)]			
		I	II	III	IV
Yolk-sac tumor	9	4 (44.4%)	1 (11.1%)	3 (33.4%)	1 (11.1%)
Embryonic carcinoma	1	0	0	1 (100.0%)	0
Dysgerminoma	14	8 (57.1%)	2 (14.3%)	4 (28.6%)	0
Immature teratoma	10	5 (50.0%)	0	4 (40.0%)	1 (10.0%)
Mixed type	5	3 (60.0%)	2 (40.0%)	0	0
Total (cases)	39	20 (51.3%)	5 (12.8%)	12 (30.8%)	2 (5.1%)

Materials and methods

General materials

Inclusion criteria: All the case data were from our hospital and pathologically confirmed, these data were further reviewed by at least one doctor with senior position. Operation-pathologic stage was based on the classification system published by Federation of Gynecology and Obstetrics (FIGO) in 2013. Exclusion criteria: Non-malignant ovarian germ cell tumors and cases with incomplete information.

A total of 39 patients with malignant ovarian germ cell tumors (MOGCTs) treated at Tianjin Central Hospital of Gynecology and Obstetrics from January 1999 to November 2009 were enrolled in this study. All the patients underwent pathological examination and the diagnosis was confirmed. According to the tumor pathological classification, 14 cases were dysgerminoma (35.9%), 10 cases were immature teratoma (25.6%), 9 cases were yolk-sac tumor (23.1%), 5 cases were mixed malignant germ cell tumors (12.8%) and 1 case was embryonic carcinoma (2.6%) (**Table 1**). Clinical data including age, cardinal symptom, sign, pathological diagnosis, stage, chemotherapy regimen and follow-up visit, etc. were collected. This research was approved by the Ethics Committee of Tianjin Central Hospital of Obstetrics and Gynecology.

Treatment

All the patients received surgery therapy. Fertility-preserving surgery was performed in the patients with the demands of fertility, and the adnexa tissue of diseased side was removed by tumorectomy. Patients without the demands of fertility underwent tumor staging surgery or cytoreductive surgery, then the abdominopelvic cavity was carefully detected. The full of uterus and its bilateral attachments, greater omentum appendix and pelvic lymph nodes were

Table 4. Histological type and surgery type of the patients

Histological type	Staging	Fertility-preserving surgery(cases)	Tumor staging or cytoreductive surgery (cases)	N
Yolk-sac tumor	I	4	0	4
	II	1	0	1
	III	1	2	3
	IV	0	1	1
Embryonic carcinoma	III	1	0	1
Dysgerminoma	I	8	0	8
	II	2	0	2
	III	2	2	4
Immature teratoma	I	5	0	5
	III	4	0	4
	IV	1	0	1
Mixed type	I	3	0	3
	II	1	1	2
Total (cases)		33	6	39

Table 5. Histological type and postoperative chemotherapy of the patients

Histological type	Staging	Chemotherapy	Without chemotherapy	N
Yolk-sac tumor	I	3	1	4
	II	1	0	1
	III	3	0	3
	IV	1	0	1
Embryonic carcinoma	III	1	0	1
Dysgerminoma	I	6	2	8
	II	2	0	2
	III	4	0	4
Immature teratoma	I	3	2	5
	III	4	0	4
	IV	1	0	1
Mixed type	I	2	1	3
	II	2	0	2
Total (cases)		33	6	39

also resected. The diameter of residual tumor foci was controlled within 2 cm by cytoreductive surgery.

BEP (bleomycin, etoposide and cisplatine) was adopted as the main chemotherapy regimen. Other chemotherapy regimens such as IEP (ifosfamide, etoposide and cisplatine) or VeIP (vincristine, ifosfamide and cisplatine) were used in the patients with uncontrolled tumor or recurrence. The treatment time lasted 4-10 chemotherapy courses.

Observational index

The follow-up visit was initiated for all the patients after the surgery, the survival time was defined as the time window from the start of surgery to death or the last follow-up visit. The survival time was counted as the day of last follow-up visit for patients who were lost in follow-up visit. The follow-ups included general conditions of the patients, pregnancy outcome of the patients with demands of fertility, recurrence or not, time of recurrence, treatment and effect after recurrence, etc.

Statistical methods

The collected data were analyzed with SPSS17.0 software, measurement data of normal distribution was presented with mean ± standard deviation (mean ± SD), and the comparison of the mean of two groups was analyzed by Student-t test. The comparison among groups of measurement data of non-normal distribution was based on non-parametric test. The comparison of sample rate of two groups using X^2 test and Fisher exact test was applied in this study. Kaplan-Meier survival curves were created to determine differences in survival. Cox regression was also performed using data that trended toward significance ($P < 0.10$) on univariate analysis and variables that were previously associated with the outcome. Univariate and multivariate logistic regression were used to determine the effects of patients' characteristics on the pregnancy. Inspection level with bilateral $\alpha < 0.05$ was considered as statistically significant.

Results

Clinical manifestation

The major clinical manifestations of MOGCT patients were abdominal mass, abdominal distension, stomachache and vaginal bleeding,

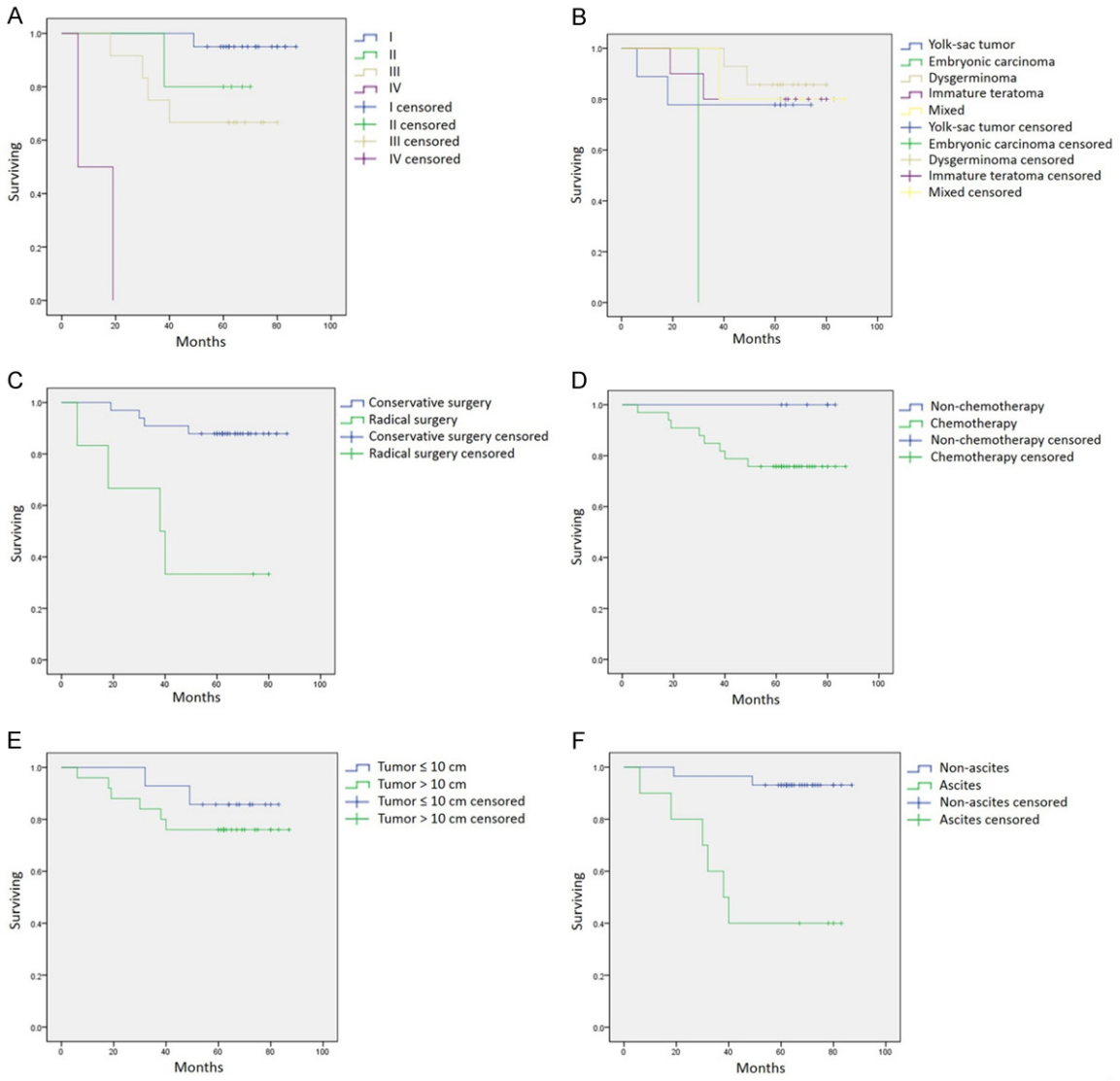

Figure 1. Kaplan-Meier survival analysis. Kaplan-Meier curves illustrate the OS of the patients influenced by (A) FIGO staging, (B) MOGCT histological type, (C) surgical method, (D) with or without chemotherapy, (E) tumor size, and (F) with or without ascites.

etc. In this study, the most common clinical manifestation was the appearance of abdominal mass, which was found in 21 cases (53.8%), followed by 8 cases (20.5%) with abdominal distension, 5 cases (12.8%) with stomachache, 3 cases (7.7%) with vaginal bleeding, and 2 cases (5.2%) had no clinical manifestations. Specific data are shown in **Table 2**.

Operation-pathologic stage

All the patients were subjected to definite pathological diagnosis after surgery, based on the classification system published by FIGO in 2013, staging conditions were as follows: 20 cases (51.28%) were stage I; 5 cases (12.82%) were stage II; 12 cases (30.77%) were stage III; 2 cases (5.13%) were stage IV and all showed the existence of pulmonary metastasis. According to the classification of histological type, yolk-sac tumor and immature teratoma III/IV had a relatively high incidence, which were 4/9 and 5/10, respectively. Only one case was embryonic carcinoma and classified in stage III. Specific data are shown in **Table 3**.

Surgical methods

A total of 33 patients (84.62%) received fertility-preserving surgery and 6 patients (15.38%) received tumor staging surgery or cytoreductive surgery. Details were shown in **Table 4**.

Table 6. Univariate logistic regression analysis of the pregnancy in patients

Factors	B	S.E.	Wald	P
FIGO staging	-1.230	0.793	2.410	0.121
MOGCT histological type	-0.474	0.428	1.224	0.269
Tumor size	-0.182	1.133	0.026	0.872
Surgical approach	-0.511	1.095	0.217	0.641

S.E., Standard error.

Postoperative chemotherapy

Postoperative chemotherapy was performed in 33 patients. Chemotherapy regimen was mainly as BEP. For the patients with uncontrolled tumor or recurrence, other chemotherapy regimens such as IEP or VelP were used. The chemotherapy courses were 4-10. Six patients didn't receive chemotherapy, including 1 stage Ia yolk-sac tumor case, 2 stage Ia class G1 immature teratoma cases, 2 stage Ia dysgerminoma cases and 1 stage Ia mixed case. See **Table 5**.

Survival analysis

All the 39 patients were followed up until November 30, 2014. Eight patients (20.5%) were dead. Six months were the shortest survival time and this patient with IV stage yolk sac tumor was ill-controlled after operation, progressing to death rapidly. The rest 7 patients died of tumor recurrence after operation. The average of progression-free survival (PFS) were 22.0±11.4 months, the average of overall survival (OS) were 29.0±14.5 months, and the longest survival time were 49 months. Up to the final day of fellow-up visit, 31 cases (79.5%) survived free of tumor and no patients were dead above 5 years after operation. Among them, 4 cases were dead receiving conservative operation and 5-year survival rate was 87.9%; 4 cases were dead receiving comprehensive tumor staging surgery or cytoreductive surgery and 5-year survival rate was 33.3%.

Kaplan-Meier survival analysis showed no significant differences in the impact of FIGO I-II staging on survival prognosis ($P > 0.05$), however, manifesting significant differences were found when compared to stage IV respectively (I vs IV, $X^2=27.072$, $P < 0.001$; II vs IV, $X^2=6.983$, $P=0.008$; III vs IV, $X^2=10.671$, $P=0.001$) and between stage I and stage III ($X^2=4.965$, $P=0.026$, **Figure 1A**). Based on MOGCT histological type, Kaplan-Meier survival analysis showed a significant difference of OS between embryonic carcinoma and dysgerminoma ($X^2=14.000$, $P < 0.001$), and between embryonic carcinoma and mixed type ($X^2=5.000$, $P=0.025$, **Figure 1B**). The univariate analysis showed that patients undergoing tumor staging surgery or cytoreductive surgery had decreased OS compared with those receiving the conservative surgery ($X^2=12.307$, $P < 0.001$, **Figure 1C**). However, no significant differences of the OS were found between patients with and without chemotherapy (**Figure 1D**) and patients had a bigger (≥ 10 cm) and smaller (< 10 cm) tumor (**Figure 1E**). In addition, patients with or without ascites showed significantly different OS ($X^2=15.509$, $P < 0.001$, **Figure 1F**).

To exclude potential confounding, Cox regression was performed concerning the variables significant on univariate analysis (FIGO staging, MOGCT histological type and ascites) as well as variables previously identified as potential confounders (age, surgical method, chemotherapy and tumor size). The result of Cox regression identified only MOGCT histological type as a predictor of OS (Wald=6.240, P=0.012).

Pregnancy analysis of the patients

We observed the pregnancy outcome of the patients with an age of 20-39 years. Of these, a total of 14 patients had a demand of fertility, and stopped chemotherapy and removed the contraceptive measures ≥ 1 year. The patients were divided into pregnancy group (8 cases, with an average age of 26.0±4.1) and non-pregnancy group (6 cases, with an average age of 25.8±5.7). Patients in both groups had compared age, underwent conservative surgery, received chemotherapy and without ascites. The operation-pathologic staging of pregnancy group was as follows: 6 cases were stage I and 2 cases were stage II; In non-pregnancy group, 3 cases were stage I and 3 cases were stage III. Univariate logistic regression analysis showed that no significant difference was found between two groups (Wald=2.410, P=0.121). In MOGCT histological type, patients in pregnancy group had three yolk-sac tumors, three dysgerminomas, one immature teratoma and one mixed type. Patients in non-pregnancy group had one yolk-sac tumor, one dysgerminoma, three immature teratomas and one mixed type. No significant differences in histological types

were found between two groups (Wald=1.224, P=0.269). In pregnancy group, three patients had a tumor ≤ 10 cm, and five had a tumor > 10 cm; In non-pregnancy group, two patients had a tumor ≤ 10 cm, and four had a tumor > 10 cm. Univariate logistic regression analysis showed no significant difference in tumor size between two groups (Wald=0.026, P=0.872). In pregnancy group, five patients received laparotomy, three patients received laparoscope approach; In non-pregnancy group, three patients received laparotomy, three patients received laparoscope approach. There were no significant differences when these two groups were compared (Wald=0.217, P=0.641). Details were shown in **Table 6**. A multivariate logistic regression analysis also showed no statistical differences between two groups.

Discussion

MOGCT patients have the common symptoms such as stomachache, vaginal bleeding, abdominal distension or pelvic masses [11-13]. The late symptoms are mostly emaciation or weak, etc. Because MOGCTs have high grade of malignancy and fast growth rate, their tumor capsules are more easily ruptured. Above half of the patients have the complication of fever [14]. Even in late MOGCT patients, the uterus and contralateral ovary are less affected. Since the gravity center of teratoma deviates frequently, pedicle torsion happens easily. It is usually misdiagnosed as acute appendicitis, indigitation or intestinal twist, etc.

Since MOGCTs have a higher incidence in adolescent and young adult women, most in this age window have the demands of fertility after marriage. Therefore, higher requirements were proposed for conventional surgical treatment [15]. The principle of conventional treatment of MOGCTs is tumor staging surgery or cytoreductive surgery. The operation extent includes uterus and its attachment on both sides. In addition, bilateral accessary, greater omentum resection, pelvic lymphadenectomy and basin abdominal peritoneal multi-point biopsy are also involved [16]. This type of surgery often leads to fertility lose perpetually and low life quality [17].

In this study, one stage I patients was dead, the 5-year survival rate was 95.0%; One stage II patients was dead, the 5-year survival rate was 80.0%; Four stage III patients were dead, the 5-year survival rate was 66.7%; Two stage IV patients were dead, the 5-year survival rate was 0%. Survival analysis showed significant differences between stage I, II, III and stage IV, respectively, and between stage I and stage III. These results showed that the patients with higher FIGO staging had a worse prognosis.

Report indicates that patients with dysgerminoma have the best prognosis, while followed by immature teratoma and yolk-sac tumor, and the prognosis of mixed and embryonic carcinoma is the worst [18]. In eight dead patients, two with yolk-sac tumor, the 5-year survival rate was 77.8%; One with embryonic carcinoma, the 5-year survival rate was 0%; Two with dysgerminoma, the 5-year survival rate was 85.7%; Two with immature teratoma, the 5-year survival rate was 80%; One with mixed type, the 5-year survival rate was 80%. The 5-year survival rate of dysgerminoma was the highest and embryonic carcinoma was the lowest in our study. Kaplan-Meier survival analysis showed a significant difference of OS between embryonic carcinoma and dysgerminoma, as well as between embryonic carcinoma and mixed type.

A total of 33 patients (84.62%) received conservative surgery. The extent of surgical resection includes unilateral ovaries and fallopian tubes, the greater omentum and pelvic lymph nodes, however, the uterus and the contralateral attachments remained to be preserved. Four cases who received conservative surgery were dead, the 5-year survival rate was 87.9%; Four received comprehensive tumor staging or cytoreductive surgery were dead and the 5-year survival rate was 33.3%, which was related to the late overall FIGO staging. The univariate analysis in this study also showed that patients undergoing tumor staging surgery or cytoreductive surgery had decreased OS compared with those receiving the conservative surgery.

To determine the influence of the above factors on the pregnancy of the patients, 14 patients having demand of fertility were divided into pregnant group and non-pregnancy group. There was no significant difference in age between two groups. Univariate logistic regression analysis showed that there were no significant differences in FIGO staging, MOGCT histological type, tumor size and surgical approach. A multi-

variate logistic regression analysis also showed no statistical differences between two groups. The above results suggested that there were no significant effects of age, surgical-pathological staging, MOGCT histological type, surgical procedures and tumor size on pregnancy.

The clinical characteristics, treatment and prognosis effect of MOGCTs were investigated, and advantage of this study is to evaluate the pregnant outcome of the patients by univariate logistic regression analysis and multivariate logistic regression analysis. Disadvantages of this study were such as the limited number of patients, and some patients were excluded because of incomplete information. Additional follow-ups are needed to evaluate long-term clinical outcomes.

In conclusion, the treatment of surgery combined with chemotherapy is the major method for malignant ovarian germ cell tumors. BEP is the preferred chemotherapy regiment after MOGCT operation. FIGO staging and MOGCT histological type are critical factors affecting the prognosis of the patients with MOGCTs. Most of patients receiving BEP chemotherapy can be naturally pregnant and the pregnant outcome is desirable. There are no significant effects of age, surgical-pathological staging, MOGCT histological type, surgical procedures and tumor size on pregnancy outcome.

Disclosure of conflict of interest

None.

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