Treatment of malignant ovarian germ cell tumors and preservation of fertility

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Summary

Objective: To explore the prognostic factors, as well as the menstrual and reproductive outcomes, of malignant ovarian germ cell tumors following a fertility-preserving treatment. *Methods:* A total of 145 patients with malignant ovarian germ cell tumors who had undergone fertility-preserving management in the past 20 years were analyzed retrospectively. The correlative factors for survival, recurrence, and reproductive status were evaluated. The median follow-up time was 9.5 years. Thirty-five cases suffered from dysgerminoma, 31 cases from endodermal sinus tumor, 63 cases from immature teratoma, two cases from embryonal carcinoma, 13 cases from mixed germ cell tumor, and one case had malignant struma. The overall five-year survival rate was 90.3%, whereas the ten-year survival rate was 89.2%. The five-year survival rates for the different stages were as follows: Stage I, 98.1%; Stage II, 5/5; Stage III, 73.3%; and recurrence, 64.1%. The five-year survival rates were 100% for dysgerminoma, 84.1% for endodermal sinuse tumors, 92.0% for immature teratoma, one of two cases for embryonal carcinoma, 76.9% for mixed germ cell tumors, and one case of malignant struma. *Results:* Thirty-five babies were delivered, whereas seven induced abortions were performed during the follow-up. The important prognostic factors included the International Federation of Gynecology and Obstetrics (FIGO) stage and standard chemotherapy. No statistical significance in the five-year survival rates was determined among the different histological types, surgery types, chemotherapy courses, and chemotherapy regimen. Fertility-preserving treatment should be considered for ovarian germ cell tumors without the limitation of the FIGO stage. *Conclusion:* Chemotherapy does not influence the menses, pregnancy, or offspring. Recurrent cases could obtain a good prognosis after the proper treatment.

Key words: Malignant ovarian germ cell tumor; Fertility; Surgery; Chemotherapy.

Introduction

Malignant ovarian germ cell tumor (MOGCT) accounts for 5% of all ovarian malignancies. These tumors are rare gynecologic tumors usually affecting young women and children. These malignancies from primordial germ cells consist of dysgerminomatous and non-dysgerminomatous tumors, including yolk sac tumor (endodermal sinus tumors), immature teratomas, mixed germ cell tumors, pure embryonal carcinomas, and malignant struma. Hysterectomy and bilateral salpingo-oophorectomy were employed prior to the advent of effective combined chemotherapy, and under most circumstances, the patients would still die within one to two years because of high malignancy. Gershenson reported that 18 of 20 patients treated with surgery alone or postoperative radioisotopes, radiation therapy, and alkylating agents died in 1984 [1]. The survival rate of ovarian MOGCT has increased dramatically because of the application and development of combined chemotherapy. The majority of patients exhibit long-term survival with reported five-year survival rates of 100% for dysgerminomatous and 85% for non-dysgerminomatous MOGCT. Reducing toxicity, improving the quality of life, and fertility preservation are crucial in young females. We report in the current paper a large, single institutional experience of more than 20 years in the management of MOGCT. We aimed to investigate the outcome and treatment methods for the preservation of reproductive function given this rare but important disease.

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Materials and Methods

Patients

A total of 286 patients with MGCTO were treated at the Cancer Institute and Hospital of the Chinese Academy of Medical Sciences between 1985 and 2004. Reproductive function was retained in 145 cases. In this study group, the tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system, and histological typing was performed according to the World Health Organization classification. After the completion of the survival period, the patients were interviewed via correspondence or telephone regarding their menstrual period and fertility. The outpatient examinations were used as a reference. The median age at the time of the first visit was 16.6 years, with an age range of 5-39 years old. Eighty-two cases were under the age of 20 (56.6%), 106 cases were unmarried (73.1%), 39 cases were married, and 19 were childless. Eighty cases were on the right-side of the ovary, 63 cases were on the left-side of the ovary, and two cases were bilateral. Stage I malignancies accounted for 106 cases (73.1%), five cases were Stage II (3.4%), 15 cases were Stage III (10.3%), and 19 were recurrences that were not treated in our hospital but merely referred (13.1%). Of the 126 cases treated in our hospital, four cases recurred, whereas four other cases were lost in the follow-up process, and one case died because of unrelated reasons (Table 1). Thirty-five cases were dysgerminoma (24.1%), 31 cases were endodermal sinus tumor (21.3%), 63 cases were immature teratoma (43.4%), two cases were embryonal carcinoma (1.4%), 13 cases were mixed germ cell tumor (9.0%), and one case was malignant struma (0.7%) (Table 2).

Surgery types

Fifty-three cases underwent unilateral salpingo-oophorectomy, omentectomy, and appendectomy. Unilateral salpingo-oophorectomy was performed in 81 cases, whereas ovarian cystectomy was performed in 11 cases. Biopsy of the contralateral ovary was performed intraoperatively in 30 cases.

Postoperative chemotherapy

The following postoperative chemotherapy was administered to 140 cases, except for five cases of immature teratoma: bleomycin sulfate, etoposide phosphate, and cisplatin (BEP) regimen in 91 cases; cisplatin, vinblastine, and bleomycin (PVB) in 25 cases; vincristine, adriamycin, and cyclophosphamide (VAC) in six cases; a single drug in 16 cases with PDD, CTX, and EADM; and other regimens for two cases. The chemotherapy courses were 1-10 courses, and median courses were 4.5. Nineteen cases were given < 3 courses, 110 cases 3-6 courses, and 11 cases > 6 courses.

Results

Survival

The follow-up work after the treatments lasted for three years to 22 years, and the median follow-up was 9.5 years. A total of 129 women are still alive, ten died, and six women were lost in the follow-up process. For the deceased cases, one Stage I patient with dysgerminoma died after seven years of postoperative and post-chemotherapeutic treatment. Only one woman with Stage I immature teratoma died after postoperative therapy and three courses of chemotherapy due to unrelated reasons. The other eight women died because of tumor within one year; one case at Stage I, two cases at Stage III, and five cases with recurrent tumor. The life-span method was used to calculate survival rate. The overall five-year survival rate was 90.3%, whereas the ten-year survival rate was 89.2%. The five-year survival rates are as follows: Stage I, 98.1%, Stage II, 100%, Stage III, 73.3%, and recurrent cases, 64.1%. Statistical significance was determined for the five-year survival rates between the different stages ($p < 0.05$).

Five-year survival rates of the different histological types were 100% for dysgerminoma, 84.1% for endodermal sinus tumors, 92.0% for immature teratoma, one of two cases for embryonal carcinoma, 76.9% for mixed germ cell tumors, and one case for malignant struma. No statistical significance was found for the five-year survival rates between the different histological types.

No statistical significance for the five-year survival rates between the different surgery types was found. Likewise, no statistical significance for the five-year survival rates between the different chemotherapy regimens and chemotherapy courses was found.

Recurrent places and treatment

Nineteen recurrent post-treatment cases in other hospitals and referred to the hospital were included in the current study, including four cases of dysgerminoma, ten cases of immature teratoma, four cases of endodermal sinus tumor, and one case of mixed germ cell tumor. Four patients relapsed post-treatment in the hospital, including one case each of immature teratoma, malignant struma, endodermal sinus tumor, and embryonal carcinoma (Table 3). The conditions of these 23 patients before recurrence were as follows: 12 cases without treatment after operation, seven cases treated with non-standard chemotherapy plans, one case treated with only one cycle of chemotherapy, and three cases used standard schedule chemotherapy for ovarian germ cell tumors.

Metastatic diseases such as in the liver, spleen, lung, and retroperitoneal lymph nodes were detected in 11 recurrent patients, and the recurrences of the other 12 cases were limited to the abdominopelvic cavity. Surgery was performed on 14 recurrent cases, whereas 20 cases were retreated with chemotherapy. However, three recurrent cases of immature teratoma did not undergo chemotherapy post-surgery. Fifteen relapsed patients have survived, six cases died, and two cases were lost to follow-up (Table 4).

Table 1. — *Clinical stages and prognosis*.

Stage	Number	Survival	Loss in follow-up	Survival rate (5-year)	Survival rate (10-year)
I	106	102	1	98.1%	96.7%
II	5	5	0	100%	73.4%
III	15	10	3	73.3%	64.1%
Recurrent	19	12	2	64.1%	

Table 2. — *Histological types and prognosis*.

Histological types	Number	Survival	Loss	Survival rate (5-year)	Survival rate (10-year)
Dysgerminoma	35	34	0	100%	96.2%
Endodermal sinus tumor	31	26	2	84.1%	84.1%
Immature teratoma	63	57	3	92.0%	92.0%
Embryonal carcinoma	2	1	–	1/2	–
Mixed germ cell tumor	13	10	1	76.9%	76.9%
Malignant struma	1	1	–	1/1	–

Table 3. — *Histological types of recurrent patients and survival*.

Histological types	Number	Survival	Decreased	Lost in follow-up
Immature teratoma	11	9	1	1
Dysgerminoma	4	4	0	0
Endodermal sinus tumor	5	1	3	1
Embryonal carcinoma	1	0	1	0
Malignant struma	1	1	0	0
Mixed germ cell tumor	1	0	1	0

Table 4. — *Treatment schedules for recurrent cases and survival*.

		Number	Survival	Decreased	Lost to follow-up
Surgery		14	11	3	
Chemotherapy schedule	without	3	3	0	0
	BEP	7	3	2	2
	PVB	3	2	1	0
	VAC	1	1	0	0
	IVP	4	3	1	0
	EADM+NVB	1	1	0	0
	TAXOL+LOP or IFO	3	1	2	0
	others	1	1	0	0

Menstruation after treatments

Eighteen cases occurred before the menarche age at the start of the therapy, but presently, all these cases have had menarche at a normal age, and the menstrual period is regular. A total of 86 cases had menoschesis during chemotherapy and recovered normally within three to six months after completion of the chemotherapy. The other patients had their regular menses during the chemotherapy.

Pregnancy and offspring

Of the 129 survival cases, 18 cases had conceived before the therapy, and 50 cases were single. Of the 61 married cases, 42 gravidities in 41 women were recorded, seven of whom had induced abortions, 35 underwent pregnancies, and one gave birth twice. All infants were in good health. The oldest is now 18 years old, and the youngest one year old. For the conceiving patients, 15 cases suffered from dysgerminoma, 12 immature teratoma, six endodermal sinus tumor, and one mixed germ cell tumor. The interval between the chemotherapy and pregnancy is within the range of six months to 18 years.

Discussion

MOGCT is a highly malignant disease. Most cases before the 1970s were treated with bilateral salpingo-oophorectomy and hysterectomy to obtain a radical cure. No effective chemotherapy was available during that period, and only treatments with adjuvant radiological therapy and alkyl agent single-drug chemotherapy were available. The majority of the patients during this period died after recurrence even during the early stages of the disease. According to reports, the survival rate of MOGCT before the 1970s was only 13% to 22%. This phenomenon indicated that the removal of the normal uterus and contralateral ovary could not improve the prognosis. The effective combination chemotherapy for MOGCT that was introduced in the 1980s, especially with the application of PVB and BEP regimens containing platinum, dramatically improved the survival rate [1-4]. The survival rates reached 87% to 100% for any type of tumor, despite the high malignancy of endodermal sinus tumor and embryonal carcinoma. Weinberg *et al*. [5] reported five-year overall survival rates of 100% for MOGCT cases. The overall five-year survival rate in the current study was 90.3%, whereas the ten-year survival rate was 89.2%. Our study showed that MOGCTs are very sensitive to chemotherapy signifying that chemotherapy is valuable in the treatment of MOGCT. No statistical significance for the five-year survival rates between the different chemotherapy regimens and chemotherapy courses was found. Single-drug and ≤ 3 courses of chemotherapy may be used in cases with dysgerminoma [6, 7].

Although the current management of MOGCT emphasized comprehensive staging in the initial operation, which consists of a unilateral salpingo-oophorectomy, omentectomy, appendectomy, multiple-punch biopsy of peritoneum, and ablation of enlarged lymph nodes, some of the patients might have been upstaged to Stage III secondary to omental and peritoneal micrometastasis, or retroperitoneal lymph node metastasis. However, this kind of tumor showed high sensitivity to chemotherapy and was reported to provide long-term survival for a vast majority of patients. Several patients with large residual disease could obtain persistent relief from effective chemotherapy. Chemotherapy might cure micrometastasis. Whether this treatment could diminish the extent of surgery and could be administered alone in the case of chorioepithelioma or lymphoma remains unresolved. Several articles have reported no significant difference in the prognosis of normally staged patients compared with incompletely staged patients [8-13]. In the current study, no difference in the survival rates between normal-staged patients and incompletely staged patients was found. Eleven patients in the group, including cases of immature teratoma, dysgerminoma, and mixed germ cell tumor were treated with unilateral ovarian cystectomy or bilateral malignant MOGCT was treated with unilateral salpingo-oophorectomy and contralateral ovarian cystectomy; all patients had disease-free survival. No significant influence in the prognosis was found whether an entire staging in the initial surgery following the application of standardized chemotherapy and dose was performed. The most essential operation should be unilateral salpingo-oophorectomy. Although Lai *et al*. [8] noted in their article that bilateral malignant disease contained within the normal ovarian tissue might be treated with cystectomy – our study has indicated that the 11 cases treated with cystectomy achieved a disease-free survival – a recommendation for cystectomy of unilateral tumors of MOGCT still cannot be made at present, particularly for high-grade malignant tumors, such as endodermal sinus tumor, embryonal carcinoma, and mixed germ cell tumor. Whether several low-grade MOGCTs containing immature teratoma and dysgerminoma could be treated with cystectomy remains to be further demonstrated. Beiner *et al*. [10] reported on cystectomy for immature teratoma of the ovary with no observed recurrence.

The combination of surgical resection and primary systemic chemotherapy cured the majority of women affected with MOGCT, and only a small number of patients relapsed. No unified recognition with the treatment of recurrent patients was established. Long-time survivors after relapse were demonstrated to be less than 5%. Lai *et al*. [8] reported five recurrent cases undertaking secondary cytoreduction that had completely no residual or less than 1 cm residual disease. Among these patients, four cases obtained disease-free survival, and one case was alive with tumor. The other six patients that had residual disease larger than 2 cm or even without secondary cytoreduction died from the disease. Of the 23 relapsed cases in our group the survival rate was 78.6%. As for the other nine cases that were treated without secondary surgery, the survival rate was 44.8%. A significant difference was determined between the survival rates ($p < 0.05$). The total effective rates have varied widely in the reports on salvage chemotherapy of recurrent MOGCT patients. Kollmannsberger *et al*. [14] reported a salvage

chemotherapy schedule using gemcitabine 1g/M² IV D1, 8 + oxaliplatin 130 mg/M² IV D1 to treat incurable male malignant germ cell tumors with a total effective rate of 46%. Miki and colleagues [15] reported a group of patients with incurable GCT treated with CPT-11 100 mg/M² to 150 mg/M² IV D1, 15,+ DDP 20 mg/M² IV D1-5, a combination chemotherapy with an effective rate of more than 50%. (Among the 20 patients, 2 cases of CR and 7 cases of PR were identified). Giorgi *et al*. [16] reported another salvage chemotherapy combined with gemcitabine 800 mg/M² + Taxol 70 mg/M² + oxaliplatin 50 mg/M² IV D1, 8, 15, repeated at every 4-week interval. Of nine platinum-resistant patients with GCT who adopted the chemotherapy plan, only one case had partial response, one case remained stable disease, and seven cases had progressive disease. In the current study, the chemotherapy regimens used BEP, PVB, and IVP for the recurrent patients. The effective rates were 42.9%, 66.7%, and 75%, respectively, which are apparently relatively high- probably because some of these patients had not been treated previously with a standard chemotherapy plan.

Large-scale case series and long-term studies are expected to determine the optimal treatment with regard to recurrent MOGCT.

In the long-term VAC regimen chemotherapy study by Gershenson *et al*. [12], the final irregular menstruation rate was 8%, slightly higher than that of the normal females (5%), and the infertility rate was 10%, similar to that of the normal females. In the current study group, 86 cases had irregular menstrual periods or menolipsis during chemotherapy, but recovered after chemotherapy. A total of 18 cases occurred before the menarche age at the start of the therapy, but presently, all these cases have had menarche at a normal age, and a regular menstrual period. Except for the cases who had conceived or not reached the marrying age, 42 gravidities in 41 women, 35 pregnancies, and seven induced abortions were recorded after the end of chemotherapy. Drugs, especially alkylating agents, have been reported to induce follicle dysfunction, and the prepubertal ovary is more resistant to the adverse effects of chemotherapy. At present, the non-alkylating drugs combined with a short-term regimen have no obvious influence on ovarian function. Successful pregnancies after treatment with chemotherapy have been well documented in other types of malignancies, including choriocarcinoma and lymphoma. The chemotherapy results for MOGCT in recent years have proved not to increase the natural abortion rate and offspring abnormality rate [17-19]. In the present study, all 35 infants were in good health, whereas the other pregnancies were stopped by induced abortion. Survival is apparently not affected by conservative surgery. Fertility is excellent after a fertility-sparing surgery and chemotherapy in patients with ovarian germ cell tumors.

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