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Original Article

A prospective clinical trial of the treatment model of malignant ovarian germ cell tumor

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Abstract: Objectives: To evaluate the therapeutic value of treatment model of conservative surgery in combination with chemotherapy for malignant ovarian germ cell tumor (MOGCT). Methods: A multi-center, prospective clinical trial was conducted on patients with MOGCT confirmed by intraoperative frozen section diagnosis during 2009 and 2013. These patients were randomly allocated into conservative surgery group (n=33) or extensive surgery group (n=36), and received either conservative or extensive surgery followed by chemotherapy. The health economics, safety, rate of regular menstruation and pregnancy, and efficacy of both models were compared. Results: (1) Health economics: The average initial hospital stays and hospital costs in conservative surgery group was significantly lower compared with extensive surgery group (P<0.01). (2) Safety: the average length of operation, amount of bleeding, recovery time of intestinal tract, and rate of operative complications in conservative surgery group was significantly lower compared with extensive surgery group (P<0.01). No significant difference in average time of indwelling urinary catheter was observed between the two groups (P>0.05). (3) The postoperative rate of both regular menstruation and pregnancy in conservative surgery group was similar to that in extensive surgery group (P>0.05). (4) Efficacy: no significant difference in the 3-year and 5-year accumulate survival rate or accumulate progressive-free survival rate was detected between the two groups (P>0.05). Conclusions: The treatment model of conservative surgery can reduce the cost of surgery and ensure the safety, and improve the quality of patients' life without affecting the prognosis of MOGCT.

Keywords: Malignant ovarian germ cell tumor, conservative surgery, treatment model, prospective, clinical trial

Introduction

Malignant ovarian germ cell tumors (MOGCT) are rapidly growing cancerous neoplasms that are derived from primordial germ cells of the ovary. MOGCTs represent 2-3% of all malignant ovarian tumors, with the highest rates in women between 15-30 years old [1]. With great advances in chemotherapy and surgery in recent years, the 5-year survival rate of MOGCT has increased from 10% to more than 90% [2], resulting in a markedly higher cure rate of the disease. The standard regimen for MOGCT treatment has become a combination of chemotherapy agents plus surgery [3]. According to traditional treatment and guidelines from National Comprehensive Cancer Network (NCCN), complete surgical staging is advocated, and fertility function-retaining surgery is a basic principle for the treatment of MOGCT, without limitation of surgical stages [4].

Conservative surgery for MOGCT consists of unilateral salpingo-oopherectomy, omentectomy, surgical staging, and debulking of metastases [5]. A number of studies have shown that conservative surgery in MOGCT patients is successful in the preservation of fertility [6-8], which has been a treatment option for patients with ovarian tumor who desire to preserve fertility. Nevertheless, it has been a hot debate whether the treatment model of conservative surgery in combination of chemotherapy is effective and whether it can improve the quality of life in patients with MOGCT. In this multi-center, prospective clinical trial, the treatment model of conservative surgery in combination with chemotherapy was compared to extensive

Table 1. Summary of information on participants in conservative and extensive surgery groups

		Conservative group (n=33)	Extensive group (n=36)	P
Age (mean (range))		27.12±14.87 years (7-73)	26.08±6.58 years (17-46)	>0.05
Dysgerminoma (n (%))		8 (24.2%)	5 (13.9%)	>0.05
Yolk sac tumor (n (%))		10 (30.3%)	12 (33.3%)	
Immature ovary teratoma (n (%))		15 (45.5%)	15 (41.7%)	
	G1	5 (15.2%)	7 (19.4%)	
	G2	6 (18.2%)	4 (11.1%)	
	G3	4 (12.1%)	4 (11.1%)	
Embryonal carcinoma (n (%))		0	1 (2.8%)	
Mixed germinoma (n (%))		0	3 (8.3%)	
Abnormal tumor marker prior to treatment (n (%))		29 (87.9%)	30 (83.3%)	>0.05
Diameter of tumor (n (%))	>20 cm	4 (12.1%)	9 (25%)	>0.05
	10-20 cm	19 (57.6%)	15 (41.7%)	>0.05
	<10 cm	10 (30.3%)	12 (33.3%)	>0.05

surgery followed by chemotherapy from the perspectives of health economics, safety, postoperative rate of regular menstruation and pregnancy, and efficacy in order to evaluate the feasibility of treatment model of conservative surgery in combination with chemotherapy in patients with MOGCT.

Material and methods

Participants

From 1st January 2009 to 31st December 2012, participants with MOGCT from the following four hospitals were screened for eligibility: No. 4th Hospital Affiliated to Guangxi Medical University, No. 1st Hospital Affiliated to Guangxi University of Science and Technology, No. 2nd Hospital Affiliated to Guangxi University of Science and Technology, and Liuzhou Hospital of Traditional Chinese Medicine. Inclusion criteria were as follows: 1. Patients with MOGCT confirmed by intra-operative frozen section diagnosis; 2. Patients with initial treatment; 3. Could tolerate extensive surgery; 4. Signed informed consent and adhered to the treatment and follow-up; 5. Without any contraindications to chemotherapy and could tolerate chemotherapy after surgery. A patient was excluded if he had malignant mixed tumor.

Interventions

Participants in conservative surgery group underwent laparotomy excision of accessories on the affected side, and/or offside ovary biopsy, and/or biopsy of para-aortic lymph node or pelvic lymph node, and excision of omentum majus. Patients in extensive surgery group underwent laparotomy complete surgical staging, and the scope of surgery included excision of accessories on the affected side, excision of omentum majus, excision of retroperitoneal lymph node, and/or excision of appendix and/or whole uterus, and excision of offside accessories. Except for immature teratoma in stage IA G1, all participants received 3-6 courses of BEP chemotherapy regimen (bleomycin + etoposide + cis-platinum) after the surgery. Two participants developed pulmonary ventilation function after receiving BEP chemotherapy regimen, and shifted immediately to VAC chemotherapy regimen (vincristine + actinomycin D + cyclophosphamide).

Follow-up and measurement

All participants were followed up till 31st December 2014. The follow up data were entered into the gynecological oncology database we developed for this study. Any participant who did not visit the hospital on schedule was subjected to a telephone interview. If any participant could not be reached for three times, her affiliation or local police station would be contacted for information. If information could not be obtained through any of these methods, the participant would be defined as loss of follow up. All participants were requested to visit the hospital once each month during the first year after their surgery, once every 3 months during the second year, once every 6 months during the third year, and once every year afterward. The criteria of relapse were defined according to the NCCN Guideline of ovarian cancer.

Table 2. Comparison of health economics outcomes of MOGC patients in the two groups

	Conservative surgery group (n=33)	Extensive surgery group (n=36)	*t*	*P*
Initial hospital stay (day)	16.27±2.95	19.91±3.78	-4.05	<0.001
Initial hospital cost (RMB)	16603.11±4312.38	24701.58±2957.77	-7.14	<0.001

Table 3. Comparison of safety factors of MOGCT participants in the two groups

	Conservative Surgery Group (n=33)	Extensive Surgery Group (n=36)	t	P
Length of operation (min)	107.63±25.57 (60~140)	265.61±80.66 (70~390)	-10.55	<0.001
Amount of bleeding (ml)	65.83±56.31 (20~200)	409.70±215.50 (10~800)	-8.76	<0.001
Recovery time of intestinal tract (h)	51.00±14.70 (24~72)	75.64±12.18 (48~96)	-6.91	<0.001
Time of indwelling urinary catheter (h)	38.00±15.69 (24~72)	45.09±11.63 (24~72)	-1.87	0.07

Table 4. Menstruation and pregnancy of MOGCT participants in two groups

	Menstruation		Pregnancy	
	Regular	Irregular	Yes	No
Conservative surgery group	21 (77.78%)	6 (22.22%)	5 (62.50%)	3 (37.50%)
Extensive surgery group	17 (77.27%)	5 (22.73%)	6 (66.67%)	3 (33.33%)

Statistical analysis

Data were analyzed by SPSS16.0 (SPSS Inc., Chicago, IL, USA). Numeration data was analyzed by χ^2 test or Fisher's exact test and measurement data was analyzed by t test. Year survival rate was calculated by the Life Tables. The survival analysis was estimated by Kaplan-Meier. *P* values smaller than 0.05 were considered statistically significant.

Results

General information

A total of 69 participants were included in this study between 1st January 2009 and 31st December 2012. These patients were allocated into conservative surgery group (n=33) or extensive surgery group (n=36) either mandatorily or according to their individual willingness. As shown in **Table 1**, there was no statistical difference in age, pathological pattern, pathological grading, tumor marker and diameter of tumor between the two groups (P>0.05). The stages of participants in conservative surgery group were unclear since there was no staging surgery. In the extensive surgery group, there were 18 participants in stage I, 3 in stage II, 13 in stage III, and 2 in stage IV.

Till 31st December 2014, there were 4 deaths out of 69 participants. The remaining 63 were followed up for a median period of 48 months (range: 16-72 months). Data classified into censored data. Two patients were lost to follow up.

Health economics outcomes

All participants received the first course of chemotherapy during their initial hospital stay. As shown in **Table 2**, the initial hospital stay in conservative surgery group ranged from 10 to 21 days with an average of 16.27±2.95 days, resulting in an initial average hospital cost of 16603.11±4312.38 RMB (range: 10679.98-22908.57 RMB). The initial average hospital stay in extensive surgery group was 19.91±3.78 days (range: 14-27 days) with an initial average hospital cost of 24701.58±2957.77 RMB (range: 18569.65-29061.23 RMB). No significant difference in either the initial hospital stay or hospital cost was observed between the two groups (P<0.01).

Safety

As shown in **Table 3**, the average length of operation, amount of bleeding and recovery time of intestinal tract in conservative surgery group were significantly lower compared with extensive surgery group (P<0.01). The average time of indwelling urinary catheter in conservative surgery group was slightly shorter than that of extensive surgery group; but there was no significant difference between two groups (P> 0.05).

Operative complications were reported in 4 patients (4/33, 12.12%) in conservative sur-

Table 5. Summary of the 4 cases of death

Order	Group	Age (year)	Chemotherapy regimen	Course	Interval of relapse (month)	Site of relapse	Causes of death	Survival time (month)
1	Conservative	15	BEP	3rd	14	Multiple metastasis	Advanced tumor	18
2	Conservative	13	BEP	4th	30	Pelvic cavity	Advanced tumor	48
3	Extensive	19	BEP	3rd	7	Pelvic cavity	Advanced tumor	24
4	Conservative	17	BEP	3rd	5	Pelvic cavity	Advanced tumor	16

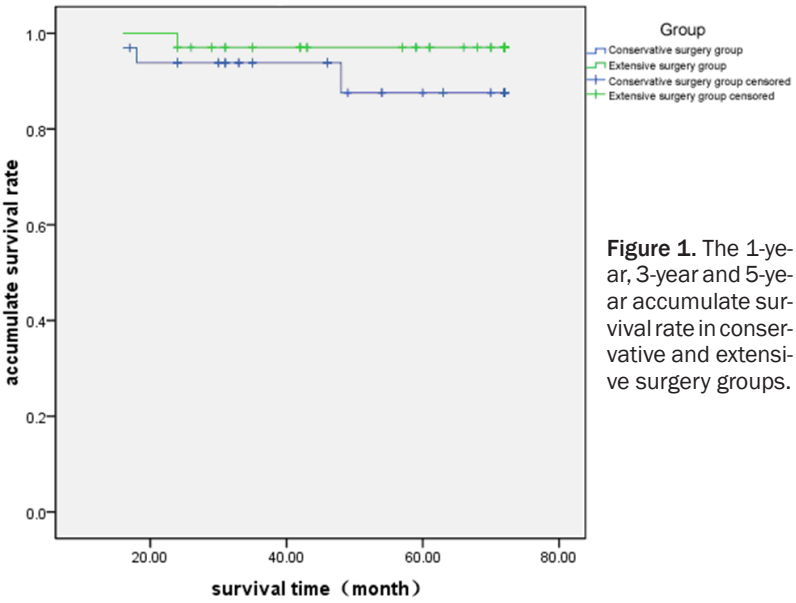

Figure 1. The 1-year, 3-year and 5-year accumulate survival rate in conservative and extensive surgery groups.

gery group including 3 cases of undesirable healing, and 1 case of retroperitoneal bleeding. In extensive surgery group, there were 17 cases of operative complications (17/36, 47.22%): 12 lymphocele in pelvic cavity, 2 ileus, 2 undesirable healing, and 1 intestinal adhesion. The overall rate of operative complications in conservative surgery group was significantly lower compared with extensive surgery group (χ^2= 10.02, P=0.002).

Postoperative rate of regular menstruation and pregnancy

Of the 69 participants, 5 did not experience menophania, and 15 were in menopause due to surgery (excision of uterus or bilateral accessories). The remaining participants stopped menstruation during the first 1-3 courses of chemotherapy, and restored menstruation in 1 month to 1 year after chemotherapy. Among them, 38 participants had regular menstruation and 11 had irregular menstruation. The rate of regular menstruation in conservative surgery group was 77.78% (21/27), which was similar to that of extensive surgery group (77.27%, 17/22; χ^2= 0.002, P=0.97; **Table 4**).

A total of 17 out of 69 patients desired pregnancy. Till 31st December 2014, 11 were pregnant, and 8 of them delivered baby. The pregnancy rate in conservative surgery group (62.50% (5/8)) was comparable to that in extensive surgery group (66.67% (6/9), χ^2=0.03, P=0.86; **Table 4**). The 20 participants who did not desire pregnancy included 5 juveniles, 12 without sex history, and 15 without fertility function (excision of uterus or bilateral accessories).

Survival analysis

Till 31st December 2014, of the 69 participants, 62 cases of survival without any tumor, 1 relapse, 4 deaths and 2 loss of follow up. As shown in **Table 5**, the 1-year, 3-year and 5-year accumulate survival rate of all participants was 97%, 95% and 92%, respectively. In conservative surgery group, there were 29 survivals without any tumor, 1 relapse, and 3 deaths, and the 1-year, 3-year and 5-year accumulate survival rate was 94%, 94% and 87%, respectively (**Figure 1**). In extensive surgery group, there were 33 survivals without any tumor, one death and 2 loss of follow up, and the 1-year, 3-year and 5-year accumulate survival rate was 100%, 97% and 97%, respectively (**Figures 1** and **2**). No significant differences in the accumulate survival rates was detected between the two groups (χ^2=1.26, P=0.26).

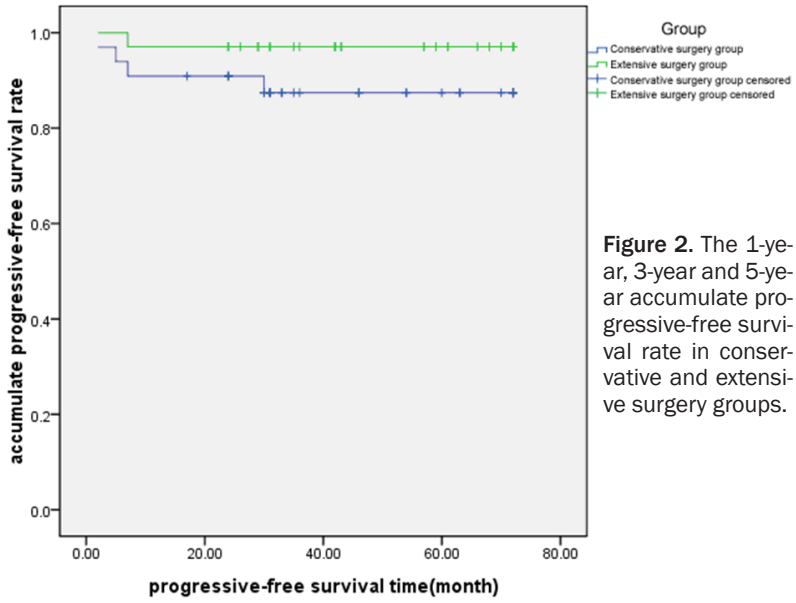

Figure 2. The 1-year, 3-year and 5-year accumulate progressive-free survival rate in conservative and extensive surgery groups.

The 1-year, 3-year and 5-year accumulate progressive-free survival rate of all participants was 94%, 92% and 92%, respectively. In conservative surgery group, the 1-year, 3-year and 5-year accumulate progressive-free survival rate was 91%, 87% and 87%, respectively (**Figure 2**). In extensive surgery group, the 1-year, 3-year and 5-year accumulate progressive-free survival rate was all 97% (**Figure 2**). There was no statistical difference in accumulate progressive-free survival rates between the two groups (χ^2=2.03, P=0.15).

Discussion

Studies have found that the majority of MOGCTs appear in one side, and rarely relapse in offside ovary and uterus. In addition, since MOGCT patients were sensitive to both BEP (bleomycin + etoposide + cis-platinum) and BVP (bleomycin + vincristine + cis-platinum) chemotherapy regimens, and the excision of offside ovary and uterus is unable to improve the prognosis of MOGCT patients, fertility function-retaining surgery is a basic principle for the treatment of MOGCT, without limitation of stages [4]. Traditional view and guidelines issued by NCCN advocate complete surgical staging. It is required that for young patients who desired pregnancy, regardless of the stages, as long as offside ovary and uterus are not affected by tumor, complete surgical staging should be conducted to retain their fertility function, which means only accessory of affected side will be excised and apply complete surgical staging at the same time [9]. For patients who are not desired pregnancy, in principle the complete surgical staging should be conducted according to requirements of epithelial ovarian cancer. It is well known that complete surgical staging is difficult, because the retroperitoneal lymph nody excision requires high surgical skills, and only physicians specialized in gynecological oncology with level four surgery qualification are qualified enough to conduct this surgery. The surgery is high-risk, slow to recover, has big surgical wound and high rate of postoperative complications. Actually, the majority of patients were nonage and young women desired pregnancy. Therefore, on the premise that the cure rate is not affected, gynecology oncologists is paying close attention to reducing scope of surgery, reducing surgical wound and improving quality of patients' life. Currently, the treatment protocol of reducing the scope of surgery is still controversial.

Meanwhile, most current studies demonstrated that postoperative chemotherapy is an independent factor of the relapse and prognosis of MOGCT patients, and there is no relationship with surgical procedures. Ding et al. have conducted a retrospective analysis on 111 MOGCT patients [10], and found that chemotherapy course is an independent factor of the prognosis of MOGCT patients. In another retrospective analysis by Han et al. [11], it has been found whether patients receive standard chemotherapy after surgery is an independent factor of the prognosis, and there is no statistical difference between the survival rate of conservative surgery group and extensive surgery group. In a study on 40 MOGCT patients [12], it has been shown that all 3 participants who relapsed had complete surgical staging and the relapse rate and survival rate was not limited by surgical stages. Wei et al. have also demonstrated that complete surgical staging is not an independent factor for the prognosis [13]. Mahdi et al. [14] reported that 9% of MOGCT patients in

clinical stage I had affected lymph glands, and 24% of clinical stage II patients had affected lymph glands, indicating their stages were increased to III after surgery. However, they also found that if the affected site was limited in ovary of early stage MOGCT, neither the excision of retroperitoneal lymph node nor lymphatic metastasis was the independent factor for prognosis. Therefore, complete surgical staging might be crucial for clear staging, which can identify potential end stage patients and introduce further chemotherapy, but is not important to improve the prognosis of MOGCT patients. Currently, there are quite few studies on surgical treatment for MOGCT due to the rareness of the disease. To our best knowledge, the current study is the first multi-centered, randomized controlled trial of surgery for the treatment of MOGCT.

In this multi-center, prospective clinical trial, we failed to conduct randomization due to ethical issues of surgical procedures. The findings of this study demonstrated that the initial hospital stay, initial hospital cost, length of surgery, amount of bleeding and recovery time of intestinal tract in conservative surgery group was significantly lower compared with extensive surgery group. The rate of operative complications in conservative surgery group was also significantly lower than that of extensive surgery group. These results indicated that conservative surgery group was superior to the extensive surgery group in health economics and surgical safety.

Further, we compared the accumulate survival rate and progressive-free survival rate in the two groups and detected no difference in either rate despite that the efficacy of conservative surgery group (3 deaths and 1 relapse) appeared to be lower compared with extensive surgery group (1 death). Two of the 3 deaths in conservative surgery group pre-terminate the treatment due to some reasons, which probably resulted in the higher death rate. Our result was inconsistent with a previous study on 26 patients with ovarian dysgerminoma in IA stage [15], in which the tumor was controlled by extensive surgery in 11.5% of patients who had previously underwent conservative surgery but had a relapse.

In conclusion, the treatment model of conservative surgery in combination with chemotherapy for the treatment of MOGCT was superior to the model of extensive surgery followed by chemotherapy in the perspective of health economics and surgical safety. There was no statistical differences in the accumulate survival rate and progressive-free survival rate between the two treatment models. The treatment model of conservative surgery in combination with chemotherapy can reduce the scope of surgery, decrease the surgical wound, and improve the quality of patients' life without decreasing the prognosis of MOGCT. However, the current study is limited by the small sample size due to the low incidence of MOGCT. Further trials with larger sample sizes are needed to validate our findings. Moreover, it is worth noting that for patients in later stages, it is still suggested to conduct surgical staging in order to guide postoperative chemotherapy.

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Disclosure of conflict of interest

None.

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