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Original Article

Malignant ovarian germ cell tumors in adolescents: 18 years of experience at a single institution

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Abstract: Malignant ovarian germ cell tumors (MOGCTs) in adolescents are rare. Although fertility-sparing surgery for such patients is suggested unequivocally, the necessity of staging surgery remains the subject of intense debate. Here, we evaluate the role of staging surgery in adolescents affected by MOGCTs and review the outcomes of these patients. We performed a retrospective study of patients aged 10-19 years who received surgery and were pathologically diagnosed with MOGCTs at OB/GYN Hospital of Fudan University between January 1997 and October 2014. Forty-two patients diagnosed with immature teratomas, dysgerminomas, endodermal sinus tumors and mixed germ cell tumors were included in this study. The majority (90.5%) of them were of apparent early-stage with lesion confined to the ovary grossly, and the majority (90.5%) received adjuvant chemotherapy. Although comprehensive staging protocols were followed in only a small number of patients (28.6%) in our cohort, the recurrence rate was low at 4.8%. Five-year overall survival and disease-free survival were 97.2% and 94.8%, respectively. Comprehensive staging or individual factors such as peritoneal washings cytology, lymph nodes dissection and omentectomy were not independent risk factors for disease-free survival (DFS). Positive peritoneal washing cytology or lymph nodes were not correlated with recurrence. Our findings show that there is a good prognosis for adolescents affected by MOGCTs and for adolescent patients receiving adjuvant chemotherapy, staging procedures may not provide any additional benefits.

Keywords: Malignant ovarian germ cell tumors, adolescents, survival, comprehensive staging, chemotherapy, fertility-sparing

Introduction

Malignant ovarian germ cell tumors (MOGCTs) are rare and account for around 5% of all ovarian malignancies [1]. These tumors consist of several histological variations and exhibit several grades of differentiation. Dysgerminomas, immature teratomas and endodermal sinus tumors (EST) are the most common types and comprise over 90% of MOGCTs [2]. Approximately 70% of patients are diagnosed during early stages [3].

MOGCTs predominate in pediatric and adolescent patients, unlike epithelial ovarian carcinomas which are more commonly seen in women of more than 40 years of age. Most of the patients afflicted with MOGCTs are nulliparous. Therefore, therapeutic modalities should be adjusted accordingly as fertility-sparing surgery is vital in the management of such cases. The National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) both suggest in their guidelines that fertility-sparing can be considered for patients with MOGCTs, even in advanced stages, on the premise that comprehensive staging procedures are also implemented at the same time [4].

The NCCN recommended that comprehensive or complete staging procedures for MOGCTs should be carried out in a protocol that is the same as the procedures used for treating epithelial ovarian cancer. Specifically, the following steps were suggested: (1) Collection of ascites or washings from the peritoneal cavity, (2) Careful examination of the peritoneum, biopsy

Table 1. Demographic information of the study population

Characteristics	No.	%
Stage		
Apparent stage I	38	90.5
Apparent stage II	1	2.4
FIGO Stage III	3	7.1
Histological types		
Immature Teratoma	16	38.1
Grade I	6	
Grade II	7	
Grade III	3	
Dysgerminoma	12	28.6
Endodermal sinus tumor	8	19.0
Mixed germ cell tumor	6	14.3
Involved ovary		
Left	15	35.7
Right	21	52.4
Both	5	11.9
Maximum diameter of the mass, mm		
≤50	1	2.4
51-250	38	90.5
251-300	3	7.1
Laparotomy		
Yes	36	85.7
No	6	14.3
Fertility-sparing surgery		
Yes	30	71.4
No	28.6	
Complete staging surgery		
Yes	12	28.6
No	30	71.4
Chemotherapy after surgery		
Yes	38	90.5
BEP	25	
PVB	13	
No	4	9.5

Abbreviations: BEP: bleomycin, etoposide, and cisplatin; PVB: cisplatin, vincristine and bleomycin.

and excision of any nodules, (3) Infra-colic omentectomy, and (4) Sampling or excision of the retro-peritoneum lymph nodes [5]. Comprehensive staging procedures are believed by some to be very important, as staging has been associated with lower recurrence rates [6]. However, a different point of view was put forward by the Children's Oncology Group (COG). Based on their own results, COG suggested that when practicing fertility-sparing surgery for children and adolescents, lymph node dissection, biopsy of the peritoneal surfaces, and omentectomy are not indispensable if grossly absent of lesions. Omitting these steps had no obvious adverse impact upon survival [5]. Even if abnormalities of the omentum or lymph nodes was suspected, biopsy is preferred instead of total excision [7].

However, apart from the guidance from COG published in 2004, there have been very few studies relating to the role of staging surgery for adolescent patients in the past decade. Three studies concluded that comprehensive staging surgery had no significant impact upon prognosis for MOGCT patients [8-10]. However, these studies included both adolescents and adults in their survey population; and one article was written in a non-English language. More importantly, a common consensus has yet not to be reached on this topic, as the NCCN still approves of comprehensive staging surgery in their latest guidelines. We therefore conducted a retrospective study in order to review the treatment, survival, and more importantly, the role of staging surgery for adolescent patients diagnosed with MOGCTs at our hospital.

Patients and methods

Forty-two patients aged 10-19 years underwent surgery and were pathologically diagnosed with MOGCTs between January 1997 and October 2014 at the OB/GYN Hospital of Fudan University, one of the largest tertiary gynecological centers in China. No patient younger than 10 years of age is treated in this hospital as they are routinely transferred to specialized pediatric centers in China. Patient data was collected retrospectively from hospital medical records, including age at diagnosis, chief complaint, ultrasonogram (USG) findings, serum tumor markers such as cancer antigen-125 (CA-125), alpha-fetal protein (AFP), and carcinoembryonic antigen (CEA) before and after surgery if available, surgical details, pathological reports, adjuvant chemotherapy, and clinical outcomes such as recurrence, death or survival.

All histological slides were reviewed by two independent pathologists. Histological type was defined according to established classifications by the World Health Organization (WHO). Stage was verified according to the

International Federation of Gynecology and Obstetrics (FIGO) classification of ovarian tumors (2015 version). Immature teratomas were graded according to the criteria developed by Norris *et al* [11].

Comprehensive staging surgery is defined earlier in this article, while fertility-sparing surgery is defined as preservation of the uterus and at least part of an ovary. Radical surgery is defined as bilateral salpingo-oophorectomy (BSO), or unilateral salpingo-oophorectomy (USO) when the contralateral ovary is congenitally dysgenesis, with or without hysterectomy (TAH).

Patients were followed-up by periodic clinical, serological, and USG examinations via the outpatient service. A telephone interview was also performed to ascertain the latest status. Disease-free survival (DFS) period and overall survival (OS) periods were defined as time intervals from the date of primary surgery to recurrence or last disease-free visit (months), and to death or last visit (months), respectively. Kaplan-Meier analysis was utilized and univariate analysis was completed with the log-rank test. Fisher's exact test was used to evaluate for correlation between recurrence and peritoneal fluid or lymph node positivity. Statistical analysis was performed by SPSS software (version 16.0, Chicago, IL, USA). A *p*-value <0.05 was defined as being statistically significant. The study was approved by the Hospital Ethics Committee.

Results

Between January 1997 and October 2014, 42 adolescent patients were pathologically diagnosed with MOGCTs; their demographic and clinico-pathological information is provided in **Table 1**. The median age was 16 years and none of our patients was sexually active. The most common histology was an immature teratoma (38.1%), followed by dysgerminoma (28.6%), EST (19.0%) and mixed germ cell tumor (14.3%). There were three dysgerminoma cases presented with gonadoblastoma in the same tumor. Twenty-two cases (52.4%) presented with a tumor in the right ovary while 15 cases (35.7%) presented a tumor in the left ovary. Both ovaries were involved in five patients (11.9%). However, although considered as unilaterally involved, one patient with a dysgeminoma had a concurrent gonadoblastoma in the contralateral ovary; in another two patients, the contralateral ovary was congenitally dysgenesis. The most common symptoms were (in descending order): pelvic mass (38.1%), pelvic pain (28.6%), abdominal distention (23.8%), dysmenorrhea (9.5%), absence of menarche (9.5%), and fever (7.1%). Four patients consulted clinicians due to the absence of menarche at the age of 16 years. Three patients complaining of pelvic pain were subsequently shown to have ovarian tumor torsion.

All patients were given a USG examination before surgery to estimate the size and gross nature of the tumor (e.g., solid, cystic, or complex). Thirty-seven (88.1%) cases were reported as complex while the others (11.9%) were solid. Maximum mass diameter ranged from 4.1 to 30 cm, with most (90.5%) measuring between 5 to 25 cm. There was no significant difference in tumor size when compared between different histological types ($p>0.05$). There were 22/33 (66.7%), 8/20 (40%), 0/8, 3/22 (13.6%) and 21/28 (75.0%) patients presenting with elevation of CA-125 (>35 U/ml), CA-199 (>35 U/ml), CA-153 (>35 U/ml), CEA (>5 ng/ml), and AFP (>10 ng/ml), respectively. Elevation of CA-125 was present in all the involved pathological types identified of our study. This value was positively correlated with stage ($p<0.05$). Elevation of CA-199 was neither correlated with stage nor type of tumor, nor CA-125 value. All patients exhibiting tumors containing an EST component showed elevation in AFP. To our surprise, 10 out of 12 patients with immature teratomas also showed elevation; and the AFP level positively correlated with tumor grade ($p<0.05$). After surgery, there was a significant decline in these tumor biomarkers in the majority of patients.

Laparotomy was carried out in 36 (85.7%) patients, while laparoscopy was performed in 6 (14.3%) patients. Most patients (30/42, 71.4%) received fertility-sparing surgery. Twelve patients (28.6%) did not receive fertility-sparing surgery: the reasons for this included advanced stage of disease in three patients, the involvement of both ovaries in five patients, tumor or dysgenesis of the contralateral ovary in three patients, and due to a decision made by the guardian of one patient.

There were 38 patients (90.5%) with lesions confined to the ovary (or ovaries) grossly. Nine patients were comprehensively staged as FIGO

Table 2. Univariate analysis: Chi-square and *p*-value for various factors (*log*-rank test) for disease-free survival

Factor	Chi-square	*p*
Histological type	3.149	0.533
AFP level higher than 500 ng/ml	2.783	0.095
Laterality	1.703	0.427
Fertility-preserving	0.869	0.351
Comprehensive staging surgery	0.583	0.445
Peritoneal fluid cytology	0.857	0.355
Omentectomy	0.000	1.000
Lymph node dissection	0.036	0.849
Chemotherapy regimen	1.214	0.270
More than 3 chemotherapy cycles	1.476	0.224

stage IA/IB, and three patients were confirmed to be FIGO stage I although incompletely staged because lymph nodes and omentum were both negative. The precise stage for the remaining 26 patients could not be determined due to the absence of lymph node dissection, or omentectomy, or both. There was one patient diagnosed with apparent stage II disease according to surgical findings with involvement of the pelvic peritoneum. Three patients had peritoneum lesions outside the pelvis were comprehensively staged as FIGO stage III disease. In total, comprehensive staging procedures were followed in 12 (28.6%) patients. Peritoneal washing cytology, omentectomy and lymph node dissection were carried out in 22, 21 and 19 patients, respectively. There were 17 patients in whom none of the above staging items was implemented. Two patients (one of apparent early-stage and one of FIGO stage III disease) were positive for peritoneal washing cytology. One patient (of FIGO stage III disease) was positive for lymph node involvement. No residual disease was left macroscopically in any of the patients.

Thirty-eight (90.5%) patients received postoperative chemotherapy for a median of 6 cycles (range, 1 to 8). A BEP (bleomycin, etoposide, and cisplatin) regimen was adopted in 25 patients while a PVB regimen (vincristine, carboplatin, and bleomycin) was adopted in 13 patients.

During the median follow-up of 61.3 months (range, 5 to 207 months), 2 patients were lost during follow-up, and 2 patients developed recurrences. One 13-year-old girl, with a 20 cm mass in the right ovary with an intact surface, died. Earlier, USO and contralateral ovary partial excision had been carried out in this patient. As incompletely staged, this patient was apparent stage I with a mixed germ cell tumor containing EST and dysgerminoma. Seven courses of PVB regimen were given following surgery. Twelve months after the initial surgery a 5 cm mass was found in the left pelvis by USG while CA-125 was 450 U/ml and AFP was 836 ng/ml. AFP continued increasing to 1898 ng/ml before secondary debulking surgery, and only slightly reduced to 1406 ng/ml post-operatively. The patient survived for less than 6 months thereafter and ultimately died.

The other recurrent case was a 16-year-old girl affected by a grade III immature teratoma in the right ovary. The CA-125 and AFP before surgery was 227.3 U/ml and >3000 ng/ml, respectively. We performed USO and comprehensive staging surgery and she was staged as FIGO stage IA. Six courses of BEP regimen were prescribed for this patient after surgery. After the third cycle both CA-125 and AFP fell to normal levels. However, after the sixth cycle (around four months after surgery), a small suspicious shadow was detected in Douglas' pouch on USG and MRI. Chemotherapy was resumed but the mass increased to more than 3 cm in diameter six months following primary surgery. A secondary debulking surgery was carried out. Pathology confirmed mature teratoma and neuronal tissue in Douglas' pouch and on the surface of the peritoneum. This patient survived without this disease during the 41-month follow-up thereafter.

Five-year OS and DFS for our patients cohort were 97.2% and 94.8%, respectively. None of the clinical factors such as histological type, laterality, fertility-sparing, comprehensive staging, peritoneal washings cytology, lymph node dissection, omentectomy, or types of chemotherapy regimen was shown to be an independent risk factor for DFS (**Table 2**). Further more, Fisher's exact test showed that the positivity of peritoneal washing cytology or lymph nodes was not correlated with recurrence. With regard to the reproductive outcomes, we report that among the 30 patients who received fertility-sparing surgery, 25 cases (83.3%) reported regular menses. One patient successfully gave birth to a full-term baby while the other patients were either unmarried or taking contraception during the follow-up period.

Table 3. Pediatric staging system for ovarian cancer by the Children's Oncology Group (COG)

Stage I	Limited to ovary (ovaries); peritoneal washings negative; tumor markers normal after appropriate half-life decline (AFP, 5 days; β-HCG, 16 hours).
Stage II	Microscopic residual disease or disease in lymph nodes <2 cm; peritoneal washings normal; tumor markers positive or negative.
Stage III	Gross residual disease or biopsy only; lymph nodes >2 cm; contiguous spread to other organs (omentum, intestine, bladder); peritoneal washings positive for malignant cells; markers negative or positive.
Stage IV	Metastatic disease, including liver.

Discussion

Malignant tumors of the ovary are rare in children and adolescents [12], representing approximately 1% of all childhood malignant tumors [13]. Most ovarian malignant tumors occurring during childhood are germ cell tumors [14]. USG is considered to be a highly valuable technique for detecting the mass and distinguishing between benign and malignant tumors, with solid nature considered a definite feature predicting malignancy [15]. However, it has been reported that cystic components are common in malignant ovarian tumors in childhood with an incidence of 57% [5]. Tumor markers are helpful but not always reliable for MOGCT screening. CA-125 levels were elevated in all of the histological types observed in our cohort and increased with stage. CA-199 was elevated in 40% of the patients but no correlation was found with stage. CA-153 and CEA seemed of limited importance as few patients showed elevation of these markers.

Elevated AFP levels usually suggest tumors containing an EST component. In our cohort, 10 out of 12 patients with an immature teratoma also showed AFP elevation and the values were positively correlated with tumor grade. The COG and Pediatric Oncology Group (POG) have reported that 29.5% to 31.5% patients diagnosed with immature teratomas were confirmed to have co-existing microscopic foci of EST, especially in grade III tumors. Furthermore, these organizations concluded that co-existing EST is the only valid risk factor for recurrence [16]. However, no concurrent microscopic foci of EST were reported in our study upon pathological examination. We speculate that a large mass volume may increase the difficulty in detecting tiny EST foci and more careful inspection should be executed. In fact, one of the two patients experiencing recurrence in our cohort was a patient with a grade III immature teratoma with markedly elevated AFP levels (>3000 ng/ml) before surgery, which strongly suggested the existence of EST.

For the treatment of MOGCTs in adolescents, surgical staging guidelines have been arbitrarily adopted from that of ovarian epithelial cancers [5]. However, it has been reported that these guidelines were seldom followed completely [5]. As described earlier in this article, the COG does not support staging procedures such as lymph node dissection and omentectomy for pediatric patients. Instead, the COG developed another staging system specifically for children and adolescents (listed in **Table 3**). For apparent early-stage patients with lesions confined to the ovary, only peritoneal fluid cytology is suggested and if negative the guidelines would designate this as COG stage I. If positive, patients would be designated as COG stage III. In our study, we saw considerable variability in surgical procedures and only 28.6% (12/42) of patients received comprehensive staging according to the criteria described earlier. We found that neither comprehensive staging surgery, nor individual factors, including not only lymph node dissection or omentectomy, but also peritoneal fluid cytology, was an independent impact factor for DFS. However, it should be mentioned that the majority (90.5%) of our patients were of apparent stage I with lesions grossly confined to the ovary. More importantly, most of these patients (90.5%) received adjuvant chemotherapy, which may have had profound influence upon outcomes.

Prior to the 1980s, the 5-year overall survival of MOGCT patients was only 20%, even for early stage tumors [17]. The introduction of platinum-based chemotherapy has resulted in significant improvements in long-term survival, even for patients of advanced stages. However, chemotherapy may cause severe latent effects. Hearing loss was the most significant morbidity [18]; renal impairment and neurotoxicity were also reported. Considering such risks, the COG and POG have made great efforts over the past decade to investigate the necessity for adjuvant therapy in early stage patients. The COG divided pediatric patients into 3 categories based on prognosis: low, intermediate and high

risk groups [18]. COG stage I MOGCT patients belong to the low risk group, and are prescribed with surveillance instead of chemotherapy after surgery [5, 18]. COG stage III patients belong to the intermediate risk group and recommendations indicate that such patients receive 3 cycles of PEB regimen following surgery. Further more, the PEB regimen is also different from the BEP regimen recommended by the NCCN as bleomycin is administered once per cycle instead of once a week [18].

However, a recent report showed that when prescribing COG stage I patients with surveillance after surgery, 48% (12/25) patients experienced persistence or recurrence of disease within 8 months although they were all ultimately salvaged after chemotherapy [7]. These results were consistent with a French study which found that when surveillance was the only approach after surgery, a success rate of only 50% could be reached in COG stage I MOGCT patients [19]. The above results indicate that for COG stage I, girls who were incompletely staged according to the FIGO criteria are at risk omitting chemotherapy. Based on the FIGO staging system, one research study has shown that for FIGO stage I patients, the risk of relapse was significantly increased (HR = 4.5) with a recurrence rate of 33.3% if observation was chosen instead of chemotherapy after surgery; and relapse occurred only in patients of stage IC or IX (who were not completely staged according to FIGO protocols) [20]. Collectively, these results supported the fact that it takes great risks to omit adjuvant chemotherapy for incompletely staged early stage patients.

In another respect, it was suggested in a recent article that for early stage patients not receiving adjuvant chemotherapy, complete staging is crucial because incomplete staging may lead to down-staging of tumors [21]. In fact, the NCCN guidelines for ovarian cancer (version 2.2015) suggest that only on the basis of comprehensive staging surgery may pediatric and young adult patients of the following situations be considered for observation as a treatment option as well as chemotherapy: stage IA, IB dysgerminoma; stage IA, grade 1 immature terotomas; stage IA embryonal tumors; or stage IA ESTs. Taking these statements together, for early stage patients it is not rational to omit complete staging surgery and adjuvant chemotherapy at the same time.

In our study, the majority (29/38, 76.3%) of the apparent early-stage patients did not receive comprehensive staging surgery, but only 2 (5.3%) patients relapsed. The recurrence rate is therefore much lower than reported results mentioned above. This may be attributed to the fact that 92.1% (35/38) of apparent early-stage patients received adjuvant chemotherapy. We speculate that for apparent early-stage adolescent patients who receive adjuvant chemotherapy, staging surgery may add no further benefit. The results of the log-rank and Fisher's exact test in our cohort both supported this conclusion. We theorize that it might be rational therefore to treat apparent early-stage adolescent patients with fertility-sparing surgery and adjuvant chemotherapy but without staging procedures.

Three patients with FIGO stage III disease in our study were precluded from fertility-sparing surgery. However, it has been suggested that fertility-sparing procedures are safe for children and adolescents with advanced stages due to the high sensitivity to chemotherapy [21]. For the five bilaterally involved patients and the three unilaterally involved patients with the contralateral ovary absent or dysgenesis, whether it is safe to spare fertility, that is, to preserve part of the involved ovary, warrants further study. Conservative surgery and chemotherapy was reported to have minimal impact on fertility in young adult women [22, 23]. Other results have suggested that the adverse effect was closely related to the number of chemotherapy cycles [24]. The optimal duration of chemotherapy is still controversial. Three cycles in a completely resected disease and four cycles for patients with residual disease is generally accepted [4]. Patients receiving fertility-sparing treatment should undergo regular and long-term follow-up in order to evaluate their ovarian reserve.

We acknowledge that our study has limitations as it was retrospective in nature and of limited size. However, this study represents data from a single institution over a long time period, and that treatment protocols were kept consistent throughout this prolonged interval.

Conclusion

In conclusion, MOGCTs in adolescents are highly curable with a satisfying 5-year OS and DFS. Most (90.5%) of the adolescent patients in our

current study were of apparent early-stage, and most (90.5%) received adjuvant chemotherapy. Although comprehensive staging protocols were followed in only a small number of patients (28.6%) in our cohort, the recurrence rate was as low as 4.8%. Comprehensive staging or individual factors such as peritoneal washing cytology, lymph node dissection and omentectomy were not independent risk factors for DFS. The positivity of peritoneal washing cytology or lymph node dissection did not correlate with recurrence. Based upon these results, we conclude that for adolescent patients who have received adjuvant chemotherapy, staging procedures may not provide additional benefit.

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Disclosure of conflict of interest

None.

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