Original Article

Survival benefit of lymphadenectomy in patients with early-stage juvenile granulosa cell tumor of the ovary: a single center retrospective cohort study

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Background: Juvenile granulosa cell tumor (JGCT) often arises in young women, which has subsequent reproductive needs. Surgery is the mainstay of treatment for JGCT. Whether lymphadenectomy is necessary for JGCT in the early stage has long been questioned. The purpose of this study is to evaluate the impact of lymphadenectomy on survival in early-stage ovarian JGCT who went through fertility-sparing surgery (FSS).

Methods: In a period of 9 years (from March 2013 to February 2022), patients who underwent FSS treatment for JGCT at the Gynecological Oncology Department of West China Second Hospital of Sichuan University were identified retrospectively. Clinical data of patients with early-stage JGCT and follow-up information from outpatient records or telephone interviews were collected. Descriptive statistics were used to describe the patient population. Treatments were evaluated for association with relapse and survival.

Results: FSS was treatment for all the included patients including cystectomy and unilateral salpingo-oophorectomy (USO). Lymphadenectomy was performed in 8 (53%) of 15 patients. Those patients with simple cystectomy or unilateral salpingectomy showed no residual disease after the computed tomography (CT) scan. Adjuvant chemotherapy (AC) was given in 8 cases. After a median follow-up time of 31.87 months (range, 2–85 months), three patients were registered relapse including two in the non-lymphadenectomy group and one in the lymphadenectomy group. The overall survival and 3-year disease-free survival rates were 93.3% and 80.0%, respectively, which are similar in the lymphadenectomy (87.5%, 100.0%) and non-lymphadenectomy groups (71.4%, 85.7%) (P=0.57, 0.47).

Conclusions: FSS is the preferred treatment of choice for JGCT, with a good prognosis. It seems lymphadenectomy was no survival benefit in early-stage JGCT. Whether lymph node dissection should be performed in JCGT patients should be considered.

Keywords: Juvenile ovarian granulosa cell tumor; lymphadenectomy; survival; ovarian cancer

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Introduction

Granulosa cell tumor (GCT) is a rare type of ovarian cancer, accounting for 3%-5% of ovarian cancers. It can be divided into two types, juvenile and adult types (1). Adult granulosa cell tumor (AGCT) is the most common and arises in women during perimenopause and post menopause. While juvenile granulosa cell tumor (JGCT) accounts for 5% of all GCT and arises in premenarchal girls or young women (1-3). JGCT, in most cases, presents at early stage, with a favorable prognosis after surgical treatment and adjuvant therapy. After surgical treatment and adjuvant therapy, JGCT has an excellent prognosis (1,4). Different from AGCT, JGCT has subsequent reproductive needs. Because of the exceptionally low incidence of this disease, the literature on the treatment and clinical course of JGCT is limited (5,6). Surgery is the mainstay of treatment for JGCT. Current evidence-based clinical practice guidelines identify fertility-preserving surgery (FSS) as the recommended treatment of JGCT (7,8). Traditionally, FSS methods include abdominal or laparoscopic exploration surgery, cystectomy or unilateral salpingo-oophorectomy (USO), omentectomy, peritoneal washing, and biopsy. While there is no consensus on the role of routine lymph node dissection. However, JGCT is reported to spread by lymphatic dissemination and is rarely observed (4,9,10). There is great controversy regarding whether routine lymphadenectomy is necessary for JGCT in the early stage. Besides, the literature reports that longer hospital stays, decreased serum hemoglobin after surgery, and increased rate of wound infection were observed more frequently in the lymphadenectomy group (11-13). Therefore, the effectiveness of lymphadenectomy in the surgery of early-stage JGCT has long been questioned. We present this article in accordance with the STROBE reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-45/rc).

Highlight box

Key findings

- There was no significant difference in the disease-free survival rate and overall survival rate of early-stage juvenile granulosa cell tumor (JGCT) patients between the lymphadenectomy group (8 cases) and the non-lymphadenectomy group (7 cases).

What is known and what is new?

- Stage is considered the most important prognostic factor, and lymphadenectomy remains as a controversial procedure in the surgical management of JGCT.
- The status of lymphadenectomy was not associated with disease-free survival in early-stage JGCT.

What is the implication, and what should change now?

- FSS is the treatment of choice for ovarian JGCT and the overall prognosis is good.
- Whether lymph node dissection should be performed in JCGT patients should be considered.

Methods

This study was carried out by cohort retrospective analysis of the data of patients with early-stage JGCT at the gynecological oncology department of West China Second Hospital of Sichuan University between March 2013 and February 2022. Early-stage JGCT was defined as the disease confined to the ovary after surgery, which includes complete surgical staging (ovarian cystectomy or unilateral salpingectomy, peritoneal washing, omentectomy or omental biopsy) and simple cystectomy or unilateral salpingectomy with no residual disease after computed tomography (CT) scan. Lymphadenectomy was an optional procedure based on the intraoperative outcome and surgeon's experience. And patients were defined into the non-lymphadenectomy group and the lymphadenectomy group. Clinical characteristics were collected from all patients regarding age, menopausal status, pregnancy and delivery history, presenting symptoms (abdominal distension and tenderness, vaginal bleeding), tumor site and diameter, preoperative serum carbohydrate antigen125 (CA125), surgery information (type, ascites, rupture), adjuvant therapy, relapse information, and treatment (surgery and adjuvant therapy). Follow-up information came from medical records or telephone interviews with patients or their families. Patients with incomplete medical files or unavailable pathology sections were excluded. In addition, a senior pathologist reviewed the pathological sections. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of West China Second Hospital of Sichuan University (Registration No. 2022095). Individual consent for this retrospective analysis was waived.

Statistical analysis

Collected data were analyzed using IBM Statistical Product and Service Solutions (SPSS, Armonk, NY, USA). Patient demographics and characteristics were analyzed using descriptive statistics. Patients were assigned to the non-

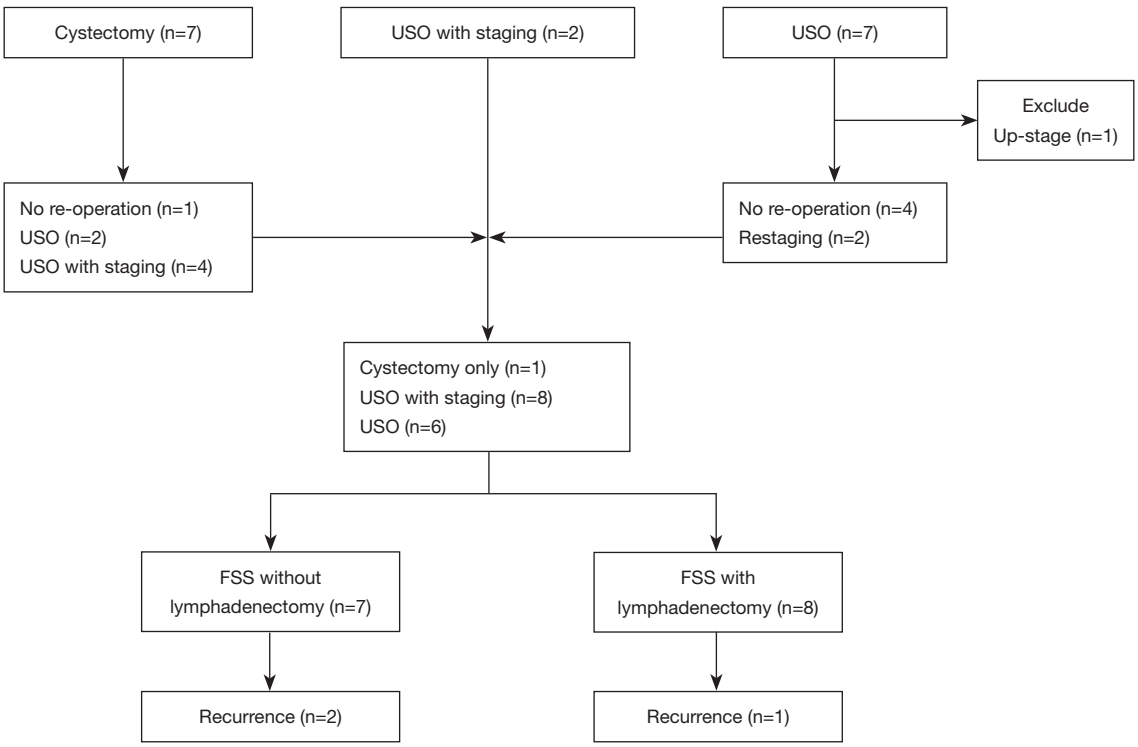

Figure 1 Initial surgical procedures in JGCT patients with early-stage. USO, unilateral salpingo-oophorectomy; FSS, fertility-preserving surgery; JGCT, juvenile granulosa cell tumor.

lymphadenectomy group and the lymphadenectomy group. The medians were compared by Mann-Whitney *U* tests and χ^2 and Fisher's exact tests were used to compare frequency distributions. Continuous data were compared using an independent sample *t*-test. A comparison of categorical data was performed using χ^2 test. Disease-free survival (DFS) was defined as the time interval between initial diagnosis and the first observation of recurrence or the date last visit. Overall survival (OS) was defined as the interval between the date of first diagnosis and the date of death or date of last visit. OS curves were calculated by the Kaplan-Meier analysis. The difference in survival between groups was compared using the log-rank test in univariate analysis. Due to the small sample size, no multivariate analysis was performed. All P values are two-sided and P<0.05 was considered to be statistically significant.

Results

Clinical characteristics

A total of 16 patients who met the inclusion criteria were treated at or referred to West China Second Hospital during the study period. We determined the surgical circumference according to the initial surgical intervention and the second surgical intervention within 2 months. FSS was the first-line surgery for all participating patients, defined as preserving the uterus and at least 1 adnexa. One patient was excluded, which was treated with USO at original surgery and diagnosed with stage III disease due to the detection of omental micro-metastasis after staging. The study flow diagram is shown in *Figure 1*. There was no missing data. Four of seven in the cystectomy group underwent surgical USO with staging and 2 patients underwent USO within 2 months. Three patients in the USO group went through surgical staging within 2 months. Those patients with simple cystectomy or unilateral salpingectomy showed no residual disease after the CT scan. At last, 15 patients with and without lymphadenectomy were included in the analysis (n=8 and 7, respectively). The clinical features of included patients are listed in *Table 1*. The most common symptoms are abdominal distension and tenderness (2,14). Some patients may present with vaginal bleeding for the elevated estrogen level (5). The mean age was 17 years (range, 3–31 years) in the present

Table 1 Demographic and clinical features of included JGCT patients

Variables	All patients (n=15)	Lymphadenectomy (n=8)	No-lymphadenectomy (n=7)	P
Age (years), mean ± SD	17.00±9.08	22.11±6.39	9.33±6.92	0.003
Pregnancy history				0.46
Yes	2	2	0	
No	13	6	7	
Delivery history				0.46
Yes	2	2	0	
No	13	6	7	
Pre-puberty				0.12
Yes	5	1	4	
No	10	7	3	
Serum CA125 level (IU/mL)				0.99
<35	9	5	4	
≥35	6	3	3	
Tumor site				0.61
Left	5	2	3	
Right	10	6	4	
Tumor diameter (cm), mean ± SD	14.23±10.37	13.32±10.81	15.17±10.42	0.64
Rupture				0.61
Yes	10	6	4	
No	5	2	3	
Adjuvant therapy				0.99
Yes	8	4	4	
No	7	4	3	

JGCT, juvenile granulosa cell tumor; SD, standard deviation; CA125, carbohydrate antigen 125.

study. There was an obvious difference in age between the lymphadenectomy group and the non-lymphadenectomy group. The mean age in the non-lymphadenectomy group [mean ± standard deviation (SD): 9.33±6.92 years] was much younger than in the lymphadenectomy group (mean ± SD: 22.11±6.39 years). Among them, five (33.33%) were pre-puberty and two (13.33%) had a pregnancy history previous. The mean tumor diameter was 14.23±10.37 cm (range, 4–35 cm). Of those, six (40%) had a higher serum CA125 level (35 IU/mL). And intraoperative or preoperative rupture occurred in 10 cases (66.66%). Eight patients (53.33%) obtained adjuvant chemotherapy (AC). Four patients in the lymphadenectomy group have received chemotherapy and 4 in non-lymphadenectomy group. Chemotherapy regimen including bleomycin, etoposide, and cisplatin (BEP) in 4 patients; bleomycin, vinca alkaloid, and cisplatin (BVP) in 1 patient; paclitaxel and carboplatin (TC) in 3 patients. Among those 8 patients who received chemotherapy, seven (87.5%) received more than three cycles and 1 (12.5%) received three or fewer cycles.

Survival analysis

During a median follow-up time of 31.87 months (range, 2–85 months), three patients (20.0%) underwent at least one relapse, including two in the non-lymphadenectomy

group and one in the lymphadenectomy group. The 3-year DFS rate and OS rate were 80.0% and 93.3%, respectively. And the status of lymphadenectomy was not associated with DFS (P=0.40) (*Figure 2*). Median time from diagnosis to relapse was 12 months (range, 6–20 months). And the sites of relapses were the pelvis and abdomen in 2 patients, sigmoid colon in 1. All the patients were treated with surgery plus chemotherapy. At the end of follow-up, one patient died of this disease, who failed to achieve complete remission, and the other 2 patients were alive, with no evidence of disease. Details of relapse information in the 3 patients are presented in *Table 2*.

Discussion

Lymphadenectomy remains a controversial procedure in the surgical management of the disease.

Although there is no prospective, controlled, and randomized research, studies have shown that the surgical treatment of JGCT suggests FSS (3). In addition, wedge biopsy from the contralateral ovary is not recommended (15,16). The stage is considered the most important prognostic factor. FSS is the treatment of choice for ovarian JGCT and the overall prognosis is good. There are several limitations to our study. Firstly, the present study is limited by its retrospective nature, and the relatively small cases could limit the generalizability to a certain extent. Secondly, the follow-up period is relatively short.

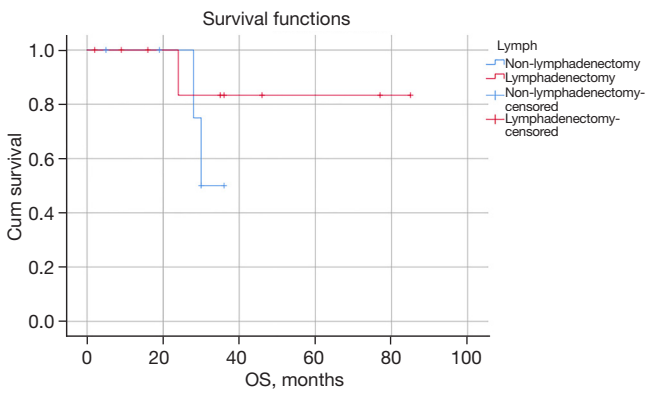

Figure 2 Overall survival according to the status of lymphadenectomy. Cum, cumulative; OS, overall survival.

Literature reports that the age range of JGCT might vary from infancy to a maximum of 67 years. But more than half of the patients are younger than 20 years. In our study, the mean age was 17 years which is similar to that of the current study population and 33.3% of patients were premenarchal girls. Lymph node metastasis is seldom observed in patients with sex-cord stromal tumor (11,16-18). Karalök *et al.* reported that none of the JGCT patients had lymph node involvement which went through pelvic and para-aortic lymphadenectomy (2). Besides, the conclusion of Dan Wang's study is consistent with the above discussion (10). In our study, none of these 8 patients with lymphadenectomy had lymphatic metastasis, and one of these patients was diagnosed with stage III disease due to the detection of omental metastases after stage. Lymphadenectomy procedure usually requires longer operative time and wider surgical incision, which may result in longer hospital stays, increase intraoperative bleeding, and increased wound infection rate (11-13,19). Besides lymphatic cysts may cause by lymphovascular circulation blocked after lymphadenectomy. Due to the low incidence, the present study and other case reports seem that lymphadenectomy had no improved effect on survival in JGCT, as reviewed in *Table 3*.

Due to the large volume of the tumor, patients mainly present with abdominal distention and pain or discomfort associated with pelvic masses. The presenting complaints

Table 2 Clinical details of patients with relapse JGCT

Case	Age (years)	Surgery	CA125 (IU/mL)	Lymphadenectomy	AC	DFS (months)	Relapse site	Treatment	Status
1	18	USO	89.7	No	TC ×3	6	Abdomen, pelvis	Surgery + AC	Death
2	18	USO	77.5	No	BEP ×6	24	Abdomen, pelvis	Surgery + AC	Alive
3	21	USO + staging	171.9	Yes	TC ×3	12	Sigmoid colon	Surgery + AC	Alive

JGCT, juvenile granulosa cell tumor; USO, unilateral salpingo-oophorectomy; CA125, carbohydrate antigen125; DFS, disease-free survival; TC, paclitaxel and carboplatin; BEP, bleomycin, etoposide and cisplatin; AC, adjuvant chemotherapy.

Table 3 Review of the studies of JGCT with relapse information according to surgery

Author, year	No. of cases	Surgery	Stage	Recurrence
Bergamini, 2021, (4)	17	USO [13], cystectomy [2], RS [2]	Stage I [17]	No recurrence
Zhao, 2019, (16)	6	USO + stage [6]	Stage I [5], stage III [1]	1 recurrence (stage III)
Wang, 2022, (10)	35	USO + stage [16], USO [15], cystectomy [4]	Stage I [35]	8 recurrences including USO [6], cystectomy [1], USO + stage [1]
Wu, 2017, (20)	8	USO + stage [3], USO [5]	Stage I [5], stage III [3]	1 recurrence (stage III)
Parikshaa, 2021, (9)	15	USO [9], BSO [1], USO + stage [1], TAH + BSO [3], cystectomy [1]	Stage I [12], stage III [2], stage IV [1]	1 died (stage IV)
Karalök, 2015, (2)	10	USO + stage [4], USO [4], TAH + BSO + stage [1], cystectomy [1]	Stage I [10]	No recurrence
Cecchetto, 2011, (21)	12	Adenectomy [8], ovariectomy [3], biopsy and ovariectomy [1]	Stage I [12]	No recurrence
Schneider, 2003, (22)	48	Ovariectomy [13], adenectomy [24], No data [11]	Stage I [39], stage II [3], stage III [1], no data [5]	3 recurrences
Vassal, 1988, (23)	15	USO [12], BSO [2], TAH + BSO [1]	Stage I [6], stage II [1], stage III [6], stage IV [1], no data [1]	4 recurrences including USO [3], TAH + BSO [1]

JGCT, juvenile granulosa cell tumor; USO, unilateral salpingo-oophorectomy; RS, radical surgery; TAH, Transabdominal Hysterectomy; BSO, bilateral salpingo-oophorectomy.

in some patients are acute lower abdominal pain suggestive of the tumor with rupture or torsion. Tumor rupture has been reported in up to 10% of cases, but the presence of intraoperative penetration of the tumor does not necessarily affect the prognosis (24,25). The incidence of tumor rupture in this study was 66.6%, which is higher than that reported in the literature. Five cases occurred preoperatively, possibly caused by the large tumor diameter (10–35 cm). And 1 case occurred intraoperatively. Pregnant women are often asymptomatic and the tumors are incidentally discovered by routine ultrasonography (6,26,27). Endocrine manifestations are also discovered in JGCT patients because JGCT is associated with estrogen production (3). In prepubertal children, peripheral precocious puberty, which includes breast enlargement and vaginal bleeding is the common clinical presentation, while in post-pubertal patients, the symptoms might include menstrual irregularities and amenorrhea (3,4,24). In our study, half of those patients present with abdominal distention and pain, and three of those post-pubertal patients present with menstrual irregularities (reduced menstrual volume, menstrual cycle disorders), and one patient was discovered in cesarean section (CS) surgery. One in five prepubertal children present with breast enlargement and one presents with vaginal bleeding. A previous study found that 10% of ovarian JGCT patients had ascites, which could be caused by tumor rupture or metastasis. In contrast with epithelial ovarian tumors, peritoneal metastases are rare, literature reviews that nearly 90% of JGCT were in stage I (14,28).

In 9 years, 20 patients were diagnosed as JGCT in our hospital, and peritoneal metastases were found in 5 patients. Due to the rarity of the tumor, current literature reports that it is difficult to distinguish JGCT from other ovarian tumors by imaging studies (2). AGCT and JGCT show similar appearances in imaging studies, which both showed a cystic-solid and multilocular mass with a relatively large size compared with the epithelial ovarian tumors on CT scan (29). The tumor diameter in our study was 14.23 cm.

Elevated serum CA125 levels have been reported in cases of JGCT (6,30). Lee reported that CA125 evaluated in AGCT was only 13.1%, while the percent was 45.5% in JGCT (31). In our study, 6 out of the 15 patients tested for tumor markers before surgery had elevated serum CA125 levels. But the diagnostic value is still uncertain.

The use of AC in early-stage disease remains unclear. Currently, patients with stage IC2 and IC3 JGCT should accept AC after surgery according to ESGO-SIOPE (The European Society of Gynecological Oncology and the European Society for Pediatric Oncology) guidelines (8,32). The chemotherapy regimen used in GCT treatment

includes BEP and TC. Six-cycle TC was recommended according to the 2020 version of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, while BEP was still recommended as the most commonly used in ESGO and SIOPE guidelines (8). In our study, 8/15 received AC after surgery, 3 patients with TC therapy, and 4 with BEP, 1 with BVP therapy. With regard to the 5-year DFS, there was no statistically significant difference between patients undergoing AC and patients not. Different from the AGCT, JGCT tends to relapse primarily within the first few years after the original surgery. And the most relapses site was the abdominal-pelvic cavity (33). Wang's study reported that the median time to relapse was 4.5 months (range, 2–52 months) and the 5-year DFS and OS rates were 74.8% and 84.3%, respectively (10). In current study, 3 patients experienced recurrence and the median time to recurrence was 12 months (range, 6–20 months). As to the treatment for relapse, 2018 European Society for Medical Oncology (ESMO) guidelines suggested that the debulking surgery with AC remains the most effective treatment (33). In our study, one patient died of their disease, who failed to achieve complete remission. The other two were DFS after surgery and chemotherapy.

Ovarian JGCT is a malignant sex-cord stromal tumor, which mostly occurs in premenarchal girls. Lymph node metastasis is seldom observed. It seems that the status of lymphadenectomy was not associated with DFS in early-stage JGCT. Further studies and longer-time follow-ups in large series are needed to define the real risk factors.

Conclusions

JGCT is a rare subtype of ovarian cancer, which occurs mainly in premenarchal girls or young women. FSS is the treatment of choice for ovarian JGCT and the overall prognosis is good. Based on our limited data that showed lymphadenectomy had no improved effect on survival in early-stage JGCT. However, further multicenter studies are required to confirm this observation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-45/rc

Data Sharing Statement: Available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-45/dss

Peer Review File: Available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-45/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm-22-45/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of West China Second Hospital of Sichuan University (Registration No. 2022095). And individual consent for this retrospective analysis was waived.

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