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Research

Keywords: Granulosa cell tumors, Recurrence, Late recurrence

DOI: https://doi.org/10.21203/rs.3.rs-449508/v1

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Abstract

Objective: To explore the clinical features and treatment of 22 patients with recurrent ovarian granulosa cell tumor (GCT).

Methods: The clinical data of 22 females with recurrent ovarian GCT and received treatments in Qilu hospital were retrospectively analyzed.

Results: During the recurrence interval, late recurrence (≥5 years) appeared in 14 patients, early recurrence (<5 years) were in 8 patients. Among the 22 recurrent patients, 8 cases had second relapses during the time of follow-up. Of the 14 late recurrent cases, 10 cases had FIGO stage I cancers, 4 had stage III cancers. Among the 8 early recurrent GCT cases, 5 had FIGO stage I cancers. FIGO stage and whether performed fertility-sparing surgery or not had significant impacts on the recurrence type (P = 0.035 and 0.016, respectively).

Conclusions: The intervals of GCT recurrence are usually long after the initial diagnosis. Continuous long-term follow-up is absolutely required, especially for those with early stage and complete surgery.

Key words: Granulosa cell tumors; Recurrence; Late recurrence

Introduction

Granulosa cell tumors of ovary (GCT) are rare sex cord-stromal ovarian tumors constituting approximately 2-3% of all ovarian malignant tumors, which are classified into two types: ovarian adult granulosa cell tumor (AGCOT) and ovarian juvenile granulosa cell tumor (JGCOT)1.

Different from other types of ovarian cancer, GCT is characterized by slow growth, local spread, and late recurrence, most patients have a favorable prognosis, especially patients in early stage. Although there were several aggressive cases reported, the overall 5-year survival rate was 85-95%2,3, and the duration of recurrence could be up to 41 years4. However, literature on the diagnosis and treatment of ovarian GCT is scarce, and there’s little evidence about recurrence in GCT.

In this paper, we presented 22 cases with recurrent granulosa cell tumor of the ovary, including 14 late recurrence cases and 8 early recurrence cases, and analyzed their oncological consequences.

Materials and methods

This study included 22 recurrent cases of 85 who was diagnosed with GCT and treated in the Gynecologic Oncology Department of Qilu Hospital of Shandong University from 2005 to 2019. 8 of 22 recurrent cases were early recurrent, which is defined as the relapse interval ≤ 5 years, and the other 14 have recurrence interval over 5 years, called late recurrence in this study. The medical records of 22 cases, including the clinical features and therapeutic approaches, were retrospectively reviewed. Follow-up examinations of all patients were conducted every three months during the first three years after treatment, and every six months thereafter. The follow-ups included the recurrence and survival status, and recurrence was defined as a new focus was found by imaging and confirmed by pathology. Staging of GCT was categorized in accordance with the International Federation of Gynecology and Obstetrics (FIGO) standard staging of ovarian tumors. The prognosis-related data were obtained.
through telephone interviews and outpatient follow-ups. The research protocol of this study was approved by the Ethics Committee at our institution.

SPSS 26.0 software (IBM SPSS, Chicago, IL) were used for data analysis. The risk factors of late recurrence were analyzed by univariate analyses using the Cox proportional hazard regression. All statistical tests were two-sided, with \( P \) values less than 0.05 considered statistically significant. All figures and tables in this article are original.

3. Results
3.1 Clinical characteristics at initial diagnosis

3.1.1 Clinical characteristics at initial diagnosis of early recurrence

The present study included 8 cases of early recurrent GCT (recurrence interval \( \leq 5 \) years). The main characteristics of early recurrent patients and tumors at initial diagnosis were summarized in Table 1.

The age of initial disease onset was 16–58 years, with a median age of 39 years. Five cases were premenopausal and three were not. All but one had given birth, and five of which had miscarriages. The most common clinical manifestations were vaginal bleeding, and pelvic masses, as well as abdominal pain and abdominal distension. All eight patients had unilateral lesion and three cases had multiple lesions.

All cases underwent surgery as the initial treatment. Three cases underwent fertility-sparing surgery, two case with unilateral salpingo-oophorectomy and one with left salpingo-oophorectomy and omentectomy. The others had a hysterectomy and bilateral salpingo-oophorectomy (HBSO). Two patients underwent lymphadenectomy and all lymph nodes were negative, showed in postoperative pathology. One in eight cases was pathologically proved to be JGCOT, and the others were AGCOT. Based on the intraoperative findings and pathological features, the eight patients were staged as following: 5 cases of stage I, including 3 cases of stage Ia, 2 cases of stage Ic, and 3 patients who had pelvic metastasis was classified as stage III.

Among 8 patients, 6 cases had chemotherapy postoperatively, and 2 cases had no adjuvant therapy. Two of the cases receiving postoperative chemotherapy were performed PEB regimen and two cases underwent PVB regimen. One patient received TC regimen and the other one received PC regimen. 3 patients received chemotherapy for four cycles or less, and 3 patients received chemotherapy for more than four cycles.

3.1.2 Clinical characteristics at initial diagnosis of late recurrence

There were 14 cases of late recurrent granulosa cell ovarian tumor. The main characteristics of patients and tumors of late recurrence at initial diagnosis were summarized in Table 2.

The median age of initial disease onset was 45 years (range 33–70). Six cases were postmenopausal at the initial treatment and eight cases were premenopausal. All fourteen cases had given birth, six of which had miscarriages. The common clinical manifestations were vaginal bleeding, abdominal pain, abdominal distension, and pelvic masses, similar to those of early recurrent cases. Five cases had multiple lesions, and one have bilateral ovarian lesions.

All cases underwent surgery as the initial treatment. Three cases underwent fertility-sparing surgery, including one case of cystectomy, one case of left salpingo-oophorectomy and one case of fertility-sparing staging surgery (left adnexectomy+ right ovarian cystectomy + omentectomy + pelvic lymph node dissection). The others had HBSO. Two patients underwent lymphadenectomy and postoperative pathology showed that all lymph nodes were negative and the remaining 12 patients had
no lymphadenectomy. All fourteen cases were AGCOT pathologically. The fourteen patients were staged as following: 10 cases of stage I, including 3 cases of stage Ia and 7 cases of stage Ic, and 4 of stage III.

Among all patients, 4 cases had no postoperative chemotherapy, and 10 cases had postoperative adjuvant therapy. The regimens were PVB, PEB, PC, CAF regimen respectively. All cases received chemotherapy for four cycles or less.

3.2 Clinicopathological features and therapeutic approaches at recurrence

3.2.1 Clinicopathological features at recurrence of early recurrent cases

The clinicopathological features at recurrence of early recurrent cases can be seen in Table 3. Among the 8 patients with early recurrence, the PFS was 12-58 months and the median was 35.5 months; the OS was 49-147 months (median 84.5 months). The age at recurrence was 43 years (median 19-59 years). Only one case (case 7) had clinical symptoms at recurrence (chest discomfort, abdominal distension, weight loss), while the other 7 cases were asymptomatic in which the recurrence was discovered by imaging examination during follow-ups.

The recurrence sites included only pelvic recurrence in four cases, and multisite recurrences in the abdominopelvic cavity in four cases. Two patients had recurrence of one single lesion, and six patients had recurrence of multiple lesions. Among the four cases in which the recurrent lesions involved the abdominal cavity, one case involved omentum majus; one case involved gastrocolic ligament; two involved mesentery. Among the patients with early recurrence, the post-recurrence therapeutic approaches included one case of surgery alone, one case of chemotherapy alone, six cases of surgery combined with postoperative chemotherapy. Seven cases underwent surgery at relapse, including cytoreductive surgery, pelvic lymph node dissection and omentectomy. The case with chemotherapy alone underwent TC regimen for 7 cycles. Among the 6 patients with post-recurrence chemotherapy, 4 patients underwent paclitaxel plus platinum-based regimens; 1 patient underwent PEB regimen, 1 underwent PVB regimen and 1 for paclitaxel only. Three patients had ≤ four-cycles chemotherapy, and four patients had > four-cycles chemotherapy. Reviewing of the pathological reports of the 8 patients with early recurrence showed that 6 patients had inhibin-A examination, all positive. Two patients had vimentin examination, both positive. 3 patients had an CR examination, all positive. 5 patients had a Ki-67 protein examination and 4 were below 30%, while 1 case was 60%. Three had second recurrences and two of them had third and fourth recurrence, in which one death was reported.

3.2.2 Clinicopathological features and therapeutic approaches at recurrence of late recurrent cases

As seen in Table 4, among the 14 patients with late recurrence, the PFS was 64-204 months and the median was 122 months; the OS was 86-264 months, with a median of 178.5 months. The median age at recurrence was 55 years (range 43-78 years). Nine cases had clinical symptoms at recurrence, while 4 cases were asymptomatic in which the recurrence was discovered by imaging examination. The other one was discovered in trauma surgery accidentally.

The recurrence sites included pelvic recurrence in 5 cases, multisite recurrences in the abdominopelvic cavity in 7 cases and abdominal recurrence in 2 cases. Three patients had recurrence of one single lesion, and 11 patients had recurrence of multiple lesions. Among the nine cases in which the recurrent lesions involved the abdominal cavity, 5 cases involved the omentum majus; 1 case involved the liver; 1 case involved the perisplenic region; 2 cases involved intestines and 2 involved mesentery; 3 cases involved the abdominal wall; 1 involved diaphragm. Among the patients with late
recurrence, the post-recurrence therapeutic approaches included 2 cases of surgery alone, 12 cases of surgery combined with adjuvant chemotherapy. All 14 cases underwent surgery at the relapse, including cytoreductive surgery, HBOC, Pelvic lymph node dissection and omentectomy. Among the 12 patients with post-recurrence chemotherapy, 10 patients underwent paclitaxel plus platinum-based regimens; 2 patients underwent a BEP regimen. Three patients had ≤ four-cycles chemotherapy, and nine patients had >four-cycles chemotherapy. Reviewing of the pathological reports of the 14 patients with late recurrence showed that all patients had inhibin-A examination, including 10 positive cases (+ - +++) and 2 negative cases. Six patients had vimentin examination, which are all positive. Eleven patients had a Ki-67 protein examination and all were below 30%. Five had second recurrences and one of them had third and fourth recurrences. No death was reported.

3.3 Risk factors analysis between early relapse and late relapse

Univariate analysis of initial clinicopathological features and initial therapeutic approaches on the recurrence type of recurrent GCT cases (early recurrence/late recurrence) showed that FIGO stage ($P = 0.035$) and with or without fertility-sparing surgery ($P = 0.016$) had significant impacts on the recurrence type. There was no significant difference in age, menstrual status, with or without abortion, lesion number, tumor diameter, FIGO stage, with or without lymphadenectomy, integrity of tumor capsule and with or without chemotherapy between patients with late recurrence and patients with early recurrence ($P > 0.05$), as shown in Table 5. Furthermore, there’s no significant difference in risk of re-replapse between late recurrence and early recurrence ($P = 0.416$).

4. Discussion

Unlike the common types of ovarian cancer, such as epithelial ovarian cancers, which are more destructive, the overall survival with GCT is more favorable. This may be at least partially due to the earlier stage at diagnosis of ovarian GCT.

Recurrence 5 years or more after a diagnosis is commonly referred to as “late recurrence” in multiple tumors, here, consistent with the naming convention, we defined “late recurrence” as the relapse interval > 5 years. GCT is indolent and characterized by large pelvic mass and late recurrence. Compared with AGCOT, JGCOT has a lower incidence rate and recurrence rate, especially late recurrence late. It has been reported that JGCOT may have late recurrence. In this study, the median interval between relapse and initial treatment of 22 patients with recurrent GCT was 87 months, which was consistent with the 5-10 years reported in the literature. Pectasides et al considered that the risk of long-term cancer-related death could reach 50%. There was a big difference in recurrence rates of GCT among different researches, 17% ~ 50%, where the reason may be that most studies are retrospective analysis, and the recurrence rate is related to the length of follow-up.

Lee et al reported 149 patients with recurrent GCT and found that the pelvic recurrence and extrapelvic metastasis accounted for 55% and 47.7% respectively. The sites of extrapelvic metastasis include peritoneal implantation, retroperitoneal metastasis, liver, lung, spleen, and other organs. Peritoneum implantation can be seen as disseminated nodule or infiltrative mass around liver, mesentery and omentum majus. 50% of the cases with retroperitoneal metastasis were lymph node metastasis. There were 6 patients with only pelvic recurrence and 16 patients with extrapelvic metastasis. The sites of extrapelvic metastasis included disseminated peritoneal implantation, retroperitoneal metastasis, liver, omentum majors, mesentery, and abdominal wall. Since it is not
uncommon for recurrent GCT to metastasize outside the pelvis, and which mainly spread in the abdominal cavity, more attention should be paid to the routine examination of the upper abdomen during the follow-up.

There is no standard treatment for recurrent GCT at present. Many researchers believe that cytoreductive surgery is the first choice for treatment at recurrence, but considering its favorable prognosis and indolent course, fertility-sparing management could be deliberated for those young patients who desire child-bearing in the future. However, in our study, we found that compared with TH and BSO, people who underwent fertility-sparing surgery may have a faster recurrence, which suggests that we should make decisions very carefully. Fotopoulou et al reported that 80% of recurrent GCT can be performed satisfactory debulking surgery, and the surgical resection rate of recurrent GCT patients is higher than that of recurrent ovarian cancer. Chua et al reported that 5 patients with recurrent GCT underwent multiple tumor reduction surgery, of which 1 case received 4 tumor reduction surgery and the tumor free survival time of the 5 patients after reoperation was 10 ~ 95 months. All the 22 patients with recurrent GCT in this study received surgical treatment, of which 9 cases recurred again. 2 of 9 cases recurred 4 times, of which 1 case died, 1 case recurred 3 times and 6 cases recurred twice.

Zhao et al reported PFS ≥ 61 months and post-recurrence therapeutic approach were independent risk factors for repeated recurrences in 40 recurrent AGCOT patients. In addition, the age at recurrence (≤50y) and post-recurrence therapeutic approach were independent risk factors for death after AGCOT recurrence. Miller et al reported that the patients with early recurrence had significantly high number of mitotic figures and nuclear atypia than those with late recurrence in 19 patients with recurrent AGCOT, while there was no significant difference in mitotic figures numbers and nuclear atypia between the patients with late recurrence and those without recurrence. For the follow-up of GCT patients after treatment, the monitoring of tumor markers should be stressed. Inhibin is expected to become a valuable tumor marker for monitoring the disease and predicting recurrence. Besides that, we found that patients with early stages tend to relapse later, therefore, the importance of regular follow-up should be emphasized for patients in the early stage of disease.

As for recurrent GCT, performing tumor reductive surgery to the most extent may prolong the survival time of patients with recurrence. Chemotherapy can be applied to the adjuvant treatment of unresectable recurrent tumors or patients with recurrent tumors after surgical resection. The BEP scheme is most commonly used. The effective rate of chemotherapy was 51% ~ 92% and platinum-based chemotherapy regimens are also selected for recurrent cases, including PVB, CAP and TP. However, some studies pointed out that although recurrent GCT has a high response rate to chemotherapy, the effect of chemotherapy on the survival of such patients is not clear. Keskin S et al reported that the combination of tamoxifen and leuprolide get good effect in the treatment of a GCT patient. Some researchers have reported the application of radiotherapy in the treatment of recurrent GCT, but most of them are palliative treatment, and most of the effective ones are localized lesions. No case in our study received radiotherapy. It has been reported that the effective rate of radiotherapy can reach 43% (6/14), but the effect of radiotherapy on the survival of patients with recurrent ovarian GCT is still controversial.

Ovarian GCT cases need long-term follow-up, even for life long, because of its characteristic of late recurrence. Postoperative follow-up should include routine examination of upper abdomen and monitoring of plasma Inhibin. Tumor reduction surgery is the first choice for the treatment of recurrent GCT. Chemotherapy, radiotherapy and hormonal therapy can also be the treatment of GCT.
Considering that patients with early stage and complete surgery are more likely to have late recurrence, follow-up should be maintained for these patients. The characteristics and treatment of recurrent GCT still need to be explored, in order to find out the best treatment methods.

**Availability of data and materials:**

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

**Author Contribution:**

Ruiying Dong, Yawen Zheng and Ying Gu conceived and designed the analysis; Yawen Zheng, Ying Gu and Xingsheng Yang analyzed the data; Wenjin Zhang collected the data helped polish the language. All the authors reviewed the final manuscript.

**Competing interests:**

The authors declare no competing interests.

**Ethics approval and consent to participate:**

The research protocol of this study was approved by the Ethics Committee at our institution (KYLL-202008-088).

**Consent for publication:**

Not applicable

**Availability of data and materials:**

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

**Funding:**

Not applicable

**Acknowledgements:**

Thanks to Dr. Kun Wang for his help in the ethics application process, and to Professor Taotao Dong for his help and polishing in the article writing process.

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