Peer Review File

Article information: https://dx.doi.org/10.21037/gpm-22-45

Reviewer A

This paper demonstrated to evaluate the effect of lymphadenectomy on surgical morbidity and survival in early-stage juvenile granulosa cell tumor (JGCT) of the ovary who underwent fertility-sparing surgery(FSS). Critically, the number of cases is exceedingly small; it would be very difficult to gain new insights from a comparison between seven and eight cases. I will mention a few things that I noticed.

Reply: Thanks for your comments. We appreciate the reviewer's insightful suggestion and agree that it would be have a higher credibility to obtain a larger research sample. JGCT is a rare subtype of ovarian cancer, which accounts for 5% of all granulosa cell tumors. Due to the exceptionally low incidence of this condition, literature about treatment and clinical course of JGCTs is scanty. The number of cases reported in the literature are small sample sizes.

There were two studies with relatively large sample sizes nearly 30 years ago (33 cases in 1997, 125cases in 1984). In the past 10 years, except the number of cases in Dan Wang' study was 35, in almost all case studies on JGCT, the number of cases was less than 20. Besides, JGCT almost occurs in premenarchal girls or young women, who has subsequent reproductive needs. Lymphadenectomy procedure usually requires longer operative time and wider surgical incision, which may result in increased intraoperative bleeding and infection rate. Lymphadenectomy still remains as a controversial procedure in the surgical management of the disease. As the reviewer comments, the relatively low number of cases could limit the generalizability of our results. It was hope to provide some new perspective for the treatment of JGCT through our research. Thanks again to the reviewer on suggesting to further improve this manuscript, we have studied comments carefully and have made corresponding corrections which we hope meet with approval.

Changes in the text: Please see page 4 of the revised manuscript, lines 4–6(**bolded and underlined**).

L81: The authors define JGCT here. However, the histologic patterns of the adult and juvenile forms are quite different. It is possible that this factor has not been taken into account.

Reply: We sincerely thank the reviewer for careful reading. As to histopathological features, compared to the adult type. The most frequently observed in JGCT was the macrofollicular arrangement, with variable-sized follicles filled with luminal eosinophilic secretion. The histopathological features also presence of abundant cytoplasmless Call-Exner bodies in JGCT. The article studied the prognostic impact of lymph node dissection in patients in early-stage JGCT, so the article did not focus on the pathological characteristics of JGCT and AGCT.

Changes in the text: Please see page 3 of the revised manuscript, lines 8-10, Page 4, line 1(**bolded and underlined**)..

L120: The postoperative stage of disease is not mentioned, but I think it is an important information.
Reply: Thanks for your comments. The objective of the study was to evaluate the effect of lymphadenectomy on surgical morbidity and survival in early-stage juvenile granulosa cell tumor (JGCT) of the ovary who underwent fertility-sparing surgery (FSS). Early-stage JGCT was defined as the disease confined to the ovary after surgery, which include 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 CT scan. One patient was treated with unilateral salpingo-oophorectomy (USO) at initial surgery and was diagnosed with stage III disease because of the detection of micro-metastasis to the omentum after staging.
Changes in the text: Please see page 4 of the revised manuscript, lines 18–21, page 6, line 4-6(**bolded and underlined**).

L120: How was the metastatic rate in cases with lymph node dissection? According to Ebina Y et al. in 2021, the more advanced the pT was, the higher the frequency of lymph node metastasis. Furthermore, the prognostic factors were significantly influenced by initial intra-abdominal findings such as dissemination and residual tumor at the time of the first surgery.
Reply: Thank the reviewer for the constructive comments and suggestions. Early-stage JGCT was defined as the disease confined to the ovary after surgery, which include 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 CT scan. One patient was treated with unilateral salpingo-oophorectomy (USO) at initial surgery and was diagnosed with stage III disease because of the detection of micro-metastasis to the omentum after staging. Of all the JGCT cases we queried, there were two cases that were not included in the study. Fertility preservation surgery was not performed due to extensive lesions. Intraoperative peritoneal metastases were found during the surgery, while no lymph node metastases was found. However, among one of them, CT examination during postoperative chemotherapy revealed enlarged lymph in the parietal abdominal aorta at the level of the renal hilum considering the possibility of node metastases. However, the prognosis of both patients was poor.
Changes in the text: Please see page 4 of the revised manuscript, lines 18–21, page 6, line 4-6, page 9, line 15-16(**bolded and underlined**).

Reviewer B

Title: "Is lymphadenectomy beneficial for the patients with Early-stage 2 Juvenile Granulosa Cell Tumor of the Ovary" - the title is a question. The question mark was missing. As it stands it may leave some doubt as to whether it is a statement. In the conclusions (line 49) there is the answer to that question: "Lymphadenectomy had no improved effect on survival."

Reply: We were really sorry for our careless mistakes. Thank you for your reminder.

Changes in the text: Please see the title.

The abstract contains all the necessary information and allows the research to be understood. I suggest that the phrase "between January 2013 and January 2022" in line 35/36 be replaced by "a period of 9 years".

Reply: We sincerely thank the reviewer for careful reading. As suggested by the reviewer, we have corrected the " between January 2013 and January 2022"into" in a period of 9 years ".

Changes in the text: Please see page 2 of the revised manuscript, lines 5-6(**bolded and underlined**).

The introduction is well written, justifies and presents the research well.
In lines 35 and 36: "Patients who underwent surgical treatment for JGCT between January 2013 and January 2022 were identified." In lines 80, 81 and 82: "This study was carried out by retrospective analysis of the data of patients with early-stage JGCT at gynecological oncology department of a tertiary center in between March 2013 and February 2022. Although one is the period of assessment and the other of occurrence, it would be better to unify the study period so as not to get confused.

Reply: Thanks for your careful checks. Based on your comments, we have made the corrections to make the word harmonize d within the whole manuscript.

Changes in the text: Please see page 2 of the revised manuscript, lines 5-6, page 4, line 17-18(**bolded and underlined**).

Materials and method, lines 90 and 91, among the patients excluded from the analysis, wasn't there a patient with stage III disease who was excluded? Wasn't this an exclusion criterion too? This patient is described in the results (lines 112 to 115)

Reply: Thank the reviewer for the constructive comments and suggestions. Early-stage JGCT was defined as the disease confined to the ovary after surgery, which include 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 CT scan. One patient was excluded, which was treated with unilateral salpingo-oophorectomy (USO) at initial surgery and diagnosed with stage III disease because of the detection of micro-metastasis to the omentum after staging. So

this case was not included in the study.
Changes in the text: Please see page 4 of the revised manuscript, lines 18-21, page 6, line 4-6(**bolded and underlined**).

Line 128: "And intraoperative or preoperative rupture was observed in 10 patients (66.66%)". High percentage. This may be better justified in the discussion, since the percentage is well above that reported in the literature.
Reply: Thank the reviewer for the constructive comments and suggestions. 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. The incidence of tumor rupture in this study was 66.6%, which is higher than that reported in the literature. 5 cases occurred preoperatively, possible caused by the large tumor diameter (10-35cm). And 1 case occurred intraoperatively.
Changes in the text: Please see page 7 of the revised manuscript, lines 21-22, page 8, line 1-4(**bolded and underlined**).

Line 135: "During a median follow-up time of 31.87 months (range: 2-85 months)".
The discussion is well prepared. It needs minor adjustments:
- Lines 154 to 156: the sentence "Tumor rupture has been reported in up to 10% of cases, but the presence of rupture does not necessarily affect the prognosis." needs a bibliographic reference
Reply: We feel sorry for our carelessness. In our resubmitted manuscript, the bibliographic reference is added. Thanks for your correction.
Specific references are listed as follows:
Reference 10 *Koukourakis G V., Kouloulias VE, Koukourakis MJ, Zacharias GA, Papadimitriou C, Mystakidou K, et al. Granulosa cell tumor of the ovary: Tumor review. Vol. 7, Integrative Cancer Therapies. 2008. p. 204–15.*
Reference 11 *Schneider DT, Calaminus G, Wessalowksi R, Pathmanathan R, Selle B, Sternschulte W, et al. Ovarian sex cord-stromal tumors in children and adolescents. Vol. 21, Journal of Clinical Oncology. 2003. p. 2357–63.*
Changes in the text: Please see page 8 of the revised manuscript, lines 1-2. (**bolded and underlined**)

- Information contained in the sentences of lines 156 to 161 require bibliographic references
Reply: We feel sorry for our carelessness. I n our resubmitted manuscript, the bibliographic reference is added. Thanks for your correction.
Specific references are listed as follows:
Reference 3 *Ndhlovu E, Liu L, Dai J, Dong X, Zhang W, Chen B. Retrospective analysis of clinicopathological characteristics of 19 ovarian juvenile granulosa cell tumor cases. Journal of Obstetrics and Gynaecology Research. 2021 Jul 1;47(7):2492–9.*
Reference 4 *Bergamini A, Ferrandina G, Candotti G, Taccagni G, Scarfone G, Bocciolone L, et al. Stage I juvenile granulosa cell tumors of the ovary: A multicentre*

analysis from the MITO-9 study. European Journal of Surgical Oncology [Internet]. 2021;47(7):1705–9. Available from: https://doi.org/10.1016/j.ejso.2021.02.003
Reference 6 *Hasiakos D, Papakonstantinou K, Goula K, Karvouni E, Fotiou S. Juvenile granulosa cell tumor associated with pregnancy: Report of a case and review of the literature. Gynecol Oncol. 2006 Feb;100(2):426–9.*
Reference 10 K*oukourakis G V., Kouloulias VE, Koukourakis MJ, Zacharias GA, Papadimitriou C, Mystakidou K, et al. Granulosa cell tumor of the ovary: Tumor review. Vol. 7, Integrative Cancer Therapies. 2008. p. 204–15.*
Reference 12 *Xu HS, Zhong E, Rotman J. Juvenile granulosa cell tumor associated with Maffucci syndrome in pregnancy: A case report. Clin Imaging. 2019 Jul 1;56:77–80.*
Reference 13 *Gaughran J, Datta A, Hamilton J, Holland T, Sayasneh A. Juvenile granulosa cell tumour in the third trimester of pregnancy. Int J Reprod Contracept Obstet Gynecol. 2020;9(2):861–6.*
Changes in the text: Please see page 8 of the revised manuscript, lines 4-9(**bolded and underlined**).

- Line 168: in the sentence "Between March 2013 and February 2022", it would be easier to read if it were replaced by "In a period of 9 years...". The period in months is already in Materials and Methods.
Reply: We sincerely thank the reviewer for careful reading. As suggested by the reviewer, we have corrected the " between January 2013 and January 2022"into" in a period of 9 years ".
Changes in the text: Please see page 8 of the revised manuscript, lines 17(**bolded and underlined**).

- Line 186: "Besides, the conclusion of Dan Wang study is consistent with the above discussion" - needs the corresponding bibliographic reference (which is in the references at the end of the article)
Reply: We were really sorry for our careless mistakes. Thank you for your reminder. In our resubmitted manuscript, the bibliographic reference is added. Thanks for your correction. Specific references are listed as follows:
Reference 22 *Wang D, Xiang Y, Wu M, Shen K, Yang J, Huang H, et al. Is adjuvant chemotherapy beneficial for patients with FIGO stage IC adult granulosa cell tumor of the ovary? J Ovarian Res. 2018;11(1):1–7.*
Changes in the text: Please see page 9 of the revised manuscript, lines 12-13(**bolded and underlined**).

The study is relevant, well-written and important in the scientific environment. The authors emphasized the limitations of the study, such as the short follow-up time. Considering the rarity of this type of tumor, the number of patients is not considered a limiting factor. The authors will have to make minor adjustments to make it even clearer. In the conclusions it is possible to see the answer to the title. This is good.

Reply: We sincerely thank the reviewer for careful reading. We have revised the text to address your concerns and hope that it is now clearer.
Changes in the text: Please see page 10 of the revised manuscript, lines 16-18(**bolded and underlined**).

Reviewer C

In their report Li and Li described detailed analysis of 15 patients with early-stage JGCTs, reporting that lymphadenectomy did not change the survival rates in this specific group. They do their best in reporting demographic and clinical patients' characteristics, describing also clinical details of women with tumor recurrences. The main bias of this research, apart from short time follow-up period, is a limited number of cases investigated. In the opinion of the Reviewer, it is difficulty to make any conclusion when you compare the groups composed of 9 /with lymphadenectomy/ and 6 /no lymphadenectomy/ patients. In my opinion, this study needs an international or even multicenter study to find out the reasonable conclusions, it they truly exist. Finally, I wonder if lymphadenectomy is necessary for early-stage JGCT of the ovary. Maybe, a case report of an interesting JGCT of the ovary will be much more appreciate in a case-specific Journal. I recommend to reject this manuscript in its present form based on my criticism outlined above.
Reply: Thanks for your comments. We appreciate the reviewer's insightful suggestion and agree that it would be have a higher credibility to obtain a larger research sample. JGCT is a rare subtype of ovarian cancer, which accounts for 5% of all granulosa cell tumors. Due to the exceptionally low incidence of this condition, literature about treatment and clinical course of JGCTs is scanty. The number of cases reported in the literature are small sample sizes.
There were two studies with relatively large sample sizes nearly 30 years ago (33 cases in 1997, 125cases in 1984). In the past 10 years, except the number of cases in Dan Wang' study was 35, in almost all case studies on JGCT, the number of cases was less than 20. Besides, JGCT almost occurs in premenarchal girls or young women, who has subsequent reproductive needs. Lymphadenectomy procedure usually requires longer operative time and wider surgical incision, which may result in increased intraoperative bleeding and infection rate. Lymphadenectomy still remains as a controversial procedure in the surgical management of the disease. As the reviewer comments, the relatively low number of cases could limit the generalizability of our results. It was hope to provide some new perspective for the treatment of JGCT through our research. Thanks again to the reviewer on suggesting to further improve this manuscript, we have studied comments carefully and have made corresponding corrections which we hope meet with approval.
Changes in the text: Please see page 4 of the revised manuscript, lines 4–6(**bolded and underlined**).