# A single-center retrospective long-term analysis of 80 cases of ovarian Sertoli-Leydig cell tumors

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*To the Editor*: Sertoli-Leydig cell tumors (SLCTs) are a rare type of sex cord-stromal tumor of the ovary, accounting for <0.5% of all ovarian tumors.[1] An accurate diagnosis and the knowledge of prognosis based on clinical and pathological features have important therapeutic implications; however, the rarity of SLCT renders collecting reliable data difficult. We aimed to analyze the features of SLCTs to clarify their relationship with the behavior of the tumor and explore reasonable modes of therapy.

This single-center retrospective study received ethical approval from the Institutional Review Board of the Peking Union Medical College Hospital (No. S-K1338), and the requirement for obtaining informed consent was waived.

Eighty patients with SLCT who were admitted at our institution between 1966 and 2019 were retrospectively reviewed. Patient information was collected from the medical records and clinical database. Pathological findings were assessed and compared with post-treatment clinical manifestation. All specimens were graded randomly by two independent pathologists who were blinded to the histological classification and original diagnosis. All cases were assigned to an International Federation of Gynecology and Obstetrics (FIGO) stage and categorized as follows: well (Grade 1), intermediately (Grade 2), and poorly (Grade 3) differentiated tumors, or undefined. Pathological staging was done according to the FIGO staging system.[2]

GraphPad Prism v.7.0 (GraphPad Software Inc., San Diego, CA, USA) was used for statistical analyses. Fisher exact test was used to analyze the categorical data. A $P$ value of <0.05 was considered statistically significant.

The mean age of the patients was 33 (6–73) years. Among the 80 patients, 46 (57.5%) were aged <30 years, and 21 (26.6%) were post-menopausal. The clinicopathological characteristics of the patients are summarized in Table 1.

Of the 48 patients (average age: 26 [10–53] years; mean tumor diameter: 7.7 [2.0–33.9] cm) showing androgenic manifestations, 44 had oligomenorrhea or amenorrhea, 24 had hirsutism, 20 presented with voice raucity, 16 had clitoromegaly, and seven showed laryngeal protuberance. A serum testosterone evaluation was performed pre-operatively for 48 patients, and 38 showed a significant elevation, with a mean level of 14.2 ± 7.1 (3.5–34.7) nmol/L. Serum testosterone was re-tested in 39 patients 1 to 10 days post-operatively, and all had normal values.

Of the 13 patients (average age: 61 [54–73] years; mean tumor diameter: 8.6 [2–19] cm) presenting with estrogenic manifestations, two who were aged >56 years still had their period, and the remaining 11 had post-menopausal hemorrhage. Eleven patients underwent diagnostic curettage, two had an irregular proliferative endometrium, four had simple hyperplasia, and two had polyps.

Nineteen patients (average age: 33 [6–59] years; mean tumor diameter: 13.4 [2–30] cm) without endocrine symptoms underwent surgery to remove abdominal masses. Seven complained pre-operatively of abdominal pain and distension, and six underwent an emergency operation because of acute and severe abdominal pain caused by a spontaneous tumor rupture.

Intact capsules were identified in 58 cases (stages IA and IB), tumor cells in ascites or ruptured tumors in 20 cases (stage IC), tumors on the omentum majus (stage IIIC) in one case, and widespread metastasis (stage IV) in one case. The average tumor diameter ranged from 7.1 to 30.0 cm [Supplementary Table 1, http://links.lww.com/CM9/A529]. There was no obvious difference between tumor components; the percentages of solid-cystic and solid components were

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**Table 1: Clinicopathological features of 80 cases of SLCTs.**

| Items | N | Percentage (%) |
|---|---|---|
| Menopausal status | | |
| Pre-menopausal | 59 | 73.8 |
| Post-menopausal | 21 | 26.3 |
| Clinical manifestation | | |
| Androgenic | 48 | 60.0 |
| Estrogenic | 13 | 16.3 |
| Non-hormonal | 19 | 23.8 |
| Tumor location | | |
| Left ovary | 34 | 42.5 |
| Right ovary | 42 | 52.5 |
| Bilateral | 3 | 3.8 |
| Not identified* | 1 | 1.3 |
| Tumor stage | | |
| IA | 56 | 70.0 |
| IB | 2 | 2.5 |
| IC | 20 | 25.0 |
| IIIC | 1 | 1.3 |
| IV | 1 | 1.3 |
| Tumor differentiation | | |
| Well | 5 | 6.3 |
| Intermediately | 24 | 30.0 |
| Poorly | 50 | 62.5 |
| Not identified | 1 | 1.3 |

*The tumor was on one side of the ovary, but the exact side was not specified in the clinical report. SLCTs: Sertoli-Leydig cell tumors.

53.75% (43/80) and 46.25% (37/80), respectively. In 77 (96.3%) of the patients, the tumors were confined to one ovary.

Five (6.3%) tumors were well differentiated, 24 (30.0%) were intermediately differentiated, 50 (62.5%) were poorly differentiated, and one (1.3%) was undefined. Of the 80 cases, six had heterologous elements (one case presented with intermediate differentiation with immature striated muscle and another with poor differentiation containing sarcoma elements). A prominent retiform pattern was found in nine cases of poor differentiation [Supplementary Table 2, http://links.lww.com/CM9/A529].

Compared with those showing androgenic or estrogenic manifestations, the group without endocrine symptoms presented with significantly larger proportions of tumors >10 cm in diameter, poorly differentiated tumors, and stage ≥IC tumors [Supplementary Table 3, http://links.lww.com/CM9/A529].

All patients underwent surgical treatment. Among the 80 patients, 6 (7.5%) initially underwent cystectomy, one of whom subsequently underwent unilateral salpingo-oophorectomy, while two had standard staging surgery (omentectomy + appendectomy + pelvic lymphadenectomy). Forty-eight (60.0%) of the patients underwent unilateral salpingo-oophorectomy, 13 of whom had standard staging surgery (omentectomy + appendectomy + pelvic lymphadenectomy), three had omentectomy, and 11 had contralateral ovarian biopsy simultaneously. One (1.3%) patient initially underwent bilateral salpingo-oophorectomy. The remaining 25 (31.3%) patients underwent total hysterectomy and bilateral salpingo-oophorectomy or cytoreductive surgery.

Of the 75 patients with intermediately or poorly differentiated tumors, 45 (60.0%) received systemic chemotherapy after the initial surgery. Two of the 30 patients who did not receive post-operative chemotherapy relapsed and received adjuvant chemotherapy after the second surgery. Regarding chemotherapy, 22 (46.8%) patients received cisplatin + etoposide + bleomycin (PEB); 7 (14.9%) received cisplatin + vinblastine + bleomycin (PVB); and the remainder received paclitaxel + cyclophosphamide (TC), cisplatin + epirubicin + cyclophosphamide (PAC), paclitaxel + cisplatin (TP), vinblastine + actinomycin + cyclophosphamide (VAC), or others (5-fluorouracil, actinomycin, melphalan, or ifosfamide).

Of the patients who received chemotherapy, eight had intermediately differentiated tumors (four cases were stage IA and four were stage IC; six cases had a tumor >10 cm in diameter; and one had heterologous elements), and 37 had poorly differentiated tumors (25 cases were stage IA, one was stage IB, nine were stage IC, one was stage IIIC, and one was stage IV; 15 cases had a tumor >10 cm in diameter, five had heterologous elements, and seven had retiform patterns). The average number of chemotherapy courses was 4.1 (1–20, including one repeated recurrence). Eight (17.8%) patients who received systemic chemotherapy after the initial surgery relapsed.

Follow-up information was available for 76 patients. Four cases were lost to follow-up within 1 year post-operatively. Seven patients died during follow-up, five of SLCT and two of other diseases, including one patient (stage IA, poor differentiation) who died of diabetic nephropathy after 21 months without evidence of ovarian tumor spread, and one (stage IA, intermediate differentiation) who died of breast cancer with multiple osseous metastases after 40 months. Sixty-nine patients survived and were free of the disease for 10 to 383 months (average 86 months) post-operatively.

Ten patients had a recurrence, nine of whom were G3, seven were stage ≥IC, six had no endocrine symptoms, six had a retiform pattern or heterologous elements (four cases had retiform patterns or heterologous elements in the recurrent tissue), six had recurrence at the abdominopelvic cavity, and four died (all were in the group without endocrine symptoms, stage IC, G3, tumor ≥10 cm). The clinicopathological characteristics of the recurrence are summarized in Supplementary Tables 4, http://links.lww.com/CM9/A530 and 5, http://links.lww.com/CM9/A529.

Of the 45 patients who underwent fertility-sparing surgery, 23 did not receive adjuvant therapy. During the treatment, four patients still had no menarche. One 10-year-old patient had had premature thelarche at 3 years of age, menarche at 6 years of age, and amenorrhea at 8 years of age. Among the other 40 patients, normal menstruation resumed within 1 to 3 months post-operatively. Of the 23 patients who received chemotherapy, three experienced irregular periods post-treatment, and one who later

relapsed had transient amenorrhea, although her normal menstruation resumed after a secondary surgery.

In total, 15 of the 19 patients who desired to get pregnant achieved satisfactory reproductive outcomes (two conceived through *in vitro* fertilization and embryo transfer). Two were pregnant, one remained infertile because her partner was infertile, and one continued birth control at the last follow-up.

The incidence of ovarian SLCT is very low, and it occurs in women of different ages; however, women of childbearing age often develop SLCT.[3] In our study, we discovered that ovarian SLCT prognosis is strongly associated with its clinical features, especially endocrine change.

About 60.0% of the patients had manifestations of androgen excess, with oligomenorrhea or amenorrhea, hirsutism, and voice raucity being the most frequent symptoms of virilization. Post-operatively, the serum testosterone level was normalized, menstruation resumed, and virilization manifestations disappeared in the patients. In our study cohort, 16.3% of the patients presented with estrogenic manifestations. The outcome in this group was better when compared with the outcomes for the other two groups. Furthermore, 23.8% of the patients did not show any endocrine abnormalities, although they experienced abdominal pain or abdominal enlargement; the outcome in this group was worse when compared with those in the other two groups.

Surgical resection is the primary treatment for ovarian SLCT. Because well differentiated tumors are almost always benign and unilateral, unilateral salpingo-oophorectomy is adequate.[4] Poorly differentiated, stage ≥IC, and ≥10 cm diameter tumors or tumors with heterologous elements or retiform patterns are correlated with a worse prognosis, and patients with these tumors are recommended to undergo standard staging surgery. However, the efficacy of pelvic lymphadenectomy remains controversial, nodal metastasis is rarely reported in the literature,[5,6] and lymphadenectomy may not have a significant influence on relapse and long-term survival.[7] In our study, no node-positive patients were found.

Given that most patients were diagnosed at reproductive ages with early-stage disease, fertility-sparing surgery was appropriate. In our cohort, 79.0% of the patients who desired to get pregnant achieved satisfactory reproductive outcomes, and none of them relapsed after childbearing.

Adjuvant chemotherapy has not been demonstrated to be beneficial in clinical practice. There was no significant difference in the rate of relapse between the groups receiving and not receiving chemotherapy ($P = 0.1728$) in our study. Drug resistance was observed in relapsed patients.

Sixty-nine patients survived and were disease-free for 10 to 383 months post-operatively. Five patients died of SLCT during follow-up. One (stage IV) died from widespread tumors 1 month after the initial surgery, while the other four died after relapse.

Ten patients had a recurrence, with an average time to recurrence of 19 months. The patients with no endocrine symptoms ($P = 0.0114$), stage ≥IC tumors ($P = 0.0035$), and tumor diameters ≥10 cm ($P = 0.0010$) had a high risk of relapse [Supplementary Tables 4, http://links.lww.com/CM9/A530 and 5, http://links.lww.com/CM9/A529], and higher proportions of poorly differentiated tumors or tumors with retiform patterns or heterologous elements are associated with the absence of endocrine symptoms [Supplementary Tables 2, http://links.lww.com/CM9/A529 and 3, http://links.lww.com/CM9/A529]. Relapsed tumors are often limited to the abdominopelvic cavity, whereas those with aggressive biological behaviors can be widespread.

In brief, our study highlighted that patients with no endocrine symptoms have worse outcomes. Fertility-preserving conservative surgeries are recommended for young patients at an early stage, whereas patients in high-risk groups (poor differentiation, beyond stage I, tumor diameter ≥10 cm, and with retiform patterns or heterologous elements) should receive adjuvant chemotherapy and long-term follow-up.

### Conflicts of interest

None.

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