

ORIGINAL RESEARCH

18 Sertoli-leydig cell tumors of the ovary: analysis of a single institution database

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Abstract

Background: An improved understanding of the clinical presentations, histological character, and therapeutic approaches relevant to ovarian Sertoli-Leydig cell tumors (SLCTs), is of value to better treat this disease. **Methods:** We reviewed the medical records of 18 ovarian SLCT patients seen in our center over the last 10 years. Combined with available literature, we conducted a retrospective study and analysis of this patient group. **Results:** We observed that the patients initially presented at ages ranging from 23 to 72 years, displayed various clinical disease manifestations, and all patients were diagnosed with stage I tumors. Most tumors were solid masses, unilateral lesions, and carried a favorable prognosis. **Conclusions:** Data gathered favor both improved clinical management and better prognostic for patients with SLCT.

Keywords

ovary; Sertoli-Leydig cell tumors; clinicopathological characteristics; surgery; prognosis

1. Introduction

Ovarian Sertoli-Leydig cell tumors (SLCTs) belong to a family of sex cord-stromal tumors, all of which exhibit a testicular pattern of differentiation [1]. It was reported that SLCTs are hormonally active and are generally characterized by the presence of testicular structures that produce androgens. Approximately 70–85% of these tumors are discovered due to the clinical signs and symptoms associated with excess androgen production, such as virilisation [2]. Although limited cases of ovarian SLCTs have been described in the literature, this tumor type primarily occurs in young women, are commonly accompanied by menstruation changes and infertility, and have malignant transformation potential. Due to the overall rarity of SLCTs, these tumors can be difficult to diagnose in a timely manner and identifying suitable treatments can be difficult, resulting in unsatisfying therapeutic outcomes. Given these issues, disease characteristics must be summarized based on the clinical data taken from SLCT patients to enhance awareness of this disease. The aim of this study was to evaluate the clinical and pathological features, treatment, and prognosis of SLCT patients treated in our hospital over the past 10 years.

2. Materials and Methods

This study was approved by the Institutional Review Board of the Beijing Obstetrics and Gynecology Hospital of China. In this study, we conducted a detailed analysis of 18 SLCT patients who were treated at the Beijing Obstetrics and Gynecology Hospital of Capital Medical University. Patients diagnosed with a sex cord-stromal tumor with a purely Sertoli cell composition were excluded from the analysis. Clinical

data, including age, symptoms and signs, surgery choice, clinical staging, pathologic type, chemotherapy regimens, and postoperative follow up were collected from patient medical records and reviewed.

All patients underwent surgical resection for the primary tumor, and SLCT was pathologically confirmed. Two experienced pathologists specializing in gynecologic oncology randomly reviewed all pathological sections. According to morphological characteristics SLCTs can be categorized into four subtypes: well-differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), and retiform. G2 and G3 tumors may also contain heterologous elements, either admixed with the sex cord areas or presented as discrete areas. All SLCTs were pathologically staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [3]. Some patients received adjuvant chemotherapy after surgery and all patients received periodic follow-up and routine clinical checks, during which complaints of symptoms, pelvic examinations, blood tumor markers, and ultrasonic examinations were performed and evaluated.

3. Results

3.1 Clinical Characteristics

A total of 18 patients with morphologically-confirmed ovarian SLCT seen in our clinic from 2009 to 2019 were retrospectively analyzed in this study. The clinicopathological features of all ovarian SLCTs studied in this report are summarized in Table 1. The ages of the patients ranged from 23 to 72 years old, with a mean age of 39.3 years. The median age was 32.8 ± 10.1 years in non-menopausal women, whereas

TABLE 1. Clinicopathological features of the 18 patients with ovarian SLCTs.

Case	Age	Mas	T	Side	Dia	Gross	CA125	Surgery	Chemo	Mons	Stage	Grade	F/U
1	30	+	547	L	3.0	S	N	Lap LSO+Staging	-	87	Ia	G2	S
2	27	-	-	L	14.8	C	N	Lap LSO+Staging	PT2	103	Ia	G2	S
3	56	+	> 1500	R	4.6	S	N	CRS	-	116	Ia	G2	S
4	53	-	-	R	8.9	S	N	Hysterectomy+BSO	-	129	Ia	G2	S
5	27	+	869	L	3.5	S	N	Hysterectomy+BSO	-	76	Ia	G2	S
6	23	+	-	R	4.5	S	N	Lap OPC	-	91	Ia	G2	S
7	25	+	120	R	4.6	CS	N	OPC	-	87	Ia	G2	S
8	52	-	-	R	17.3	C	N	CRS	PT4	87	Ia	G2	S
9	54	-	-	L	1.9	S	N	Lap USO	BEP6	124	Ia	G3	D
10	48	-	-	R	10.0	CS	N	CRS	BEP3 PT3	76	Ia	G2	S
11	36	-	-	L	4.9	S	N	Lap USO	-	72	Ia	G2	S
12	31	+	494	R	9.0	CS	34.4	Lap USO +Staging	BEP3	25	Ia	G3	S
13	72	-	-	L	5.3	CS	N	Lap USO	-	49	Ia	G3	S
14	56	-	-	L	4.5	S	N	Lap Hysterectomy+BSO	-	51	Ia	G3	S
15	34	-	-	L	9.5	CS	N	USO	-	97	Ia	G3	S
16	24	-	-	L	5.5	S	N	Lap OPC	-	33	Ia	G1	S
17	26	-	-	R	5.5	CS	N	Lap OPC	-	44	Ia	G2	S
18	34	+	-	L	4.4	S	N	Lap USO	-	44	Ia	G2	S

Abbreviations: Mas, Masculinization; T, Testosterone; E2, Estradiol 2; L, left; R, right; C, Cystic; S, solid; CS, cystic and solid; N, normal; Lap, laparoscopy; OPC, Oophorocystectomy; USO, Unilateral salpingo-oophorectomy; BSO, Bilateral salpingo-oophorectomy; CRS, cytoreductive surgery, including hysterectomy, BSO, omentectomy, appendectomy, pelvic lymph node dissection; Chemo, chemotherapy; PT, paclitaxel+cisplatin; BEP, cisplatin + etoposide + bleomycin; Mons, months after surgery; F/U, follow up; S, survival; D, dead; Dia, diameter.

the median age of postmenopausal women was 56.8 ± 9.1 years, and these patients presented approximately 10.8 years after the onset of menopause. Of these 18 patients, 11 (61.1%) were younger than 36 years at initial diagnosis, 5 (27.8%) were postmenopausal, and 4 (22.2%) were married but infertile. The SLCT cases accounted for 0.38% of all primary ovarian tumors treated in our hospital over this period of time.

Based on clinical symptoms, we divided all patients into 3 groups. The first group included 5 patients presenting with androgenic manifestations, including 4 (22.2%) with amenorrhea and 2 (11.1%) with signs of virilization, such as a deepening of the voice. The serum testosterone level of 5 of these patients was measured before and after surgery. Serum testosterone levels ranged from 7.1 ± 5.1 ng/mL (range = 1.41–6 ng/mL) before the surgery, but reduced to normal levels within 3–10 days after surgery. The mean mass size was approximately 4.9 ± 2.4 cm (range = 3–9 cm). The average age of patients in this group was 33.8 ± 12.6 years (range = 25–56 years).

The second group included 11 patients who presented with estrogenic manifestations, including 10 patients with irregular menstruation and 1 patient with amenorrhea. Serum estrogen levels were measured before surgery in 6 patients from this group and the median estrogen concentration was within normal range for all patients. The average age of these 11 patients was approximately 42.4 ± 16.8 years (range = 24–72 years), and the mean diameter of the mass present in these patients was 7.2 ± 3.6 cm (range = 1.9–14.8 cm).

The third group included 2 patients who presented with either abdominal pain and/or a palpable abdominal mass. Each patient had postmenopausal hormone levels. The ages of these 2 patients were 48 and 52 years, and the mean diameter of the mass was 13.7 ± 5.2 cm. There was no regularity in the size of tumors with different differentiation (Table 2).

TABLE 2. Relationship between tumor differentiation and size.

Grade	G1	G2	G3
Dia	5.5 ± 0	7.1 ± 4.6	6.1 ± 3.1

In regards to SLCT tumor subtype, the mean diameter of tumor masses classified as G1 tumors was 5.5 ± 0 cm, while the diameter of G2 and G3 tumors was 7.1 ± 4.6 cm, and 6.1 ± 3.1 cm, respectively.

Within all patients included in this study SLCT tumors occurred unilaterally. Most tumors were solid in nature (Fig. 1), and an average diameter of 6.7 ± 1.1 cm (range = 1.9–17.3 cm) was measured. No tumor rupture was observed in any of these tumors and all were staged as Ia neoplasms. Only 1 case was G1, and it consisted of solid Sertoli cells tubules and clusters of Leydig cells within a fibrous stroma. The 12 G2 SLCTs principally consisted of testicular tubules (Figs. 2 and 3). The 5 G3 cases included in this study were largely composed of a sarcomatoid stroma. No heterogenous elements

were identified in any of the cases included in this study. A total of 9 patients underwent molecular analysis, and all cases were typically positive for vimentin and pan-cytokeratin, and we also noted that cells were positive for the sex cord marker α -inhibin (Fig. 4).



FIGURE 1. Grossly, the SLCTs presented as a cystic-solid mass (fluid has been removed), with yellowish nodules.

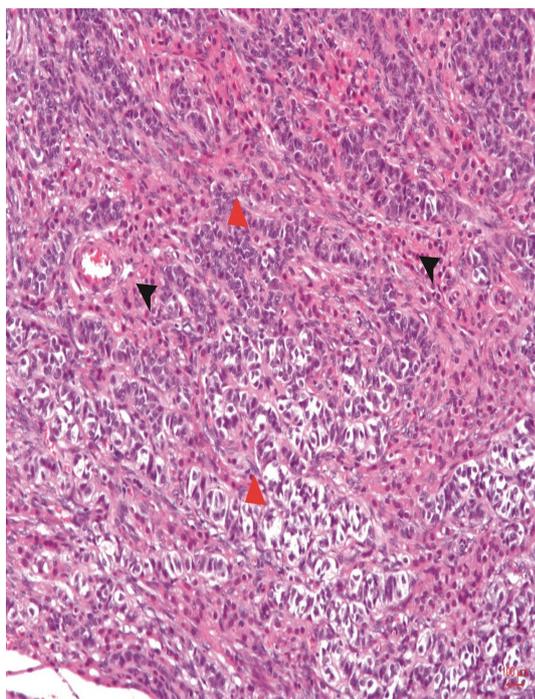


FIGURE 2. Ovarian lesion with Sertoliform tubules adjacent to Leydig component, Leydig cells (black arrow), Sertoli cells (red arrow) (10×10 HE).

3.2 Treatment Protocols

Two patients in the androgenic manifestation group were treated by unilateral salpingo-oophorectomy (USO), 5 patients were treated by oophorectomy, and 3 of the

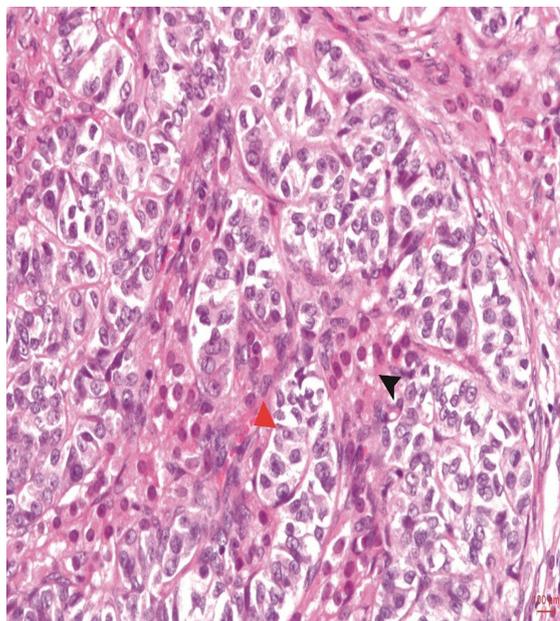


FIGURE 3. Microscopically, Leydig cells (black arrow) are scattered in background of Sertoli cells (red arrow), which arrange in closed tubules. The Sertoli cells have vacuolated cytoplasm filled with lipid (10×20 HE).



FIGURE 4. Diffuse cytoplasmic immunoreactivity for α -inhibin can be found in SLCTs (10×10 HE).

postmenopausal patients underwent hysterectomy and bilateral salpingo-oophorectomy (BSO). Cytoreductive surgery (CRS) was performed in 2 patients. Others were 3 staging surgeries and 3 hysterectomy and BSO surgeries. In addition, 4 patients who were treated by oophorectomy had a mean age of 24.5 years, and each refused a second USO surgery.

A total of 11 cases were treated using laparoscopy, 5 cases with laparotomy, 1 case with laparoscopy followed by laparotomy, and 1 case by sequential laparotomy and laparoscopy. The differences between the operative times, blood transfusion volumes, postoperative recovery, and hospital costs indicated that surgical effects were similar between laparoscopy and laparotomy approaches. A total of 6 patients diagnosed with G2 or G3 ovarian SLCT subtypes received postoperative chemotherapy.

3.3 Patient Follow-Up

All patients were followed after surgery, starting every 3–6 months for the first 5 years and then once per year thereafter. The median follow-up time was 77.3 months (range = 25–129 months). No SLCT-related deaths were noted among the 17 surviving patients, but 1 patient included in this study died in a car accident. During routine clinical checks, menstruation complaints were evaluated, pelvic examination, blood tumor marker tests, and ultrasonography examinations were performed. Among the 17 surviving patients, no recurrence was noted through December, 2021. In 9 of 12 patients who underwent fertility-sparing surgery and did not receive chemotherapy, all 9 patients achieved normal menstruation within 3 months, postoperatively. The remaining 3 patients resumed regular menstruation 6 to 7 months after the final cycle of chemotherapy. Of the 4 patients with infertility prior to surgery who received fertility-sparing surgery and with whom we had available follow-up information, 2 patients experienced full-term pregnancies, and the other 2 patients remained infertile after surgery for personal reasons.

4. Discussion

Ovarian sex cord-stromal tumors are rare neoplasms of the female genital tract. Tumors of this type account for fewer than 0.5% of all primary ovarian neoplasms. SLCTs can occur at any age, ranging from 6 months to 84 years. Over 75% of SLCTs arise during the second or third decades of life, and the average age at clinical diagnosis is approximately 25 years. Fewer than 10% of SLCTs occur before menarche or after menopause [4]. In this study, we found that the median age of SLCT diagnosis was 39.3 years (range: 23–72 years). The median age was approximately 32.6 years among non-menopausal women, whereas the median age of postmenopausal women was approximately 56.8 years. The age of SLCT patients in this study was older than that previously reported in the literature, especially among the premenopausal group.

The principal cytological feature of SLCTs are uncontrolled proliferation of Sertoli and Leydig cells within the ovary. SLCTs can be subdivided into G1, G2 and G3 subtypes based on the degree of tubular differentiation observed within the Sertoli cell component. This feature decreases with increasing tumor grade, and in contrast, the quantity of primitive gonadal stroma increases in higher-grade tumors. Similarly, the number of Leydig cells also decrease with increasing tumor grade [1]. SLCTs tend to show obvious intercellular edema, which can be overlooked as a benign finding. In frozen

sections, SLCT is often misdiagnosed as edematous ovarian stroma. This represents a diagnostic pitfall that clinicians should be aware of, especially as diagnosis of gestational SLCT is challenging. For example, the corpus luteum and simple cysts are still frequently observed during pregnancy, ranging from 11 to 41% of patients examined. These features are also observed in ovarian tumors complicating pregnancies, of which approximately 5% of these tumors are malignant. Meantime, as Juvenile granulosa cell and SLCTs are the most commonly encountered sex-cord stromal tumors [5], differential diagnosis is particularly important.

Most symptoms and signs of SLCTs present clinically as endocrine manifestations [6]. Many SLCTs have been identified in association with androgenic manifestations, such as the development of acne, temporary balding, and deepening of the voice. Some patients with SLCTs display estrogenic manifestations, such as menorrhagia or postmenopausal bleeding. However, approximately 40% of SLCTs were associated with no hormonal production and only presented as an abdominal mass or pain [7]. Evidence of androgen excess is observed in over 43% of cases. After surgery, feminine characteristics can promptly return, however, the disappearance of masculine features can be slow to occur [8]. In our study, 27.2% of SLCT patients had androgenic manifestations, and estrogenic manifestations accounted for 66.7%, with the remaining ~6% of patients displaying an abdominal mass. In this study, patients with androgenic manifestations were not the primary clinical manifestation observed, in contrast to previous reports.

Preoperative diagnosis of SLCT has proven exceedingly difficult. In patients with female endocrine abnormalities and pelvic neoplasms, SLCT should be considered. In addition to clinical and laboratory evidence of androgen or estrogen excess, ultrasonography has been regarded as a useful imaging technique for the initial assessment of SLCT. Other imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), are more useful for tumor staging [9]. SLCTs may be cystic, solid, or cystic solid masses, and approximately 60% of ovarian SLCTs masses are cystic solid in nature. We found that 10 of the SLCTs included in this study were solid masses, accounting for 55.5% of the total cases examined. It has been reported in the literature that the mean diameter of SLCT is 13.5 cm, and that these masses can grow up to 50 cm in tumors of the G3 histological subtype [3]. In our study, the average SLCT diameter was 6.7 cm, and all masses were identified by ultrasonography prior to diagnosis.

SLCTs are commonly unilateral and typically confined to the ovary at the time of diagnosis. Stage I SLCTs comprised nearly 90% of the total tumors diagnosed, and less than 3% of SLCTs invaded tissue outside of the ovary [10]. In this study, all SLCT cases were diagnosed as stage I, were unilateral in nature, and the tumor was restricted to the ovary. Perhaps owing to the rarity of this tumor type, no consensus currently exists regarding the optimal management of stage I disease [11]. Rupture or extra-ovarian SLCT tumors are commonly associated with G3 tumors or recurrent SLCTs [4]. In one study, the G2 and G3 tumors were 22% and 59%, respectively, of the tumors included in this report, with no G1 tumors reported in 207 cases of SLCT. The recurrence rate of G3

SLCTs is 100%, and only one-third of patients with G3 SLCT survived. Similarly, tumors with heterogenous elements are often associated with poorer outcomes [12]. G1 SLCTs are commonly smaller in size, with a mean diameter of 5 cm, whereas G2 and G3 tumors have an average diameter of 15 cm [13]. In this study, G2 or G3 tumors were the most common subtypes observed. Specifically, we found that most of the 18 patients included in this study had tumors of the G2 subtype, 5 patients had the G3 subtype, and only 1 patient presented with a G1 subtype tumor.

Standard management guidelines for ovarian SLCTs remain uncertain. The recommended treatment of SLCTs varies with patient age, fertility condition, tumor differentiation and stage. Surgery is often the first-line treatment method for SLCTs and, in young women for whom the preservation of fertility is desired, USO is often performed if the tumor is stage IA and of the G1 subtype [14]. Patients with G2 or G3 tumors with fertility requirements may choose to undergo USO plus standard staging surgery such as omentectomy, appendectomy, and pelvic lymphadenectomy [15, 16]. G2 or G3 patients with no fertility requirements may choose total hysterectomy, BSO, and standard staging surgery [17].

Currently, there is limited experience in the postoperative management of SLCT, so adjuvant therapy is controversial and its use requires further study [17]. Chemotherapy is not appropriate for stage I and G1 patients, but it is recommended for patients with features associated with poorer prognosis such as advanced staging, moderate to poor tumor grading, heterogenous elements, high mitotic profiles, and tumor rupture [18]. The most common chemotherapeutic regimen is bleomycin, etoposide, and platinum compounds (BEP) [19, 20]. Other regimens include cisplatin, adriamycin, and cyclophosphamide (PAC), or cisplatin, vinblastine, and bleomycin (PVB) [21]. Radiotherapy (RT) is of unknown value for SLCT. In this study, 6 Stage Ia G2 or G3 patients received platinum-containing regimens including BEP or paclitaxel and cisplatin (PT), and these cases showed good outcomes with no recurrence. Recommended options of for postoperative treatment of SLCT outlined in the 2021 NCCN Ovarian Cancer Guideline include RT for limited disease or platinum-based chemotherapy such as BEP or PT regimens.

Sertoli cells are typically positive for vimentin and pan-cytokeratin, in addition to the sex cord markers α -inhibin, calretinin, steroidogenic factor 1 (SF1), Wilms tumor protein 1 (WT1), and forkhead box protein L2 (FOXL2) to varying degrees [22, 23]. Compared with Leydig cells, Sertoli cells tend to stain less diffusely and intensely for α -inhibin. Additionally, staining for α -inhibin may be weak and focal or completely absent in G3 subtype of the tumor. According to Al-Hussaini *et al.* [24] calretinin is thought to be another particularly helpful marker for the identification of SLCTs. Recently, Karnezis *et al.* [25] sought to establish a molecular classifier based on the somatic mutation status of *DICER1* and *FOXL2* genes combined with clinicopathological features, and this classification method has been accepted by the World Health Organization Fifth Edition. Karnezis *et al.* [25] suggested the existence of at least 3 molecular SLCT subtypes, associated with distinct clinicopathologic features: *DICER1*-mutant (presenting in younger patients with more androgenic symptoms,

G2/G3 subtype, retiform, or heterologous elements); *FOXL2*-mutant (presenting in postmenopausal patients, with abnormal bleeding, G2/G3 subtype, without retiform or heterologous elements); and *DICER1/FOXL2*-wildtype (presenting at intermediate ages, without retiform or heterologous elements, and includes all G1 tumors). In one study, *DICER1* mutations were found in 4 of the 8 genetically analyzed SLCTs, and *FOXL2* mutations were found in 2 cases. This study also reported that the sensitivity was approximately 50% and that all cases associated with these gene mutations were G2 or G3 [26]. As such, FOXL2 is generally used with serum inhibins to distinguish sex-cord stromal tumors from non-sex-cord stromal tumors, rather than to compare different SLCTs [27].

Patients with androgenic manifestations should be followed-up, and serum testosterone levels should be evaluated every 3 months during the first year, every 4 months during the second year, every 6 months during the third year, and annually for the rest of their life. Most tumor recurrences occur within 36 months, but recurrence has been reported as late as 35 years after initial diagnosis, thus, lifelong follow-up is of clear importance. Detailed symptoms, physical examination, serum tumor markers, and ultrasonic examinations of the abdomen and pelvis should be performed and, if necessary, CT or MRI may also be ordered. The prognosis of SLCTs is generally good and depends on the stage and degree of tumor differentiation. Of the 17 surviving patients included in this study, all remained free of recurrence to date.

5. Conclusions

SLCT is a rare sex cord-stromal tumor. Most SLCT tumors occur during reproductive ages and present with hormonal abnormalities, pelvic mass, or pain. SLCT frequently occurs unilaterally, are typically confined to the ovary, and 90% cases are diagnosed as stage I tumors. *DICER1* and *FOXL2* mutation testing can be helpful for the differential diagnosis of ovarian SLCT, and these findings can be widely applied to clinical practice. Surgery is the most important treatment approaches, and postoperative therapy may be applied when appropriate. Alternate treatment approaches should be considered to achieve a minimally invasive, standardized management strategy.

ABBREVIATIONS

BEP, cisplatin+etoposide+bleomycin; BSO, bilateral salpingo-oophorectomy; C, cystic; Chemo, chemotherapy; SLCTs, Sertoli-Leydig cell tumors; CRS, cytoreductive surgery (including hysterectomy, BSO, omentectomy, appendectomy, and pelvic lymph node dissection); CS, cystic and solid; CT, computed tomography; Dia, diameter; E2, estradiol; G1, well-differentiated; G2, moderately differentiated; G3, poorly differentiated; Lap, laparoscopy; L, left; Mas, masculinization; Mons, months after surgery; MRI, magnetic resonance imaging; N, normal; OPC, oophorocystectomy; PET, positron imaging tomography; PT, paclitaxel + cisplatin; R, right; S, solid; T, testosterone; USO, unilateral salpingo-oophorectomy; F/U, follow up; S, survival; D, dead.

AUTHOR CONTRIBUTIONS

WL and XZZ designed the research study. YMW gave administrative support. LS and JWM collected the data. WL and SLY was responsible for data analysis and interpretation. WL and XZZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Beijing Obstetrics and Gynecology Hospital, Beijing Maternal and Child Health Care Hospital/Capital Medical University Ethics Board (Approval number 2020-KY-046-01).

ACKNOWLEDGMENT

We would like to express our gratitude to all those in the Gynecologic Oncology and Pathology' department of Beijing Obstetrics and Gynecology Hospital Who helped during the writing of this manuscript. We would like to thank all the peer reviewers for their opinions and suggestions.

FUNDING

This study was funded by grants from Beijing Obstetrics and Gynecology Hospital, Capital Medical University [No. fcy201627], from National Natural Science Foundation of China [No. 81001150], from Beijing Municipal Administration of Hospitals Incubating Program [No. PX2019054] and from Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support [No. ZYLX201705].

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Li W, Yang S, Su L, Miao J, Wu Y, Zheng X. 18 Sertoli-Leydig Cell Tumors of the Ovary: Analysis of a Single Institution Database. *European Journal of Gynaecological Oncology*. 2022; 43(3): 134-140. doi: 10.22514/ejgo.2022.018.