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Original Article

Clinicopathologic features of ovarian Sertoli-Leydig cell tumors

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Abstract: Background: Ovarian Stertoli-Ledig cell tumor (SLCT) is a rare type of sex cord-stromal tumor of the ovary. The present study was to evaluate clinicalopahologic features and prognosis of patients with Sertoli-Leydig cell tumor treated by surgery and adjuvant chemotherapy during short term follow-up. Methods: A total of sixteen patients with ovarian Sertoli-Leydig cell tumor treated at the Obstetrics and Gynecology Hospital, Shanghai, China, between Jan 2001 and Dec 2011 were reviewed. The clinical data, treatment and prognosis were obtained from medical records. Results: The median age of the patients with ovarian Sertoli-Leydig cell tumor was about 27.5 years old in non-menopausal women, while the median age of menopausal women was about 63 years old. The most common complaint was with hormonal-related symptoms in the form of secondary amenorrhea and infinity, features of virilization, abdominal mass or irregular vaginal bleeding. All of sixteen patients underwent surgical staging and all were found to have stage I disease at the time of diagnosis. Eleven patients with intermediate and two patients with poorly differentiated tumors received adjuvant chemotherapy. There were differences found in operative time, blood loss and postoperative recovery time between laparotomy and laparoscopy. There were no disease-related deaths and all patients were under complete remission at the last follow-up. Conclusions: Ovarian Sertoli-Leydig cell tumors could happen in any period age of women. However, the tumors typically occur in the single side while still at the early stage, a favorable outcome could be achieved by surgery and adjuvant chemotherapy. Laparoscopy has similar surgical effects as laparotomy, but has a number of advantages.

Keywords: Ovarian Sertoli-Leydig cell tumors, clinicopathologic features, surgery, chemotherapy

Introduction

Ovarian Sertoli-Leydig cell tumors, also known as androblastoma, belong to the sex cord-stromal tumors which exhibit a testicular pattern of differentiation. Ovarian Sertoli-Leydig cell tumors are rare and account for less than 1% of all primary ovarian tumors [1]. Ovarian Sertoli-Leydig cell tumors typically occur as unilateral ovarian mass in young women, although well or intermediate differentiation. Patients with Sertoli-Leydig cell tumor often present with an abdominal pain and a series symptoms of defeminization and progressive masculinization such as amenorrhea, deepening of the voice, hirsutism, a male pattern hair growth, and clitoromegaly. Because of the scarcity of SLCT, it is difficult to diagnose early and accurately, and hard to carry on the suitable treatment and counter prognosis by a standardized approach. As a result, it is necessary to build a perfect diagnosis and prognosis system based on the clinical and pathologic features for patients with Sertoli-Leydig cell tumor. The aim of the present study was to evaluate clinical and pathologic features, treatment and prognosis of 16 patients suffered with the rare tumor, and treated in the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, PR of China.

Materials and methods

The present study was carried on according to the protocol approved by the ethics committee at The Obstetrics and Gynecology Hospital of Fudan University, Shanghai, PR of China.

In the present study, we analyzed the clinical data from 16 patients, who were diagnosed as patients with ovarian Sertoli-Leydig cell tumors

Table 1. Clinicopathological features of 16 patients with ovarian sertoli-ledig cell tumors

No	Age	Clinical manifestation			Hormone		Histopathology						Therapy			Follow-up		
	Year	mas	fem	INF	T nmol/L	E2 pg/L	Side	Diameter cm	Gross	Stage	Grade	CA125 IU/mL	Surgery		Chemo therapy	Months	Fertility	Outcomes
1	16	+	-	S	7.3	/	left	20	cs	Ia	G2	N	Lap	L-USO	TP	360	-	survive
2	17	+	-	S	5.2	30	right	8.5	cs	Ia	G2	93	Lap	R-USO	PVB	49	-	survive
3	19	+	-	S	6.9	/	right	10	cs	Ia	G2	61	Lap	OPC	PVB	114	-	survive
4	24	+	-	S	13.6	82	right	30	cs	Ia	G2	92.9	TV-Lap	R-USO	PEB	27	-	survive
5	25	+	-	+	3.6	/	left	4	S	Ia	G1	75	TV-Lap	L-USO	/	54	1	survive
6	27	+	-	+	21.9	/	left	4	cs	Ic	G2	N	TV-Lap	L-USO	PEB	38	-	survive
7	43	-	-	+	/	/	right	6	c	Ia	G2	N	Lap	CRS	PVB	123	-	survive
8	49	+	-	+	3.2	/	left	9	cs	Ic	G2	39	Lap	CRS	PVB	82	-	survive
9	49	-	+	-	/	673	left	7.5	cs	Ia	G1	N	Lap	CRS	/	123	-	survive
10	49	-	-	P	/	/	left	7.5	cs	Ia	G3	54.41	TV-Lap	CRS	PVB	97	-	survive
11	59	-	-	P	0.16	/	left	17	cs	Ia	G2	N	Lap	CRS	PEB	34	-	survive
12	61	-	+	P	/	192	right	1.5	S	Ia	G2	N	TV-Lap	CRS	PEB	24	-	survive
13	64	-	+	P	0.22	165	right	10	S	Ia	G1	63	Lap	CRS	/	55	-	survive
14	68	-	+	P	/	129	right	2.7	S	Ia	G2	N	TV-Lap	CRS	PEB	22	-	survive
15	77	-	+	P	0.21	/	right	4	cs	Ia	G3	N	Lap	CRS	PC	67	-	Dead
16	77	-	+	P	/	97	left	8	cs	Ia	G2	36	Lap	CRS	/	84	-	survive

Abbreviations: Mas: Masculinization, including oligomenorrhea or amenorrhea, virilization with a deepening of the voice and hirsutism; Fem: Feminization, including post-menopausal hemorrhage; INF: Infinity; S: Single; P: Postmenstrual; T: Testosterone; E2: Estradiol; C: Cyst; S: Solid; CS: Cyst and solid; N: Normal; USO: Unilateral salpingo-oophorectomy; OPC: Oophorocystectomy; CRS: Cytoreductive surgery, including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, peritoneal biopsies, and staging pelvic lymph node dissection; TP: Paclitaxel + cisplatin; PVB: Cisplatin + vinblastine + bleomycin; PEB: Cisplatin + etoposide + bleomycin; PC: Cyclophosphamide + cisplatin.

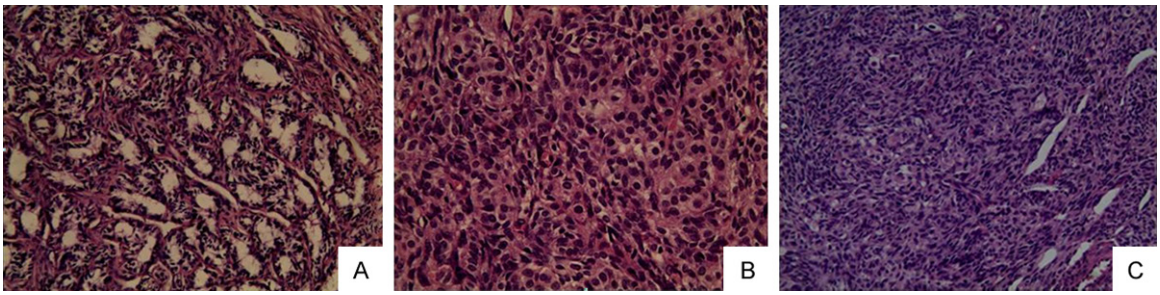

Figure 1. STLCs specimens were showed under the microscope (HE staining 200×). A. Well-differentiated (grade 1); B. Moderately-differentiated (grade 2); C. Poorly-differentiated (grade 3).

and treated in the Obstetrics and Gynecology Hospital of Fudan University during the years 2001-2011. The cases of sex cord-stromal tumor with annular tubules, and pure Sertoli cell tumors were excluded. Clinical data, including age, date of initial diagnosis, presenting symptoms and signs, type of surgery, stage at presentation, histological type, chemotherapy regimens, relapse details, menstrual functions, and fertility of all patients were collected from patient medical records and retrospectively reviewed (**Table 1**).

Two experienced pathologist specializing in gynecologic oncology evaluated all pathology specimens randomly. These tumors are categorized into four subtypes, based on how they look under the microscope (**Figure 1**). These factors are tumor grade and a particular pattern or appearance that the pathologist can identify: 1. Well-differentiated (grade 1); 2. moderately differentiated (grade 2); 3. Poorly-differentiated (grade 3); 4. Retiform pattern (a very characteristic appearance under the microscope). More than 97% of SLCTs are grade I. In other words, they are found very early in the overwhelming majority of cases [2]. SLCTs were pathological staged in accordance with the International Federation of Gynecology and Obstetrics staging system [3].

The initial treatment of SLTC is surgery and adjuvant chemotherapy is a more important approach. The patients in this study all had been followed up since the day of surgery every three months. Routine clinical check-ups, including complains of menstruation, pelvic examination, blood tumor marker and ultrasonography examination were performed and evaluated periodically.

Data were collected and then analyzed using SAS 9.2 (SAS Institute, Cary, North Carolina). The t-and Wilcox-tests were used to assess the categorical data.

Results

Clinical characteristics

Sixteen patients diagnosed as ovarian Sertoli-Leydig tumor were treated in our hospital between 2001 and 2011. The median age was 27.5 ± 12.2 years old in non-menopausal women, while the median age of postmenopausal women was 63.0 ± 10.9 years old about 6 years after menopause. Of the 16 patients, 6 (37.5%) were younger than 30 years old and single, 7 (43.8%) were post-menopausal, and 4 (25%) married but infertile. The incidence of STLCs in sex cord-stromal tumors was about 13.5%, accounting for 0.38% of all of the primary ovarian tumors in the Obstetrics and Gynecology Hospital between 2001 and 2011.

According to the clinical symptoms, we divided the patients into three groups. Seven patients in the first group showed androgenic manifestations. 5 (31.3%) had oligomenorrhea or amenorrhea, and 2 (12.5%) showed virilization with a deepening of the voice and hirsutism. Serum testosterone level was tested before and after surgery in the seven patients. We found that the median level of testosterone concentration was as high as 9.75 ± 6.86 ng/ml (range 3.6 to 21.9 ng/ml) before operation, and reduced to normal level in the ten days after the operation. The mean diameter of the mass in this group was about 11.79 ± 9.73 cm (range 4 to 30 cm). The average age of this group is about 31.5 ± 12.2 years (rang 16 to 49 years). 4 patients in this group were married but inferlity.

There were six patients presented with estrogenic manifestations as the second group. All of the six patients had post-menopausal hem-

Table 2. Pathological features between endocrine function groups

Endocrine function	Number of cases	Average age (years)	Mass diameter (cm)	CA125 (IU/mL)
Androgenic manifestation	7	31.5 ± 12.2	11.79 ± 9.73	80.5 ± 15.5
Estrogenic manifestation	6	59.6 ± 11.0	5.62 ± 3.36	48.1 ± 12.8
No endocrinal features	3	51.7 ± 4.9	10.17 ± 5.97	25.7 ± 9.1

orrhage about 6 year after menopausal. Serum estrogen level was tested before surgery in the six patients. The median level of estrogen concentration was on the normal level. The average age of the six women was about 59.6 ± 11.0 years (range 49 to 77 years), the age of post-menopausal was about 51.7 ± 4.9 (range 45 to 58 years), and the mean diameter of the mass in this group was about 5.62 ± 3.36 cm (range 1.5 to 10 cm).

Three patients were present with a palpable abdominal mass, abdominal distention, or abdominal pain, but without any endocrine symptoms. The three patients had normal serum testosterone level. The average age of this group was about 50.3 ± 8.1 (range 43 to 59 years), and the mean diameter of the mass was about 10.17 ± 5.97 cm (range 6 to 17 cm).

Seven of the sixteen patients had high levels of the tumor markers CA125, four with androgenic manifestations (80.5 ± 15.5), and three with estrogenic manifestations (48.1 ± 12.8) (**Table 2**).

Histopathological features

All of the 16 cases occurred in one side ovary. Most of them had solid and cystic components, with an average diameter of 7.13 ± 4.59 (range 1.5 to 30 cm). 14 of the 16 cases were identified with intact capsules (stage Ia) and two cases were ruptured during surgical operation (stage Ic). Only three cases were well-differentiated which consisted of solid or hollow tubules composed of Sertoli cells and a delicate fibrous stroma containing clusters of Leydig cells. Eleven moderately-differentiated SLCTs were composed of testicular tubules, observed in all stages of gonadogenesis. Two poorly-differentiated neoplasms were largely composed of sarcomatoid stroma with pleomorphic stroma and rudimentary tubule formation. These also met the qualifications for retiform elements (< 90% of the tumor). A heterogonous element (mucinous cystadenoma) was present in one poorly-differentiated SLCT. Mucinous cystadenoma is rarely associated with other sex cord stromal tumors, with the exception of the sporadic reports of benign or malignant mucinous epithelial tumors occurring in intimate association with granulosa cell tumors [6, 7].

Treatment

There were still no exact guidelines regarding clinical management of SLTC. Given ovarian Sertoli-Leydig cell tumors typically occur in unilateral side with mass varying from 0.8 to 30 cm and in young patients, surgical intervention that maintain fertility should be discussed [4]. According to the patient age, productive will and stage, we performed different surgery ranges and modes. For young women, unilateral salpingo-oophorectomy (USO), removal of a single ovary and fallopian tube while preserving the uterus and other adnexa, was recommended if the tumor is detected in stage I. Hysterectomy and bilateral salpingo-oophorectomy, concomitant with pelvic lymph node dissection, were indicated for more advanced stages. The operation and adjuvant chemotherapy were also recommended for all poorly differentiated SLCTs, intermediately differentiated tumors with intraoperative evidence of rupture, mesenchymal heterogonous elements containing subtypes, and for perimenopausal or postmenopausal women [5].

As all the 16 patients had stage Ia or Ic tumors confined to one ovary, 5 patients in androgenic manifestations group had unilateral salpingo-oophorectomy, 1 had oophorocystectomy and 1 stage Ic had cytoreductive surgery, including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy, peritoneal biopsies, and staging pelvic lymph node dissection. Cytoreductive surgery was performed in all six patients in the estrogenic manifestations group and in the no-endocrine symptom group.

Six cases were performed by laparoscopy, and the rest were performed by laparotomy directly.

Table 3. Surgery pathway evaluation

Characteristic	Surgery pathway	Number of cases	Average blood loss (ml)	*P*-value	Average operating Time (h)	*P*-value	Average hospital Time (d)	*P*-value
USO	Laparotomy	3	193.3 ± 51.3		79.7 ± 5.7		7.7 ± 0.6	
	Laparoscopy	3	66.7 ± 28.9	0.043	47 ± 2.6	0.013	4.3 ± 0.6	0.01
CRS	Laparotomy	7	316.7 ± 76.4		152.3 ± 6.8		9.3 ± 0.6	
	Laparoscopy	3	210 ± 36.1	0.048	163.3 ± 20.8	0.319	5.7 ± 0.7	0.008

The differences in the operative time, blood loss, postoperative recovery time and cost of hospitalization between laparotomy and laparoscopy showed that laparoscopy had similar surgical effects as laparotomy, but had a number of advantages (**Table 3**). Only the three well-differentiated SLCT patients did not receive chemotherapy. Platinum-based chemotherapy (PEB; carboplatin on day 1, etoposide and bleomycin on day 3) was administered to thirteen patients for 4 cycles.

Follow-up

All of the patients in this report had been followed up since the day of surgery every three months. The median follow-up was 84.6 months (range 25 to 361 months). One patient died of car accidence, and no tumor-related death occurred in the other fifteen patients. With the data of routine clinical check-ups, including complaints of menstruation, pelvic examination, blood tumor marker and ultrasonography examination, the fifteen patients were found no recurrence of SLTC till Sep 2013. Of the six patients undergoing fertility-sparing surgery, only one did not receive chemotherapy and got normal menstruation with 3 months postoperatively. The rest of the five patients resumed regular menstruation 6 to 8 months after the last chemotherapy cycle. Of the 4 patients with infertility before the operation, two had cytoreductive surgery, and the rest two patients had follow up information. One had experienced full-term pregnancy, and one remained infertile after 38 month.

Discussion

Ovarian sex cord-stromal tumors are rare kinds of neoplasm of the upper female genital tract. Sertoli-Leydig cell tumor of ovary belongs to sex cord-stromal tumors of ovary and accounts for less than 0.5% of all primary ovarian neoplasms [1].

It is reported that SLTCs can occur in any age period ranging from 6 months to 75 years old. Over 75% of SLTCs happened during the second and third decades of women's life, and the average age of clinical diagnosis is about 25 years old. There were less than 10% of STLCs took place prior menarche or postmenopause [1]. In the present study, we found that the median age of STLCs was roughly 45 years (range 16 to 77 years). The median age was about 27.5 years old in non-menopausal women, while the median age of postmenopausal women was about 63 years old.

STLCs typically occur unilaterally, mostly were confined to ovary. Bilateral ovarian STLCs were rare accounting for roughly 1.5% of all STLCs. Moreover, nearly 90% of STLCs were classified as stage I at the time of clinical diagnosis, and less than 3% of all STLCs spread over the ovary [8]. In the study of 16 patients, all cases were classified as stage I and confined to one side ovary.

STLC is characterized by uncontrolled proliferation of naturally occurring Sertoli and Leydig cells of varying degrees of differentiation in the ovary. Clinically, symptoms and signs of SLCTs mostly related to endocrinal manifestations [9]. One-third (33-38%) of STLCs could be identified for androgenic manifestation associating with a loss of female secondary sex characteristics, including atrophy of the breasts and disappearance of female body contours followed by progressive masculinization supervenes, including acne, temporal balding, deepening of the voice, and enlargement of the clitoris. These symptoms are the results of androgen excess. Such virilization is usually accompanied by elevated levels of serum testosterone produced by Sertoli-Leydig cells. Occasionally, SLCTs have estrogenic manifestations, such as menorrhagia/metrorrhagia or postmenopausal bleeding. However, there were still approximately 50% of

SLCTs had no hormonal production and only presented with abdominal mass or pain [10]. Elevated serum levels of testosterone and estrogen can be often identified in approximately 80% of patients with ovarian SLCTs and endocrinal manifestations [11, 12]. Testosterone serum levels greater than 7 nmol/L are generally associated with an androgenic neoplasm from ovaries, adrenals, or elsewhere [13].

According to the serum hormonal level and clinical symptoms, we divided the patients into three groups. First, seven patients showed androgenic manifestations. 5 (31.3%) had oligomenorrhea or amenorrhea, and 2 (12.5%) showed virilization with a deepening of the voice and hirsutism. The median level of testosterone concentration was as high as 11.7 ± 8.9 ng/ml (range 2.8 to 20.6 ng/ml) before operation, and reduced to normal level in the ten days after the operation. Second, six patients presented with estrogenic manifestations. All of the six patients had post-menopausal hemorrhage about 6 year after menopausal. The median level of estrogen concentration was on the normal level. Three patients were present with a palpable abdominal mass, abdominal distention, or abdominal pain, but without any endocrine symptoms. The three patients had normal serum testosterone level.

The diagnosis of STLCs before surgery is exceedingly difficult. When a women presented with a complaint of endocrinal manifestations with abdominal mass, we should take care of STLCs. Beside the clinical and laboratory proofs of androgen or estrogen excess, ultrasound remains the preferred imaging method, and transvaginal or transrectal ultrasound appears to achieve better morphologic features of adnexal masses than abdominal sonography, because of its high sensitivity and cost-effectiveness [14, 15].

SLCTs typically exhibit solid or sonographic appearance and mostly unilateral mass [1, 3]. Components of SLCTs can be purely solid, purely cystic, or mixed [1]. Mixed (solid and cystic) components are most commonly encountered in roughly 60% of all ovarian SLCTs [1]. Average SLCT diameter is 13.5 cm and can reach as huge as 50 cm in poorly differentiated histological variants [1]. However, as the size of STLCs can sometimes be undetectable by ultrasonic, other imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron imaging tomography (PET) scans can be used for better recognization of SLCTs.

The neoplastic Sertoli and Leydig cells in the ovary exhibit varying degrees of differentiation which include well differentiated, moderately differentiated, poorly differentiated, and with heterogonous elements [16]. Sometimes, SLCTs are complicated by rupture or spread outside the ovary and it is more common in association with poorly differentiated tumors or recurrence of the malignant SLCTs [1]. In Young and Scully study of 207 cases, none of the well-differentiated, 11% of intermediately-differentiated, 59% of poorly-differentiated and about 19% of tumors with heterogonous elements were clinically malignant. Patients with poorly-differentiated SLCTs have a recurrence rate of 100% and only a third of cases could be survival [1]. Tumors with heterogonous mesenchymal elements (i.e., skeletal muscle or cartilage) or neuroblastoma are associated with a poor outcome [17]. In contrast, the occurrence of gastrointestinal epithelium or carcinoid elements does not alter the prognosis [18]. The presence of retiform elements seems to be an unfavorable prognostic factor.

Standard management guideline of ovarian STLCs is still uncertain. Recommended treatment of Sertoli-Leydig cell tumor varies with patient age, tumor stage, and differentiation. Surgery is the initial method to deal with STLCs. Fertility-sparing surgery (unilateral salpingooophorectomy) can be carried out in all well-differentiated ovarian SLCTs. Patients desiring fertility but exhibiting moderately or poorly differentiated ovarian SLCTs can be considered for unilateral salpingo-oophorectomy plus standard staging surgery (omentectomy, appendectomy, and pelvic lymphadenectomy) [19, 20]. Patients who do not desire fertility or poorly-intermediately differentiated with intraoperative evidence of rupture, and mesenchymal heterogonous elements containing subtypes should be considered for total hysterectomy, bilateral salpingooophorectomy in addition to complete standard staging surgery [21].

Due to limited information about effectiveness of postoperative therapy, adjuvant therapy remains questionable and requires further

evaluation [22]. Radiotherapy is of unknown value [4]. Adjuvant therapy is not indicated for patients with stage I and G1 STLCs, but postoperative chemotherapy is recommended for patients with poor prognostic factors such as advanced disease staging, moderate-to-poor tumor grading, high mitotic profile, existence of heterogonous elements and tumor rupture [1-3]. The most frequently used chemotherapeutical regimen is cisplatin, etoposide, and bleomycin (PEB) [23, 24]. Other regimens also exist such as (1) cisplatin, Adriamycin, and cyclophosphamide (PAC), and cisplatin, vinblastine, and bleomycin (PVB) [25]. In our study, the Stage Ia and G2-3 patients received platinum-containing regimens (PEB: carboplatin on day 1, etoposide and bleomycin on day 3), PVB, TP and PC. However, for the small number of cases, no difference of efficiency was found among these regimens.

Recently, tumor markers have been evaluated as diagnostic and prognostic indicators for SLCTs. Inhibin-α is positive in ovarian granulosa cells and testicular Leydig interstitial cells, and is useful in diagnosing SLCTs. Vimentin is one of the intermediate filaments, mainly distributed in the tumors of mesenchymal origin, and is mainly used for diagnosing tumors of mesenchymal source, such as SLCTs. Therefore, both Inhibin-α and vimentin expression may be helpful immunohistochemical stains to aid in the pathologic diagnosis [26]. According to Movahedi-Lankarani and Kurman, the new tumor marker calretinin may aid in monitoring patients with ovarian sex cord-stromal neoplasms [27]. Calretinin is thought to be another particularly helpful marker in identifying the tumors [28]. In addition, it has been shown that SLCTs stain positive for WT-1 and CD56 [29]. Recently, Williams suggested that a FOXL2-negative, and calretinin-or inhibin-α-positive immunophenotype is associated with SLCT and other steroid cell tumors [30]. Accordingly, patients with Sertoli-Leydig cell tumors can be followed with serum FOXL2 (a transcription factor expressed mainly in the adult ovary and critical for the development of granulosa cells), inhibin-α, calretinin, and testosterone levels. Patients should be followed up on serum testosterone levels every 3 months during the first year, every 4 months during the second year, every 6 months during the third year, and thereafter annually for rest of their life. As most recurrences occur within 36 months but are known to occur as late as 35 years, lifelong follow-up is necessary [31]. During follow-up visits, detailed history, examination, serum testosterone levels and ultrasound examination of the abdomen and pelvis are done. If required, CT or MRI of the abdomen or pelvis may also be ordered. Our 15 remaining patients remained free of recurrence after 5-years of follow-up.

In conclusion, STLC is a rare gonadal tumor belonging to the sex cord-stromal type. The vast majority of SLCTs present with hormonal magnification or abdominal mass or pain and be diagnosed during reproductive age, frequently unilateral, mostly confined to ovary and nearly 90% classified as stage I grade 1 at the time of clinical diagnosis. Further studies of SLCTs are still of major importance. Surgical staging should be optimal, postoperative therapy may be advisable, extensive alternate treatments should be assembled to achieve a minimally invasive, standardized management.

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Disclosure of conflict of interest

None.

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