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Original Research

Survival outcomes of sex cord-stromal tumors of the ovary

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Summary

Objective: To evaluate the role of retroperitoneal lymphadenectomy and the survival outcomes of malignant ovarian sex cord-stromal tumors (SCSTs). *Materials and Methods:* Patients with malignant SCSTs of the ovary who underwent surgery between January 2005 and March 2017 were retrospectively reviewed. The authors analyzed stage, histology, clinical presentation, type of surgery, the role of lymphadenectomy, five-year disease-free survival, and five-year overall survival. *Results:* Fifty-four patients with malignant SCSTs of the ovary were identified in this study. Retroperitoneal lymph node dissection was performed in 30 (55.6%) patients. No lymph node metastasis was detected. At the median follow-up time of 35 months, the five-year disease-free survival and the five-year overall survival was 88.7% and 92.4%, respectively. *Conclusion:* The survival outcomes of women with ovarian sex cord-stromal malignancies are favorable. No lymph node metastasis is detected in this study. Retroperitoneal lymphadenectomy may be omitted in a surgical staging procedure for these patients.

Key words: Ovarian sex cord-stromal tumor; Survival outcomes; Chemotherapy.

Introduction

Ovarian sex cord-stromal tumors (SCSTs) are a rare gynecologic neoplasm, comprising 1.2 percent of all ovarian malignancies [1]. The most common histology is granulosa cell tumors (GCT), followed by Sertoli-Leydig cell tumors and theca cell tumors [2]. Ovarian SCSTs are primary present in biphasic age groups, adolescents and fifth to the sixth decades of life. Characteristics of SCSTs are the early stage of presentation, slow progression, late recurrence, and favorable long-term prognosis. Prognostic factors of SCSTs include stage, age, tumor size, and residual disease [3-5]. SCSTs are hormonal secreting tumors that produce estrogen, progesterone, and androgen. Excessive estrogen production leads to an increased incidence of isosexual precocious puberty, endometrial hyperplasia, and associated risk for endometrial cancer [6]. The incidence of malignant ovarian SCSTs most likely occurs in younger age groups with good response to chemotherapy of bleomycin, etoposide, and cisplatin (BEP) regimen [7]. The standard treatment for such tumors is fertility-sparing surgery in patients who have a desire to preserve fertility and complete surgical staging procedure in patients with a completed family. With this method of treatment, the tenyear survival rates were 86% to 96% in early-stage and 26% to 49% in advanced stage diseases [8].

The authors conducted this retrospective study to analyze the role of retroperitoneal lymphadenectomy and the survival outcomes of patients with malignant ovarian SCSTs who were treated in this center.

Materials and Methods

This study was approved by the Research Ethics Committee of Faculty of Medicine, Chiang Mai University. A retrospective analysis of patients with malignant ovarian SCSTs who were treated between January 2005 and March 2017 at Chiang Mai University Hospital was carried out. All cases were identified from the clinical database of the Gynecologic Oncology Division. Clinical charts, operative reports, and pathology reports were reviewed. Stages were assigned according to the 2012 FIGO staging system [9]. The characteristic data included age at first diagnosis, stage, histology, clinical presentation, type of surgery, lymph node status, concurrent endometrial lesions, adjuvant treatments, and survival outcomes. All pathological specimens were examined by gynecologic pathologists in the present hospital. Adjuvant treatments were at the discretion of the attending gynecologic oncologists.

The inclusion criteria were patients with the pathologic diagnosis of malignant SCSTs of the ovary undergoing tumor debulking surgery with or without adjuvant chemotherapy. Exclusion criteria included patients with non-stromal ovarian cancer and pregnancy. The authors also excluded the patients whose medical records were incomplete and those who were lost to follow up. The types of the surgery in the study were divided into four groups; 1) complete surgical staging which included total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), and lymph node sampling or lymphadenectomy (pelvic and/or para-aortic), omentectomy, and peritoneal washing, 2) TAH and BSO or unilateral SO (USO) without lymph node sam-

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Table 1. — *Clinico-pathological variables of patients with malignant ovarian sex cord-stromal tumors*

Clinico-pathological variables (n=54)	Outcome*
Age of diagnosis	
Median (yrs) (range)	56 (12 - 80)
Clinical presentation	
Pelvic mass	34 (63.0)
Abnormal bleeding	8 (14.8)
Abdominal pain	12 (22.2)
Tumor size (cm)	
Median (range)	13 (4 - 30)
Tumor site	
Unilateral	49 (90.7)
Bilateral	5 (9.3)
Surgery	
Complete surgical staging	25 (46.3)
TAH and USO/BSO without lymphadenectomy	14 (25.9)
USO with lymphadenectomy	4 (7.4)
USO without lymphadenectomy	11 (20.4)
Stage	
I	47 (87.0)
II	1 (1.9)
III	5 (9.2)
IV	1 (1.9)
Histology	
Adult granulosa cell tumor	38 (70.4)
Juvenile granulosa cell tumor	6 (11.1)
Sertoli - Leydig cell tumor	5 (9.2)
Sex cord tumor with annular tubule	2 (3.7)
Unclassified sex cord-stromal tumor	3 (5.6)
Lymph node removal	
Pelvic	15 (27.8)
Pelvic and para-aortic	15 (27.8)
Number of nodes removed	
Median (range)	9 (1 - 40)
Lymph node status	
Negative	30 (100)
Positive	0
Concurrent endometrial lesion	
Endometrial hyperplasia	5 (9.2)
Endometrial cancer	1 (1.8)
Residual disease	
Optimal	48 (88.9)
Sub – optimal	6 (11.1)
Recurrence	
Local	1 (1.8)
Distant	3 (5.5)
Adjuvant chemotherapy	
None	31 (57.5)
BEP regimen	22 (40.7)
Single carboplatin	1 (1.8)

**Outcomes were presented as number (percentage), except for age, tumor size and total number of nodes removed presented as median (range); TAH, Total abdominal hysterectomy; USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy; BEP, Bleomycin, etoposide, and cisplatin.*

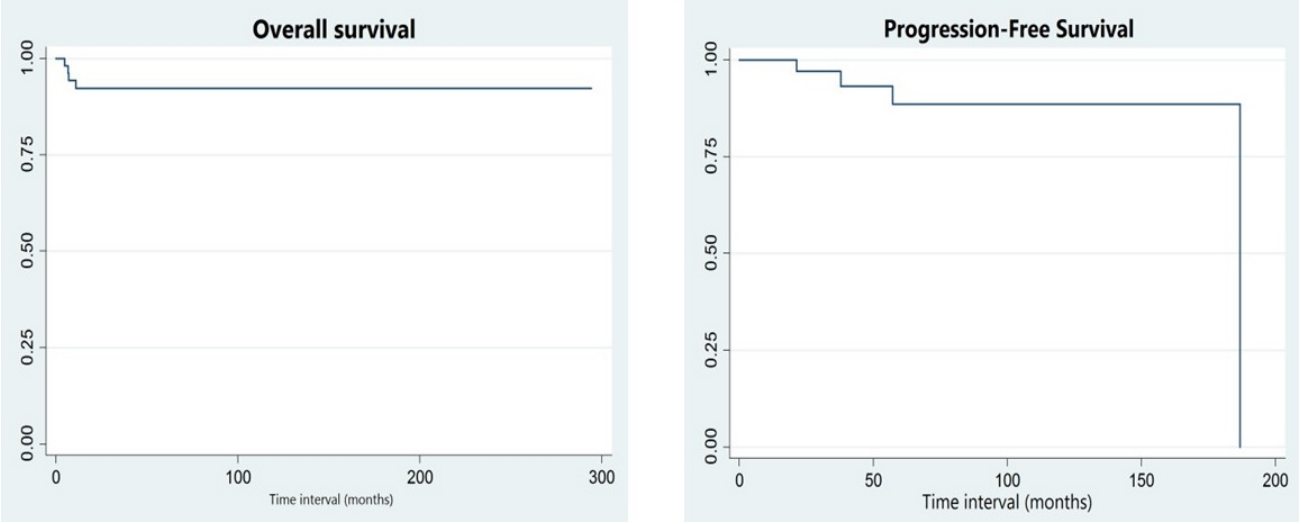

Figure 1. — Kaplan-Meier survival analysis for five-year overall survival and five-year progression-free survival (A = overall survival, B = progression-free survival).

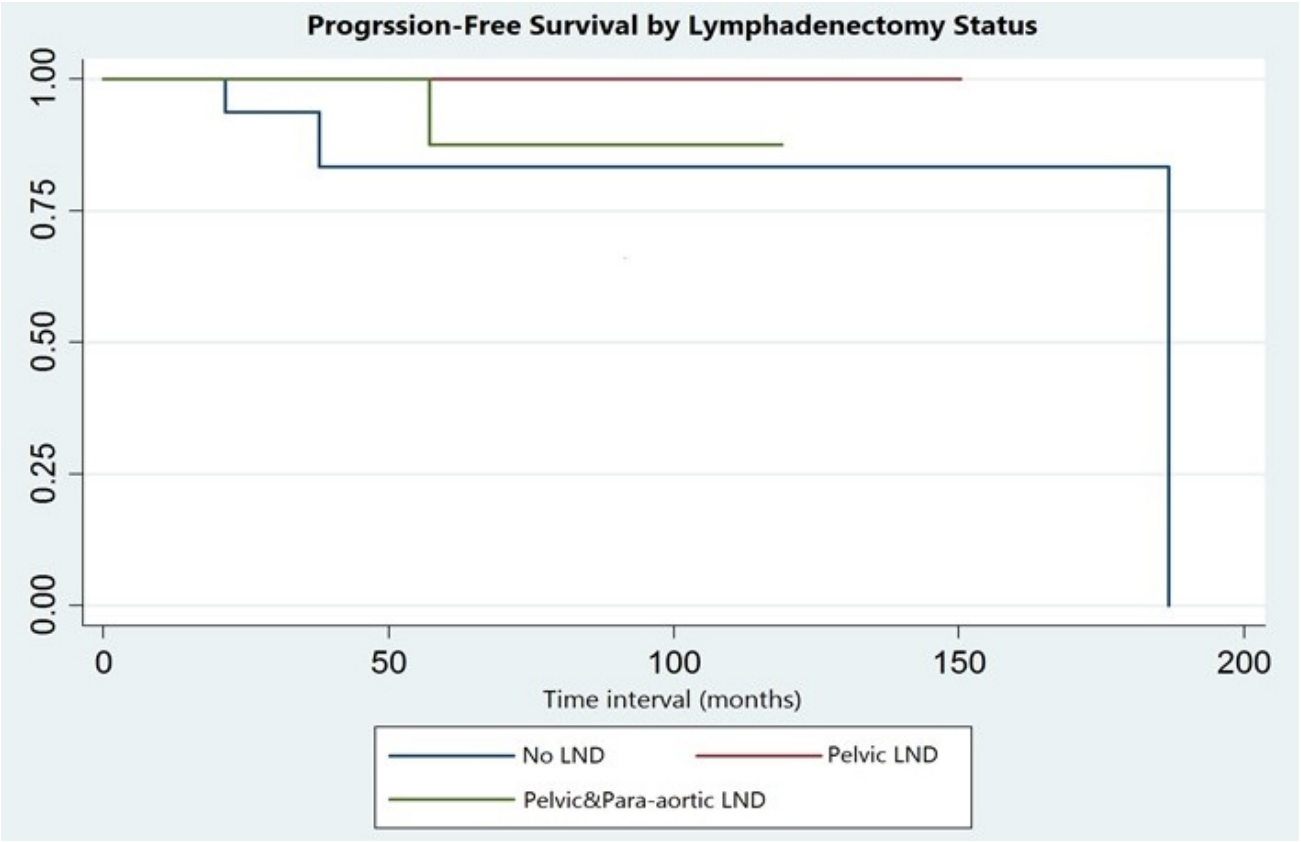

Figure 2. — Fiver-year progression-free survival stratified by lymphadenectomy status ($p = 0.51$).

pling or lymphadenectomy, 3) fertility sparing surgery included USO with lymph node sampling or lymphadenectomy (pelvic and/or para-aortic), and 4) fertility sparing surgery included USO without lymph node sampling or lymphadenectomy.

The response evaluation criteria in solid tumors (RECIST) criteria were used for the evaluation of response after treatment. After completed treatment, all women were followed every three months for one year, every four months in the second year, every six months up to five years, and yearly thereafter. The surveillance after treatments consisted of history taking, physical examination, imaging studies, including computed tomography of the whole abdomen and chest X-ray, as indicated.

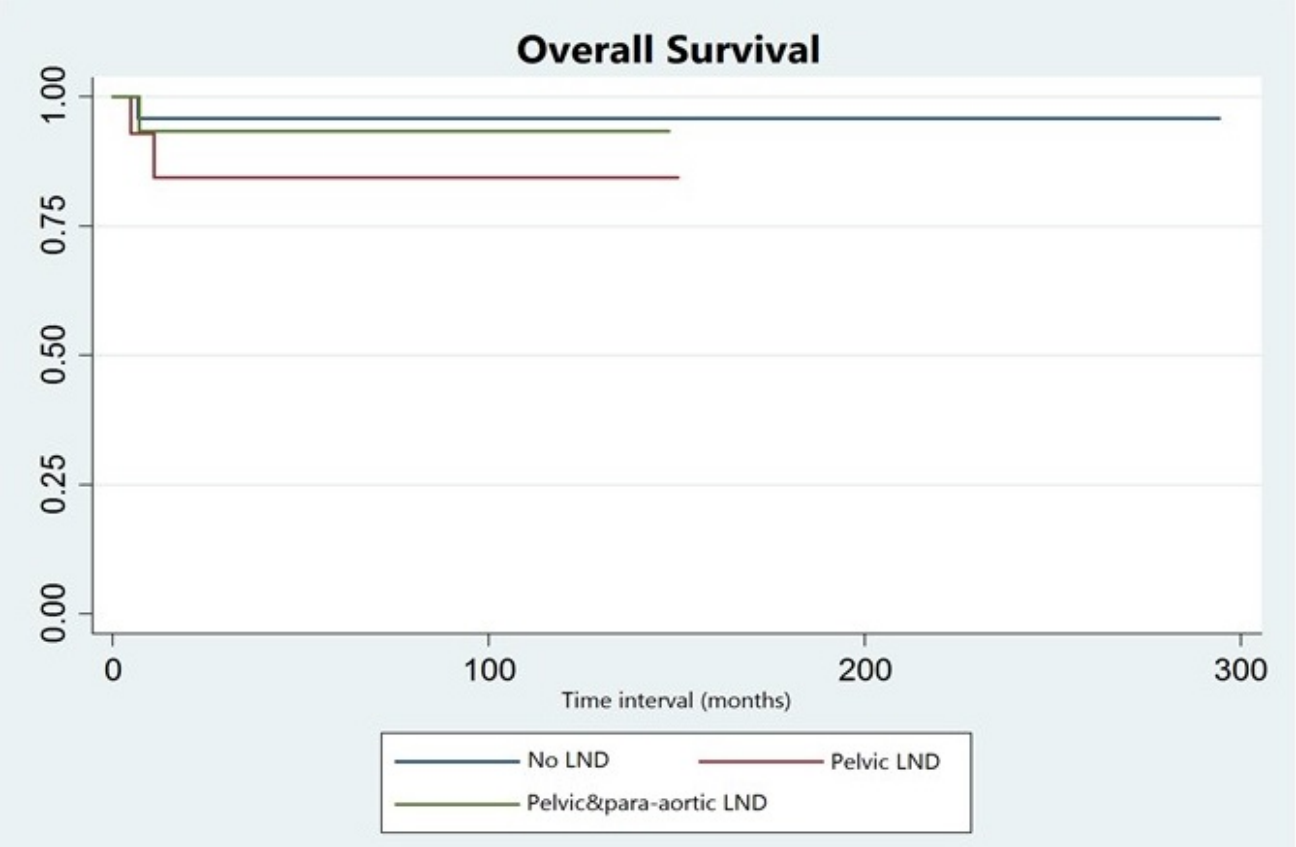

Figure 3. — Five-year overall survival stratified by lymphadenectomy status ($p = 0.46$).

The period between the date of surgery and the date of recurrence diagnosis, or the date of the last follow up was defined as the disease-free interval. Overall survival was calculated by employing the period between the date of surgery and the date of death or date of last follow up. The overall survival and the disease-free survival were analyzed using the Kaplan-Meier methods and the difference was tested for statistical significance using the log-rank test. The data were tabulated and the median range for variables was calculated. The proportion was used to describe categorical data. Descriptive data were listed as median (range) and discrete data were reported as number (percentage). The p-value of < 0.05 was considered statistically significant. All analyses were performed using STATA SE version 11.0.

Results

The authors identified 61 patients with the pathologic diagnosis of malignant ovarian SCSTs. Seven patients were excluded because of incomplete medical records. The clinico-pathological variables of 54 patients are shown in Table 1. The median age of the study group was 56 years. Adult GCT was the most common histology, accounting for 70.4% followed by juvenile GCT (11.1%). Of the 54 patients, 39 (72.2%) patients underwent hysterectomy and adnexectomy, while 15 (27.8%) patients underwent fertilitysparing surgery. For those who had the hysterectomy with adnexectomy, 25 (64.1%) also had complete surgical staging procedure performed. For women who had fertilitysparing surgery, four (26.7%) also had nodal sampling or resection procedure. Overall, retroperitoneal node dissection was performed as part of the staging procedure in 30 (55.6%) patients (15 patients had only pelvic node dissection and 15 patients had both pelvic and para-aortic node dissection). The median number of lymph nodes removed was nine (range 1-40). All lymph nodes were histologically negative for malignancy. Forty-seven (87.0%) patients had Stage I diseases. Five patients with Stage III had gross intra-abdominal disease without lymph node metastasis. Among two patients with Stage IV, one had pulmonary metastasis and the other had liver metastasis. Furthermore, one patient with adult GCT had concurrent Stage IA endometrial carcinoma and Stage IA endometrioid fallopian tube carcinoma. In this patient, the endometrial tissue showed endometrioid adenocarcinoma with a background of atypical endometrial hyperplasia. Five patients with endometrial hyperplasia were diagnosed preoperatively. Twenty-two patients received adjuvant chemotherapy consisting of BEP. Only one patient received single carboplatin due to renal insufficiency.

Of the four patients whose disease recurred, one had a local recurrence in the pelvic cavity. She had Stage IIIC adult GCT with residual tumor at cul-de-sac after TAH with

BSO. The remaining three patients experienced distant recurrences at liver parenchyma (2) and omentum (1). Two patients had prior Stage IC and the other had prior Stage IIIC disease. These three cases had adult GCT. Two patients received prior complete surgical staging and one underwent prior fertility-sparing surgery. The time interval after treatment completion to recurrence was 4–15 years. All patients whose disease recurred were alive with no evidence of lymph node metastasis.

With the median follow-up of 35 months, the five-year progression–free survival (PFS) was 88.7% and five-year overall survival (OS) was 92.4% (Figure 1). The five-year PFS was 83.3%, 100%, and 87.5% for patients without lymph node removal, patients with pelvic lymph node removal, and patients with pelvic and para-aortic lymph node removal, respectively ($p = 0.51$) (Figure 2). The five-year OS was 95.8%, 84.8%, and 93.3% for patients without lymph node removal, patients with pelvic lymph node removal, and patients with pelvic and para-aortic lymph node removal, respectively ($p = 0.46$) (Figure 3).

Discussion

Patients with malignant ovarian SCSTs in this study appeared to have a good prognosis. Over 87% of the patients presented with early-stage disease. Nearly 90% of the patients had optimal debulking surgery. No lymph node metastasis was found among patients undergoing nodal dissection. Also, no evidence of recurrence occurred in the lymph node-bearing area. Treatment results after recurrence were favorable and all patients are still alive until now. The five-year DFS and five-year OS were 88.7% and 92.4%, respectively.

In general, malignant SCSTs of the ovary are typically diagnosed with early-stage and have a good prognosis. The average age at diagnosis of sex cord-stromal neoplasms was 50 years in the SEER data [1] which was like the present study (median age 56 years)**.** The most common presenting symptoms of the patients in the present study were pelvic mass and pelvic pain. This is consistent with the findings from previous studies, which reported that over 80% of the SCSTs patients presented with such symptoms. Of note, patients may have abnormal uterine bleeding from estrogen secreting ovarian SCSTs. The reported incidence of concurrent endometrial hyperplasia and endometrial cancer in patients with GCTs was 25.5-29% and 5.9-7.5%, respectively [10, 11]. In the present study, concurrent endometrial lesion of GCTs was noted in six (15.8%) patients, in whom, five with endometrial hyperplasia. The remaining patient with ovarian GCT had associated primary endometrioid adenocarcinoma of the endometrium and primary endometrioid adenocarcinoma of the fallopian tube.

Aside from usually being diagnosed at early-stage, malignant sex cord-stromal neoplasms of the ovary tended to have a late recurrence, if it occurred at all. Most of the patients in this study were apparently in early-stage and all the recurrence occurred late. Recurrent disease was diagnosed in 7.4% of the patients in this study. Among four women with recurrences, one had local recurrence in the pelvic cavity and three had a distant recurrence in liver and omentum. The time interval to recurrence was 4-15 years and all had prior adult GCT. Early-stage, age < 50 years, tumor size < 10 cm, and no residual disease were important prognostic factors for improved survival in patients with SCST of the ovary in the previous studies [3-5]. In this study, all recurrences occurred in women aged > 50 (range 50 – 64) years, tumor size 10–20 cm, Stage IC in two patients and Stage IIIC in two patients. However, three patients had no residual disease after debulking surgery, and one patient had residual disease > 1 cm.

Ovarian sex cord-stromal malignancies may spread by local or regional extension, but nodal metastases are rare in the previous reports [2, 12-15]. In the present study, there appeared to be a significant variation in the number of lymph nodes removed, ranging from 1 to 40 nodes, with the median number of resected nodes of nine. There was no documented nodal metastasis in the present series. Complications of pelvic and para-aortic lymphadenectomy such as lymphocyst, lymphedema, nerve and vascular injuries, increased blood loss, and increased operation time have been reported [16]. Accordingly, due to the very low incidence of lymph node involvement in malignant ovarian SCSTs, despite the limited data, it appears that pelvic and para-aortic lymphadenectomy may be safely omitted.

Despite the lack of evidence showing survival benefit, postoperative adjuvant therapy is typically advised for patients with Stage II–IV SCSTs given the risk of disease progression and recurrence. The recommended chemotherapy involves platinum-based treatment including BEP regimen or etoposide plus cisplatin, and paclitaxel plus carboplatin [17]. In the present institute, the BEP regimen is the mainstay of adjuvant treatment for Stage II–IV patients.

The strength of the present study was that all patients were treated at a single institution. Therefore, variations in operative techniques and treatment protocol were minimal. Moreover, all pathologic specimens were evaluated by expert gynecologic pathologists. However, certain limitations exist. The design of this study was the retrospective with a short median follow-up time. Besides, this study contained a relatively small sample size owing to the rarity of this type of ovarian neoplasms.

In conclusion, the survival outcomes of women with ovarian sex cord-stromal malignancies are favorable. No lymph node metastasis was detected in this present study. Retroperitoneal lymphadenectomy may be omitted in surgical staging procedure for patients with malignant ovarian SCSTs.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by Research Ethics Committee

of Faculty of Medicine Chiang Mai University (approval number: OBG-2559-04017).

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Conflict of interest

The authors declare no conflict of interest.

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References

[1] Quirk JT., Natarajan N.: "Ovarian cancer incidence in the United States, 1992-1999". *Gynecol Oncol*., 2005, *97*, 519.
[2] Brown J., Sood AK., Deavers MT., Milojevic L., Gershenson DM.: "Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted?". *Gynecol Oncol*., 2009, *113*, 86.
[3] Chan JK, Zhang M, Kaleb V, Loizzi V, Benjamin J, Vasilev S, et al.: "Prognostic factors responsible for survival in sex cord stromal tumors of the ovary—a multivariate analysis". *Gynecol Oncol*., 2005, *96*, 204.
[4] Meisel JL, Hyman DM, Jotwani A, Zhou Q, Abu-Rustum NR, Iasonos A, *et al.*: "The role of systemic chemotherapy in the management of granulosa cell tumors". *Gynecol Oncol*., 2015, *136*, 505.
[5] Zhang M, Cheung MK, Shin JY, Kapp DS, Husain A, Teng NN, *et al.*: "Prognostic factors responsible for survival in sex cord stromal tumors of the ovary—an analysis of 376 women". *Gynecol Oncol*., 2007, *104*, 396.
[6] Evans AT 3rd, Gaffey TA, Malkasian GD Jr, Annegers JF.: "Clinicopathologic review of 118 granulosa and 82 theca cell tumors". *Obstet Gynecol*., 1980, *55*, 231.
[7] ACOG Committee Opinion: number 280, December 2002.: "The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer". *Obstet Gynecol*., 2002, *100*, 1413.
[8] Cronjé HS, Niemand I, Bam RH, Woodruff JD.: "Review of the granulosa-theca cell tumors from the emil Novak ovarian tumor registry". *Am J Obstet Gynecol.,* 1999, *180*, 323.
[9] Prat J.: "Staging classification for cancer of the ovary, fallopian tube, and peritoneum". *Int. J. Gynaecol. Obstet*., 2014, *124*, 1.
[10] Ottolina J, Ferrandina G, Gadducci A, Scollo P, Lorusso D, Giorda G, *et al.*: "Is the endometrial evaluation routinely required in patients with adult granulosa cell tumors of the ovary?". *Gynecol Oncol*., 2015, *136*, 230.
[11] van Meurs HS, Bleeker MC, van der Velden J, Overbeek LI, Kenter GG, Buist MR.: "The incidence of endometrial hyperplasia and cancer in 1031 patients with a granulosa cell tumor of the ovary: longterm follow-up in a population-based cohort study". *Int. J. Gynecol. Cancer,* 2013, *23*, 1417.
[12] Kleppe M, Amkreutz LC, Van Gorp T, Slangen BF, Kruse AJ, Kruitwagen RF.: "Lymph-node metastasis in stage I and II sex cord stromal and malignant germ cell tumours of the ovary: a systematic review". *Gynecol Oncol*., 2014, *133*, 124.
[13] Nasioudis D, Kanninen TT, Holcomb K, Sisti G, Witkin SS.: "Prevalence of lymph node metastasis and prognostic significance of lymphadenectomy in apparent early-stage malignant ovarian sex cord-stromal tumors". *Gynecol Oncol*., 2017, *145,* 243.
[14] Park JY, Jin KL, Kim DY, Kim JH, Kim YM, Kim KR, et al.: "Surgical staging and adjuvant chemotherapy in the management of patients with adult granulosa cell tumors of the ovary". *Gynecol. Oncol*., 2012, *125*, 80.
[15] Thrall MM, Paley P, Pizer E, Garcia R, Goff BA.: "Patterns of spread and recurrence of sex cord-stromal tumors of the ovary". *Gynecol. Oncol*., 2011, *122*, 242.
[16] Di Re F, Baiocchi G.: "Value of lymph node assessment in ovarian cancer: Status of the art at the end of the second millennium". *Int. J. Gynecol. Cancer*, 2000, *10*, 435.
[17] Schumer ST, Cannistra SA.: "Granulosa cell tumor of the ovary". *J. Clin. Oncol*., 2003, *21*, 1180.

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