Published in final edited form as:

Gynecol Oncol. 2011 August ; 122(2): 242–245. doi:10.1016/j.ygyno.2011.03.020.

Patterns of Spread and Recurrence of Sex Cord-Stromal Tumors of the Ovary♦

Melissa M. Thrall, M.D.¹, Pamela Paley, M.D.², Ellen Pizer, M.D., Ph.D.³, Rochelle Garcia, M.D.⁴, and Barbara A. Goff, M.D.¹

¹Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, WA

²Pacific Gynecology Specialists, Seattle, WA

³Cellnetix Pathology and Laboratories, Seattle, WA

⁴Department of Pathology, University of Washington School of Medicine, Seattle, WA

Abstract

Objective—Sex cord-stromal tumors are an uncommon type of ovarian neoplasm and limited data are available in the literature to guide clinical management. Recent published series suggested a lack of lymph node involvement and recommended abandonment of the lymph node dissection as part of the primary surgical staging of these tumors. To confirm these findings we evaluated pathologic findings in women undergoing surgical management of sex cord-stromal tumors in the Seattle metropolitan area.

Methods—A retrospective multi-institutional review of all patients treated with sex cord-stromal tumors at University of Washington Medical Center and Swedish Medical Center in Seattle was conducted. Information was collected on the pathology, evaluation and treatment of these patients.

Results—A total of 87 patients were available for analysis, the majority of whom had adult granulosa cell tumors (82%) and Sertoli-Leydig cell tumors (13%). Of these patients, 68% had complete or partial surgical staging procedures, and 47 patients had some nodal tissue examined as part of the initial or restaging procedure. All nodes examined were negative. Tumor size was significantly associated with risk of recurrent disease, with a 20% increase in the hazard of recurrence for each increase of tumor size of 1 cm (HR 1.20, 95% CI 1.11-1.07)

Conclusions—This study confirms the finding that lymph node metastasis are rare in sex-cord stromal tumors. These findings support the hypothesis that routine lymphadenectomy provides limited additional information in the management of these patients and can be omitted from the primary surgical staging procedure or secondary restaging procedures.

♦Presented at the Thirty Ninth Annual Meeting of the Western Association of Gynecologic Oncologists, Santa Barbara, California, June 9-12, 2010

© 2010 Elsevier Inc. All rights reserved.

*Corresponding Author: Melissa M. Thrall: mthrall@uw.edu, phone 206-543-3669, Fax 206-543-3915, University of Washington School of Medicine, Department of Obstetrics and Gynecology Box 356460, Seattle WA 98195-6460 .

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest to report.

Keywords

Ovarian sex cord stromal tumor; Lymph node metastasis; Prognostic factors

Introduction

Sex cord-stromal tumors (SCST) are rare ovarian tumors that represent approximately 7% of all ovarian malignancies[1]. These malignancies are often low grade and are frequently diagnosed in younger patients. Given these features and the rarity of these tumors, they are often diagnosed by pathology following surgery, which is often only a unilateral oophorectomy or ovarian cystectomy. While fertility sparing surgery is generally regarded as appropriate in apparently early stage disease, a staging procedure to include omentectomy, biopsies and pelvic and para-aortic lymph nodal dissection has been historically recommended for all patients with ovarian malignancies[2, 3].

In a recently published series of 262 patients, 58 patients had lymph nodes sampled as part of their primary surgery, all of which were negative[4]. As such, these investigators recommended abandonment of the pelvic and para-aortic lymph nodal dissection as part of the primary surgical staging of these tumors. A previously published case series reported four patients having positive nodes of 55 having sampling, however it is not clear from this report if these were isolated nodal metastasis[5]. Additionally a report of 68 patients with granulosa cell tumors, most of whom were not completely surgically staged, documented 15% of recurrences involved the retroperitoneum[6]. Before a paradigm shift can be widely endorsed in the management of sex cord-stromal tumors we felt strongly that confirmation of patterns of spread be evaluated in another large series of patients.

In this retrospective review, we aimed to report the experience with a large series of these rare tumors in two large medical centers where surgical staging was frequently performed.

Methods

All patients with ovarian sex cord-stromal neoplasms treated from 1/1/1990-9/2/2009 at the University of Washington Medical Center (UW) and Swedish Medical Center (SMC) in Seattle, Washington were identified. Institutional review board (IRB) approval was obtained from both institutions (UW IRB #37297; SMC IRB 4884 S-09). Pathology databases were used to identify patients. All available computerized and paper medical records, including inpatient and outpatient visits at either institution were reviewed. Data was collected on patient characteristics, clinical findings and all treatment received for primary or recurrent disease.

Patients were excluded if they had a concomitant diagnosis of another malignancy that was not a SCST or an endometrial primary. In order to be included in the analysis patients needed to have at least one clinical visit at either institution and have review of their pathology at the corresponding institution. Patients were classified as not having staging if only a unilateral salpingo-oophorectomy or ovarian cystectomy was performed. Complete staging was defined as at least a unilateral salpingo-oophorectomy, pelvic washings, peritoneal biopsies, omental sampling and pelvic and para-aortic lymph nodal sampling. All other operations were classified as partial staging. Completeness of staging was based on either the primary surgical procedure or a secondary staging procedure if this occurred within 90 days of diagnosis without interval therapy. Patients with grossly advanced abdominal disease were considered completely staged even if a nodal dissection was not performed.

Descriptive statistics were calculated for all subjects. Kaplan Meyer survival methods were used and the log-rank test was used to determine differences in survival curves. Multivariate analysis using Cox proportional hazard regression was used. All p values are 2 sided. STATA SE version 11.0 (College Station, TX) was used for all calculations.

Results

Ninety-four patients were identified with sex-cord stromal tumors. Two patients were not included due to a second, non endometrial primary and five patients had incomplete medical records. The clinical characteristics of the remaining 87 patients included in the analysis are listed in Table 1. The majority of the patients had adult granulosa cell tumors (AGCT, n=71) and Sertoli-Leydig cell tumors (SLCT, n=11). Additionally there were 2 patients each with mixed and unclassified sex cord stromal tumors and one patient with a juvenile granulosa cell tumor. Of the patients with granulosa cell tumors, 6 (8.5%) had concurrent endometrial carcinomas and none had endometrial hyperplasia. Most of these endometrial carcinomas were diagnosed pre-operatively and all of these patients had complete or partial staging procedures.

Of the 87 patients in this analysis, 27 (31%) had no surgical staging, 11 (13%) had partial staging and 49 (56%) had complete staging or grossly advanced disease (Figure 1). There were 8 patients who had two surgical staging procedures and two of these patients were upstaged as a result of the second surgery. Of the two patients upstaged, one had microscopic omental involvement and one had disease remaining in the ovary following a primary ovarian cystectomy. Of the 59 patients that had complete or partial staging procedures, 47 had at least one lymph node examined. Among patients having lymph node removal, the number of nodes obtained was not reported in 11 patients and in the remaining patients the median number of nodes removed was 14 (range 3-80). Final stage of disease for the 59 patients that had either a complete or partial staging procedure was stage I in 50 patients (57%), stage II in 6 patients (7%), stage III in 2 patients (2%) and stage IV in 1 patient (1%). One additional patient had grossly advanced abdominal disease and thus was classified as stage III without a nodal dissection. Among women with stage II disease, 2 had gross extra-ovarian disease with involvement of a uterine nodule and a rectosigmoid nodule. The remaining 4 patients had disease diagnosed microscopically only from peritoneal biopsies in the cul de sac, pelvic sidewall and uterosacral ligament. Similarly, among women with stage III disease, one had grossly advanced abdominal disease and the other two had diagnosis by biopsy only (diaphragmatic peritoneum and microscopic omental involvement). The patient with stage IV disease had pulmonary metastasis in addition to gross abdominal involvement.

Among the 47 patients having some lymph nodal tissue examined, there were no patients with nodal involvement. This includes the 8 patients that had a secondary staging procedure following primary surgery. Of the 87 patients in this analysis 15 were treated with adjuvant therapy following surgery. Most women receiving adjuvant therapy had stage IC or higher disease. 3 un-staged patients were treated based on high risk features such as high grade disease or tumor rupture. The most common regimen administered was bleomycin/etoposide/cisplatin (n=10). Two patients were treated with radiation therapy, one with an unknown agent, one with melphalan and one with cisplatin and paclitaxel.

Of the 87 patients in this analysis, one had persistent disease following surgery and 7 had no additional follow up information following surgery. Of the remaining 79 patients, median follow up was 20.6 months (range 0.23-323 months). 18 patients had at least one episode of disease recurrence with a median time to recurrence of 46.6 months. These recurrences were observed between 2.6 and 186 months following diagnosis. Of the 18 patients with disease

recurrence, 2 had isolated retroperitoneal recurrences. These recurrences occurred at 28 and 66 months, neither of these patients had nodal sampling as part of their primary surgery. One patient was a 56 year old with a 12cm apparent stage IA high grade Sertoli-Leydig tumor with a previous hysterectomy who had partial staging including bilateral salpingo-oophorectomy, omentectomy and an ileocecal resection (negative pathology, severe adhesions at surgery). This patient recurred at 28 months with a retroperitoneal mass and at surgery had involvement of the left iliopsoas muscle, left adrenal gland, left common iliac and internal iliac nodes. The other was 39 years old, with a 7cm adult granulosa cell tumor who had only an abdominal hysterectomy and left salpingo-oophorectomy. She recurred after 66 months with an isolated retroperitoneal mass that was near the left kidney. Neither of these patients was treated with adjuvant chemotherapy. The majority of recurrences among the remaining patients were either unifocal or multifocal pelvic or abdominal tumors and two patients had liver and/or vaginal apex involvement. There was no difference in the distribution of the sites of recurrence between those having nodes or not at the time of initial surgery.

Median survival in this cohort was 130 months. Within this patient population age and stage did not predict survival. Tumor size <10cm was strongly predictive of survival compared to tumors 10 cm or larger ($p=0.006$, Figure 2). Tumor size was available for 70 of the women, 37 of whom had tumors 10cm or larger. Median survival was 177 months for women with tumors smaller than 10 cm, and 101 months for those whose tumors were 10 cm or larger. No recurrences were observed for women whose tumors were less than 7cm. In a multivariate regression analysis, adjusting for age and stage, size remained significant with an almost 20% increase in the hazard ratio (HR) for death with each 1cm increase in tumor size (HR 1.198, 95%CI 1.106-1.065).

Discussion

Sex cord-stromal tumors are rare ovarian neoplasms that are often unsuspected and incompletely staged at the time of primary surgery. These malignancies are typically diagnosed at an apparently early stage and generally have a favorable prognosis. In our series just under half of women were below the age of 50 at the time of diagnosis and fertility sparing surgery is often desired among these women. Thus gynecologic oncologists are frequently faced with decisions regarding the need for additional staging procedures in this patient cohort. Our study confirms the recently reported findings by Brown et al. that these tumors were not noted to spread to pelvic or para-aortic lymph nodes as there were no involved nodes observed among any of the 47 women that had nodal tissue evaluated[4].

Secondary surgical staging, especially for women whose primary surgery consisted only of an ovarian cystectomy or unilateral salpingo-oophorectomy is likely still an important part of treatment and management of women with un-staged SCSTs. In this series, of the 8 women who had secondary staging, 2 were noted to have additional disease, one of which was in the residual ovary following ovarian cystectomy. This is similar to the findings of Brown et al where 4 patients were noted to have recurrent disease in residual ovarian tissue[4]. Furthermore, 6 of the 10 women in our series diagnosed with stage 2 or higher disease had only microscopic extra-ovarian disease, emphasizing the continued importance of secondary staging even if lymphadenectomy is not required.

Recurrent disease was diagnosed in 20% of the patients in this study. Among women with recurrences, 2 were noted to have isolated retroperitoneal disease recurrence at 28 and 66 months. Neither of these women had a lymph node dissection at the time of primary recurrence. Nodal involvement at the time of recurrent disease was documented in 5% of cases in another series [4]. In this report, half of the women with nodal involvement at the

time of recurrence had documented negative nodes at primary surgery and the other had no nodal evaluation. Overall these data appear to support the conclusion that the incidence of microscopic nodal involvement at the time of primary surgery is extremely low and it seems unlikely that a routine nodal dissection will impact recurrence risk.

Tumor size was found to be the most important predictor of death from disease in this study with no disease recurrences noted among women with primary tumors less than 7cm. Tumor size has been noted to be an important prognostic factor in many reports [5, 7-9]. In these series, tumors greater than 10-15cm were associated with an increased risk of recurrence and death from disease. Conversely other authors have suggested that tumor size is not an important prognostic factor after adjusting for other clinical factors such as stage [10, 11]. In our analysis, stage did not correlate with a difference in survival. Stage has been previously demonstrated to be one of the most important predictors of survival [12, 13]. The majority of the patients in this analysis presented with stage I disease and we had a limited power to detect a difference due to stage. Age has not been consistently correlated with survival among women with SCST [5, 9, 14, 15]. Our study also did not demonstrate a correlation between age and risk of death from disease.

This study has all of the limitations that are an inherent in retrospective chart reviews. This series covers almost 20 years and it is likely that temporal change in practice patterns increases the difficulty of evaluating outcomes related to care provided. However this long time period also allows us to maximize the ability to identify recurrent disease given the tendency for these tumors to recur many years after diagnosis.

Overall, our study findings support the rarity of lymph node involvement in SCST and support the hypothesis that the routine removal of pelvic and para-aortic lymph nodes may be omitted from the surgical staging of this malignancy. Tumor size appears to be a very strong predictor of death from disease and careful evaluation of women with larger lesions, especially over 7cm is warranted.

Acknowledgments

This work is supported by the National Cancer Institute (NCI) at the National Institutes of Health, Dr. Thrall is the recipient of an NCI-funded postdoctoral fellowship (T32-CA009515-26). The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

- [1]. Koonings PP, Campbell K, Mishell DR Jr, Grimes DA. Relative frequency of primary ovarian neoplasms: a 10-year review. *Obstet Gynecol.* 1989; 74:921-6. [PubMed: 2685680]
- [2]. NCCN. Practice guidelines in Oncology v.2.2011 Ovarian Fallopian Tube and Primary Peritoneal Carcinomas. 2011.
- [3]. Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. *Gynecol Oncol.* 1994; 55:S62-72. [PubMed: 7530680]
- [4]. Brown J, Sood AK, Deavers MT, Milojevic L, Gershenson DM. Patterns of metastasis in sex cordstromal tumors of the ovary: Can routine staging lymphadenectomy be omitted? *Gynecol Oncol.* 2009; 113:86-90. [PubMed: 19162310]
- [5]. Chan JK, Zhang M, Kaleb V, Loizzi V, Benjamin J, Vasilev S, Osann K, Disaia PJ. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary--a multivariate analysis. *Gynecol Oncol.* 2005; 96:204-9. [PubMed: 15589602]
- [6]. Abu-Rustum NR, Restivo A, Ivy J, Soslow R, Sabbatini P, Sonoda Y, Barakat RR, Chi DS. Retroperitoneal nodal metastasis in primary and recurrent granulosa cell tumors of the ovary. *Gynecol Oncol.* 2006; 103:31-4. [PubMed: 16537089]

- [7]. Fox H, Agrawal K, Langley FA. A clinicopathologic study of 92 cases of granulosa cell tumor of the ovary with special reference to the factors influencing prognosis. *Cancer*. 1975; 35:231–41. [PubMed: 1109770]
- [8]. Stenwig JT, Hazekamp JT, Beecham JB. Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. *Gynecol Oncol*. 1979; 7:136–52. [PubMed: 437566]
- [9]. Evans AT 3rd, Gaffey TA, Malkasian GD Jr, Annegers JF. Clinicopathologic review of 118 granulosa and 82 theca cell tumors. *Obstet Gynecol*. 1980; 55:231–8. [PubMed: 6243409]
- [10]. Malmstrom H, Hogberg T, Risberg B, Simonsen E. Granulosa cell tumors of the ovary: prognostic factors and outcome. *Gynecol Oncol*. 1994; 52:50–5. [PubMed: 8307501]
- [11]. Miller BE, Barron BA, Wan JY, Delmore JE, Silva EG, Gershenson DM. Prognostic factors in adult granulosa cell tumor of the ovary. *Cancer*. 1997; 79:1951–5. [PubMed: 9149022]
- [12]. Zhang M, Cheung MK, Shin JY, Kapp DS, Husain A, Teng NN, Berek JS, Osann K, Chan JK. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary--an analysis of 376 women. *Gynecol Oncol*. 2007; 104:396–400. [PubMed: 17030354]
- [13]. Zanagnolo V, Pasinetti B, Sartori E. Clinical review of 63 cases of sex cord stromal tumors. *Eur J Gynaecol Oncol*. 2004; 25:431–8. [PubMed: 15285297]
- [14]. Bjorkholm E, Silfversward C. Prognostic factors in granulosa-cell tumors. *Gynecol Oncol*. 1981; 11:261–74. [PubMed: 7250754]
- [15]. Ohel G, Kaneti H, Schenker JG. Granulosa cell tumors in Israel: a study of 172 cases. *Gynecol Oncol*. 1983; 15:278–86. [PubMed: 6832637]

Figure 1.
Staging of women with Sex Cord-Stromal Tumors

Figure 2.
Kaplan-Meier survival analysis based on primary tumor size.

Table 1

Patient Characteristics*

	n(%)
No. of patients	87
Median age (range)	50 (13-88)
Histology	
Adult granulosa cell tumor	71 (82%)
Sertoli-Leydig cell tumor	11 (13%)
Juvenile granulosa cell tumor	1 (1%)
Mixed sex cord-stromal cell tumor	2 (2%)
Unclassified sex cord-stromal tumor	2 (2%)
Stage (after all staging procedures)	
I	50 (57%)
II	6 (7%)
III	3 (3%)
IV	1 (1%)
Unstaged	27 (31%)

* Not all % add up to 100% due to rounding.