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Research article

Prognostic factors in sex cord stromal tumors of the ovary

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Abstract

Objective: To evaluate prognostic factors that impact the survival of women with ovarian sex cord stromal tumors (SCST).

Study Design: A retrospective single institutional review of all patients with SCST from 1982 to 2008 at our institution was conducted. Data were collected on patient characteristics, clinical findings, and all treatment received. Kaplan–Meier and Cox proportional hazards analyses were used to determine the predictors for survival.

Results: SCST constituted 5.8% of all ovarian cancers in our institution during the study period. The median age was 51 years (range 15–95). Adult granulosa cell tumors (n=52) were the most frequent histological subtype. In addition, there were 14 patients with Sertoli-Leydig cell tumors, two with Juvenile granulosa cell tumors, one with sex cord tumor with annular tubules, and one with steroid cell tumor. The median follow-up period was 58

(range 1–362) months. Fifty were stage I, two stage II, 15 stage III and three stage IV. There were two cases of persistent disease following surgery, 18 cases of recurrence and six cases of disease-related death. The median time to relapse was 75 months (range: 18–208). The 5-year overall and disease free survivals were 76% and 68%, respectively. In univariate analysis, factors affecting the recurrences were FIGO stage (p=0.02) and postoperative residual tumor (p=0.002), while age, tumor size, extent of the surgery (standard staging/ conservative staging), lymphadenectomy, histology and grade were not. On multivariate analysis, only postoperative residual tumor (p=0.002) remained significant prognostic factors for improved disease-specific survival.

Conclusion: Postoperative residual tumor and early-stage disease are important predictors for improved disease free survival in patients with SCST. If there are no residuals, fertility sparing surgery for early staged patients with SCST wishing to preserve fertility appears to be a safe alternative.

Keywords: Sex cord stromal tumors; Sertoli-Leydig tumors; Granulosa cell tumors; Ovary.

Introduction

Ovarian sex cord-stromal tumors (SCST) represent 1.2 - 8% of ovarian neoplasms. These tumors are heterogeneous and are usually functional since most can synthesize hormones (estrogens, androgens) [1-6]. They affect patients of any age and may have estrogenic or virilizing effects. The optimal management of these tumors is limited by their low incidence, and the multiplicity of their histological patterns. The principles treatment are usually developed on the basis of observations of small groups of patients and information extrapolated from management of epithelial ovarian tumors. Surgery is the cornerstone of treatment; it allows to confirm the diagnosis and to realize, in most cases, the first therapeutic act and the staging. To select patients who should receive postoperative therapy, an understanding of prognostic factors is essential [2, 3, 5].

Materials and methods

All patients with ovarian sex cord-stromal neoplasms treated from January 1982 to December 2008 were identified. Patients were excluded if they had a theca-fibroma tumor. Pathology databases were used to identify patients. All available computerized and paper medical records were reviewed. Data were collected on patient characteristics, clinical findings, and all treatment received.

The primary standard surgery consisted of total hysterectomy with bilateral adnexectomy and infra colic omentectomy. The fertility sparing surgery consisted of unilateral adnexectomy with infra colic omentectomy. The cytoreductive surgery included at least a total hysterectomy with bilateral adnexectomy, infra gastric omentectomy with extensive peritonectomy carrying away all the carcinomatosis nodules. In all cases, the lymph nodes dissection was not performed unless in case of palpable masses or in case of associated endometrial cancer. The surgery is optimal if there is no residual tumor more than 1 cm.

Descriptive statistics were calculated for all subjects. Kaplan–Meier 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. A two-sided p-value <0.05 was considered statistically significant. SPSS version 20 was used for all calculations.

Results

A total of 70 women with SCST were identified. The clinicopathologic characteristics of these women are listed in **Table 1**. The majority of the patients had adult granulosa cell tumors (AGCT; n=52) and Sertoli–Leydig cell tumors (SLCT; n=14). In addition, there were two patients with juvenile granulosa cell tumor (JGCT), one patient with a sex-cord tumor with annular tubules and one with a steroid cell tumor not otherwise specified. Two patients had concurrent endometrial carcinomas (1 AGCT and 1 SLCT) and none had endometrial hyperplasia. The median age was 51 years (range: 15–95).

Of the 70 patients in this analysis, 54 (77%) received standard primary surgical staging that included a hysterectomy, whereas 16 (23%) underwent fertility sparing surgical staging. Surgery was complete or optimal in 61 patients (87%).

Among the 19 patients having some lymph nodal tissue examined, two (10%) patients had a nodal involvement. Seventy two percent of patient presented with stage I disease, 3% with stage II, 21% with stage III, and 4% with stage IV cancers. Of the 50 patients with information on grade, 64% had grade 1 disease, 20% had grade 2 disease and 16% had grade 3 disease. The median tumor size was 13.8 cm (range: microscopic–40 cm).

Of the 70 patients in this analysis, 24 (34%) were treated with adjuvant therapy following surgery. Most women receiving adjuvant therapy had stage IC or higher disease. One patient with stage Ia was treated based on high grade disease. All patients received platinium based chemotherapy and the most common regimen administered was bleomycin /etoposide/ cisplatinum (n=14). No patient received radiotherapy.

The median follow-up period was 58 months (range 1–362 months). Two patients had persistent disease following surgery and 18 patients (26%) had at least one episode of disease recurrence with a median time to recurrence of 75 (range: 18 - 208) months.

The overall 5-year and 10-year survival for all patients was 76% and 66%. The 5-year and 10-year disease-free survival (DFS) was 68% and 40% (Figure 1 and 2). The prognostic factors responsible for survival are summarized in **table 2**. Age was not an important predictor for survival; for, younger women ≤36 years vs. >36 years had a DFS of 72% vs. 48%, respectively (p=0.62). Patients with tumors ≤14 cm had better 5-year DFS than those with tumors >14 cm (70% vs. 51%), the difference was not statistically significant (p=0.6). Patients with early-stage (Stage I–II) disease had a 5-year and 10-year DFS of 77% and 43%, compared to only 44% and 29% for those with advanced stage disease (p=0.029) (Figure 3). The 5-year DFS for patients who underwent fertility sparing surgery was 56% compared to 67% for patients who underwent radical surgery, the difference was not statistically significant (p = 0.81). There was no difference in the outcome of women who had lymphadenectomy vs. those who did not have lymph node surgery (p=0.62). Postoperative residual tumor was strongly predictive of

survival. Patients with no postoperative residual tumor had a 5-year DFS of 75 % compared to 0 % in those with postoperative residual tumor (p=0.002) (Figure 4). Histology and grade were not associated with a decreased survival. In a multivariate regression analysis, the only independent predictor of DFS was the residual tumor at the end of surgery.

Discussion

Several prognostic factors have been reported for SCST. Studies to define prognostic factors were often frustrated by the relative rarity of these tumors.

The prognostic significance of age in SCST has been controversial. Large studies have shown an improvement of prognosis in patients whose age is less than 40 years [3, 6-10]. Zhang and colleagues in a study about 376 women with SCST, found that patients whose age is less than or equal to 40 years had a better survival than those who were older than 40 years (93 % vs. 84 %, $p < 0.001$) [6]. In contrast, several studies did not find any significant impact of age on survival [4, 8, 11-13]. In this current series of 70 women, younger women age $\leq$ 36 years had a better survival but without statistically significant difference.

Tumor size greater than 10 to 15 cm is associated with inferior survivals in some reports. In the study by Miller and colleagues concerning 70 patients, larger tumor size was associated with decreased progression-free survival, but this difference was no longer important in multivariate analysis after accounting for stage of disease [14]. In two series of 83 and 89 patients, Chan and Lee showed that tumor size $\geq$ 10-12 cm contributed to decreased survival rates in both univariate and multivariate analysis [8, 15]. In the study by Thrall and colleagues about 87 SCST which 37 were greater than 10 cm, tumor size was an independent predictor of survival. The median survival was 177 months for women with tumors less than 10 cm and 101 months for the others. In addition, no recurrence was observed in women with tumors less than 7 cm. Tumor size was significantly associated with a risk of recurrence of the disease, with a 20% increase in the risk of recurrence for each increase in tumor size of 1 cm [4]. However, Zhang and al. showed that tumor size was not a significant prognostic factor for decreased survival in women with tumor size greater or less than 10 cm (5 year-survival of 89% vs. 91%, p=0.42) [6]. Similarly, we were unable in this study to validate the prognostic significance of tumor size in SCST. The same results were obtained in other studies [13, 16].

Evans et al. indicated that the extent of the surgery seems to affect the rate of recurrences. Indeed, the recurrence rate reported was 17% for patients who had a standard staging and 24% for those who had conservative surgery [12]. However, the majority of experts have claimed that standard surgical treatment including a hysterectomy does not improve the prognosis of SCST [6, 17, 18]. In the multi-institution series by Zhang, in the 132 patients younger than 50 diagnosed with stage I disease, 61 (46%) underwent standard surgical treatment while 71 (54%) had a fertilty-sparing procedure. The prognosis for both groups was extremely favorable with equivalent 5-year survivals of 97% and 98% (p=0.61) [6]. In our series, the 5-year DFS for patients who underwent fertility sparing surgery was 56% compared to 67% for patients who underwent radical surgery (p=0.81). These data suggest that a more conservative approach involving unilateral salpingo-oophorectomy with careful staging may

be reasonable in younger women with early-stage disease who desire to retain fertility. Moreover, it is prudent to perform an endometrial biopsy to exclude a concurrent uterine cancer [1-5, 19].

Most authors agree on the fact that survival is better in the early stages of disease. In different series, the overall 5-year survival varies from 90-95% and the overall 10-year survival from 85 to 95 % for stage I disease. The survival rate reported at 5 years and 10 years for stage III /IV range from 22 to 50 % and from 17 to 33 %, respectively [6-10, 12, 13, 16, 20]. Our results are consistent with those in the literature; patients with early-stage (Stage I–II) disease had a 5-year and 10-year DFS of 77% and 43%, compared to only 44% and 29% for those with advanced stage disease (p=0.029), but this difference was no longer important in multivariate analysis.

Postoperative residual tumor has been shown to be the most important prognostic factor in most studies; the fullest possible tumor resection improves survival [8, 15, 19, 21]. In the study by Schneider et al., four of 15 patients with incomplete resection showed recurrence, whereas all patients completely resected remained disease free with long-term follow up [21]. To Chan et al., the absence of residual disease was a significant predictor for improved survival (p = 0.002) [8]. Similarly, in the study by Lee et al. about 89 cases of adult granulosa cell tumors, postoperative residual tumor contributed to decreased survival rates in both univariate and multivariate analysis [15]. In this current series, women with no postoperative residual tumor had a 5-year DFS of 75 % compared to 0 % in those with postoperative residual tumor (p=0.002). Postoperative residual tumor remained as independent risk factor for survival in multivariate analysis.

The histological grade was reported as an important prognostic factor for Sertoli–Leydig cell tumors. The poor prognostic factors reported by Young and Scully on 207 cases of SLCT are: grade and the presence of heterologous elements. The 5-year DFS was 89% for the moderately differentiated forms and 81% for tumors with heterologous elements [18]. In MITO study, Sigismondi et al. reported an overall 5-year survival of 100% for patients with SLCT grade 1 and 77.8% for women with SLCT grade 2-3 [7]. Similarly, Zhang et al. reported that patients with grade 1-2 disease had a 5- year survival advantage of 32% compared to those with grade 3 tumors (96 % vs 64%, p<0,001) [6]. In this current report, we were unable to validate the prognostic significance of grade in SCST.

Other prognostic factors have been reported in the literature such as: mitotic index, cellular atypia, aneuploidy, necrosis, absence of Call-Exner bodies in granulosa cell tumors, lymphovascular invasion low microvessel density, high Ki-67 index and p53overexpression. Clearly, molecular analyses may further elucidate the differences in outcomes of women with SCST.

Conclusion

This analysis confirms that early-stage disease and substantially postoperative residual tumor are important predictors for improved disease free survival in patients with SCST. Since these tumors are usually unilateral and tend to present at a younger age, fertility-sparing procedures are an important consideration. If there are no residuals, conservative surgical treatment for early-staged women wishing to retain fertility appears to be a safe alternative.

References

[1] V Zanagnolo, B Pasinetti, and E Sartori, Clinical review of 63 cases of sex cord stromal tumors. Eur J Gynaecol Oncol, 2004. 25: 431-8.

[2] C R Koulouris and R T Penson, Ovarian stromal and germ cell tumors. Semin Oncol, 2009. 36: 126-36.

[3] I Ray-Coquard, P Pautier, E Pujade-Lauraine, P Meeus, P Morice, I Treilleux and al., [Rare ovarian tumours: therapeutic strategies in 2010, national website observatory for rare ovarian cancers and delineation of referent centers in France]. Bull Cancer, 2010. 97: 123-35.

[4] M M Thrall, P Paley, E Pizer, R Garcia, and B A Goff, Patterns of spread and recurrence of sex cord-stromal tumors of the ovary. Gynecol Oncol, 2011. 122: 242-5.

[5] D M Gershenson, Current advances in the management of malignant germ cell and sex cord-stromal tumors of the ovary. Gynecol Oncol, 2012. 125: 515-7.

[6] M Zhang, M K Cheung, J Y Shin, D S Kapp, A Husain, N N Teng and al., Prognostic factors responsible for survival in sex cord stromal tumors of the ovary--an analysis of 376 women. Gynecol Oncol, 2007. 104: 396-400.

[7] C Sigismondi, A Gadducci, D Lorusso, M Candiani, E Breda, F Raspagliesi and al., Ovarian Sertoli-Leydig cell tumors. a retrospective MITO study. Gynecol Oncol, 2012. 125: 673-6.

[8] J K Chan, M Zhang, V Kaleb, V Loizzi, J Benjamin, S Vasilev and al., Prognostic factors responsible for survival in sex cord stromal tumors of the ovary--a multivariate analysis. Gynecol Oncol, 2005. 96: 204-9.

[9] J T Stenwig, J T Hazekamp, and J B Beecham, Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. Gynecol Oncol, 1979. 7: 136-52.

[10] H Fox, K Agrawal, and F A Langley, 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.

[11] G Ohel, H Kaneti, and J G Schenker, Granulosa cell tumors in Israel: a study of 172 cases. Gynecol Oncol, 1983. 15: 278-86.

[12] A T Evans, 3rd, T A Gaffey, G D Malkasian, Jr., and J F Annegers, Clinicopathologic review of 118 granulosa and 82 theca cell tumors. Obstet Gynecol, 1980. 55: 231-8.

[13] E Bjorkholm and C Silfversward, Prognostic factors in granulosa-cell tumors. Gynecol Oncol, 1981. 11: 261-74.

[14] B E Miller, B A Barron, J Y Wan, J E Delmore, E G Silva, and D M Gershenson, Prognostic factors in adult granulosa cell tumor of the ovary. Cancer, 1997. 79: 1951-5.

[15] Y K Lee, N H Park, J W Kim, Y S Song, S B Kang, and H P Lee, Characteristics of recurrence in adult-type granulosa cell tumor. Int J Gynecol Cancer, 2008. 18: 642-7.

[16] H Malmstrom, T Hogberg, B Risberg, and E Simonsen, Granulosa cell tumors of the ovary: prognostic factors and outcome. Gynecol Oncol, 1994. 52: 50-5.

[17] S T Schumer and S A Cannistra, Granulosa cell tumor of the ovary. J Clin Oncol, 2003. 21: 1180-9.

[18] R H Young and R E Scully, Ovarian Sertoli-Leydig cell tumors. A clinicopathological analysis of 207 cases. Am J Surg Pathol, 1985. 9: 543-69.

[19] A Ayhan, M C Salman, M Velipasaoglu, M Sakinci, and K Yuce, Prognostic factors in adult granulosa cell tumors of the ovary: a retrospective analysis of 80 cases. J Gynecol Oncol, 2009. 20: 158-63.

[20] H Fox, Pathologic prognostic factors in early stage adult-type granulosa cell tumors of the ovary. Int J Gynecol Cancer, 2003. 13: 1-4.

[21] D T Schneider, G Calaminus, R Wessalowski, R Pathmanathan, B Selle, W Sternschulte and al., Ovarian sex cord-stromal tumors in children and adolescents. J Clin Oncol, 2003. 21: 2357-63.

Table 1: Clinicopathologic characteristics

	n (%)
Number of patients	70
Median age (range)	51 (15-95)
Surgery	
Fertility sparing surgery	16 (22.9%)
Surgical staging with hysterectomy	54 (77.1%)
Stage at diagnosis	
Stage I	50 (71.5%)
Stage II	2 (2.8%)
Stage III	15 (21.4%)
Stage IV	3 (4.3%)
Histology	
Adult granulosa cell tumor	52 (74.3%)
Sertoli–Leydig cell tumor	14 (20%)
Juvenile granulosa cell tumor	2 (2.8%)
Sex-cord tumor with annular tubules	1 (1.4%)
Steroid cell tumor not otherwise specified	1 (1.4%)
Tumor size (range)	13.8cm (microscopic - 40cm)
Grade of disease	
Grade 1	32 (45.7%)
Grade 2	10 (14.3%)
Grade 3	8 (11.4%)
Unknown	20 (28.6%)

Table 2: Prognostic factors responsible for survival (univariate analysis)

Prognostic factor	**OS**	**DFS**
Age	NS	NS
Tumor size	0,02	NS
Surgery (standard/conservative)	NS	NS
Lymph node surgery	NS	NS
Stage	0,002	0,02
Postoperative residual tumor	<0,0001	0,002
Histology	NS	NS
Grade	NS	NS

Abbreviations. NS: Not significant, OS: Overall survival, DFS: Disease-free survival.

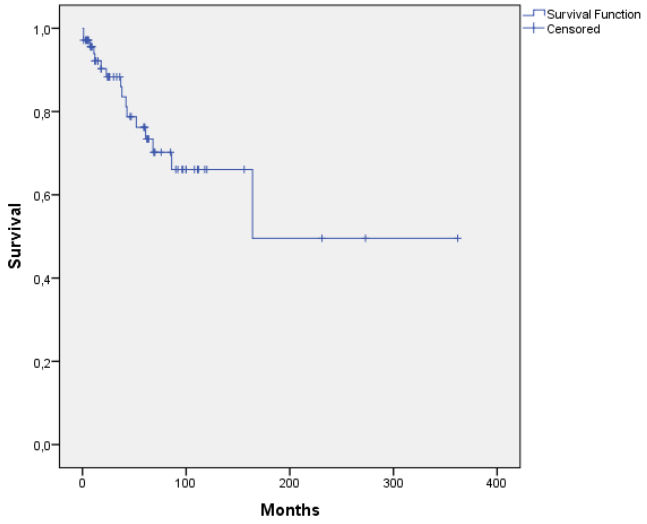

Fig. 1: Overall survival

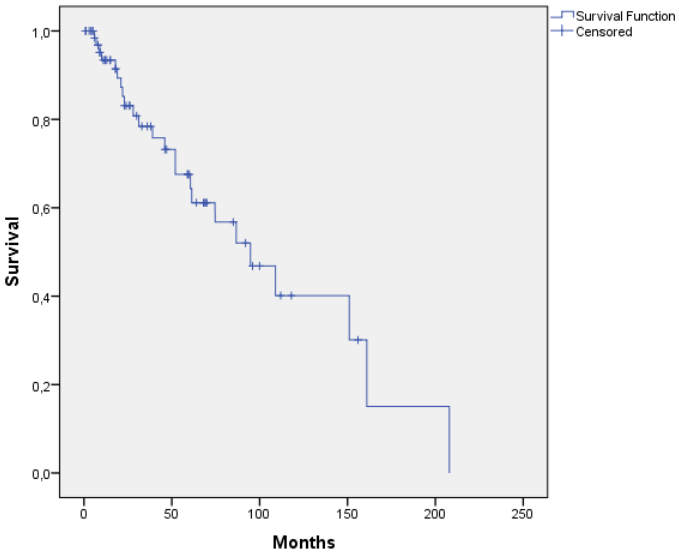

Fig. 2: Disease free survival

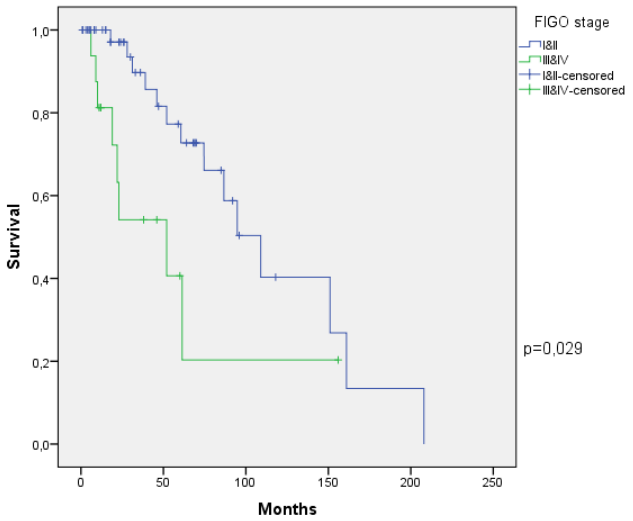

Fig. 3: Disease free survival according to stage

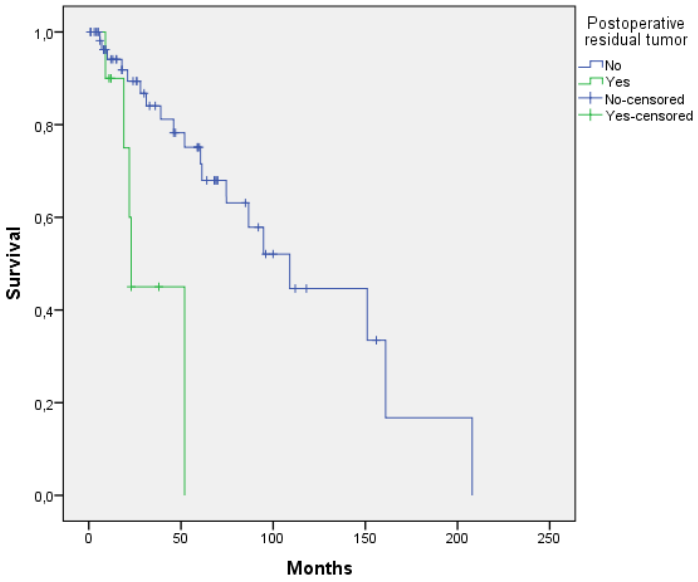

Fig.4: Disease free survival according to postoperative residual tumor