ORIGINAL ARTICLE

OUTCOMES AMONG PATIENTS WITH SEX CORD STROMAL TUMOUR OF OVARY: EXPERIENCE FROM PAKISTAN

Sohail Sarwar, Neelam Siddiqui, Sohail Ather, Abdul Hannan, Amir Ali Syed, Waleed Zafar

Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore Pakistan

Background: Ovarian sex cord-stromal tumours (SCST) are relatively uncommon neoplasms that account for approximately 5–7% of all primary ovarian tumours. The aim was to report experience with sex cord stromal tumours (SCST) of ovary in a low and middle income country. **Methods:** Clinical records of 56 patients with histopathologically-established SCST of ovary admitted to a tertiary care cancer hospital in Pakistan between April 1995 and December 2011 were reviewed. **Results:** Median age at presentation was 41 years (Range 4–77). Forty one (73%) patients were premenopausal and 15 (26.8%) were postmenopausal. The most common presenting complaint was abdominal pain (28.1%). Thirty seven patients (66%) had stage–I, 2 had stage II and III each, and 15 (26.8%) had stage IV disease. Five years survival in patients with early stage (stages I & II) was 91% while in those in the late stage (III & IV) was 84% (p=0.79). Histopathologically, 49 patients (85.7%) had Granulosa cell tumour, and 7 (12.5%) had Sertoli Lyedig cell tumour. CA-125 was high only in 8 patients (14.3%). Adjuvant chemotherapy was given in 16 (28.6%). Thirty six (64%) were disease free at last follow up, 10 (18%) succumbed to disease and 10 (18%) were alive with disease. On univariate and multivariate analyses, late stage at presentation was the sole factor significantly associated with mortality. **Conclusion:** Ovarian sex cord-stromal tumours of ovary are relatively uncommon malignancies with good prognosis if diagnosed early and treated adequately. Survival in our study was comparable to those reported elsewhere. Among various factors, late stage of tumour at presentation was found to be the only factor significantly associated with mortality.

Keywords: Sex Cord Stromal Tumour, Ovary, Granulosa cell tumour, Prognosis

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INTRODUCTION

Ovarian sex cord-stromal tumours (SCST) are relatively uncommon neoplasms that account for approximately 5–7% of all primary ovarian tumours.[1] They are a diverse group of neoplasms composed of cells derived from gonadal sex cords (Granulosa and Sertoli cells), specialized gonadal stroma (theca and Lyedig cells), and fibroblasts. The morphology of these tumours varies, depending on the cell type present, and can range from entirely glandular i.e. well-differentiated Sertoli cell tumours to entirely spindled e.g., cellular fibromas. This variegated presentation and the fact that some of these tumours are uncommon can lead to difficulties in their correct diagnosis. Immunohistochemical studies may be helpful in those situations where conventional microscopic findings fail to establish a clear diagnosis.[2–4]

Surgery remains the cornerstone of treatment for patients with sex-cord stromal tumours. Conservative surgical approach with unilateral salpingo-oophorectomy is appropriate for patients who want to preserve their fertility and who do not have an extra ovarian spread of malignant cells.[5,6] Partly because of the rare nature of these malignancies, very limited data have been reported from low and lower-middle income countries regarding presentation and treatment outcomes in SCST of ovaries. In this study, we present retrospective data from 56 patients with histopathologically established sex cord stromal tumours of ovary seen at a cancer hospital in Lahore, Pakistan over a period of 16 years.

MATERIAL AND METHODS

We carried out a review of records for all patients who presented with a histopathologically diagnosed ovarian SCST and were treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), Lahore, Pakistan between January 1996 and December 2011. All available computerized and paper medical records, including inpatient and outpatient visits were reviewed. We excluded patients who did not follow up after the first visit or whose staging workup was incomplete. Using a standardized data extraction form, clinical data including age and stage at diagnosis, presenting complaints, menopausal status, tumour markers, histopathology, treatment modalities, disease recurrence and status at last follow up was extracted. Data were entered into Microsoft Excel (Microsoft Corporation, Version 2007) and was analyzed using STATA SE version 11.0 (College Station, TX). Descriptive statistics were calculated for all subjects. Outcomes were identified as dead, alive with disease or alive without disease. Bivariate and multivariate multinomial regression analyses were done to explore

the association of various demographic and clinical factors to the outcomes. All analyses were done at two-sided p=0.05 and final model for multivariate analysis was selected using forward selection and Akaike Information Criterion.

RESULTS

A total of 1406 cases of ovarian cancer were identified. Out of these, 56 (3.98%) patients were diagnosed as having SCST. The median follow up for the entire sample was 24.5 months. The demographic characteristics of the patients are reported in table-1.

Table-2 gives an account of patients by clinical characteristics and outcome with 49 (87.5%) patients with granulosa cell tumours.

Details of the treatment received by the patients and the outcomes are presented in table-3. Table-4 presents the results of bivariate multinomial regression analyses. The outcomes in these analyses were alive without disease till the last follow up, alive with disease at the last follow up, or death during follow up. The median follow up for the entire sample was 24.5 months (range: 12–6354 days). Among the factors studied for association with the outcome were age of the patient, status of menopause, stage of the tumour, type of surgery performed and whether the tumour was a Granulosa cell tumour or a Sertoli-Leydig cell tumour.

Factors to include in the final model were selected based on forward selection using Akaike Information Criterion. Column two in table-4 reports the odds of being alive with disease compared to being alive without disease while column 4 reports the odds of being dead compared to being alive without disease. In the bivariate analysis, none of the factors were significantly associated with being alive without disease. However, compared to those with stage-I or II tumours, those with stage-III or IV tumours were 12 times (95% CI: 2.3–62.6) more likely to have died than to be alive without disease. All other associations were not significant.

Table-5 presents the results of multivariate analyses. Again, the only significant association was that compared to those with stage-I or II tumours, those with stage-III or IV tumours were 13 times (95% CI: 2.0–85.0) more likely to have died than to be alive without disease.

Table-1: Demographic Characteristics

Characteristics	n (%)
Age at diagnosis (years)	
0–9	1 (1.8)
10–19	3 (5.4)
20–29	7 (12.5)
30–39	16 (28.6)
40–49	13 (23.2)
50–59	12 (21.4)
60+	4 (7.1)
Menopause	
Premenopausal	41 (73.2)
Post-menopausal	15 (26.8)
Predominant symptoms	
Asymptomatic	7 (12.5)
Abdominal pain	18 (32.1)
Abdominal distension	6 (10.7)
Menstrual disturbance/ Vaginal bleeding	16 (28.6)
Hirsuitism	3 (5.3)
Primary infertility	6 (10.7)

Table-2: Patients by clinical characteristics, outcome

Characteristic	n (%)
Tumour type	
Granulosa cell tumour	49 (87.5)
Sertoli-Leydig cell tumour	7 (12.5)
Stage	
1a	32 (57.1)
1b	1 (1.8)
1c	4 (7.1)
II	2 (3.6)
III	2 (3.6)
IV	15 (26.8)
Follow up	
1 year	16 (28.6)
2 years	12 (21.4)
3 years	6 (10.7)
4 years	4 (7.1)
5 years	6 (10.7)
More than 5 years	12 (21.4)
Mean Follow up in Months (Range)	24.5M (12-6354)
Outcome	
Alive without disease	36 (64.3)
Alive with disease	10 (17.8)
Dead	10 (17.8)

Table-3: Treatment and outcomes

Characteristic	Total n (%)	Alive without disease n (row %)	Alive with disease N (row %)	Dead n (row %)
Treatment				
Surgery alone	39 (69.6)	26 (66.7)	8 (20.5)	5 (12.8)
Surgery and Chemotherapy	17 (30.4)	10 (58.8)	2 (11.8)	5 (29.4)
Types of surgery performed				
Total abdominal hysterectomy with bilateral salpingo-oophorectomy	31 (55.4)	16 (51.6)	6 (19.3)	9 (29.0)
Total abdominal hysterectomy with unilateral salpingo-oophorectomy	6 (10.7)	6 (100)	0 (0)	0 (0)
Oophorectomy/Others	19 (33.9)	14 (73.7)	4 (21.0)	1 (5.3)

Table-4: Factors associated with outcomes (Results from bivariate multinomial regression)

Factor	Odds Ratio of Alive with disease[1]	Standard Error	Odds Ratio of Dead[1]	Standard Error
Age group (Compared to > 30 years)				
30 years or above	1.1	1.0	2.6	2.9
Post-menopausal (Compared to pre-menopausal)	1.8	1.4	4.1	3.1
Surgery type (Compared to TAH)				
Fertility preserving surgery	1.0	0.77	0.17	0.19
Tumour Stage (Compared to stage I or II)				
Stage-III or IV	3.4	3.0	12*	10.1
Granulosa cell tumours (Compared to SLCT)	1.4	1.7	1.4	1.7
***: Significant at 99% level of confidence [1]:, Compared to alive without disease, TAH: Total Abdominal Hysterectomy**				

Table-5: Factors associated with outcomes (Results from multivariate multinomial regression)

Factor	Odds Ratio of Alive with disease[1]	Standard Error	Odds Ratio of Dead[1]	Standard Error
Age group (Compared to > 30 years)				
30 years or above	0.86	0.85	0.54	0.70
Post-menopausal (Compared to pre-menopausal)	1.5	1.3	3.4	3.3
Surgery type (Compared to TAH)				
Fertility preserving surgery	0.96	0.75	0.12	0.14
Tumour Stage (Compared to stage I or II)				
Stage III or IV	3.2	2.8	13.0*	12.4
Granulosa cell tumours (Compared to SLCT)	1.3	1.4	0.96	0.93
***: Significant at 99% level of confidence [1]:, Compared to alive without disease, TAH: Total Abdominal Hysterectomy**				

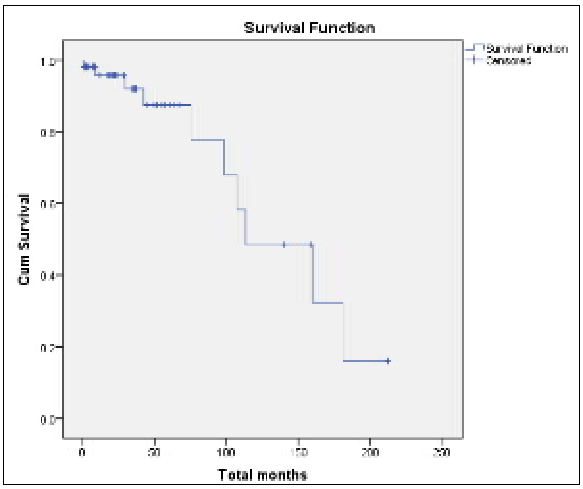

Figure-1: Kaplan Meier Survival Curve

DISCUSSION

Ovarian SCST are relatively uncommon malignancies. Most studies of these tumours are retrospective and involve small numbers of patients.[7,12] The behaviour of these tumours is similar to other rare tumours; they occur at an earlier age, present at an early stage, grow in an indolent fashion and respond well to treatment.[7] There are very few studies that have reported experience with SCST in low and lower middle income countries. In this study we have presented 16 years of retrospective data on patients presenting with SCST in a cancer institution in Lahore, Pakistan. Overall, 56 patients presented with SCST over this period. Most female patients had granulosa cell tumours, were aged 30–59 years, were pre-menopausal, and had presented with either abdominal pain or menstrual disturbances. There was a bimodal distribution in terms of tumour stage, with more than half the patients presenting in stage-I, and a quarter in stage-IV. In terms of treatment, most patients were treated with surgery alone involving total abdominal hysterectomy with bilateral or unilateral salpingo-ophorectomy. A third of the patients received fertility-sparing surgery. Among various factors, presentation with stage-III or IV was the only significant factor in predicting a patient's risk of death from the tumour.

In almost all studies done on ovarian SCST, Granulosa cell tumours (GCT) is the most frequent type followed by Sertoli Leiding cell (SLCT) and rarely gonadoblastoma or thecoma-fibroma groups.[8] Our data indicate a similar pattern with most patients having GCT followed by SLCT. We did not find patients with other types of SCST perhaps because of a small sample size of patients. The effect of age on prognosis in SCST is still debated. In two major studies, Stenwing *et al* and Fox *et al* found decreased survival in older patients.[9,10] Specifically, patients older than 40 had a corrected survival of 64% compared to 81% in those younger than 40. Bjorkholm *et al*, have, however, found no significant impact of age on survival among 198 patients. In our study, we also did not find any association of age with the likelihood of death. Tumour stage has been previously demonstrated to be one of the most important predictors of survival.[11,12] Most patients presenting at an early stage do better and have longer survival as compared to those with advanced stage. Our study strengthens this finding. Among various factors, we found tumour stage to be the only factor significantly associated with mortality.

Surgery is the mainstay of treatment in SCST. All of our patients underwent surgery and 40% among those required completion surgery at a later stage as initial operation was inadequate, or was done to obtain biopsy sample only. Fertility sparing surgery is an important consideration in treatment of young patients. Some evidence suggests that fertility-sparing procedures may be offered to young patients.5,6 In this study, we did not find any association between fertility-sparing surgery and risk of recurrence or death. Prospective, preferably randomized controlled, studies are needed to resolve the question of the efficacy of fertility-sparing surgery in SCST treatment. Of the 56 women in our study, 17 were offered chemotherapy following surgery. None of the patients were offered neoadjuvant chemotherapy. Among these patients, all 8 patients with stage-IV disease had died by the time of data collection and 2 with stage- III were alive with disease recurrence. All patients with early stage disease who received chemotherapy were alive.

This study has several limitations. First, this is a retrospective report necessitated by the slow indolent nature of these rare tumours. Second, this study covers almost 16 years and treatment protocols offered to the patients have undergone modifications over time thus affecting the outcomes. Finally, it was difficult to complete a 5 year follow up for all the patients. Among the reasons that patients were lost to follow up were non-availability of patient contact details and patients living in other cities that were unable to come for follow up appointments. Despite these limitations, this is one of the few studies that report clinical outcomes of patients with ovarian SCST from a low income country. Another strength of this study is the relatively long follow up period with almost a quarter of the patients being followed up for longer than 5 years.

CONCLUSION

Sex cord stromal tumours of the ovary are relatively uncommon malignancies with good prognosis if diagnosed early and treated adequately. Among various factors, late stage of tumour at presentation was found to be the only factor significantly associated with mortality.

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Conflict of Interest Statement: To the best of our knowledge, none of the authors have any conflict of interest to report.

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.
2. Deavers MT, Malpica A, Liu J, Broaddus R, Silva EG. Ovarian sex cord-stromal tumours: an immunohistochemical study including a comparison of calretinin and inhibin. Mod Pathol 2003;16(6):584–90.
3. Baker PM, Oliva E. Immunohistochemistry as a tool in the differential diagnosis of ovarian tumours: an update. Int J Gynecol Pathol 2005;24(1):39–55.
4. McCluggage WG, Young RH. Immunohistochemistry as a diagnostic aid in the evaluation of ovarian tumours. Semin Diagn Pathol 2005;22(1):3–32.
5. Savage P, Constenla D, Fisher C, Shepherd JH, Barton DP, Blake P, *et al*. Granulosa cell tumours of the ovary: demographics, survival and the management of advanced disease. Clin Oncol (R Coll Radiol)1998;10:242–5.
6. Ohel G, Kaneti H, Schenker JG. Granulosa cell tumours in Israel: a study of 172 cases. Gynecol Oncol 1983;15:278–6.
7. Bouffet E, Dyon JF, Armari C, Bost M. Granulosa cell tumours of the ovary in children and adolescents. Multicentre retrospective study in 40 patients aged 7 months to 22 years. Arch Fr Pediatr 1992;49:793–8.
8. Evans AT, 3rd, Gaffey TA, Malkasian GD, Jr, Annegers JF. Clinicopathologic review of 118 granulosa and 82 theca cell tumours. Obstet Gynecol 1980;55:231–8.
9. Stenwig JT, Hazekamp JT, Beecham JB. Granulosa cell tumours of the ovary. A clinicopathological study of 118 cases with long-term follow-up. Gynecol Oncol 1979;7:136–52.
10. Fox H, Agrawal K, Langley FA. A clinicopathologic study of 92 cases of granulosa cell tumour of the ovary with special reference to the factors influencing prognosis.Cancer 1975;35:231–41.
11. Zhang M, Cheung MK, Shin JY, Kapp DS, Husain A, Teng NN, *et al*. Prognostic factors responsible for survival in sex cord stromal tumours of the ovary--an analysis of 376 women. Gynecol Oncol 2007;104:396–400.

Address for Correspondence:

Dr. Sohail Sarwar, Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, 7-A Block R-3, Johar Town, Lahore, Pakistan
Tel: +92-42-35905000
Email: sohails@skm.org.pk