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Clinicopathological features and prognostic factors of ovarian sex-cord stromal tumors

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Summary

Objective: In this study the authors aimed to evaluate the clinicopathological features and prognostic factors of sex-cord stromal tumors (SCST). *Materials and Methods:* The medical and pathological records of patients with SCST who were operated and followed up in a tertiary university clinic between March 1991 and October 2013 were reviewed. Clinical, surgical and pathological characteristics, follow-up data of the patients, and the effect of this parameters on survival were investigated. *Results:* One hundred and three women with a mean age of 45 ± 12.8 (range 16-78) were included. Histopathological diagnosis was found as granulosa cell tumor in 95 (92.2%), Sertoli-Leydig cell tumor (SLCT) in six (5.8%), Leydig cell tumor (LCT) in one, and Sertoli cell tumor (SCT) in one of the cases. Sixty-eight percent of the patients had Stage I, 8.7% Stage II, 15.5% Stage III, and 6.8% had Stage IV disease. On univariate analysis; stage, age greater than 50 years, suboptimal cytoreduction, bilaterality, and non-BEP chemotherapy were determined as poor prognostic indicators. On multivariate analysis, age, stage, and optimal cytoreduction were found to be independent prognostic factors for overall survival, while only optimal cytoreduction was detected as an independent prognostic factor for disease-free survival (DFS). Fertility-sparing surgical procedures (FSS) were performed in 22 patients (21.4%). Among these 22 cases 16 (72.7%) pregnancies (13 resulted in a live birth and three in abortion) were achieved through a median period of 72 months (24-240). *Conclusion:* It was concluded that the most effective parameters on survival were stage and optimal cytoreduction. FSS is an effective approach for preserving the reproductive functions of young patients with SCST.

Key words: Sex-cord stromal tumors; Granulosa cell tumor; Prognostic factor; Overall survival (OS); Disease-free survival (DFS); Fertility-sparing surgery.

Introduction

Ovarian sex-cord stromal tumors (SCST) are a rarely seen tumors with heterogeneous biology derived from the ovarian stroma. These tumors comprise only about 7% of all primary ovarian tumors [1]. The mean age is somewhat younger than that of epithelial ovarian cancers (EOCs). In contrast to EOCs, SCSTs are often diagnosed at an earlier stage. They are characterized with slow growth pattern and late recurrence; thus, their prognosis and survival are generally favorable [2]. According to their origin, SCSTs have potential to produce hormones, like estrogen or androgen. For this reason they are categorized as functional ovarian neoplasms [3]. Surgery is the main treatment of SCSTs. Complete resection including total hysterectomy + bilateral salpingo-oophorectomy is recommended in patients who complete their fertility. Unilateral salpingo-oophorectomy can be performed in patients who are willing to preserve their fertility. Due to the detection potential of early-stage disease, surgery is usually curative. In advanced stages, adjuvant chemotherapy is necessary. Characteristic morphology is the main diagnostic step and various immunohistochemical markers are useful for differential diagnosis [3]. The most important prognostic factor appears to be the stage of disease. Other prognostic factors are age, intraperitoneal disease, bilaterality, tumor size, grade, and optimal cytoreduction [4]. However, the role of these prognostic factors has not been clearly determined due to the low number of cases series.

The aim of this study was to retrospectively evaluate the clinicopathological features, prognostic factors, treatment modalities, and survival outcomes of this rare tumor group .

Materials and Methods

The study was designed as a retrospective investigation in patients with SCSTs who were diagnosed, treated, and followed up at the Gynecologic Oncology Unit of the University Hospital of Çukurova University from March 1991 to October 2013. Ethical approval for this study was obtained from the Research Ethics Committee of Çukurova University Faculty of Medicine. Patients' archival files, pathology records and the Gynecologic Oncology Unit data cards, and computer and clinical files were assessed and 103 cases with SCST were included. The data analysis included a) demographic

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Table 1. — *Distribution and survival analysis of the basic and clinical parameters of patients.*

Parameters		n	%	Mean survival (months)	95% CI*	*p**	*p***
Age (years)	< 40	25	24.3	111.7 ± 4.5	102.8−120.6	< 0.001	0.299
	40-49	37	35.9	145.3 ± 12.0	121.7−168.9		
	≥ 50	41	39.8	43.5 ± 5.6	32.5−54.5		
	Total	103	100				
Parity	Nulliparous	31	30.1				
	Multiparous	72	69.9				
Familial cancer history	No	43	41.7				
	Yes	60	58.3				
Menopausal status	Perimenopausal	26	25.2	80.0 ± 7.1	65.9−94	< 0.001	0.012
	Postmenopausal	36	35	58.3 ± 12.0	34.7−81.8		
	Reproductive	41	39.8	136.8 ± 6.8	123.5−150.2		
Admission complaints	Abdominal or pelvic pain	31	30.1				
	Mass	15	14.6				
	Bloating, tension	16	15.5				
	Vaginal bleeding	30	29.1				
	Incidental	11	10.7				
Endocrinologic symptoms	No endocrinologic symptoms	30	29.1				
	Hirsutism	10	9.7				
	Weight gain	22	21.4				
	Menstrual disorder	29	28.2				
	Diabetic symptoms	12	11.7				
Additional disease history	Diabetes	17	16.5	77.6 ± 19.9	38.5−116.8	< 0.001	0.117
	Hypertension	20	19.4	60.4 ± 8.7	43.2−77.6		
	Obesity	8	7.8	30.8 ± 13.5	4.3−57.3		
	Asthma	6	5.8	78.3 ± 34.4	10.7−145.9		
	Polycystic ovarian syndrome	8	7.8	89.4 ± 11.2	67.4−111.5		
	No disease	44	42.7	132.1 ± 7.5	117.2−147.0		
Ascites	Yes	38	36.9	125.7 ± 10.8	104.4−147.0	0.059	0.125
	No	65	63.1	72.4 ± 8.2	56.2−88.7		

*p**: comparison of the total survival; *p***: comparison of DFS of the parameters; CI: confidence interval.

features (age, parity, menopausal status, cause of hospital admission, history of comorbid disease, endocrine symptoms, and family history), b) surgical approach (surgical procedure, type of cytoreduction, ascites, intraoperative, and postoperative complications), c) pathological findings (tumor localization, size, histological type, stage, grade, pelvic and para-aortic lymph node involvement, and cytologic evaluation), d) adjuvant treatments, and e) follow-up data [recurrence, pregnancy outcome, disease-free survival (DFS), and overall survival (OS)]. Patients who had no routine examinations within the last six months were contacted by phone and their status was checked. Optimal cytoreduction was defined as the absence of visible residual tumor or < one cm tumor. DFS was considered as the period between the operation and relapse. OS was considered as the time period between the pathological diagnosis and death. Survival times were stated as months. Histopathological examinations of the surgical specimens were evaluated by an experienced gynecopathologists (DG). Histopathological types were categorized as; granulosa cell tumor (GCT) - Sertoli Leydig cell tumor (SLCT) - Leydig cell tumor (LCT), and Sertoli cell tumor (SCT). Tumor staging was made according to the surgical pathological staging system proposed by International Federation of Gynecology and Obstetric (FIGO) 1988. Tumor size was assessed with the largest diameter of the tumor and then divided into three groups (≤ 5 cm, 5-10 cm, and >10 cm). Tumor localization was noted as right, left, and bilateral. Postoperative pregnancy status was recorded.

Statistical methodology

Univariate analysis of survival rates were carried out by the Kaplan-Meier method. Significant variables in the univariate analysis were reassessed with multivariate analysis using the Cox regression model. Log rank test was performed to compare the survival curves between groups. Statistical significance of each factor of the regression coefficients was tested with Wald test. SPSS 20.0 Evaluation Version (Statistical Package for Social Sciences) software package was used in the statistical analysis of the data.

Results

A total of 103 patients with SCST (GCT n=95, SLCT n=6, LCT n=1, and SCT n=1) were included in this analysis. SCST consisted 8% of all ovarian cancers (n=1270) followed at the present clinic during the study period. Median follow-up was 39 (3-240) months.

Mean age was 45.57 ± 12.8 (16-78) years. The most common symptom was abdominal and/or pelvic pain (30.1%) followed by abnormal vaginal bleeding (29.1%). Endocrinologic symptoms including menstrual disorders (28.2%), weight gain (21.4%), diabetic symptoms (11.7%), and hirsutism (9.7%) were determined. Basic and clinical

Table 2. — *Surgical and pathological tumoral characteristics and survival analysis.*

Characteristics		n	%	Mean survival	%95 CI	*p**	*p***
Tumor diameter (cm)	< 5	10	9.7	95.0 ± 3.4	66.2−119.3	0.470	0.097
	5-10	66	64.1	123.1 ± 11.5	88.3−101.6		
	> 10	27	26.2	86.0 ± 13.9	58.6−113.4		
Tumor localization	Right	45	43.7	123.2 ± 14.8	94.1−152.4	0.036	0.001
	Left	48	46.6	104.8 ± 9.9	85.2−124.3		
	Bilateral	10	9.7	50.2 ± 10.9	28.7−71.7		
Stage	1	71	68.9	139.7 ± 9.8	120.3−159.1	< 0.001	< 0.001
	2	9	8.7	108.3 ± 18.9	71.1−145.4		
	3	16	15.5	56.9 ± 9.0	39.1−74.6		
	4	7	6.8	20.5 ± 5.7	9.3−31.6		
Surgery type	FSS	22	21.36			0.017	0.721
	TAH+BSO/USO	25	24.27				
	Staging surgery	46	44.66				
	Re-staging surgery	10	9.70				
Cytoreduction	Optimal	85	82.5	135.9 ± 8.7	118.8−152.9	< 0.001	< 0.001
	Suboptimal	18	17.5	36.1 ± 6.9	22.4−49.9		
Omentum metastasis	Yes	20	67	65.4 ± 13.8	38.4−92.5	< 0.001	
	No	34	33	146.5 ± 9.3	128.2−14.8		
Lymph node metastasis	Yes	12	22	59.3 ± 12.2	35.2−83.3	< 0.001	
	No	42	78	138.9 ± 9.1	120.9−156.9		
Peritoneal metastasis	Yes	8	8.4	41.0 ± 12.5	16.3−65.7	< 0.001	
	No	87	91.6	136.8 ± 8.5	120.0−153.7		
Intraoperative complication	Intestinal injury	4	3.9				
	Vascular injury	4	3.9				
	No complication	95	92.2				
Postoperative complication	Wound infection	7	6.8				
	Acute gastrointestinal bleeding	1	1.0				
	Vein thrombosis	2	1.9				
	Pleural effusion	4	3.9				
	Intestinal obstruction	5	4.9				
	No complication	84	81.6				
Chemotherapy	-	59	57	138.3 ± 11.6	115.4−161.2	0.004	0.002
	+	44	43	82.8 ± 9.8	63.6−102.0		
	BEP	27	61	96.3 ± 12.8	71.2−121.4	0.003	0.001
	Non-BEP	17	39	55.6 ± 8.9	38.1−73.0		
Cytology	Positive	27	26.2	63.9 ± 9.3	45.6−82.2	0.008	0.156
	Negative	27	26.2	94.3 ± 6.6	81.4−107.2		
	No cytology	49	47.6				

*p**: comparison of the total survival; *p***: comparison of DFS of the parameters; CI: confidence interval.

characteristics are shown in Table 1. Hirsutism was the only endocrinologic symptom presented in the other histopathological types and this difference was statistically significant ($p = 0.001$).

All patients underwent surgery. Mean operation time was 120.28 ± 36.35 (60-240) minutes. Total abdominal hysterectomy + bilateral/unilateral salpingo-oophorectomy (TAH+BSO/USO) were done in 25 (24.3%), staging surgery (TAH+BSO+infracolic/total omentectomy±lymphadenectomy) in 46 (44.7%) and re-staging surgery in ten (9.7%) patients. Fertility sparing surgery (FSS= USO±infracolic omentectomy±lymphadenectomy) was performed in 22 (21.4%) patients who desired to maintain their fertility. Surgery was optimal in 85 (82.5%) cases. Wound infection was the most common postoperative complication (6.8%).

Tumor diameter was between five and ten cm in more than half of the cases (64.1%). Tumor was bilateral in 10 (9.7%) cases. The majority of the cases was in early stage (68.9% Stage I and 8.7% Stage II), only 22.3% of the cases was in advanced stage (15.5% Stage III and 6.8% Stage IV). Distribution of the surgical procedures and pathological findings of the tumor and survival analysis are shown in Table 2.

Characteristics of patients who underwent FSS are shown in Table 3. This procedure was performed in 22 cases. Mean age of the cases performed FSS was 28 (16-40) and most of them were single. Majority of the cases were Stage I. Bleomycine+etoposide+platinum chemotherapy (BEP CT) was administered in six (27%) patients. A total of 16 (72.7%) pregnancies (13 resulted in a live birth and three

Table 3. — *Characteristics of fertility sparing surgery cases.*

Case no	Age	Stage	Surgery detail	Histopatho-logical type	Chemo-therapy	Pregnancy	Recurrence
1	20	I	USO + omentectomy + BPLND	GCT	No	Live birth after 4 years	No
2	16	I	USO	SLCT	No	Live birth after 10 years	No
3	31	I	USO	GCT	No	No	No
4	16	I	USO	GCT	No	Live birth after 3 years	No
5	38	I	USO + omentectomy + BPPLND	GCT	No	Live birth after 2 years	No
6	31	II	USO + omentectomy + BPPLND	GCT	BEP	Live birth after 4 years	Recurrence after 5 years
7	19	III	USO + omentectomy + BPPLND	GCT	BEP	Live birth after 9 years	No
8	32	I	USO + omentectomy + BPLND	GCT	No	Twice spontaneous abortion	No
9	23	III	USO + omentectomy + BPPALND	GCT	BEP	Live birth after 6 years	No
10	19	I	USO + omentectomy + BPPALND	LCT	No	Live birth after 7 years	No
11	37	I	USO + omentectomy + BPPALND	GCT	No	Missed abortion	No
12	23	I	USO	GCT	No	Live birth after 6 years	No
13	37	I	USO + omentectomy + BPPALND	GCT	No	Spontaneous abortion	No
14	39	I	USO	GCT	No	No	No
15	40	I	USO + omentectomy + BPPALND	GCT	No	No	No
16	19	I	USO + omentectomy	GCT	No	Live birth after 8 years	No
17	24	II	USO + omentectomy + BPPALND	GCT	BEP	No	Recurrence after 5 years
18	36	I	USO + omentectomy	SLCT	No	No	No
19	18	I	USO	SCT	BEP	Live birth after 5 years	No
20	34	I	USO + omentectomy + BPPALND	GCT	No	Live birth after 2 years	No
21	28	I	USO	GCT	BEP	Live birth after 6 years	No
22	38	I	USO + omentectomy + BPPALND	GCT	No	No	No

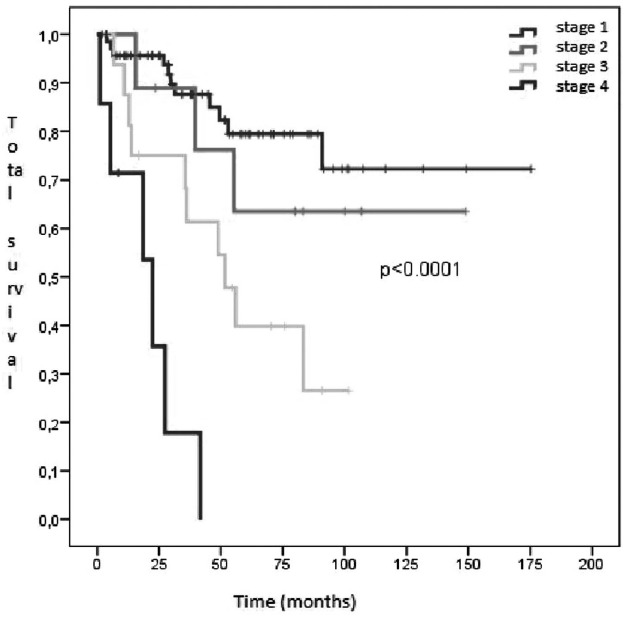

Figure 1. — OS of SCST according to stages.

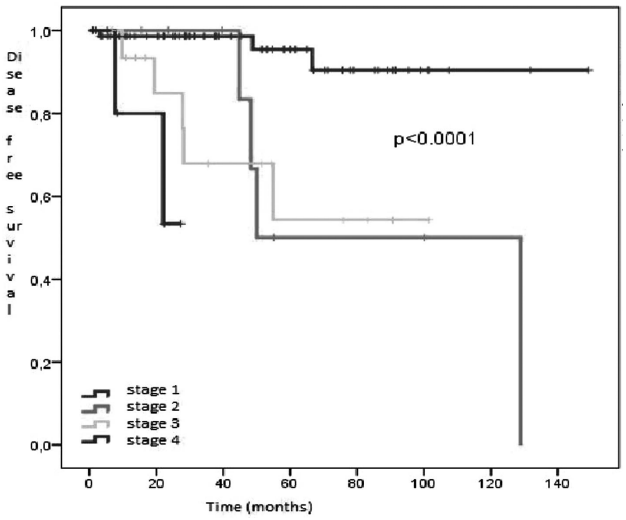

Figure 2. — DFS of SCST according to stages.

with abortion) were detected through a median period of 72 (24-240) months. Recurrence presented in two of the FSS cases. Both of these cases were Stage II GCT and had received BEP CT.

Chemotherapy was given to 44 (42.7%) patients (27 BEP, 17 non-BEP), radiotherapy (RT) was given in combination with CT in two patients. Recurrence was detected in 14 (13.6%) cases, five of which were in the vaginal cuff. Secondary surgery was applied in ten of these patients. On univariate analysis, age, menopausal status, comorbid disease, stage, tumor differentiation, positive cytology, type of surgery, suboptimal cytoreduction, the presence of bilateral tumor, omental, peritoneal and lymph node metastasis, and adjuvant chemotherapy were determined to be statistically significant prognostic factors for OS. On the other hand,

Table 4. — *Multivariate analysis of total survival.*

Factors		*p*	HR	95% CI	
				Upper band	Lower band
Age years)	< 40	0.037	Ref.		
	40-49	0.243	4.673	0.351	62.176
	50+	0.035	25.408	1.253	515.169
Stage	I	0.047	Ref.		
	II	0.252	0.424	0.097	1.842
	III	0.824	1.141	1.35	3.669
	IV	0.027	3.775	2.78	18.167
Cytoreduction	Optimal	< 0.001	Ref.		
	Suboptimal	0.000	8.344	3.139	22.180

HR: hazard ratio; CI: confidence interval.

menopausal status, the presence of bilateral tumor, stage, grade, cytoreduction, tumor localization, metastatic disease and adjuvant chemotherapy were found to be statistically significant prognostic factors for DFS. Stage was detected as one of the most significant prognostic factors both for OS and DFS ($p < 0.001$) (Figures 1 and 2). Five-year OS rates were determined as 80%, 63%, and 40% for patients with Stage I, II, and III, respectively. Two-year survival was 20% in cases with Stage IV disease. Multivariate analysis illustrated that age, stage, and optimal cytoreduction were the most significant factors for OS (Table 4). The only independent prognostic factor for DFS was optimal cytoreduction. Although, patients with GCT had longer OS when compared to the others, difference was not statistically significant ($p = 0.659$).

Discussion

SCST are a rarely seen heterogeneous tumor group derived from the ovarian stroma and the sex cords. Unlike EOC, they are characterized with slow growth pattern and low malignancy potential and patients with SCSTs have better prognosis [1, 3]. It is very well known that SCSTs constitute approximately 7% of all primary ovarian tumors [1]. Similar to the available data, the present cases with SCST constituted 8% of primary ovarian tumors seen in the study period. The most commonly seen SCSTs are GCTs and consist of 70% of all SCSTs [1,5]. In the present study, GCTs were detected in the majority of the cases with SCSTs (92%).

SCSTs may occur in all age groups, although their incidence increases in the perimenopausal period [3]. In accordance with literature, the present patients' mean age was 45.57 ± 12.8 (16-78) years, although age has been found to be significant prognostic factor in some studies, but not in others [4, 6]. In the present study, age was determined as a significant prognostic factor for OS ($p < 0.001$), but not for DFS ($p = 0.299$). Abdominal pain (30.1%) and bleeding disorders (29.1%) were the common complaints in the present study, consistent with literature [7]. SCSTs are unilateral in 95% of cases [2, 3]. Bilaterality has been found to be associated with poor clinical outcome [8]. Ninety percent of the present cases had unilateral tumor. Bilateral tumor involvement has been reported as a significant poor prognostic factor both for OS and DFS and predictive for up to 50% of recurrence risk.

SCSTs are usually medium-sized tumors [9]. Similarly in the present study, five- to ten-cm tumor diameter was the most commonly detected in all stages and there was no smaller than five cm tumor in cases with Stage IV disease. Sun *et al.* reported that residual tumor and tumor diameter were related with recurrence of the disease [7]. However, the present authors did not find a statistically significant correlation between tumor diameter and stage ($p = 0.470$). Stage, tumor diameter, and postoperative residual tumor have been reported as independent risk factors for recurrence in multivariate analysis by Shim *et al.* [10]. In the present study, cytology was evaluated in 54 (52.4%) cases. Recurrence rate was found to be 22.1% and 7.4% of the patients with positive and negative cytology, respectively. With univariate analysis, positive cytology was detected to be a significant prognostic factor for OS ($p = 0.008$). Although, DFS was found to be better in cases with negative cytology, but statistically not significant ($p = 0.156$).

Stage and residual tumor have been defined as the most important prognostic factors in many studies [2-4]. In the present study, stage was found to be significant independent prognostic factor for OS but not for DFS. FSS can be performed in early stage and selected individual advanced cases. Similar results have been obtained with FSS as compared to patients treated with radical surgery [11]. In the present study, FSS was performed in 22 cases. This type of surgery is of great importance in patients. TAH+BSO is recommended if fertility is not desired or in postmenopausal patients. Most commonly, USO+omentectomy+BPPLND were applied to these cases. Although, protecting fertility is the main aim, staging is important for predicting prognosis. Full staging (washing and taking cytology, biopsies of suspicious peritoneal areas, omentectomy, and BPPLND) should be considered in predicting patients with high risk of recurrence [2]. Park *et al.* showed that five-year- DFS was 100% in cases experienced staging surgery and 84% in cases who did not [12]. However Sun *et al.* reported that surgery type and adjuvant treatment had no effect on survival outcomes [7]. In the present work, no statistically significant difference was noted in DFS rates according to the type of surgery ($p = 0.721$). On the other hand, OS rates of patients treated with FSS were significantly higher than those treated with radical surgery ($p = 0.017$). This result can be explained by early stage of the cases treated with FSS.

In a study by Kleppe *et al.*, 578 patients were evaluated. LND was administered to 86 of them and no metastases were detected. LND was performed in 25 cases in a total of

93 early-stage (Stage I-II). Kleppe *et al.* reported that incidence of LN metastasis is low in patients in Stage I-II SCST [13]. Also SCST in a study by Park *et al.*, no metastases were found. Thus, they noted that LND is not necessary in cases with early-stage disease [12]. Lymphadenectomy was carried out in 54 (52,4%) of the present cases. Metastases were detected in 12 (22%) of them and all of these 12 patients had Stage III-IV disease; this is compatible with available data. It seems that LND is not mandatory in cases with early-stage disease, and BPPLND is necessary in cases with advanced stage disease.

Optimal cytoreduction has been found to be an important prognostic factor for survival in many studies [4,12,14]. In our work, optimal cyotreduction was done in 85 (82,5%) cases, whereas, five-year OS was 75% in these patients, it was 20% in cases with suboptimal surgery. This difference was statistically significant both for OS and DFS.

BEP is the acceptable regimen for SCSTs [12]. Ranganath *et al.* indicated that DFS was longer in patients who received CT without statistically significant difference [14]. In the present study, five-year OS rate was 45% in patients who received CT and 80% in those who did not. This difference was statistically significant both for OS ($p = 0.004$) and DFS ($p = 0.002$). This result can be explained by advanced stage and poor prognostic factors in patients who received CT. In addition, recurrence was 27.3% in patients who received CT and 3.4% in patients who did not. In the present work, CT was given to 44 (42.7%) patients. BEP CT was used in 27 (61.3%) and non-BEP CT in 17 (38.7%) of them. With univariate analysis, survival was longer in BEP CT arm and this finding was statistically significant ($p = 0.003$). Furthermore, recurrence rate was 22.2% in BEP and 35.3% in non-BEP arm, and this outcome was statistically significant ($p = 0.001$).

SCSTs are slowly growing tumors and late recurrences have been reported even after 25 years [2, 3, 15, 16]. It is indicated that debulking surgery followed by combination chemotherapy should be given in case of recurrence [2]. Only local pelvic recurrences were seen in 14 (13.6%) of the present cases. Mean recurrence time was 39.4 (10-127) months; 64,2% of patients who detected recurrence had advanced stage disease. This result emphasized that stage has prognostic importance and long-term follow-up is mandatory in these cases.

Conclusion

FSS is an effective approach for preserving the reproductive functions of young patients with SCST. Stage, > 50 years of age, suboptimal cytoreduction, bilaterality, and non-BEP chemotherapy in cases requiring CT were determined to be poor prognostic factors with univariate analysis. Age, stage, and optimal cytoreduction were found to be independent prognostic factors with multivariate analysis. It was concluded that the most effective parameters on survival are stage and optimal cytoreduction.

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