Clinicopathological features and prognostic factors of the uterine sarcomas: 20 years of experience at Çukurova University

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Summary

Objective: Uterine sarcomas (US) are rare, malignant, and aggressive tumors of the uterus. In this study the authors aimed to evaluate retrospectively the clinical and pathologic features and to investigate the prognostic factors of the US patients who were treated in their department in the last 20 years. *Materials and Methods:* The archive files, medical, and pathological records of the 132 US patients who were operated on and regularly followed up in the clinic between March 1991 – March 2011 were reviewed. Clinical features, operation characteristics, pathological findings, adjuvant therapies, and follow-up data of the patients and their effects on survival were investigated. Analysis of disease-free survival (DFS) and overall survival (OS) were calculated using Kaplan-Meier and Cox regression tests. The *p* value was taken < 0.05 to maintain the statistical significance level for all results. *Results:* Seventy of the patients were diagnosed with leiomyosarcomas (LMS), 33 were with carcinosarcomas, 12 were with endometrial stromal sarcomas (ESS), nine were with undifferentiated endometrial sarcomas, five were with adenosarcomas, and three were with botryoid rhabdomyosarcomas. The average patients' age was 53,7±12,6 (17-78). Aboutywo-thirds of the patients were in postmenopausal and one-third were in premenopausal period. Vaginal bleeding was detected as the most common reason for patients' admission (68,9%). All cases underwent surgery and a procedure of total abdominal hysterectomy + bilateral salpingo-oophorectomy (TAH + BSO) was performed for most of them (88%). The mean duration of follow-up was 36 months (4-198). The two- and five-year OS rates were 65% and 36%, respectively, with a median time of 37 months (95% CI, 28-45). The two- and five-year DFS rates were 59% and 33%, respectively, with a median time of 29 months (95% CI, 18-40). *Conclusion:* As a result of multivariate analysis, while age, stage, lymphovascular space invasion (LVSI), and lymphadenectomy were found to be independent prognostic factors affecting DFS, only stage was detected as an independent prognostic factor for OS.

Key words: Endometrial stromal sarcoma; Carcinosarcoma; Leiomyosarcoma; Prognostic factors; Uterine sarcoma.

Introduction

Sarcomas are malignancies originating from the tissues of the embryonic mesoderm. Uterine sarcomas (US) develop from myometrial smooth muscle, endometrial stroma or more rarely from any of the connective tissue elements [1]. US compose one percent of all gynecological and three to seven percent of the uterine malignancies [2]. Their incidence is reported as less than two per 100,000 per year [3].

Although US can be seen in ages between 18-95, the peak is 50-60 years. Sixty to 70 percent of the patients are postmenopausal and 90% of them are over 45 years [4, 5]. Vaginal bleeding is generally the primary complaint [1]. More than half of the patients consult when they are in Stage I [6]. Although US have high rates of diagnosis in the early stage, they are aggressive tumors and they have poor prognosis compared to endometrial cancer. These tumors also have a high propensity for local recurrence and distant metastasis [2,7].

US can be classified into four main histological types: 1) carcinosarcoma (CS) or malignant mixed Müllerian tumor, 2) leiomyosarcoma (LMS), 3) endometrial stromal sarcoma (in the current terminology, endometrial stromal sarcoma (ESS) replaces the term "low-grade ESS" and undifferentiated endometrial sarcoma (Un-ES) replaces the term "high-grade ESS"), and 4) adenosarcoma (AS) [2, 8, 9]. However, in the last years, CS is referred as an aggressive type of the endometrial carcinoma which exhibits sarcomatous metaplasia. Nevertheless, CS has been included in most of the current retrospective studies and reviews on the US [1]. Furthermore, according to the latest World Health Organization classification (2003), CS is still classified as a uterine sarcoma. Additionally, to obtain more significative comparative results, the authors also have included carcinosarcomas in this study.

Because US are a rarely seen heterogeneous tumor group, standardized treatment model is not available. However, surgery is accepted as the cornerstone of the treatment. Although there is no consensus regarding the surgical procedure, total extrafascial hysterectomy + bilateral salpingo-oophorectomy is considered to be the standard procedure of surgery. Additional treatments such as adjuvant chemotherapy (CT) and radiotherapy (RT) are also still controversial [1, 3].

Due to their rarity, large series of randomized prospective studies on US are unavailable. Hence, each center is

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Table 1. — *Distribution of the patients' age, parity and menopausal status according to their hisopathological types.*

Histopathological type n %		LMS 70 (53.0)	CS 33 (25.0)	ESS 12 (9.1)	Un-ES 9 (6.8)	AS 5 (3.8)	Other 3 (2.3)	Total 132 (100)	*p*
Age	Mean±SD	50.2±11.8	61.2±10.0	46.7±11.9	62.0±8.3	58.6±15.6	46.6±19.2	53.7±12.6	
	Median	52	62	47	65	61	50	55	0.000
	(min-max)	(17-76)	(32-78)	(29-75)	(46-71)	(35-77)	(26-64)	(17-78)	
Parity	Mean±SD	4.5±3.3	5.4±3.6	4.0±1.9	3.4±4.3	3.6±3.2	3.6±2.3	4.5±3.3	
	Median	4	5	4	0	3	5	4	0.553
	(min-max)	(0-12)	(0-14)	(1-9)	(0-9)	(0-9)	(1-5)	(0-14)	
Menopaual status	Premenopausal n (%)	30 (42.9)	3 (9.1)	8 (66.7)	1 (11.1)	1 (20.0)	1 (33.3)	44 (33.3)	0.001
	Postmenopausal n (%)	40 (57.1)	30 (90.9)	4 (33.3)	8 (88.9)	4 (80.0)	2 (66.7)	88 (66.7)	

SD: standard deviation, Min: minimum, Max: maximum.

required to analyze their own experience and compose their series. Thus, it can be possible to make an evaluation about the various prognostic factors and treatment outcomes by comparing them among these series. For this purpose, the authors aimed to investigate retrospectively, the clinical, surgical and pathological features, performed treatments, and survival outcomes of the patients who were diagnosed with US, operated, and followed up in the authors' clinic between the years 1991 and 2011.

Materials and Methods

Approval to conduct this study was obtained from the Research Ethics Committee at Çukurova University Faculty of Medicine. The study was designed as a retrospective analysis of the uterine sarcoma patients diagnosed, treated, and followed up at the Gynecologic Oncology Unit of the University Hospital of Çukurova University during the 20-year period from March 1, 1991 to March 31, 2011. The Gynecologic Oncology Unit records were reviewed and 156 cases of uterine sarcoma were determined. Patients' archival files, pathology records and the Gynecologic Oncology Unit data cards, and computer and clinical files were assessed. Sixteen patients with irregular registration or follow-up data and eight patients with uncertain diagnosis were excluded. Study was carried out with the remaining 132 patients. These 132 patients'; a) clinical features (age, parity, menopausal status, reason for admission, family history, concomitant malignancy, radiation history), b) operational information (the surgical procedure, optimization of cytoreduction, ascites, operation time, operative complications, postoperative hospital stay), c) pathological findings (tumor localization, location, size, histological type, stage, grade, mitotic index, necrosis, presence of cellular atypia, depth of myometrial invasion, pelvic and para-aortic lymph nodes involvement, lymphovascular space invasion (LVSI), cytologic property), d) adjuvant treatments (CT, RT), and e) follow-up data (recurrence and its site, need for secondary surgery) were evaluated and survival were investigated.

According to the records, 79 of the patients had died and the remaining were alive during this research. Sixteen patients who did not have their routine examinations in the last three months were contacted by phone and their latest situation was checked. Patients were divided into two groups according to the preservation of the ovaries: ovary protective (TAH/TAH+USO) and non-protective (TAH+BSO) procedures. Optimal cytoreduction was defined as the absence of visible residual tumor. Disease-free survival (DFS) was considered as the period between the operation time and relapse or recurrence dates. In patients with non-optimal cytoreduction, the DFS was taken to be zero. Overall survival (OS) was considered as the period between the pathological diagnosis and death dates. Survival times were expressed in months.

Histopathological examinations of the surgical specimens were evaluated by an experienced gynecopathologists in the authors' medical faculty. Tumor staging was determined according to the surgical pathological staging system which had been revised by International Federation of Gynecology and Obstetric (FIGO) in 2009. US were graded as "low" and "high". Number of the mitotic figures was divided as <10, 10-20, and >20. Tumor size was assessed with the largest diameter of the tumor and then categorized into three groups (≤ 5, 5-10, and >10cm).

Statistical methodology: data were tested according to their compliance for the normal distribution. Continuous variables with normal distribution were analyzed using t test and one-way ANOVA for the independent variables. Mann Whitney U and Kruskall Wallis tests were used in the analysis of the continuous variables with abnormal distribution. Categorical variables were compared using the Chi-square test. Univariate analysis of survival rates were carried out by the Kaplan-Meier method. Variables which were found to be significant in the univariate analysis were evaluated with multivariate analysis using the Cox regression method. Log rank test was performed to compare the survival curves between groups. For all tests, $p < 0.05$ was considered statistically significant. Results were summarized as mean ± standard deviation (median and minimum-maximum values were added where necessary), numbers, and percentages. SPSS 17.0 Evaluation Version (Statistical Package for Social Sciences) software package was used in the statistical analysis of the data.

Results

The study was conducted with 132 patients which accounted about 3% of all gynecologic malignancies (4,342) and 12% of the uterine malignancies (1,083) treated during the study period in the authors' department. The mean follow-up period was 36 months (4 - 198). The histological subtypes of the US were as follows: 70 (53%) cases with LMS, 33 (25%) with CS, 12 (9.1%) with ESS, nine (6.8%) with Un-ES, five (3.8%) with AS, and three (2.3%) with other sarcomas. The mean age of the patients at the diagnosis time was 53.7 ± 12.6 years (17-78). The mean parity

Table 2. — *Distribution of the tumor localization, location, and stage according to the histopathological types*

Histopathological type			LMS	CS	ESS	Un-ES	AS	Other	Total	*p*
Tumor localization	Submucosal	n	16	28	2	4	4	1	55	
		%	23.9	93.3	40.0	33.3	80.0	33.3	45.1	
	Intramural	n	32	2	3	7	1	1	46	
		%	47.8	6.7	60.0	58.3	20.0	33.3	37.7	0.000
	Subserosal	n	19	0	0	1	0	1	21	
		%	28.4	0.0	0.0	8.3	0.0	33.3	17.2	
	Total	n	5	67	30	12	5	3	122	
Tumor location	Isthmus	n	14	6	0	2	1	2	25	
		%	21.2	23.1	0.0	40.0	20.0	66.7	21.4	
	Corpus	n	39	13	10	3	4	0	69	
		%	59.1	50.0	83.3	60.0	80.0	0.0	59.0	0.223
	Fundus	n	13	7	2	0	0	1	23	
		%	19.7	26.9	16.7	0.0	0.0	33.3	19.7	
	Total	n	66	26	12	5	5	3	117	
Stage	I	n	46	15	10	5	5	1	82	
		%	65.7	45.5	83.3	55.6	100.0	33.3	62.1	
	II	n	10	1	0	1	0	1	13	
		%	14.3	3.0	0.0	11.1	0.0	33.3	9.8	-
	III	n	8	10	1	3	0	1	23	
		%	11.4	30.3	8.3	33.3	0.0	33.3	17.4	
	IV	n	6	7	1	0	0	0	14	
		%	8.6	21.2	8.3	0.0	0.0	0.0	10.6	

of all patients (4.57) was close to the mean parity of LMS (4.5): the largest proportion among the subtypes. While premenopausal patients were dominant (66.7%) only in the ESS cases, postmenopausal patients consisted the majority of the other histological subtypes. Patients' distribution according to their histological subtypes, age, parity, and menopausal status is shown in Table 1.

The most common symptoms were vaginal bleeding (68.9%), bloating or pelvic mass (16.7%), and abdominal or pelvic pain (10.6%). Ten patients (7.6%) had family history of cancer. Four patients (3%) had personal history of metachronous malignancy: three of them were breast cancer and the other was rectal cancer. Only the patient with rectal cancer had a history of pelvic RT as an adjuvant therapy.

All the patients underwent surgery. TAH + BSO was administered to 116 (88%) patients. Only TAH or TAH with unilateral salpingo-oophorectomy (USO) was performed in the remaining 16 patients in order to preserve one or both of the ovaries. Lymph node dissection (LND) was carried out in 46 (35%) patients and ten of them were found to be positive. Pelvic and para-aortic LND (PPLND) was applied to 31 cases and in 15 cases only pelvic LND was performed. Omentectomy was administered to 39 (29.5%) of the patients. Additional surgical procedures (e.g. bowel resection, splenectomy, vaginectomy) were required in 19 (14%) patients. Both of postoperative hospital stay and operation times were statistically longer in case of LND ± omentectomy ± additional surgical procedures were per-

Table 3. — *Distribution of the pathological characteristics of the uterine sarcomas.*

Pathological characteristics		n (%)
Grade	Unknown	59 (44.7)
	1	31 (23.5)
	2	6 (4.5)
	3	36 (27.3)
Mitosis count	Unknown	33 (25.0)
	<10	28 (21.2)
	10-20	30 (22.7)
	>20	41 (31.1)
Marked cellular atypia	Unknown	19 (14.4)
	No	49 (37.1)
	Yes	64 (48.5)
Necrosis	No	16 (12.1)
	Yes	116 (87.9)
Myometrial invasion	No	4 (3.0)
	<% 50	55 (41.7)
	>% 50	73 (55.3)
LN involvement	Unknown	86 (65.2)
	No	36 (27.3)
	Yes	10 (7.6)
LVSI	No	95 (72.0)
	Yes	37 (28)
Tumor size	Unknown	8 (6)
	<5 cm	24 (18.2)
	5-10 cm	66 (50.0)
	>10 cm	34 (25.8)

Table 4. — *Patients' disease-free and overall survival rates according to their clinical, surgical, and pathological characteristics.*

Parameter		N/n	Disease-free survival				Overall survival			
			X/M	2 years (%)	5 years (%)	*p*	X/M	2 years (%)	5 years (%)	*p*
Age	≤50	51/27	86/41	62	43	0.034	86/51	72	44	0.023
	>50	81/52	32/23	46	26		39/31	61	30	
Menopausal status	Premenopause	44/23	89/41	63	45	0.041	90/51	72	48	0.021
	Postmenopause	88/56	32/23	46	25		39/31	61	28	
Surgical procedure	TAH/TAH+USO	16/7	62/97	-	-	0.115	78/115	69	-	0.104
	TAH+BSO	116/72	64/27	50	28		61/36	67	32	
Omentectomy	No	93/59	46/23	47	30	0.097	51/34	64	33	0.148
	Yes	39/20	90/42	66	41		94/42	70	42	
LND	No	86/59	37/23	45	24	0.013	45/31	62	29	0.024
	Yes	46/20	101/66	66	48		102/66	72	51	
Additional surgery	No	113/64	70/32	54	36	0.111	68/40	69	37	0.066
	Yes	19/15	36/21	40	17		40/24	46	22	
Cytoreduction	Nonoptimal	12/12	-	-	-	-	11/7	8	-	0.000
	Optimal	120/67	-	-	-	-	71/41	71	40	
Tumor localization	Submucosal	55/31	69/41	59	39		82/42	70	44	
	Intramural	46/26	49/32	55	35	0.009	57/44	73	38	0.040
	Subserosal	21/15	35/6	25	10		36/21	33	16	
Tumor location	Isthmus	25/16	35/32	55	25		40/41	63	37	
	Corpus	69/37	77/50	57	38	0.381	79/51	67	43	0.573
	Fundus	23/16	31/22	46	23		44/37	67	31	
Histopathological type	LMS	70/42	71/24	49	34		72/36	61	37	
	KS	33/22	32/24	49	25	0.109	36/34	63	23	0.083
	ESS	12/6	71/54	85	46		83/89	91	57	
	Un-ES	9/7	19/7	22	-		28/24	44	-	
Stage	I+II	95/45	84/60	63	48	0.000	89/66	76	52	0.000
	III+IV	37/34	15/8	24	0		22/18	37	0	
Grade	Low	31/16	79/54	75	39	0.001	83/66	89	53	0.000
	High	42/29	25/12	39	12		30/27	51	17	
Mitosis count	<10	28/12	101/89	78	53		102/97	85	57	
	10-20	30/19	52/29	57	29	0.002	55/50	59	39	0.001
	>20	41/28	25/11	34	-		31/28	53	-	
Cellular atypia	No	49/27	63/41	63	35	0.135	66/50	76	39	0.151
	Yes	64/40	71/17	44	30		72/29	60	32	
Necrosis	No	16/5	63/-	93	62	0.006	65/-	100	57	0.008
	Yes	116/74	59/23	45	29		59/31	60	33	
Tumor size	≤ 5 cm	24/9	112/66	70	59		113/69	80	60	
	5-10 cm	66/44	50/24	47	27	0.032	54/34	66	29	0.026
	>10 cm	34/20	31/12	46	17		36/24	49	24	
Myometrial invasion	<% 50	59/30	85/54	64	45	0.003	95/66	77	50	0.001
	>% 50	73/49	35/23	41	20		42/28	55	22	
Lymph node involvement	No	36/11	126/-	76	56	0.000	127/-	85	60	0.000
	Yes	10/9	14/6	20	0		19/12	25	0	
LVSI	No	95/51	76/41	61	40	0.000	78/50	76	44	0.000
	Yes	37/28	22/9	30	-		26/15	38	9	
Cytology	Negative	19/9	93/44	72	37	0.000	94/51	84	38	0.000
	Positive	2/2	-/-	-	-		-/-	-	-	
Ascite	No	122/71	70/33	54	35	0.047	68/40	67	38	0.009
	Yes	10/8	18/8	25	-		22/19	48	-	
RT	No	84/43	90/37	55	43		71/41	64	46	
	Primary	36/26	42/24	43	15	0.253	47/29	64	18	0.202
	Secondary	12/10	42/27	58	22		55/36	70	42	
KT	No	50/21	99/97	77	56		101/69	79	60	
	Primary	65/45	42/12	36	20	0.000	42/28	54	22	0.000
	Secondary	17/13	22/12	31	0		34/34	64	11	

N: number of total patients, n: number of dead patients, X: mean, M: median

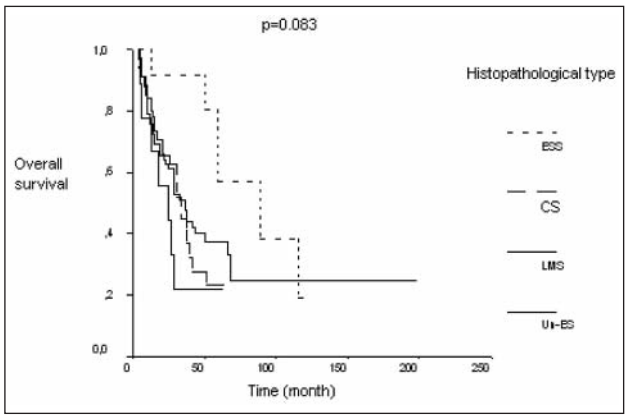

Figure 1. — Overall survival of the uterine sarcoma subtypes.

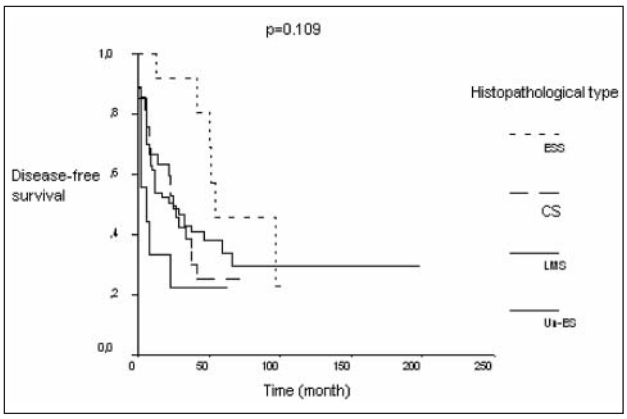

Figure 2. — Disease-free survival of the uterine sarcoma subtypes.

formed. Blood transfusion (15.2%) and wound infection (7.6%) were the most seen complications. Surgery was evaluated as non-optimal in 12 (9%) patients.

Fifty-five of the US were submucosal, 46 intramural, and 21 subserosal. The localization of the remaining ten cases was unknown. Nearly half (47.8%) of the LMS tumors were intramural. Also, more than half (58.3%) of the Un-ES's were intramural. Most of the CS tumors (93.3%) and the AS tumors (80%) were submucosal. While 60% of the ESS tumors were intramural, 40% of them were submucosal. Uterine corpus was the place where 69 of the US were located in. Twenty-five of the US were located in the low segment (or isthmus) and 23 were in the fundus. The remaining 15 cases' locations were not known. The distribution of the localization and location of the US according to their histological types is shown in Table 2. Most of the patients were assessed as early stage (62.1% Stage I and 9.8% Stage II). High stages were preponderant only in the patients with CS type (Table 2).

In eight patients, tumor diameter was not assessed. The mean tumor diameter of the remaining 124 cases was 8.2 ± 4.4 cm (1.5 - 25 cm). In half of the cases, tumor diameter was between five and ten cm. Thirty-one patients were evaluated as low grade and 42 patients as high grade. Grade was unknown in 59 patients. While mitosis number was unknown in 33 cases, 28 patients had <10 mitosis count, 30 patients had 10-20 mitosis count, and 41 had >20 mitosis count. Marked cellular atypia was found in 64 patients (48.5%). Necrosis was seen in most of the cases (88%). Ascite was seen only in ten patients (four LMS, six CS). Out of 21 patients whose cytology results were known, two positive cytology were detected and both of them were CS. Pathological findings of the patients are summarized in Table 3.

Recurrences were determined in 58% of the patients during the follow-up time. Local pelvic recurrences were found in 21 (16%) patients and six of them were in the vaginal cuff. Recurrence was determined in the abdomen in 17 cases. Lungs were the place of recurrence in 17 cases, also. The recurrence of 21 cases was seen in more than one region. Recurrence was seen in 61.4%, 51.5 %, 50%, 77.8% and 40% of the LMS, CS, ESS, Un-ES, and AS patients, respectively, and there was no statistical difference among them. The median time to recurrence was 27 months for all US patients. This period was calculated as 24, 24, 54, and seven months for LMS, CS, ESS, and Un-ES patients, respectively. Adjuvant RT was given to 48 (36%) patients. While 36 of these patients underwent primary adjuvant RT, 12 of them received secondary adjuvant RT. Primary adjuvant CT was administered to 65 (49.2%) patients and secondary adjuvant CT was administered to 17 (12.9%) patients. Only 16 patients underwent secondary surgery.

The two- and five-years OS rates were 65% and 36%, respectively, with a median time of 37 months (95% CI, 28-45). The two- and five-year DFS rates were 59% and 33%, respectively, with a median time of 29 months (95% CI, 18-40). Age, menopause status, LND, tumor localization, stage, grade, mitosis count, necrosis, tumor size, myometrial infiltration, lymph node status, LVSI, peritoneal cytology, ascite, and adjuvant CT were all statistically significant in the univariant analysis of both of OS rates and DFS rates (Table 4). Cytoreduction was assessed for the DFS rates and found to be statistically significant. Although there was no statistical significance for any of OS or DFS rates among the histological subtypes, ESS patients' survival rates were clearly superior to those with LMS, CS, and Un-ES patients (Figures 1, 2). As a result of multivariate analysis, while age, stage, LVSI, and lymphadenectomy were found to be independent prognostic factors affecting DFS, only stage was detected as an independent prognostic factor for OS (Tables 5, 6).

Table 5. — *Multivariate analysis of disease-free survival.*

Parameter	*p*	HR	95% CI	
			Minimum	Maximum
Age	0.045	5.0	1.03	24.11
LND	0.017	4.8	1.32	17.28
Tumor localization (submucosal)	0.819			
Tumor localization (intramural)	0.853	1.2	0.26	5.1
Tumor localization (subserosal)	0.813	0.8	0.07	7.32
Stage	0.010	5.4	1.5	19.29
Grade	0.620	1.5	0.28	8.19
Mitosis count (<10)	0.274			
Mitosis count (10-20)	0.988	1.0	0.19	5.34
Mitosis count (>20)	0.171	3.3	0.59	18.81
Tumor size (<5cm)	0.181			
Tumor size (5-10cm)	0.064	7.0	0.89	54.73
Tumor size (>10)	0.108	6.7	0.65	69.8
Myometrial invasion	0.172	2.6	0.65	10.57
LVSI	0.026	7.1	1.26	40.6

HR: *Hazard Ratio*, CI: Confidence interval.

Table 6. — *Multivariate analysis of overall survival.*

Parameter	*p*	HR	95% CI	
			Minimum	Maximum
Age	0.104	3.2	0.78	13.35
LND	0.178	2.5	0.66	9.16
Tumor localization (submucosal)	0.955			
Tumor localization (intramural)	0.763	1.2	0.3	5.1
Tumor localization (subserosal)	0.832	1.2	0.16	9.83
Stage	0.012	4.1	1.35	12.47
Grade	0.590	0.6	0.15	2.9
Mitosis count (<10)	0.282			
Mitosis count (10-20)	0.754	1.3	0.25	6.69
Mitosis count (>20)	0.145	4.0	0.61	26.4
Tumor size (<5cm)	0.403			
Tumor size (5-10cm)	0.221	2.9	0.52	16.3
Tumor size (>10)	0.197	3.8	0.5	29.0
Myometrial invasion	0.489	1.6	0.42	5.91
LVSI	0.091	4.5	0.78	25.73

HR: *Hazard Ratio*, CI: Confidence interval.

Discussion

US are uncommon and aggressive gynecological malignancies. Due to the rarity and diversity of histologic types**,** a treatment strategy has not yet been established. Most of the treatment guidelines are based on small and retrospective studies. In this study 132 patients of US treated in the present hospital during the last 20 years were evaluated. LMS is found to be the most frequent subtype of the US, followed by CS and ESS. This histological distribution was in accordance with the literature [2, 10-12].

Generally, US are encountered at older ages. However, LMS and ESS can be seen at younger ages than CS and AS [2, 6, 11, 13]. In the present study, similar to the findings in the literature, the mean age of diagnosis for LMS, ESS, CS, and AS was 50.2 ± 11.7, 46.7 ± 11.9, 61.2 ± 10, and 58.6 ± 15.6, respectively. Age was detected as a significant prognostic factor in the study by Koivisto-Korander *et al.* [14]. Kapp *et al.* stated that prognosis was worse in the patients > 52-years-old [11]. In the univariate analysis of the present series, age was significant for both of OS and DFS. However, in the multivariate analysis age was identified as a significant prognostic factor for DFS, but not for OS. It appears that prognosis of postmenopausal women are worse than the premenopausal ones [11, 15-18]. In correlation with the literature, univariate analysis shows that postmenopausal women's OS and DFS outcomes were statistically inferior to those in premenopausal women. Nevertheless, these results were not significant according to the multivariate analysis.

Classically, radiation history is considered as a risk factor for sarcomas. Actually, most of the US**,** which thought to be developed secondary to pelvic radiation**,** consist of carcinosarcomas [6, 19]. In the present study, only one patient with CS had a history of pelvic radiotherapy. Personal cancer history was found in three percent and familial cancer history was in 7.6% of the cases. These rates were lower than in other studies [1, 14, 20].

Surgery is the primary treatment of US. A procedure consisting of TAH+BSO+complete staging which include taking cytology, biopsies from suspected places, omentectomy, and BPPLND**,** is recommended in carcinosarcomas [3]. However, there is no consensus about the radicality of the surgical procedure in the other histological subtypes. If there is no macroscopic involvement of the ovaries, it is reasonable to preserve them in the premenopausal women with LMS who wish to retain their fertility [2, 3, 15, 21, 22]. In the largest serial of LMS patients, 341 cases (with Stage I or II disease) who were < 50 years old had been reported. Among these 341 patients there was no difference in five-year DFS between those who did or did not undergo BSO [11]. Ovarian conservation is more complicated in ESS subtype, since their estrogen receptor expression is variable [23, 24]. Furthermore, the role of BSO on survival is debatable [3, 21, 25-27]. Spano *et al.*, indicated that recurrence risk was high in the patients whose ovaries were preserved [28]. The present study included 16 patients (12 LMS, three ESS, and one AS) one or both of whose ovaries were protected. No difference was found in DFS or OS of these patients when compared with those who underwent BSO. Positive lymph nodes are rare without visible extrauterine disease in the LMS patients [3, 11, 15, 22, 29]. Adnexial or lymph node involvement was identified as

three percent in early stage leiomyosarcomas in a review paper by Amant *et al.* [26]. In the study by Kapp *et al.,* 6.6% of the patients who underwent LND had lymph node metastasis. LN metastasis was accompanied with extrauterine disease in 70% of these patients. No impact of LND on DFS was revealed [11]. Gadducci stated that the rate of occult LN metastasis ranged from four to 11 percent in LMS patients who did not have visible disease outside the uterus [22]. Giuntoli *et al.* researched 208 cases of LMS. Lymphadenectomy was performed to 36 of them. LN metastasis was found in four (11%) patients and three of them had extrauterine disease [15]. DFS and OS were statistically similar between the women with LMS who did or did not undergo LND in a study by Ayhan *et al.* [30]. According to all these data**,** it seems unnecessary to perform routinely lymphadenectomy in leiomyosarcomas. On the other hand, significance of lymphadenectomy in women with ESS is uncertain. LN metastasis ranged from 0-33% among these patients [21, 31-33]. This wide interval can be explained by small sample sizes of the studies and the fact that most studies were carried out with US rather than ESS. Shah *et al.* investigated the role of lymphadenectomy in 384 cases of ESS (100 of them underwent LND). There was no difference on survival rates between patients who had positive or negative lymph nodes [25]. In an analysis of Surveillance, Epidemiology, and End Results (SEER) made by Chan *et al.*, 831 ESS patients were evaluated. LND was applied to 282 patients and lymph node metastasis was detected in 9.9% of them. Lymph node involvement was considered to be an independent prognostic factor which affected survival negatively. However, no significant difference on survival was found between patients who underwent lymphadenectomy and those who did not [34]. Data about the incidence of LN involvement in Un-ES subtype is limited. A series consisted of 320 cases of Un-ES, pelvic and/or para-aortic LND was administered to 143 patients and lymph nodes were positive in 18% of them. Metastatic lymph nodes were related with low survival time (eight vs 24 months) [25]. A study of GOG identified that lymph node involvement rates were 15% and 21% in homologous and heterologous CS patients, respectively [35]. Also, Temkin *et al.* determined that metastatic regional lymph nodes were about 20% of the CS patients in their series [36]. Nemani *et al.* established that lymphadenectomy had positive impact on survival of the CS patients (54 vs 25 months) [37]. Hence, a complete debulking is suggested in CS's. In the present study, LND was performed in 46 cases (22 LMS, 19 CS, three ESS, one AS, one rhabdomyosarcoma). In other words LND was applied to 31.4%, 57.6% ,and 25% of the LMS, CS and ESS patients, respectively. Lymph nodes were positive in ten patients (two LMS, eight CS). Both of the LMS cases had extrauterine disease. Metastatic lymph nodes were identified in eight (42%) of the 19 CS cases who underwent lymphadenectomy. This rate is approximately two times higher than that reported in the literature. This difference can be explained by the fact that most of the present CS cases who underwent LND were in advanced stage. Univariate analysis revealed that there was a significant difference in both of DFS and OS rates between patients who underwent LND and those who did not. Furthermore, LND was found to be an independent prognostic factor for DFS but not for OS on multivariate analysis. Additionally, survival rates were statistically inferior in patients with positive nodes. Omentectomy was administered in 39 cases and there was no significant difference in DFS or OS rates between them and those who did not undergo omentectomy. Non-optimal cytoreduction was reported in 12 cases. These patients' survival rates were quite inferior comparing to the others'.

Investigation of the effect of uterine sarcomas' localization (submucosal, intramural, subserosal) and location (isthmus, corpus, fundus) upon survival was particular for this study. No significant impact on survival rates was reported according to the tumor location. On the other hand, univariate analysis elicit that tumor localization was a significant indicator for DFS and OS. Survival rates were distributed according to the tumor localization as follows; submucosal > intramural > subserosal. As submucosal tumors yield to vaginal bleeding and thus to early diagnosis, it is reasonable to have higher survival rates than the others. However, tumor localization was not found to be a significant prognosticator on multivariate analysis.

Literature is not quite clear about the impact of histopathological type on clinical outcomes, prognosis or survival. The differences of survival rates according to histopathological types were found to be significant in some studies [7, 20, 35, 38], and insignificant in others [14, 39, 40]. Nevertheless, generally it is considered that ESS subtype has a good prognosis than others [6, 21, 40-42]. Likewise, AS subtype is also suggested to have good prognosis [43, 44]. Although, no statistically-significant difference on DFS or OS between histopathological subtypes was obtained in the present series, there was a pronounced superiority on survival rates of ESS and AS subtypes.

Prospective studies about the effect of postoperative adjuvant RT are restricted with EORTC study which included 219 cases of Stage I or II US (99 LMS, 92 CS, 30 ESS). This study reported that adjuvant RT treatment was associated with reduced local recurrences, but it did not influence survival [45]. Using the SEER database, Brooks *et al.* conducted a study with 2,677 patients and they reached the conclusion that adjuvant RT was associated with increased survival. Five-year survival rates were 55% in Stage II patients who had adjuvant RT vs 31% in those who did not and 33% vs 25% for Stage III-IV patients [6]. Adjuvant RT (primary or secondary) was given to 48 (36%) patients in the present study and no significant effect on survival was observed in these patients. This may be attributed to the fact that the patients were heterogeneous, especially regarding stage and histological type.

Although a positive effect of adjuvant CT was obtained in some studies [46, 47], similar conclusions were not reached in others [15, 38, 48]. Adjuvant CT (primary or secondary) was administered to 82 (62.1%) patients in the present study. Both DFS and OS rates were superior in the patients who did not receive adjuvant CT as compared to those who did. This result can be explained by the fact that a) primary adjuvant CT was given only to high-risk Stage I and more advanced stages, b) secondary adjuvant CT was used in case of relapse or recurrence, and c) the heterogeneous group of the patients.

The two- and five- year OS rates of the present series were 65% and 36%, respectively, with a median time of 37 months (95% CI, 28-45). The two- and five-year DFS rates were 59% and 33%, respectively, with a median time of 29 months (95% CI, 18-40). These rates were in accordance with the literature [1, 4, 14, 16, 48, 49]. Stage emerges as the most important prognostic factor in many studies [3,11, 16, 35, 37, 41, 49]. In the present study, stage was determined as an independent prognostic factor as well for both DFS (HR 5.4, 95% CI 1.5-19.29; $p = 0.010$) and OS (HR 4.1, 95% CI 1.36-12.47; $p = 0.012$). Beside the stage, age, menopausal status, LND, tumor localization, grade, mitosis count, necrosis, tumor size, myometrial invasion, LVSI, lymph nodes' involvement, cytologic property, and ascite status were identified as significant prognosticators for both DFS and OS in univariate analysis. However, multivariate analysis elicit that only stage, age, LND, and LVSI were found to be independent factors for DFS and only stage was detected as an independent factor for OS. Similar results were achieved by other researchers [1, 11, 14, 16, 35, 41, 49-51].

Conclusion

As a result of multivariate analysis, while age, stage, LVSI and lymphadenectomy were found to be independent prognostic factors affecting DFS, only stage was detected as an independent prognostic factor for OS. Although no statistically-significant difference in DFS or OS among histopathological subtypes was obtained in the present series, there was a pronounced superiority on survival rates of ESS and AS subtypes.

Due to their rarity, large series of randomized prospective studies on US are unavailable. Hence, each center is required to analyse its own experiences and to compose their series. Thus, it can be possible to make an evaluation regarding the various prognostic factors and treatment outcomes in order to develop a consensus about the appropriate treatment modalities. For the same purpose, randomized and prospective multi-institutional studies should also be planned.

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