RESEARCH COMMUNICATION

Prognostic Factors and Treatment Outcomes in 93 Patients with Uterine Sarcoma from 4 Centers in Turkey

Ayşe Durnalı[1], Saadet Tokluoğlu[2], Nuriye Özdemir[3], Mevlüde İnanç[4], Necati Alkış[1], Nurullah Zengin[3], Özlem Uysal Sönmez[1], Mehmet Küçüköner[5], Anatolian Society of Medical Oncology (ASMO)

Abstract

Introduction: Uterine sarcomas are a group of heterogenous and rare malignancies of the female genital tract and there is a lack of consensus on prognostic factors and optimal treatment. Objective and Methodology: To perform a retrospective evaluation of clinicopathological characteristics, prognostic factors and treatment outcomes of 93 patients with uterine sarcomas who were diagnosed and treated at 4 different centers from November 2000 to October 2010. Results: Of the 93 patients, 58.0% had leiomyosarcomas, 26.9% malignant mixed Mullerian tumors, 9.7% endometrial stromal sarcomas, and 5.4% other histological types. According to the last International Federation of Gynecology and Obstetrics (FIGO) staging, 43.0% were stage I, 20.4% were stage II, 22.6% were stage III and 14.0 % were stage IV. Median relapse free survival (RFS) was 20 months (95% confidence interval (CI), 12.4-27.6 months), RFS after 1, 2, 5 years were 66.6%, 44.1%, 16.5% respectively. Median overall survival (OS) was 56 months (95% CI, 22.5-89.5 months), and OS after 1, 2, 5 years was 84.7%, 78%, 49.4% respectively. Multivariate analysis showed that age ≥60 years and high grade tumor were significantly associated with poor OS and RFS; patients administered adjuvant treatment with sequential chemotherapy and radiotherapy had longer RFS time. Among patients with leiomyosarcoma, in addition to age and grade, adjuvant treatment with sequential chemotherapy and radiotherapy after surgery had significant effects on OS. Conclusion: Uterine sarcomas have poor progrosis even at early stages. Prognostic factors affecting OS were found to be age and grade.

Keywords: Uterine sarcoma - leiomyosarcoma - malignant mixed Mullerian tumor - prognostic factors - Turkey

Asian Pacific J Cancer Prev, **13**, 1935-1941

Introduction

Uterine sarcomas account for 1% of female genital tract cancers and 2-5% of uterine malignancies (Major et al., 1993; Tavassoli & Devilee, 2003). This heterogenous group of tumors derives from uterine mesodermal tissue and because of their rarity and histopathological diversity, there is a lack of consensus on prognostic factors and optimal treatment. Uterine sarcomas were classified into 4 main types: malignant mixt mullerian tumors (MMMT), accounting 40% of cases, also called carcinosarcomas, leiomyosacomas (LMS, 40% of cases), endometrial stromal sarcomas (ESS, 10-15% of cases) and undiferentiated sarcomas (5-10% of cases). Recently, many authors have proposed that MMMT should be classified as a subtype of endometrial carcinoma, due to the fact that their clinical behaviour looks like carcinoma (lymphatic dissemination pattern and response to platinum based chemotherapy) (Sleijfer et al., 2007). But MMMT behave more aggressively than endometrial carcinomas and they have been still included in most retrospective studies and reviews of uterine sarcomas. In last International Federation of Gynecology and Obstetrics (FIGO) classification system three new classifications have been developed: staging for LMS and ESS, staging for adenosarcomas, staging for carcinosarcomas (Prat, 2009). Carcinosarcomas are staged as endometrial adenocarcinomas.

The aim of this study is to provide retrospective evaluation of clinicopathological characteristics and prognostic factors and treatment outcomes of the patients with uterine sarcoma.

Materials and Methods

This study was designed as retrospective analysis of the patients with uterine sarcoma who were diagnosed and treated from November 2000 to October 2010. The patients were from 4 different centers in Turkey. The main parameters recorded were patient characteristics

*[1]Medical Oncology Department of Dr A.Y.Ankara Oncology Training and Research Hospital, Ankara, [2]Medical Oncology Department of Güven Hospital, Ankara, Turkey, [3]Medical Oncology Department of Ankara Numune Training and Research Hospital, Ankara, [4]Medical Oncology Department of Erciyes University Faculty of Medicine, Kayseri, [5]Medical Oncology Department of Dicle University Faculty of Medicine, Diyarbakır, Turkey *For correspondence: aysadurnali@gmail.com*

(age, menopausal status, body mass index (BMI), parity, patient's history of other malignancies and medical diseases), presenting symptoms, serum level of cancer antigen 125 (CA125), date and type of surgical procedure, presence or absense of residual tumor after surgery, pathological data of tumor (histological type, size, grade, mitotic index, results of peritoneal cytological examination, presence or absence of lymphovascular space invasion (LVSI), myometrial invasion and lymph node involvement), date of recurrence, treatment after recurrence, date of last medical examination and date of death. Histopathological classification of uterine sarcomas were according to WHO classification (Tavassoli & Devilee, 2003): MMMT (Carcinosarcoma), LMS, ESS, other histopathological types. Some patients were diagnosed after FIGO 2009 staging system therefore we used this staging system in this study and we restaged the patients diagnosed before that time according to FIGO 2009 staging system. Relaps free survival (RFS) was calculated as the time in months from the date of diagnosis to either the date of recurrence or the date of last follow-up. Overall survival was calculated as the time in months from the date of diagnosis to either the date of death or the date of last follow-up. CA125 levels greater than 35 U/mL were considered as positive.

Data were analyzed using SPSS version 11,5. Survival rates were calculated using the Kaplan-Meier method and survival curves were compared using log-rank test. Variables showing significant differences after univariate analysis were evaluated with multivariate analysis by using Cox regression analysis. Hazard Ratios (HR) and 95% Coinfidence Interval (CI) were calculated for each variable. P value less than 0.05 was considered significant.

Results

This study included 93 uterine sarcoma patients: 54 patients (58.0%) with LMS, 25 patients (26.9%) with MMMT, 9 patients (9.7%) with ESS, 5 patients (5.4%) with other histological types (2 with adenosarcoma, 1 with undifferenciated sarcoma, 1 with Ewing sarcoma, 1 with rabdomyosarcoma). Patient characteristics are summarized in Table 1. Mean age of patients was 53.4 years (range 18-80 years). Mean age and rate of postmenopausal status

Table 1. Patient and Tumor Characteristics

Characteristics	All sarcomas (n=93)	Leiomyosarcoma (n=54)	MMMT (n=25)	ESS (n=9)	Other histologic types (n=5)	P value*
Age, years [mean(range)]	53.4 (18-80)	50.8 (34-72)	61.4 (41-80)	47.8 (28-65)	52.6 (18-80)	0.001
Parity, n (%)						
Parity ≥ 1	69 (74.2%)	38 (70.4%)	18 (72%)	9 (100%)	4 (80%)	0.504
Parity = 0	6 (6.5%)	3 (5.6%)	2 (8%)	0 (0%)	1 (20%)	
Not recorded	18 (19.3%)	13 (24.0%)	5 (20%)	0 (0%)	0 (0%)	
Menopause, , n (%)						
Premenopausal	40 (43.0%)	28 (51.8%)	3 (12%)	7 (77.8%)	2 (40%)	<0.001
Postmenopausal	50 (53.8%)	23 (42.6%)	22 (88%)	2 (22.2%)	3 (60%)	
Not recorded	3 (3.2%)	3 (5.6%)	0 (0%)	0 (0%)	0 (0%)	
Body mass index, kg/m^2, n (%)						
Normal,18.5-24.9	17 (18.3%)	9 (16.7%)	4 (16.0%)	1 (11.1%)	3 (60%)	0.234
Overweight-obese, ≤25.0	63 (67.8%)	36 (66.6%)	17 (68.0%)	8 (88.9%)	2 (40%)	
Not recorded	13 (13.9%)	9 (16.7%)	4 (16.0%)	0 (0%)	0 (0%)	
Medical disease[a], n (%)						
Absent	47(50.5%)	32 (59.3%)	8 (32%)	6 (66.7%)	1 (20%)	0.044
Present	46 (49.5%)	22 (40.7%)	17 (68%)	3 (33.3%)	4 (80%)	
Stage, n (%): I	40 (43%)	26 (48.1%)	7 (28%)	5 (55.6%)	2 (40%)	0.001
II	19 (20.4%)	14 (25.9%)	2 (8%)	3 (33.3%)	0 (0%)	
III	21 (22.6%)	5 (9.3%)	14 (56%)	1 (11.1%)	1 (20%)	
IV	13 (14.0%)	9 (16.7%)	2 (8%)	0 (0%)	2 (40%)	
Grade: I	14 (15.1%)	5 (9.3%)	2 (8.0%)	6 (66.7%)	1 (20%)	0.015
II	17 (18.3%)	12 (22.2%)	4 (16.0%)	0 (0%)	1 (20%)	
III	54 (58.1%)	33 (61.1%)	15 (60.0%)	3 (33.3%)	3 (60%)	
Not reported	8 (8.6%)	4 (7.4%)	4 (16.0%)	0 (0%)	0 (0%)	
Tumor size, Mean,cm (range)	8.44 (1-19)	8.83 (2-17.5)	7.80 (1-18)	7.75 (1.5-19)	8.87 (6-12)	0.380
Myometrial invasion, n (%)						
None	7 (7.5%)	3 (5.6%)	2 (8.0%)	0 (0%)	2 (40%)	0.416
< or ≥ 50%	76 (81.7%)	43 (79.6%)	22 (88.0%)	9 (100%)	2 (40%)	
Not reported	10 (10.8%)	8 (14.8%)	1 (4.0%)	0 (0%)	1 (20%)	
Recurrences, n (%)	59 (63.4%)	35 (64.8%)	15 (60%)	7 (77.8%)	2 (40%)	0.540
Follow-up, n (%)						
Alive, remission	24 (25.8%)	11 (20.4%)	9 (36%)	2 (22.2%)	2 (40%)	
Alive with disease	20 (21.5%)	12 (22.2%)	4 (16%)	2 (22.2%)	2 (40%)	
Lost to follow-up	15 (16.1%)	9 (16.7%)	5 (20%)	1 (11.1%)	0 (0%)	
Exitus	34 (36.6%)	22 (40.7%)	7 (28%)	4 (44.4%)	1 (20%)	

* P value between different histologic type,Abbreviations: MMMT, malignant mixed mullerian tumor; ESS, endometrial stromal sarcoma; [a]Including hypertension, diabetes mellitus, cardiac diseases, chronic obstructive lung diseases, thyroid diseases

Table 2. Surgical Management and Adjuvant Treatment[a]

Characteristics	All[b] (n=93)	Leio- (n=54)	MMMT (n=25)	ESS (n=9)	Other[c] (n=5)
Primary operation, n					
No surgery	4	2	1	0	1
HT	7	5	0	2	0
HT-BSO/USO	82	47	24	7	4
Lymph node evaluation	42	19	16	5	2
Omentectomy	48	22	18	5	3
No residual tumor	74	41	20	9	4
Adjuvant therapy, n					
Not done	25	13	6	4	2
Chemotherapy(CT)	34	20	11	1	2
Radiotherapy(RT)	11	9	2	0	0
Sequential CT+RT	21	12	6	2	1
Hormonotherapy	2	0	0	2	0
Chemotherapeutic regimens, n					
İfosfamide+doxorubicin	43	28	11	3	1
Taxan+platinum	3	0	3	0	0
Doxorubicin+ platinum	2	0	2	0	0
Cyclophosphamide+doxorubic	1	1	0	0	0
VAC regimen	2	2	0	0	0
Cyclophosphamide+etaposide	1	1	0	0	0
Other multiagent regimens	2	0	1	0	2

MMMT, malignant mixed Mullerian tumor; ESS, endometrial stromal sarcoma; HT, hysterectomy; BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy, VAC, vincristin+actinomycin-D+cyclophosphamide, [a]Values are given as number of patients, [b]All sarcomas, [c]Other histologic,

of MMMT group was higher than that of other groups (61.4 years, p = 0.001 and 88.0%, p <0.001 respectively). One patient had history of prior pelvic radiation owing to prior cervix carcinoma and 1 patient had received tamoxifen owing to prior breast cancer. Three patients had history of prior other malignant diseases (1 patient with cervix carcinoma, 1 patient with breast carcinoma, 1 patient with thyroid papiller carcinoma). Forty-six patients had medical diseases (including hypertension, diabetes mellitus, cardiac diseases, chronic obstructive lung diseases, thyroid diseases). Rate of having medical diseases was higher among patients with MMMT (68%, p = 0.044). Of the 86 patients whose presenting symptoms had been recorded, 85 patients were symptomatic at the time of diagnosis. Most frequent symptoms were abnormal vaginal bleeding (47 patients, 54.7%) and abdominal pain (30 patients, 34.8%). The mean BMI was 28.1 (range 19.0-39.8). Forty six of all patients had available records of serum CA 125 levels, CA 125 level was elevated in 16 (33.3%) of them. According to FIGO staging, 40 patients (43.0%) were stage I; 19 patients (20.4%) were stage II; 21 patients (22.6%) were stage III; 13 patients (14.0%) were stage IV. The patients with LMS ve ESS were mostly stage I-II disease (74% and 88.9% respectively), whereas the patients in MMMT group were mostly stage III-IV disease (64%), p=0.001.

Tumor characteristics are shown in Table 1. Mean size of tumor in all patients was 7.95cm (ranging from 1.0 to 19.0). Fourteen (16.5%) patients had grade 1 disease, 17 (20%) patients had grade 2 disease and 54 (63.5%) patients had grade 3 disease. In group of patients with ESS, 66.7% of patients had grade 1 disease, while in LMS and MMMT group, the rate of grade 3 disease was 66% and 71.4% respectively (p=0.015).

Mean mitotic count (per 10 High Power Field, HPF) of all patients was 13.9 (range 2-42). In LMS group mean mitotic count was highest (15.6, p=0.02).

Eighty-nine patients underwent primary surgical treatment and tumor cells were completely removed in 74 patients. Surgical procedures are listed in Table 2. In MMMT group, 16 of 25 patients (64%) underwent pelvic and/or paraaortic lymph node dissection. Of the 89 patients who underwent primary surgical treatment, 68 patients received adjuvant therapy: 34 patients received only adjuvant chemotherapy, 11 patients received only radiotherapy, 2 patients received only hormonotherapy and 21 patients received sequential chemotherapy and radiotherapy (Table 2).

After median follow-up time of 11 months (range 1-92 months), 59 (63.4%) patients had recurrent diseases. Of these patients, 10 patients (16.9%) had pelvic recurrences, 41 patients (69.5%) had distant metastasis, 8 patients (13.6%) had both pelvic and distant metastasis; 34 patients had distant organ metastasis (lung, liver, brain). Recurrence site had no significant effect on survival time. Recurrences in LMS group were mostly in the lungs (57.1%). After recurrence 1 patient had underwent only surgery; 3 patients had underwent surgery and chemotherapy;14 patients had underwent surgery and sequential chemotherapy and radiation therapy; 24 patients received only chemotherapy; 3 patients received only radiation therapy; 12 patients received only best supportive care. Median RFS was 20 months (95% CI, 12.4-27.6 months) and RFS after 1, 2, 5 years were 66.6%, 44.1%, 16.5% respectively. Univariate analysis of survival rates showed that age ≥60 years (p=0.009), elevated CA 125 levels (p<0.001), presence of residual tumor after surgery (p<0.001), high grade tumor (p=0.006), presence of necrosis (p=0.005), advanced FİGO stage (p=0.047) were significantly associated with poor RFS, adjuvant treatment with sequential chemotherapy and radiotherapy had associated with longer RFS (p=0.009).

Median OS was 56 months (95% CI, 22.5-89.5 months). Cumulative RFS and OS is shown in Figure 1. OS after 1, 2, 5 years were 84.7%, 78%, 49.4% respectively. OS did not differ significantly between histological types (p= 0.917) (Figure 1). Univariate analysis of survival rates showed that age ≥60 years (p=0.002), elevated CA 125 levels (p <0.001), presence of residual tumor after surgery (p <0.001), high grade tumor (p=0.015), tumor size ≥10cm (p=0.010), presence of necrosis (p=0.024), advanced FİGO stage (p=0.006) were significantly associated with poor OS. However, parity, BMI, menopausal status, presence of comorbid diseases, type of primary operation and adjuvant therapy, peritoneal cytology (benign or malign), number of mitosis, presence or absence of LVI and lymph node involvement were not significantly associated with OS. Cumulative OS for each stage and for each histological type of uterine sarcoma is shown in Figure 1.

Multivariate analysis showed that age ≥60 years (p=0.004) and high grade tumor (p=0.035) were

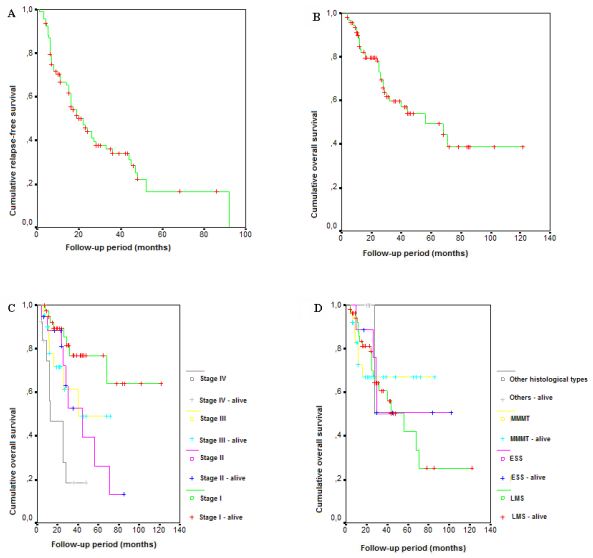

Figure 1. Relapse-Free Survival (A) and Overall Survival (B) for all Uterine Sarcomas; Overall Survival for Each Sarcoma Stage (p=0.516) (C) and for Each Sarcoma Subtype (p=0.917) (D).

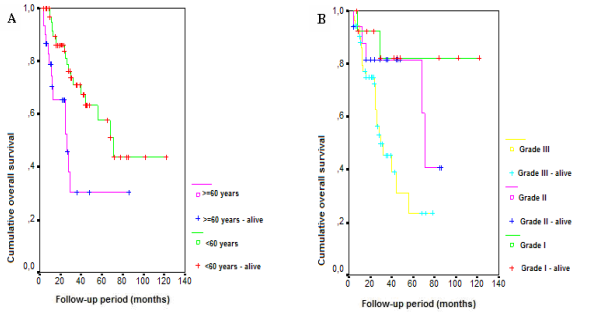

Figure 2. Overall Survival for Age Groups(p=0.014) (A) and for Grade (p=0.045) (B).

Table 3. Multivariate Analysis for Relapse-free Survival and Overall Survival

Variable	Hazard ratio	95% CI	P value
Relapse-free Survival			
Age ≥60 vs <60 y	3.19	1.46-6.99	0.004
Residual tumor	1.44	0.43-4.80	0.546
Grade	2.29	1.05-4.95	0.035
Presence tumor necrosis	4.07	0.92-17.9	0.063
Sequential chemotherapy and radiotherapy			
	0.17	0.056-0.52	0.002
Stage	0.93	0.61-1.42	0.768
Overall Survival			
Age ≥60 vs <60 y	6.6	1.46-26.7	0.014
Residual tumor	1.57	0.18-13.6	0.681
Size ≥10cm vs <10cm	3.94	0.76-20.3	0.102
Grade	6.18	1.04-36.7	0.045
Presence tumor necrosis	0.68	0.05-8.82	0.774
Stage	0.72	0.26-1.94	0.516

significantly associated with poor RFS. Patients who were administered adjuvant treatment with sequential chemotherapy and radiotherapy had longer RFS time (p=0.002). On multivariate analysis of RFS, p values for stage II versus stage I, for stage III versus stage I and stage IV versus stage I were 0.021, 0.146 and 0.007 respectively. Multivariate analysis of OS showed that only 2 factors, age ≥60 years (p=0.014) and high grade tumor (p=0.045) were significantly associated with poor OS (Figure 2). Results of multivariate analysis are shown in Table 3. On multivariate analysis of OS, p values for stage II versus stage I, for stage III versus stage I and stage IV versus stage I were 0.018, 0.087 and <0.001 respectively.

When we analyzed only LMS group, 3 factors had significantly positive effect on OS: age <60 years (p=0.022, HR:4.52, 95% CI:1.24-16.50), low grade tumor (p=0.019, HR:5.18, 955 CI: 1.30-20.51) and adjuvant sequential chemotherapy and radiotherapy after surgery (p=0.020, HR: 0.149, 95% CI: 0.03-0.74).

Discussion

Uterine sarcomas are rare diseases. In this study, 93 patients with uterine sarcomas who were diagnosed and treated for 10 year-period were analyzed. The histopathological distribution of our patients demonstrated that LMS was most frequent (58%), followed by MMMT (24%). In previously published studies, percentage of LMS and MMMT in all uterine sarcomas reported as 40% and 40% (D'Angelo and Prat, 2010); 22% and 48% (Benito et al., 2009); 33% and 30% (Ghaemmaghami et al., 2008), respectively. Usually patients with uterine sarcomas are diagnosed at older ages, mean age of our patients was 53.4 (18-80 years) and our MMMT group was older (mean age 61.4). In other studies, similar findings have been reported (Ali & Wells, 1993; Sartori et al., 1997; Park et al., 2008; Benito et al., 2009). Most frequent symptom at presentation was abnormal vaginal bleeding like some other studies (Chavenic et al., 1999; Tsikouras et al., 2008; Benito et al., 2009; D'Angelo & Prat, 2010).

Our three patients had personal history of other malignancies, Benito et al and Koivisto-Korander et al have been reported higher occurence of previous cancer in this group of patients (Koivisto-Korander et al., 2008; Benito et al., 2009). Patients in MMMT group were mostly postmenopousal (88%), whereas rate of postmenapousal patients in LMS and ESS group were lower (45.1% and 22.2% respectively). This result is convenient with other studies (Benito et al., 2009; D'Angelo & Prat, 2010). Among our patients, the rate of having medical disease in MMMT group was also higher than that of LMS and ESS group (68% versus 40.7% and 33.3%, respectively).

Total hysterectomy and bilateral salphingooferectomy is usually reported as the most effective treatment for uterine sarcomas (Sleijfer et al., 2007; Gaducci et al., 2008 Tsikouras et al., 2008). Addition of lympadenectomy to this procedure is indicated for MMMT group, because of high incidence of lymph node metastasis which was reported as 15-21% (Ali & Wells, 1993; Sartori et al., 1997; Menczer et al., 2005; Temkin et al., 2007; Gaducci et al., 2008). For localized leiomyosarcoma, the incidence of involvement of lymph node is rare, therefore lympadenectomy is not recommended (Gaducci et al., 2008). In our study, 16 patients (62.5%) in MMMT group underwent lymphadenectomy procedure and lymph node metastasis was found in 37.5% of them. But we found no significant effect of lymphadenectomy or any other type of primary surgical procedure on survival rates.

Our multivariate analysis showed that histological

types of uterine sarcomas had no significant effect on survival. In literature, there are different findings about prognostic value of histological type. Most autors found no significant difference in clinical outcome according to histological type except low grade ESS (Salazar & Dunne, 1980; Echt et al., 1990; Wolfson et al., 1994). In some studies, it was reported that MMMT had poorer prognosis than other types (Ghaemmaghami et al., 2008; Benito et al., 2009). Conversely, Olah et al. reported that prognosis of LMS was poorer than that of MMMT (Olah et al., 1992). In our study, although there was no statistical difference between OS of different histological types; in numerical value, survival rate of LMS at 1 year- period was higher than that of MMMT (87.7% vs 72.4%), but after 5 year-period survival rate of MMMT was better than that of LMS (66.9% vs 41.9%). RFS and OS rates for each histological type of uterine sarcoma are shown in Table 3. OS rates of MMMT tend to be same after 2 and 5 years, while that of LMS were decreasing. In the study of Benito et al. there was somewhat similar results about this aspect: OS rates of MMMT group after 2, 5, 10- year period were same (26%), while that of LMS decreasing over time, 72%, 42%, 21% respectively (Benito et al., 2009). It might be suggested that almost all deathts in MMMT group occur within 2 years, then survival rates tend to be stable until 5-10 years. But making such a conclusion requires further larger-long term studies.

As reported in other studies (Chavenic et al.,1999; El Husseiny et al., 2002; Kokawa et al., 2006; Koivisto-Korander et al., 2008; Tsikouras et al., 2008), in our study most patients were diagnosed at early stages (stage I-II, 63.4%). Most of the patients in LMS group and ESS group were diagnosed at stage I-II (74.1% and 88.9% respectively), while MMMT group was mainly diagnosed at advanced stages (stage III-IV, 64%). We used the new FIGO staging system. Therefore, in terms of stage, comparison of our study with previous studies may not be rationale. Some of the previous studies have reported that tumor stage is most significant prognostic factor for uterine sarcomas (Gaducci et al., 2008; Park et al., 2008; Benito et al., 2009; D'Angelo & Prat, 2010; Sharma et al., 2011). In our study, there were some conflicting findings about stage. Survival results of patients at different stages were shown in Table 4. Survival results of stage III group was better than that of stage II after 2 years period. This finding may be explained by 2 factors: firstly our stage III group was mostly composed of patients with MMMT (70%) and survival results of MMMT group was better than that of LMS group after 2 years. Secondly according to new staging system, some of LMS and ESS patients at stage II and stage III of previous system were included in stage I and stage II respectively. When we analyzed only LMS group to eradicate the effect of MMMT group on survival, stage III group continued to deteriorate the results. There was no significant effect of tumor stage on survival after multivariate analysis.

In a review (D'Angelo & Prat, 2010), it was concluded that the role of adjuvant therapy on survival of uterine sarcomas was uncertain, adjuvant radiation therapy might be useful in improving local control. Some studies showed improved outcome by administrating adjuvant chemotherapy with different regimens (Nagell et al., 1986; Odunsi et al., 2004; Gaducci et al., 2008; Matoda et al., 2011), whereas some studies did not show (Omura et al., 1985; Hempling et al., 1995). In a Gynecologic Oncology Group (GOG) study including 65 patients with uterine MMMT, adjuvant chemotherapy with ifosfamide and cisplatin was associated with 7-year progression-free survival and OS of 54% and 52% respectively (Sutton et al., 2005). In a phase II study, pelvic radiation "sandwiched" between chemotherapy was reported as efficacious treatment (Einstein et al., 2012). In a retrospective study of 49 patients with uterine MMMT, adjuvant sequential chemotherapy and radiotherapy significantly decreased mortality rate compared to adjuvant chemotherapy alone (Menczer et al., 2005). Our study suggested that adjuvant sequential chemotherapy and radiotherapy for uterine sarcomas improved RFS and had no effect on OS. When we analyzed only LMS group, adjuvant treatment with sequential chemotherapy and radiotherapy was associated with better OS.

Recurrence rates for uterine sarcomas have been reported as 50%-71% (Tsikouras et al., 2008; Koivisto-Korander et al., 2008; El Husseiny et al., 2002; Benoit et al., 2005), recurrence rate in our study was 63.4% and median time to recurrence was less than 2 years (11 months) as reported in a review (Gaducci et al., 2008). In previous studies, recurrence sites of relapsed patients were pelvic recurrence (14-30%); distant recurrences (33-44%), pelvic and distant recurrences (25-53%) (Gaducci et al., 2008). Among our relapsed patients, 13.6% of patients had pelvic recurrences, 69.5% of patients had distant recurrences, 13.6% of patients had both distant and pelvic recurences.

In our study and also in literature, uterine sarcomas have poor prognosis, 5-year OS in previous studies was ranging between 27-51% (Schwartz & Thomas, 1989; Chavenic et al., 1999; Pautier et al., 2000; El Husseiny et al., 2002; Livi et al., 2003; Benoit et al.,2005; Koivisto-Korander et al., 2008; Tsikouras et al., 2008). 5-year OS in our study was 49.4%. There is no consensus on prognostic factors of uterine sarcomas. Several studies have found no effecet of age on survival (Peters et al.,1984; El Husseiny et al., 2002; Park et al., 2008), whereas some studies reported that patients younger than age 50 years had longer survival (Nagell et al., 1986; Kokawa et al., 2006). In our study patients younger than age 60 years had significantly longer RFS and OS.

Some studies reported that tumor grade (Ghaemmaghami et al., 2008), tumor size (George et al., 1986; Rovirosa et al., 2002; Benito et al., 2009), depths of myometrial invasion (Rovirosa et al., 2002; Sagage et al., 2004; Park et al., 2008), LVSI (Major et al., 1993; Rovirosa et al., 2002; Park et al., 2008) had significant effect on prognosis of uterine sarcomas. In our study grade had significant effecet on RFS and OS. Age and grade were found to be independent prognostic parameters for our LMS group, too.

In conclusion, our study confirms that uterine sarcomas are rare malignancies with poor prognosis, the prognosis is poor even at early stages and adjuvant treatment with sequential chemotherapy and radiotherapy improves

RFS in whole group of uterine sarcomas, and sequential adjuvant chemotherapy and radiotherapy improves OS in LMS group. Our multivariate analysis indicates that advanced age (age ≥60) and high grade tumor is associated with poor prognosis. For each histological types of uterine sarcomas, mean age, sypmtoms and stage at presentation and effect of adjuvant treatment on survival may be different. Therefore each histological type should be analyzed seperately, and to investigate prognostic factors and optimal management of uterine sarcomas multi-centered, long term studies are needed.

Acknowledgement

The authors declare no conflict of interest.

References

Ali S, Wells M (1993). Mixed müllerian tumors of the uterine corpus: a review. *Int J Gynecol Cancer*, **3**, 1-11.

Benito V, Lubrano A, Arencibia O, et al (2009). Clinicopathologic analysis of uterine sarcomas from a single institution in the Canary Islands. *Int J of Gynecology & Obstetrics*, **107**,44-9.

Benoit L, Arnould L, Cheynel N, et al (2005). The role of surgery and treatment trends in uterine sarcoma. *Eur J Surg Oncol*, **31**, 434-42.

Chavenic L, Deniaud E, Plancher C, et al (1999). Uterine sarcomas: The Curie Institute experience. Prognosis factors and adjuvant treatments. *Gynecol Oncol*, **72**, 232-7.

D'Angelo E, Prat J (2010). Uterine sarcomas: A review. *Gynecol Oncol*, **116**, 131-9.

Echt G, Jepson J, Steel J, et al (1990). Treatment of uterine sarcomas. *Cancer*, **66**, 35-9.

Einstein MH, Klobocista M, Hou JY, et al (2012). Phase II trial of adjuvant pelvic radiation "sandwiched" between ifosfamide or ifosfamide plus cisplatin in women with uterine carcinosarcoma. *Gynecol Oncol*, **124**, 26-30.

El Husseiny G, Al Bareedy N, Mourad WA, et al (2002). Prognostic factors and treatment modalities in uterine sarcoma. *Am J Clin Oncol*, **25**, 256-60.

Gaducci A, Cosio S, Romanini A, Genazzani AR (2008). The management of patients with uterine sarcoma: a debated clinical challenge. *Crit Rev Oncol Hematol*, **65**, 129-42.

George M, Pejovic MH, Kramar A (1986). Uterine sarcomas: prognostic factors and treatment modalities- study on 209 patients. *Gynecol Oncol,* **24**, 58-67.

Ghaemmaghami F, Zarchi MK, Gilani MM, et al (2008). Uterine sarcoma: Clinicopathological characteristics, treatment and outcome in İran. *APJCP*, **9**, 421-6.

Hempling RE, Piver MS, Baker TR (1995). Impact on progression-free survival of adjuvant cyclophosphamide, vincristine, doxorubicin(adriamycin) and dacarbazine (CYVADIC) chemotherapy for stage I uterine sarcoma. A prospective tiral. *Am J Clin Oncol*, **18**, 282-6.

Koivisto-Korander R, Butzow R, Koivisto AM, Leminen A (2008). Clinical outcome and prognostic factors in 100 cases of uterine sarcoma: experience in Helsinki University Central Hospital 1990-2001. *Gynecol Oncol*, **111**, 74-81.

Kokawa K, Nishiyama K, Ikeuchi M, et al (2006). Clinical outcomes of uterine sarcomas: results from 14 years worth of experience in the Kinki district in Japan (1990-2003). *Int J Gynecol Cancer*, **16**, 1358-63.

Livi L, Paiar F, Shah N, et al (2003). Uterine sarcoma: twenty-seven years of experience. *Int J Radiat Oncol Biol Phys*, **57**, 1366-73.

Major FJ, Blessing JA, Silverberg SG, et al (1993). Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. *Cancer*, **71**, 1702-9.

Matoda M, Takeshima N, Nomura H, et al (2011). The treatment of uterine leimyosarcoma: clinical outcomes of 18 cases and the efectiveness of chemotherapy. *Eur J Gynaecol Oncol*, **32**, 647-50.

Menczer J, Levy T, Piura B, et al (2005). A comparison between different postoperative treatment modalities of uterine carcinosarcoma. *Gynecol Oncol*, **97**, 166-70.

Odunsi K, Moneke V, Tammela J, et al (2004). Efficacy of adjuvant CYVADIC chemotherapy in early-stage uterine sarcomas: results of long term follow up. *Int J Gynecol Cancer*, **14**, 659-64.

Olah KS, Dunn JA, Gee H (1992). Leimyosarcomas have a poorer prognosis than mixed mesodermal tumours when adjusting for known prognostic factors: the result of a retrospective study of 423 cases of uterine sarcoma. *Br J Obstet Gynecol*, **99**, 590-4.

Olah KS, Gee H, Blunt S, et al (1991). Retrospective analysis of 318 cases of uterine sarcoma. *Eur J Cancer*, **27**, 1095-9.

Omura GA, Bleesing JA, Major F, et al (1985). A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol*, **3**,1240-5.

Park J-Y, Kim D-Y, Suh D-S, et al (2008). Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989-2007. *J Cancer Res Clin Oncol*, **134**, 1277-87.

Pautier P, Genestie C, Rey A, et al (2000). Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of a grading score validated for soft tissue sarcoma. *Cancer*, **88**, 1425-31.

Peters WA 3rd, Kumar NB, Fleming WP, Morley GW (1984). Prognostic features of sarcomas and mixed tumors of the endometrium. *Obstet Gynecol*, **63**, 550-6.

Prat J (2009). FİGO staging for uterine sarcomas. *Int J Gynecol Obstet*, **104**, 177-8.

Rovirosa A, Ascaso C, Ordi J, et al (2002). Is vascular and lymphatic space invasion a main prognostic factor in uterine neoplasms with a sarcomatous component? A retrospective study of prognostic factors of 60 patients stratified by stages. *Int J Radiat Oncol Biol Phys*, **52**, 1320-9.

Sagage S, Yamashita K, Ishioka S, et al (2004). Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. *Oncology*, **67**, 33-9.

Salazar OM, Dunne ME (1980). The role of radiation therapy in the management of uterine sarcomas. *Int J Radiat Oncol Biol Phyis*, **6**, 899-902.

Sartori E, Bazzurini L, Gadducci A, et al (1997). Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. *Gynecol Oncol*, **67**, 70-5.

Schwartz SM, Thomas DB (1989). A case-control study of risk factorsfor sarcomas of the uterus. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. *Cancer*, **64**, 2487-92.

Sharma DN, Rath GK, Kumar S, et al (2011). Clinical outcome of patients with uterine sarcomas. J Cancer Res Ther, 7, 270-4.

Sleijfer S, Seynaeve C, Verweij (2007). Gynaecological sarcomas. *Curr Opin Oncol*, **19**, 492-6.

Sutton G, Kauderer J, Carson LF, et al (2005). Gynecologic Oncology Group. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*, **96**, 630-4.

Tavassoli FA, Devilee P (2003). Pathology and Genetics of Tumors of the Breast and Female Genital Organs. World Health Organization Classification of Tumors. Lyon, France: IARC Pres

Temkin SM, Hellmann M, Lee YC, Abulafia O (2007). Early-stage carcinosarcoma of the uterus: the significance of lymph node count. *Int J Gynecol Cancer*, **17**, 215-9.

Tsikouras P, Liberis V, Galazios G, et al (2008). Uterine sarcoma: a report of 57 cases over a16-year period analysis. *Eur J Gynecol Oncol*, **29**, 129-34.

Van Nagell JR Jr, Hanson MB, Donaldson ES, Gallion HH (1986). Adjuvant vincristine, dactinomycin, and cyclophosphamide therapy in stage I uterine sarcomas. A pilot study. *Cancer*, **57**, 1451-4.

Wolfson AH, Wolfson DJ, Sittler SY, et al (1994). A multivariate analysis of clinicopathologic factors for predicting outcome in uterine sarcomas. *Gynecol Oncol*, **52**, 56-62.