

## RESEARCH ARTICLE

# Adult Urological Soft Tissue Sarcomas: A Multicenter Study of the Anatolian Society of Medical Oncology (ASMO)

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### Abstract

**Objective:** To analyze clinicopathological characteristics, prognostic factors and survival rates of the patients with urological soft tissue sarcomas treated and followed up in Turkey. **Materials and Methods:** For overall survival analyses the Kaplan-Meier method was used. From medical records, nine prognostic factors on overall survival were analysed. **Results:** For the 53 patients (34 males, 19 females) whose charts were reviewed, the median age was 53 (range 22 to 83) years. Most frequently renal location (n=30; 56.6%) was evident and leiomyosarcoma (n=20, 37.7%) was the most frequently encountered histological type. Median survival time of all patients was 40.3 (95% CI, 14.2-66.3) months. In univariate analysis, male gender, advanced age ( $\geq 50$  years), metastatic stage, unresectability, grade 3, renal location were determined as worse prognostic factors. In multivariate analysis, metastatic stage, unresectability and grade 3 were determined as indicators of worse prognosis. **Conclusions:** Urological soft tissue sarcomas are rarely seen tumours in adults. The most important factors in survival are surgical resection, stage of the tumour at onset, grade and location of the tumour, gender and age of the patients.

**Keywords:** Urologic sarcoma - survival - prognostic factors - Turkey.

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### Introduction

Soft tissue sarcomas (STSs) of mesodermal origin constitute less than 1% of all malignant tumours (Dugandzija et al., 2014). Nearly 2% of STSs involve urological system and only 2% of all urological tumours have a STS histology (Izumi et al., 2010). Only scarce literature information is available about urological STS and a small series has been reported from Turkey (Berkmen and celebioglu, 1997). STS is a heterogeneous group with more than 60 histological types (Duman et al., 2012). Among STSs involving extremities and urological system, most frequently malignant fibrous histiocytomas and leiomyosarcomas are seen (Dotan et al., 2006,

Stefanovski et al., 2002, Ngan et al., 2013).

Due to scarcity of urological STSs, currently it has not a standardized treatment modality. In case reports, small series and literature reviews surgical resection has been considered the basic treatment modality (Dotan et al., 2006; Izumi et al., 2010; Ko et al., 2012). Prognostic factors effecting survival in STSs have been thoroughly analyzed (Stefanovski et al., 2002; Stojadinovic et al., 2002; Cheung et al., 2014). However, very few studies have analyzed prognostic factors effecting survival in urological STSs (Froehner et al., 2013).

In this study, we have planned to analyze clinicopathological characteristics, prognostic factors and survival rates of the patients with urological

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## Materials and Methods

**Study Design:** This study was approved by the local Institutional Review Board (April 2013). Beginning from May 1, 2013, data of patients with STS followed up between the years 1999 and 2014 in 15 separate centers of medical oncology in Turkey were collected. At the last data collection date (July 1, 2014), the actual health state, dates of the patients' last visits and if happened, their dates of death were checked up and updated. From medical

**Table 1. Patient Characteristics**

	All patients (n = 53)
Median age	53 (22-83)
Gender	
Male	34 (64.2%)
Female	19 (35.8%)
Primary tumor site	
Renal	30 (56.6%)
Bladder	7 (13.2%)
Paratesticular	7 (13.2%)
Testis	5 (9.4%)
Spermatic cord	3 (5.7%)
Prostat	1 (1.9%)
Histological type	
Leiomyosarcoma	20 (37.7%)
Liposarcoma	13 (24.5%)
Rhabdomyosarcoma	7 (13.2%)
Malignant fibrous histiocytoma	4 (7.5%)
Unclassified	4 (7.5%)
Rare types	5 (9.6%)
Tumor diameter	
<5 cm	12 (22.6%)
5-10 cm	14 (26.4%)
≥10 cm	17 (32.1%)
Unknown	10 (18.9%)
Grade	
1	19 (35.8%)
2	2 (3.8%)
3	30 (56.6%)
Unknown	2 (3.8%)
Stage at diagnosis	
Local	10 (18.9%)
Metastatic	43 (81.1%)
Surgery	
Yes	42 (79.3%)
No	11 (20.7%)
ECOG performance status	
0	22 (41.5%)
1	17 (32.1%)
2	14 (26.4%)

**Table 2. Univariate and Multivariate Analysis of All Patients' Survival Rates (n = 53)**

Variable	Univariate analysis		Multivariate analysis
	P-value	Hazard Ratio (95% Confidence interval)	P-value
Resection (Yes,no)	0.002	19.6(1.6-234.4)	0.019
Stage (local, metastatic)	0.004	10.71(1.2-95.36)	0.033
Grade (1 vs. 3)	<0.001	3.38(1.84-6.21)	<0.001
Gender (male vs. female)	0.02		0.48
Age (<50 years, ≥50 years)	0.042		0.36
Tumor location (renal, other)	0.025		0.181
Histopathology(leiomyosarcoma, other)	0.188		
Tumor diameter (0-<5 cm, 5-10 cm, ≥10 cm)	0.57		
ECOG performance status (0 vs 1,2)	0.47		

records, information about age, gender, tumor size, location, histopathologic features and grade of the tumour of the patients included in the assessments were obtained. The 2002 criteria of The World Health Organization were used for histopathological diagnosis of all patients (Jo and Fletcher et al., 2014). For those with established grades, The French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system was used (Neuville et al., 2014). Additionally, treatment modalities (sytotoxic agents, chemotherapeutic regimen, surgery and radiotherapy), time to disease progression, death and the last date of the control visit in the outpatient clinic were recorded.

**Inclusion criteria of the study were as follows:**

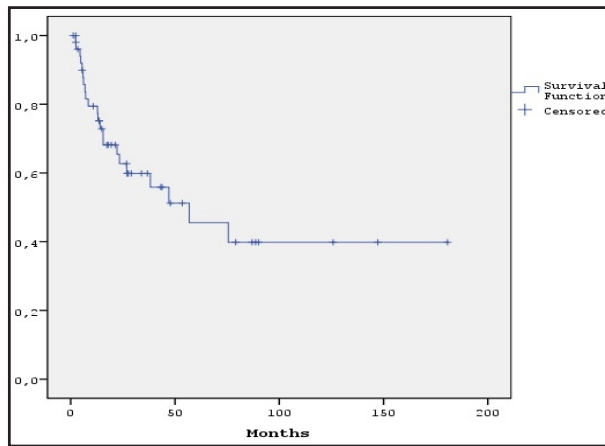
(1) Patients with histologically confirmed soft tissue sarcomas, (2) Primary location in the urological system (paratesticular, testicular, renal, prostate, bladder, spermatic cord), (3) Age ≥18. Exclusion criteria: (1) Sarcomas involving skeletal system (excl. extra-osseous Ewing's sarcoma and chondrosarcoma), (2) Dermatofibrosarcoma protuberance.

**Statistical Analyses:** Data were analyzed using the Statistical Package for Social Sciences 15.0 for Windows (SPSS Inc., Chicago, IL). Overall survival (OS) was defined as the time elapsed from the date of operation or diagnosis up to death or the last follow-up visit. In OS analyses, Kaplan-Meier method was used. For the calculation of the differences between survival rates univariate log-rank test and in multivariate analysis Cox proportional hazards model were used and P<0.05 was considered to be the level of statistical significance. In prognostic factor analysis, the following parameters were evaluated: gender (male, female), age (<50, ≥50), stage (local, metastatic), diameter (0-5 cm, 5-<10 cm, ≥10 cm), grade (1-3), histopathology (leiomyosarcoma, other), location (kidney, other) and resectability (yes, no), of the tumour, Eastern Cooperative Oncology Group(ECOG) Performance status (0,1+2),

## Results

### General patient characteristics and treatment options

This series consisted of 53 cases with a male/female ratio of 1.8. Patients' characteristics are shown in Table 1. Most frequently renal location was detected. Leiomyosarcoma was the most frequently encountered histological type. Ewing's sarcoma, fibrosarcoma, desmoplastic round cell, myogenic sarcoma, angiomyxosarcoma were rarely



**Figure 1. Mean Survival Curve of All Patients**

seen types. According to their location, most frequently encountered tumors were leiomyosarcoma (n=11; 36.6%) in the kidney, liposarcoma (n=4; 57.1%) in the bladder, rhabdomyosarcoma (n=3; 42.8%) in paratesticular region, liposarcoma (n=3; 100%) in the spermatic cord and desmoplastic round cell tumour (n=1; 100%) in the prostate.

Forty-two patients underwent either complete (n=33) or incomplete (n=9) resections. Some of these patients received adjuvant (n=17) or neoadjuvant (n=7) chemotherapy. Adjuvant chemotherapies in order of decreasing frequency were ifosfamide-doxorubicin (n=11 patients), VAC (vincristine-adriamycin-cyclophosphamide) - IE (ifosfamide-etoposide) combination (n=3) and VAC combination (n=3) chemotherapies. As neoadjuvant chemotherapy all patients received ifosfamide-doxorubicin chemotherapies.

Palliative chemotherapy was applied for 33 patients with metastasis detected at onset or developed later. Palliative chemotherapies used were in order of decreasing frequency as follows: dacarbazine, paclitaxel and combinations ifosfamide-doxorubicin or gemcitabine-docetaxel.

#### *Survival and prognostic factor analysis*

Median follow-up period was 29 (range, 1 to 121) months and 22 patients died during the follow-up period. Median survival time of all patients was 40.3 (95% CI, 14.2-66.3) months. Median and 1.5-year-survival rates of all patients were 93.4 and 63.5%, respectively (Figure 1).

In all groups, 9-factor univariate analysis was performed and its results are shown in detail in Table 2. In univariate analysis male gender, advanced age ( $\geq 50$  years), metastatic stage, unresectability, grade 3, renal location were determined as worse prognostic factors. The significant 6 factors were studied in multivariate analysis and metastatic stage, unresectability and grade 3 were determined as indicators of worse prognosis.

## **Discussion**

Urological STSs are very rarely seen. In this article, a multi-center series encompassing 53 patients with these tumours is presented. In this series, age and gender characteristics are similar to those reported for other

urological sarcomas. In other words, as reported in 4 large series on urological sarcomas, the disease peaks at 6th decade with a male gender predominancy (Dotan et al., 2006; Izumi et al., 2010; Lee et al., 2012; Froehner et al., 2013).

Leiomyosarcoma is the most dominant histological type among urological STSs (Dotan et al., 2006; Izumi et al., 2010; Froehner et al., 2013). This dominance is especially most marked for renal STSs and also in large series of renal sarcomas (Vogelzang et al., 1993; Wang et al., 2011). Our series also confirms this finding. Among urological sarcomas, liposarcoma is the second most dominant histological type which is more frequently seen in the vesical and spermatic cord regions as demonstrated in two large series with outcomes similar to our series (Coleman et al., 2003; Spiess et al., 2007). In our series rhabdomyosarcoma was the most frequently seen tumour type in the paratesticular region, which was also confirmed by the outcomes of Korkes et al. (2009). On the other hand, in our series higher histological grade was detected in more than 50% of our patients and similarly, in other large urological STS series, higher histological grade appeared to be the dominant type (Dotan et al., 2006; Izumi et al., 2010; Lee et al., 2012; Froehner et al., 2013).

In urological STS, 5-year survival rate ranged between 48 and 66%, while for STSs located in other anatomical regions it is over 75% which also reflect on median survival rates (Stojadinovic et al., 2002; Gross et al., 2005; Mondaini et al., 2005; Dotan et al., 2006; Izumi et al., 2010; Cho et al., 2011; Gronchi et al., 2011; Lee et al., 2012). In other words, median survival times vary between 31 and 91 months (2,5,18). In our series, 5-year survival rate (63%) and median survival time (40 months) resemble those of the previously performed urological STS series.

As is the case with all STSs, resectability of the tumour is the most important determinant of the survival in urological STS. Unresectability was found to be correlated with 9.7, 2.6 and 2-fold higher mortality rates in urological STS series of Lee et al., Izumi et al. and Dotan et al., respectively (Dotan et al., 2006; Izumi et al., 2010; Lee et al., 2012). Similarly, in our series resectability was detected as the most important predictor of survival in our multivariate analysis.

On the other hand, one of the other most important determinants of survival in urological STS is the stage of the tumor at diagnosis. In their large series, Dotan et al. and Lee et al., correlated detection of metastasis at the time of diagnosis with risk of death (Dotan et al., 2006, Froehner et al., 2013, Lee et al., 2012). As a confirmation of this finding, based on the results of our series metastatic stage increased risk of death for 10-fold.

In the present study, higher histological grade was associated with worse prognosis. In their studies, Cho et al., Dotan et al. and Froehner et al. determined higher histological grade as a worse prognostic factor which also confirmed the results of our study (Dotan et al., 2006; Cho et al., 2011; Froehner et al., 2013). On the other hand, in two separate series conducted by Froehner et al., lower grade had been found to be correlated with longer survival and improved prognosis (Froehner et al., 2000; Froehner et al., 2014). In fact, similar findings can be encountered

in large STS series (Coindre et al., 1996; Stefanovski et al., 2002).

In urological STS series performed so far, a relationship between gender of the patients and survival rates has not been determined (Dotan et al., 2006; Izumi et al., 2010; Cho et al., 2011; Froehner et al., 2013, ). However in 2 major STS series (Coindre and Stefanovski), female gender was found to be associated more closely with better prognosis and survival (Stefanovski et al., 2002, Coindre et al., 1996). In our series, in confirmation of these two major series, female gender was also associated with better prognosis.

In urological series, the impact of tumour location on prognosis has been investigated. Mondaini et al. (2005) detected that prostatic plus renal STSs had predicted worse prognosis and survival when compared with paratesticular STSs. (Mondaini et al., 2005). On the other hand, in these two major renal STS series very short median survival times (9 and 28 months, respectively) were estimated which indicates poorer prognosis of renal STSs when compared with other urological STSs. (Vogelzang et al., 1993; Wang et al., 2011). In our series, renal STSs had a worse prognosis relative to other urological STSs.

Age is a prognostic factor for survival in all tumour types. In their vesical STS series of 183 patients, Rodriguez et al. determined poorer prognosis with aging (Rodriguez et al., 2014). In their series, the patients aged over 50 years had a poorer prognosis.

This study, due to its retrospective design, has many limitations. The study included only the patients of the ASMO member centers and differences exist between centers as for patients' management. Besides, scarce number of patients precluded evaluation of the effects of adjuvant and neoadjuvant treatments on survival.

Urological STSs are very rarely seen tumours in adults and leiomyosarcoma and liposarcomas are remarkable as the most dominant histological types with mostly higher grades. On the other hand, the most important factor in survival is surgical resection, other important factors that struck our attention were stage of the tumour at onset, grade and location of the tumour, gender and age of the patients. Surgical resection is the cornerstone in the treatment of urological STS and further studies, which will analyze the impact of adjuvant treatments in the management of urological STSs, are needed.

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