Original Article

Clinical and pathological features of patients with resected synovial sarcoma: A multicenter retrospective analysis of the Anatolian Society of Medical Oncology

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ABSTRACT

Background: Synovial sarcoma (SS) is a rare disease and compared with other soft-tissue sarcomas has a relatively high mortality rate. The optimal management of this disease and prognostic factors associated with patient outcome remains controversial.

Aims: We aimed to evaluate the factors affecting the outcomes of SS patients in the adjuvant setting.

Patients and Methods: In this Turkish multicenter study, we assessed the data of 69 SS patients regarding prognostic factors for SS patients retrospectively.

Results: Our study included 69 localized SS patients (38 males and 31 females) with a median age of 34.5 years (minimum-maximum: 14-68 years). Overall survival (OS) and disease free survival (DFS) rates for 5 years were 64% and 25%, respectively. All patients under went surgical treatment; 64 patients were treated with a wide excision and 5 patients had an amputation. According to the univariate analysis, adverse prognostic factors for OS were male sex, higher mitotic activity, high Ki-67 levels, trunk localization and inadequate surgical margins. In multivariate analysis, none of these factors had independent significant association with OS. Prognostic factors for DFS; in the univariate analysis were higher mitotic activity, high Ki-67 levels and inadequate surgical margins. Only higher mitotic activity (≥10 high-power field) was significantly associated with worse DFS in the multivariate analysis (hazard ratio: 0.30, % confidence interval: 0.11-0.80, $P = 0.017$).

Conclusion: Our study confirms that high mitotic activity is significantly associated with decreased DFS. The question of whether the chemotherapy provides a survival advantage in patients having adverse prognostic factors requires confirmation in randomized trials.

KEY WORDS: Ki-67, mitotic activity, synovial sarcoma

INTRODUCTION

Synovial sarcomas (SS) are rare tumors with incidence of 5-10% of all soft-tissue sarcomas.[1,2] SS harbors a high-risk of local recurrence and it also carries a high-risk of developing distant metastasis later in the course of the disease.[3] The optimal treatment of SS still has not been well-defined. The issue of whether chemotherapy after surgery has any beneficial role still remains highly debated.[4,5] In order to better characterize, the prognostic factors, this multi-institutional retrospective analysis of 69 patients was undertaken by the Anatolian Society of Medical Oncology.

PATIENTS AND METHODS

Patients

Between July 2003 and April 2012, a total of 96 patients with the diagnosis of SS from 11 cancer centers were retrospectively evaluated. The diagnosis of SS was made by histological typing based on the World Health Organization and 1995 Enzinger and Weiss classification also immunohistochemistry had been used by local pathology. Baseline assessment variables including demographic data such as age and gender, history and physical examination, serum chemistry, pathologic results, treatment types received and outcome data were collected by reviewing medical records at each center and were then entered into a comprehensive data base. We excluded 27 (28%) patients with metastatic disease at diagnosis and 69 (72%) were analyzed.

Prognostic factors and outcomes

Patients were re-staged by the seventh edition of the American Joint Committee on Cancer staging manual histologic subtypes were divided into monophasic, biphasic and poorly differentiated. Histologic grade, Ki-67% levels (>10), mitotic

activity (<10/high-power field [HPF] or >10/HPF), surgical margins (inadequate margin was defined as positive margin or tumor present 2 mm or less from the linked margins), tumor size (maximum diameter <5 cm or >5 cm) were analyzed. Tumor sites were sub classified into extremity and trunk. The types of surgical procedure were divided to amputation and wide excision. We analyzed the effect of chemotherapy, radiotherapy and surgical procedures on the outcomes of the patients after treatment.

Statistical analysis

Overall survival (OS) time was calculated from the time of diagnosis to death or last follow-up visit. Disease free survival (DFS) was calculated from the date of definitive surgery to the date of the first local recurrence or the first distant metastasis or death on follow-up. The probability of OS and DFS were estimated by using the Kaplan-Meier method (Kaplan and Meier, 1958). As prognostic variables the following parameters were analyzed by the log-rank test: Age, gender, tumor site and size, type of pathology, grade, mitotic activity, Ki-67 levels, surgical margins, surgical procedure, chemotherapy and radiotherapy. All statistical analyses were performed using the SPSS 17.0 statistical software (SPSS, Chicago, IL, USA).

RESULTS

Patient demographics

The study included 38 males (55.1%) and 31 females (44.9%) with a median age of 34.5 years (minimum-maximum 14-68 years). Twenty (29%) patients had a tumor <5 cm while 49 patients (71%) had tumors >5 cm. The distribution of tumors by anatomic sites was as follows: 6 (8.7%) tumors were located in the upper extremities; 36 (52.1%) tumors were located in the lower extremities; 8 (11.5%) tumors were located in the pelvis; 14 (20.2%) tumors were located in the abdomen-thorax and 5 (7.5%) tumors were located in the head and neck regions. The most frequent histologic subtype was the monophasic subtype with 33 cases (47.8%). Nineteen (27.5%) patients had a tumor with mitotic activity <10/HPF and 21 (30.4%) patients tumors mitotic activity was recorded as >10/HPF and for 29 patients the mitotic activity rate was unknown. Ki-67 index was reported as low in 21 patients (30.4%), whereas three patients (4.3%) had high Ki-67 levels. Patients were staged by the seventh edition of the American Joint Committee on Cancer staging manual. Six (8.7%) patients had stage I, 37 (53.6%) patients had stage II and 26 (37.7%) patients had stage III disease [Table 1].

All patients under went surgical treatment, 64 (92.8%) patients were treated with a wide excision and five patients had a (7.2%) amputation. Fifteen (21.7%) patients had positive surgical margins while 54 (78.3%) patients had negative surgical margins. Thirty six patients (52.2%) received post-operative external-beam radiation therapy; the median dose was 55 Gy (range 50-64 Gy). All the 15 patients with positive surgical margins and additionally 21 patients with tumors larger than 5 cm received radiotherapy. Forty eight (69.6%) patients received adjuvant chemotherapy. All chemotherapy protocols were doxorubicin based with a combination of ifosfamide or cisplatin.

Table 1: Patients characteristic

Characteristic (*n*=69)	Value (%)	
Female/male	31/38	44.9-55.1
Median age years;	34.5;	
minimum-maximum	14-68	
Pathology		
Monophasic	33	47.8
Biphasic	28	40.6
Poorly	8	11.6
Tumor size		
<5 cm	20	29.0
>5 cm	49	71.0
Grade		
1-2	35	50.7
3	34	49.3
Stage		
1	6	8.7
2	37	53.6
3	26	37.7
Sites		
Extremity	42	60.9
Trunkal	27	39.1
Surgical margins		
Adequate	54	78.3
Inadequate	15	21.7
Chemotherapy	48	69.6
Radiotherapy	36	52.2

Treatment outcomes

The median follow-up for all patients was 2.6 years (minimum-maximum: 0.3-8.8 years). Nineteen (26.4%) patients died from the disease. Figures 1 and 2 show the actuarial OS and DFS rates. OS rates for 3 and 5 years were 68% and 64%, respectively. Most of the recurrence occurred in the first 3 years. DFS rates for 3 and 5 years were 59% and 25%, respectively.

Prognostic factors on survival

According to the univariate analysis, adverse prognostic factors for OS were male sex, higher mitotic activity, high Ki-67 levels, trunk localization and inadequate surgical margins [Table 2]. All these factors were individually associated with decreased OS. High Ki-67 levels were also found to be associated with decreased OS; however, the number of reported cases with a Ki-67 score was inadequate. When we put the important prognostic factors in the Cox regression analysis none of these factors had independent significant association with OS.

Prognostic factors for DFS in the univariate analysis were higher mitotic activity, high Ki-67 levels and inadequate surgical margins [Table 3]. Only higher mitotic activity was significantly associate with worse DFS in the multivariate analysis (hazard ratio: 0.30, % confidence interval: 0.11-0.80, $P = 0.017$).

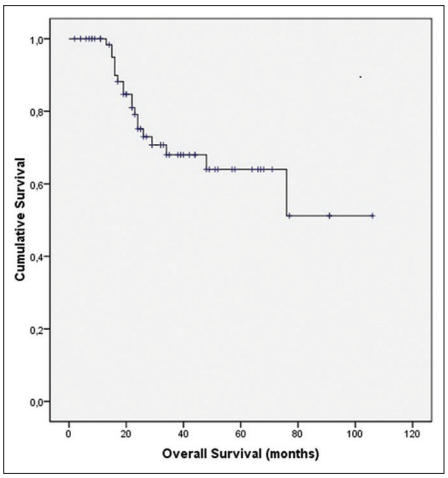

Figure 1: Kaplan-Meier curve of overall survival

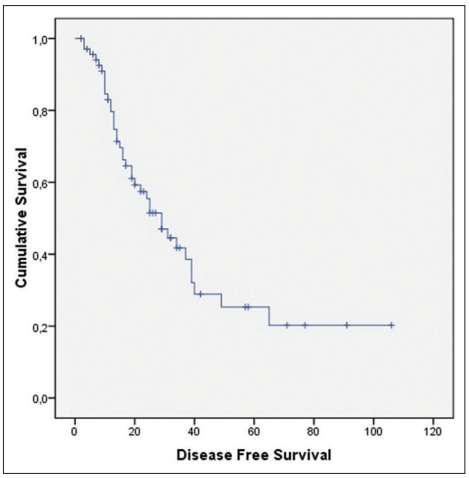

Figure 2: Kaplan-Meier curve of disease free survival

Table 2: Univariate analysis of OS

Variable	OS (%) 3 years	OS (%) 5 years	*P* value
Gender			
Female	84	84	0.046
Male	53	46	
Age			
<40	69	63	0.808
>40	71	65	
Tumor size			
<5 cm	74	64	0.354
>5 cm	64	64	
Grade			
1-2	70	70	0.536
3	66	56	
Mitosis			
<10	89	89	0.032
>10	58	39	
Sites			
Extremity	78	78	0.031
Trunk	48	41	
Surgery			
Amputation	100	100	0.222
Excision	65	61	
Surgical margins			
Adequate	78	74	0.003
Inadequate	28	28	

OS=Overall survival

Table 3: Univariate analysis of DFS

Variable	DFS (%) 3 years	DFS (%) 5 years	*P* value
Gender			
Female	53	32	0.073
Male	32	19	
Age			
<40	45	22	0.726
>40	37	30	
Tumor size			
<5 cm	45	38	0.274
>5 cm	40	17	
Grade			
1-2	40	40	0.180
3	43	12	
Mitosis			
<10	47*	31*	0.020
>10	24*	24*	
Sites			
Extremity	45	29	0.310
Trunk	36	21	
Surgery			
Amputation	33	-	0.518
Excision	42	24	
Surgical margins			
Adequate	47*	28*	0.005
Inadequate	21*	-	

*Statistically significant. DFS=Disease free survival

When the impact of adjuvant chemotherapy and radiotherapy on the survival rates were individually assessed by univariate analysis neither of them were found to have a significant effect on patient outcome.

Toxicities

The toxicity profiles of the adjuvant chemotherapy protocols were analyzed and hematologic toxicity was found to be the most common toxicity [Table 4].

DISCUSSION

There is much controversy regarding the prognostic factors in the setting of localized SS throughout the literature. SS is a rare disease therefore before planning of a large and long term prospective study we designed a multicenter retrospective study aiming to collect data about the outcomes of patients with SS. We aimed to elucidate whether data obtained from a multicenter study design would be available for determination of clinically relevant prognostic factors.

In this study, the OS and DFS rates for 3 and 5 years were 68-64% and 59-25% respectively. Recent literature reports similar 5 year OS and DFS survival rates for localized disease.[6-8]

Many studies demonstrated different prognostic factors in this disease since 1960. Some studies promote the prognostic factors; whereas some of them did not. One of the reasons behind the different outcomes reported in these studies, especially in the older studies, is the heterogeneity of the

Table 4: Chemotherapy toxicities

Grade	FEN (%)*	Neutropenia (%)	Thrombocytopenia (%)	Vomiting (%)
1-2	-	12	8	18
3-4	9	14	2	-

FEN=*Febrile Neutopenia

study groups. Data of patients with primary, recurrent and metastatic SS, adult and pediatric patient groups are pooled in the same statistical analysis.[9-13] Although our study was a retrospective evaluation like most of other studies and patients were operated in different surgical centers, the majority of the patients received the same chemotherapy and radiotherapy protocols. This homogenization of the treatment protocol adds value to the analyzed data. In more recently published studies study groups consisted of larger series of patients with similar clinical settings compared to previously published studies. However, studies from these large single center studies needed very long periods of time, usually expanding more than 15 years, for collecting enough number of patients.[8,10,14]

In the previously published retrospective studies, the following prognostic factors were evaluated; age, tumor size, anatomic location, positive surgical margin, histopathological type and mitotic activity rate.[6,7,10] In addition to these classical factors some more controversial prognostic factors such as depth, type of surgery performed and type of adjuvant treatment were also assessed.[8,14]

In our study, gender was found to be one of the factors affecting the prognostic outcome in univariate analysis. Although in some studies, the gender difference was not found to be a prognostic factor[5,6,8,10,14] in one of the largest reviews published by Trassard *et al*. male sex was found to be an adverse prognostic factor.[7] SYT-SSX1 fusion transcript has a higher prevalence in males and it has been shown to be independently associated with an increased risk of early distant recurrence.[15]

Although age was reported as an adverse prognostic factor in studies comparing pediatric and young aged patients with the adult population,[5] this finding is not consistently verified in other studies.[6,8,13] In a study by Chen *et al*. which had a patient group with a similar mean age value, older age was reported as a poor prognostic factor; however, the distribution of age in the study group is not homogenous.[5] We could not demonstrate a correlation between older age (>40 years old) and poor prognosis. One plausible explanation for this finding is that the age distribution of our study group was fairly uniform and patients younger than 25 years old were under-represented.

We found a correlation between larger tumor size and worse OS; however, this did not attain statistical significance. In most of the studies, tumor size was reported as an independent adverse prognostic factor;[15-18] however, tumor size was not associated with poor outcome in all studies.[6,13,19] In our patient, population all cases with positive surgical margins with a tumor size lower than 5 cm died due to disease progression. This could have blunted the effect of the tumor size on the outcome of patients.

Some studies concluded that prospective and multi-institutional studies in this uncommon tumor will help to demonstrate the prognostic factors. In our search of the literature, we found only two prospective studies.[4,8] In one of these studies, monophasic subtype and metastatic disease at presentation were the only independent prognostic factors related with survival.[4,8] The other prospectively designed, which included more than 100 patients reported tumor size larger than or equal to 5 cm and tumor invasion of bone, nerve and vascular structures as independent adverse prognostic factors. We did not find any association between histological subtype and outcome of patients. This is in accordance with several other reports in the literature.[7,20,21]

We did not find an association between survival and tumor grade. There are contradictory statements in the literature regarding the significance of the relation between tumor grade and survival. Much of this contradiction seems to be related to factors included in the grading process of SS. A statistically significant correlation between tumor grading performed according to French Federation of Cancer Centers FNCLCC histological grading system was reported in a study by the Sarcoma Group of the French Federation of Cancer Centers.[7] In a more recently published study by Italiano *et al*. recruiting more than 200 patients, also reported that grading is an independent prognostic factor.[22] However in a previous study by Singer *et al*. who utilized cellularity, pleomorphism, presence of necrosis and mitotic activity for grading, tumor grade was not found to be a prognostic factor effecting survival.[10]

Although mitotic activity is one of the factors in the grading of the tumor, in several studies, it was found to be an independent prognostic factor having a significant effect on survival.[7,10,20,23,24] In our study, it was inversely associated with both OS and DFS and importantly the relation between mitotic activity and DFS remained significant also in multivariate analysis.

The study by Canter *et al*. which included a large number of SS patients reported that primary tumor site was the only independent adverse predictor of disease-specific death in multivariate analysis and claimed to be the first study reporting this association.[15] In fact, previously, Trassard *et al*. also showed that truncal localization was adversely associated with disease-specific survival.[7] Although, truncal localization was found to be significantly associated with OS in univariate analysis in our study, the significance was lost in multivariate analysis.

Ideally, the biopsy and the definitive surgical resection should be performed by a team of orthopedic oncology specialists because surgical margin positivity is found to be highly correlated with event free survival.[19,20] In large studies with a patient population having a positive surgical margin ratio similar to our study group clear surgical margin was reported as a good prognostic factor.[10] However, in the two prospectively designed studies surgical margin positivity either lost its significance in multivariate analysis[8] or was not found to be associated with survival.[4]

Recently, French Sarcoma group reported in their retrospective study about the effect of neo/adjuvant chemotherapy in resected SS and stated that chemotherapy does not improve the outcome in the localized setting. French Sarcoma group had also demonstrated that radiotherapy improved local relapse-free survival, but not OS. The role of adjuvant chemotherapy in patients with localized disease after local excision remains unproven. We have failed to detect a specific subgroup of patients driving benefit from adjuvant chemotherapy. The use of chemotherapy was not associated significant difference in DFS. The same analysis for patients with tumors having higher > 10 mitotic figures and truncal versus extremity localization also failed to demonstrate statistically significant differences in OS and DFS. This finding is in accordance with several retrospectively designed published literature.[4,6,8,13,15-17] On the contrary Canter *et al*. in their study reported that adjuvant chemotherapy improved survival for patients resected with curative intent. Chemotherapy seems to improve the survival of patients for the first 3 years; however, the beneficial effect observed weans after 5 years follow-up.[15] In another study aiming to investigate the effect of chemotherapy on survival rates also reported that stage IIB/III patients might benefit from adjuvant chemotherapy.[5]

The variables, which were significant on univariate analysis, were not identified as independent prognostic factors on multivariate analysis. The relatively short follow-up period may have caused this observation. The factors promising to carry prognostic features should be evaluated in a long-term prospective study.

In conclusion, this study confirms that high mitotic activity is significantly associated with decreased OS. Current adjuvant chemotherapy protocols do not have a high toxicity profile however the answer to the question of whether the chemotherapy provides a survival advantage in patients having adverse prognostic factors requires confirmation in randomized trials.

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