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Prognostic Relevance of Tumor Localization in Patients with Synovial Sarcoma

Doğan BAYRAM[a], Gökhan UÇAR[a], Serhat SEKMEK[a], Emre HAFIZOĞLU[a], İsmet SEVEN[a], Fahriye Tuğba KÖŞ[a], Öznur BAL[a], Efnan ALGIN[a], Burak CİVELEK[a], Doğan UNCU[a]

[a]Clinic of Medical Oncology, Ankara City Hospital, Ankara, Türkiye

ABSTRACT Objective: Synovial sarcoma, an aggressive subtype of soft tissue tumors, mainly occurs in young individuals. In patients with synovial sarcoma, the tumor is predominantly localized in the lower extremities, cases. The present study aimed to investigate the contribution of tumor localization to the prognosis of patients with synovial sarcoma and to determine the factors affecting patient survival. **Material and Methods:** We retrospectively analyzed the clinical data of 35 patients with synovial sarcoma who were treated at our clinic between February 2000 and October 2022. Overall survival (OS) and the factors affecting patient survival were investigated. **Results:** The primary site of tumor mass localization was the limb in 19 patients (54.3%) and an extrinsic site in 16 patients (45.7%). The most common extrinsic site of tumor mass localization was the lung in 22.9% patients, followed by intra-abdominal localization in 8.6% patients. Of the 35 patients, 88.6% patients had undergone surgery, and 34.3% patients had received adjuvant chemotherapy, namely the Ifosfamide-Mesna-Doxorubicin regimen. The median OS was 51.1 months. Tumor localization to the limb, presence of curative surgery, and an Eastern Cooperative Oncology Group performance status score of 0-1 were found to be the independent prognostic factors affecting the OS. **Conclusion:** In the present study, the survival rate of patients with tumor localization in the limb was higher than that of patients with tumor localization at an extrinsic site. Local recurrence and progression rates were lower with curative surgery. The prognosis of patients who could not be treated curatively was poor.

Keywords: Synovial sarcoma; tumor localization; curative surgery; adjuvant chemotherapy

Synovial sarcoma is a sporadic soft tissue tumor characterized by indeterminate differentiation. It represents approximately 5-10% of all soft tissue tumors.[1] The incidence of synovial sarcoma in adults is 1.42/1,000,000 individuals, and approximately 1000 new cases of synovial sarcoma are diagnosed each year in the United States.[2]

Synovial sarcoma has similar incidence rates in both sexes, and it is most frequently detected during the third decade of life.[3] Synovial sarcoma is known to be an aggressive tumor, with a 5-year survival rate of approximately 60%. However, the 10-year survival rate is <50%.[4]

Synovial sarcoma most frequently occurs in the limbs, and it is commonly observed in structures near the knee joint in the lower extremities. Synovial sarcoma can also occur in visceral organs, the central nervous system, peripheral nerves, peritoneum, mediastinum, retroperitoneum, and oral cavity. Synovial sarcoma has a slow growth pattern, and the most common symptom is pain.[5] Approximately 13% of the patients with synovial sarcoma show distant metastases at the time of diagnosis, with the lung being the most prevalent metastatic site.[2]

Curative surgery plays a critical role in the treatment of patients with localized and low-risk synovial sarcoma. The choice of surgical approach depends on the tumor's location and may involve either amputation or extremity preservation techniques. In surgery for treating synovial sarcoma, it is typically adequate

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Correspondence: Doğan BAYRAM
Clinic of Medical Oncology, Ankara City Hospital, Ankara, Türkiye
E-mail: drdoganb@gmail.com

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to perform a wide excision with clear surgical margins of 1-2 cm, similar to the approach used for other soft tissue tumors. In tumors closely associated with neurovascular structures or bone, the epineurium, adventitia, or periosteum are also used as margins to allow a functional limb after surgery.[6]

Although the role of adjuvant chemotherapy (CT) in soft tissue tumors remains controversial, studies have shown its contribution to overall survival (OS) and disease-free survival (DFS), particularly in high-risk patients.[7] Adjuvant CT should be considered in patients with intermediate-and high-risk tumors (>5 cm, nodal involvement, and positive surgical margin). Ifosfamide-doxorubicin is the most commonly used adjuvant chemotherapeutic regimen. Neoadjuvant CT can be considered as an induction therapy to improve the outcome of surgery in high-risk synovial sarcoma localized in the extremity and chest wall.[8]

CT is used to treat metastatic or unresectable synovial sarcoma. Doxorubicin is a component of the primary systemic therapy used for treating metastatic synovial sarcoma. This approach achieves a response rate of 16-27% and results in a median OS (mOS) of approximately 18 months.[9] Moreover, previous studies have shown that eligible patients receiving the ifosfamide-doxorubicin regimen experience a higher median progression-free survival (PFS) and OS than those receiving doxorubicin monotherapy. Pazopanib and trabectedin are among the second-line treatment options.[8] Previous research has indicated that in patients with metastatic or unresectable synovial sarcoma, the OS and PFS outcomes achieved with the gemcitabine-docetaxel combination are similar to those achieved with single-agent doxorubicin.[10] In the present study, we present the demographic characteristics, survival results, and treatment modalities of patients with synovial sarcoma who were treated in our clinic.

MATERIAL AND METHODS

PATIENTS

In our clinic, 810 patients with sarcoma were treated and followed up between February 2000 and October 2022; of these, 35 patients were followed up for treating synovial sarcoma. The clinical data of these 35 patients were retrospectively analyzed in our study. We evaluated the age, gender, comorbidities, tumor localization, treatment, recurrence, and disease progression of the patients. Additionally, we investigated OS, DFS, PFS, and prognostic factors affecting the OS of patients with synovial sarcoma.

In the present study, the staging of synovial sarcoma was based on the American Joint Committee on Cancer tumor staging system (8th edition). This system determines the stage of the primary tumor by considering factors such as the anatomical region, tumor size (T), involvement of nearby lymph nodes (N), and the existence of distant metastasis (M).[11]

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS Version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Two groups were compared using the Mann-Whitney *U* test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Survival analysis was performed using the Kaplan-Meier method with the log-rank test. Survival time was estimated within a 95% confidence interval (CI) range. A significance level of $p<0.05$ was considered statistically significant. OS was defined as the duration from the date of diagnosis to the date of death from any cause or the date of the last follow-up. DFS was defined as the period from the date of surgery to the date of recurrence or the date of the last follow-up for patients who underwent curative surgery.

ETHICS

This study was approved by the institutional ethics committee. All procedures adhered to the ethical standards established by the responsible committee and the most recent Declaration of Helsinki. Because this was a retrospective study design, informed consent was not obtained from the patients. The requirement for informed consent was waived by the Clinical Research Ethics Committee of Ankara City Hospital (date: January 11, 2023, no: E1-3205).

RESULTS

PATIENT CHARACTERISTICS

Table 1 presents the clinicopathological characteristics of the patients. Of the 35 patients, 71.1% underwent curative surgery, and the most frequent surgical procedures were tumor mass excision (71%) and limb amputation (9.8%). Adjuvant CT was used in 34.3% of the patients. Neoadjuvant CT was used in 1 patient (2.9%). The Ifosfamide-Mesna-Doxorubicin (IMA) CT protocol was used as an adjuvant CT in all patients. The most frequently used first-line CT regimen in patients with metastasis was IMA (46.7%), followed by the Ifosfamide-Mesna-Etoposide regimen (20%). Table 2 shows the details of the CT regimens administered to the patients.

Among the 25 patients who underwent curative surgery, 14 patients (56%) showed recurrence during the follow-up period. Tumor progression occurred during follow-up in all 10 patients who were metastatic at the time of diagnosis or could not be treated curatively.

SURVIVAL ANALYSIS AND TREATMENT EFFECT

The median follow-up duration for all patients was 191.4 months (range: 1.1-275.6 months) (95% CI: 129.8-235), and the mOS was 51.1 months (range: 1.1-275.6 months) (95% CI: 25.8-76.5) (Figure 1). The 5-year survival rate was 45.5%, and the 10-year survival rate was 37.9%. The mOS of patients with tumors located in the limb was 105.4 months (range: 3.5-275 months), while it was 43.8 months (range: 1.1-189 months) in patients with tumors located at extrinsic sites (Figure 2).

In the univariate analysis with factors such as age, gender, smoking, and alcohol use, laboratory values, adjuvant CT, and radiotherapy, no significant relationship was observed in terms of the mOS. However, a significant relationship was found between the mOS and the location of the primary mass (p=0.006), Eastern Cooperative Oncology Group (ECOG) performance status (p=0.001), tumor stage (p=0.021), and curative surgery (p=0.007). Based on the statistically significant parameters identified in the univariate analysis through Cox regression analysis, the ECOG performance score [hazard ratio (HR): 0.239, 95% CI: 0.079-0.723, p=0.011], the location of the primary mass (HR: 0.297, 95% CI: 0.108-0.822, p=0.019), and curative surgery (HR: 0.185, 95% CI: 0.061-0.566, p=0.003) were determined as the independent prognostic factors that significantly influenced the OS of the study patients (Table 3).

The mOS of the 25 patients who underwent curative surgery was 111.1 months (range: 3.5-275 months) (95% CI: 0-236.3), and the median DFS (mDFS) was 52.7 months (95% CI: 38.0-137.3). The mDFS of patients with tumor localization in the extremity site and the non-extremity site was 99.5 months (range: 2-242 months) and 31.5 months (range: 2.6-189 months); however, the observed difference was not statistically significant (p=0.2).

The median PFS (mPFS) of patients receiving second-line CT for the metastatic disease was 8.5 months (range: 2.0-233 months) (95% CI: 5.4-13.9). The longest mPFS was observed for patients receiving the Ifosfamide-Mesna-Etoposide regimen (9.6 months), while the shortest mPFS was observed for the patients receiving the Gemcitabine-Docetaxel regimen (2.2 months); however, no statistically significant difference in mPFS was observed between the CT regimens.

DISCUSSION

Synovial sarcoma, a rare type of soft tissue tumor, is most commonly diagnosed in individuals during their third decade of life. It has a similar frequency of occurrence in both males and females.[3] In the present study, consistent with previous findings, the median age of the study patients was 42 years, and there was a relatively balanced distribution of both women and men in the study group. Vlenterie et al. investigated the effect of age on the prognosis of patients with synovial sarcoma and found that an increased age at diagnosis is a poor prognostic factor.[12] The present study found no significant relationship between age and OS. The reasons for the difference in these two studies were the low number of patients in our study and the relative age of the patients.

In the present study, the mOS was 51.1 months, the 5-year survival rate was 45.5%, and the 10-year

TABLE 1: Clinicopathological features of all patients and details of treatments.

		n=35	%
Age* (Year)		42	(19-81)
Gender	Male	18	51.4
	Female	17	48.6
ECOG performance status	0	9	25.7
	1	17	48.6
	2	7	20.0
	3	2	5.7
	4	0	0.0
Comorbidity	None	22	62.8
	Hypertension	5	14.3
	Diabetes mellitus	2	5.7
	Asthma	1	2.8
	Chronic renal failure	1	2.8
	Rheumatoid arthritis	1	2.8
	Coronary artery disease	1	2.8
	Behçet's disease	1	2.8
	Neurofibromatosis	1	2.8
Cigarette	Yes	10	28.6
Alcohol	Yes	2	5.7
Initial symptom	Hoarseness	2	5.7
	Shortness of breath	9	25.7
	Swelling	17	48.6
	Local Pain	2	5.7
	Melena	1	2.9
	Stomach ache	3	8.6
	Vaginal bleeding	1	2.9
Anemia	There is	10	32.3
Location of the primary audience	Lower limb	14	40.0
	Lung	8	22.9
	Upper limb	5	14.3
	Intraabdominal	3	8.6
	Mediastinum	1	2.9
	Hypopharynx	1	2.9
	Endometrium	1	2.9
	Gastric	1	2.9
	Ovarian	1	2.9
Distant metastasis in diagnosis	Yes	3	8.6
Stage	1A	3	8.6
	1B	3	8.6
	2	0	0.0
	3A	8	22.9
	3D	18	51.4
	4	3	8.6
Applied treatments	Neoadjuvant CT-Curative surgery	1	2.9
	Curative surgery	24	68.5
	Palliative surgery	6	17.1
	Palliative CT	1	2.9
	Palliative radiotherapy	1	2.9
	Palliative support	2	5.7
Surgery performed	Mass excision	22	70.9
	Amputation	3	9.6
	Lung lobectomy	2	6.5
	Pneumectomy	2	6.5
	TAH-BSO	2	6.5
Surgical margin	Negative	25	80.6
	Positive	6	19.4
Radiotherapy	No	26	74.3
	Yes	9	25.7
Adjuvant chemotherapy	No	23	65.7
	Yes	12	34.3

*n is presented as median, % as minimum-maximum; ECOG: Eastern Cooperative Oncology Group; CT: Chemotherapy; TAH-BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy.

TABLE 2: Treatment modalities used for patients with synovial sarcoma.

	n=35 (%)
Adjuvant chemotherapy	12
Ifosfomid-Mesna-Doxorubicin	12 (100)
First-line chemotherapy regimens	15
Ifosfomid-Mesna-Doxorubicin	7 (46.7)
Ifosfomid-Mesna-Etoposide	3 (20)
Cyclophosphamide-Doxorubicin	2 (13.3)
Gemcitabine-Docetaxel	2 (13.3)
Cyclophosphamide-Epirubicin-Vicristine-Dacarbazine	1 (6.7)
Second-line chemotherapy regimens	6
Gemcitabine-Docetaxel	3 (50)
Pazopanib	2 (33.3)
Cisplatin-Vinorelbine	1 (16.7)
Third-line chemotherapy regimens	3
Pazopanib	2 (66.7)
Cyclophosphamide-Etoposide	1 (33.3)

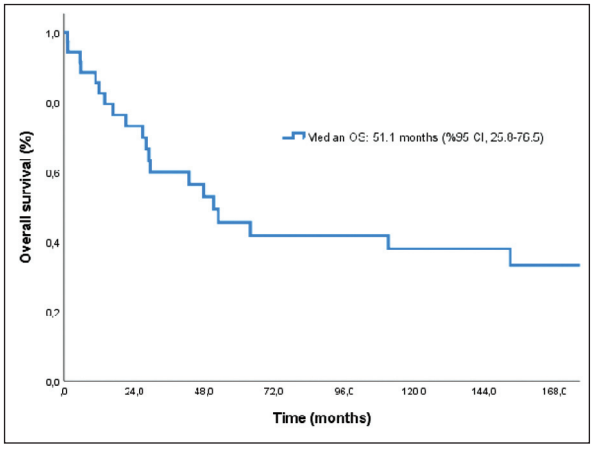

FIGURE 1: Kaplan-Meier survival curve for the overall survival of all patients.

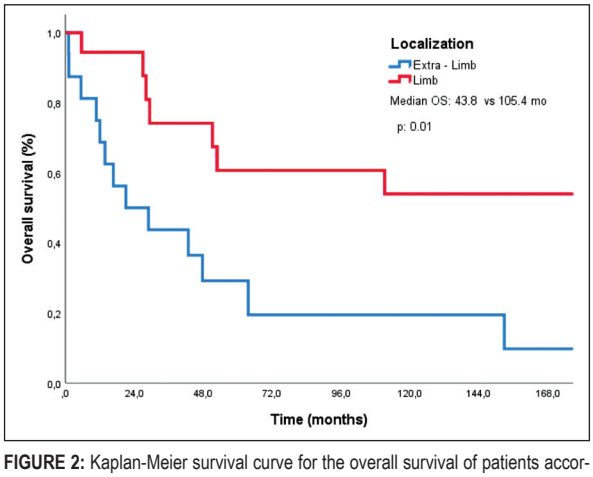

FIGURE 2: Kaplan-Meier survival curve for the overall survival of patients according to tumor localization.

survival rate was 37.9%. In the study of Guadagnolo et al., the 5-year survival rate of 150 patients with synovial sarcoma was 76%, while the 10-year survival rate was 58%; furthermore, all the patients were non-metastatic.[6] In the study of Ferrari et al., the 5-year survival rate was 64.3%, while the 10-year survival rate was 49.7%. Furthermore, in another study, 6% of the patients were metastatic at the time of diagnosis.[13] The survival rates in these two studies were higher than that in our study. In the present study, the metastatic rate of patients was higher than those reported in these two studies. None of the metastatic patients in our study could be treated curatively, and tumor progression was noted in all patients during follow-up. Spillane et al. reported that the OS rate was lower in patients with a large tumor diameter and with metastatic tumors.[14] The tumor stage also affects the prognosis of patients with synovial sarcoma, as observed for other tumors.

In the present study, the primary tumor was located in the lower limb, upper limb, and lungs in 40%, 14.3%, and 22.9% of the patients, respectively. Although synovial sarcoma can occur in any part of the body, the most common localization site is the lower limb, as noted in our study. Similar to our study, Guadagnolo et al. reported that the location of the primary mass was mostly the lower limb (58%).[6] In the study of Sultan et al., the most common tumor localization in 1,055 adult patients with synovial sarcoma was the extremity (68%). Only 4.7% of the patients showed tumor localization in the lungs and pleura. Survival was significantly higher in patients with tumors located in the limbs than in patients with tumors located in the extrinsic site.[4]

In the study of Vlenterie et al., 65.7% of the 613 study patients had a primary mass located in the limb. No relationship was observed between tumor localization and survival.[12] Trassard et al. reported no difference in the survival rate of the patients according to tumor location.[15]

In our study, we assigned patients to two groups according to primary mass localization: limb and extrinsic site. The OS rate was significantly lower in patients with extrinsic site tumors (p=0.019). Patients with tumor localization in the extremity had a lower mean age and lower ECOG performance scores. Cu-

TABLE 3: Univariate and multivariate analyses of factors affecting the overall survival of patients with synovial sarcoma.

	n=35 (%)	Median-OS (months 95% CI)	Univariate p value	Multivariate HR (95% CI)	p value
Age groups					
≤42	19 (54.3)	52.7 (10.5-95.0)	0.583		
>42	16 (45.7)	42.8 (1.9-83.7)			
Gender					
Male	18 (51.4)	42.8 (9.1-76.5)	0.072		
Woman	17 (48.6)	102.5 (51.0-154.1)			
ECOG					
0-1	26 (74.3)	63.6	0.001*	0.239 (0.079-0.723)	0.011 *
2-4	9 (25.7)	11.9 (0-30.5)			
Comorbidity					
No	22 (62.9)	52.7 (34.1-71.4)	0.970		
Yes	13 (37.1)	51.1 (0-201)			
Smoking					
No	25 (71.4)	52.7 (0-133.6)	0.579		
Yes	10 (28.6)	28.9 (4.3-54.3)			
Alcohol					
No	25 (71.4)	52.7 (27.9-77.6)	0.070		
Yes	10 (28.6)	16.6			
Anemia					
No	25 (71.6)	52.7 (32.1-73.4)	0.920		
Yes	10 (28.4)	28.0 (15.2-40.8)			
Leukocytosis					
No	26 (74.3)	63.6 (0-197.3)	0.157		
Yes	9 (25.7)	28.0 (24.8-31.2)			
Lymphocytosis					
No	30 (85.7)	66.3 (0-136)	0.315		
Yes	5 (14.3)	26.9 (4.8-49.0)			
Neutrophilia					
No	27 (77.1)	51.1 (20.9-81.3)	0.363		
Yes	8 (22.9)	28.0 (0-58.7)			
Elevated creatinine					
No	32 (91.4)	51.2 (15.5-86.8)	0.759		
Yes	3 (8.6)	63.6 (38.1-89.1)			
Elevated AST					
No	31 (88.6)	52.8 (28.5-77.0)	0.865		
Yes	4 (11.4)	29.3 (0-59.1)			
Elevated ALT					
No	29 (82.9)	47.7 (12.9-82.5)	0.86		
Yes	6 (17.1)	110.0			
Elevated calcium					
No	33 (94.3)	81.4 (51.4-111.5)	0.586		
Yes	2 (5.7)	8.77 (0-74.7)			
Elevated ALP					
No	25 (71.4)	52.7 (23.9-81.6)	0.795		
Yes	10 (28.6)	51.1 (21.4-80.9)			
Elevated LDH					
No	26 (74.3)	63.6 (39.4-87.8)	0.376		
Yes	9 (25.7)	29.3 (25.5-33.0)			
Location of mass					
Limb	19 (54.3)	105.4 (59.5-151.4)	0.006*	0.297 (0.108-0.822)	0.019*
Extra-Limb	16 (45.7)	43.8 (15.1-72.4)			
Stage					
1-2	6 (17.1)	98.7 (11.1-186.3)	0.021*	0.034 (0.0-3.5)	0.964
3-4	29 (82.9)	29.3 (0-35.6)			
Adjuvant chemotherapy					
Yes	12 (34.3)	28.9 (9.0-48.7)	0.162		
No	23 (65.7)	52.7 (0-183.0)			
Curative surgery					
Yes	25 (71.4)	111.1 (0-236.3)	0.007*	0.185 (0.061-0.566)	0.003*
No	10 (28.6)	16.6 (0-38.4)			
Radiotherapy					
Yes	26 (74.3)	47.7 (18.2-77.2)	0.360		
No	9 (25.7)	63.6 (31.8-95.4)			

ECOG: Eastern Cooperative Oncology Group; OS: Overall survival; CI: Confidence interval; HR: Hazard ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; *: Statistically significant.

rative surgery was performed in 60% of patients with limb localization and 40% of patients with extrinsic site localization. Surgical margin positivity was higher in the extrinsic site group. Moreover, patients with extrinsic site localization had a more advanced stage tumor at the time of diagnosis.

In the present study, both OS (p=0.003) and DFS were significantly higher in patients who underwent curative surgery with negative surgical margins. Singer et al. examined the contribution of the surgical margin to patient survival; tumor resection with negative surgical margins was shown to contribute to patient survival.[16] Negative surgical margins are indicative of local control. Lewis et al. reported that the rate of local recurrence was significantly higher in patients who could not undergo curative surgery with negative surgical margins.[17] In the study of Gundle et al., the 10-year local recurrence rates were as follows: 8%, 21%, and 44% in patients with negative surgical margins, positive microscopic surgical margins, and positive macroscopic margins, respectively. Adjuvant radiotherapy showed its effectiveness in reducing the risk of local recurrence following surgeries where positive microscopic or millimeter-close surgical margins were achieved.[18] Biau et al. revealed that individuals with positive surgical margins experienced a 3.3-fold greater risk of local recurrence, together with an elevated risk of mortality.[19]

In the present study, no significant relationship was observed between CT and patient survival. Similar to our study, Guadagnolo et al. also reported that CT did not contribute to patient survival.[6] Although the contribution of CT to patient survival could not be demonstrated in the study of Lewis et al., Ferrari et al. reported that the 5-year DFS rate was higher in patients receiving CT.[13,17]

Previous studies have also shown the contribution of the neoadjuvant CT, namely the Ifosfamide-Mesna-Doxorubicin, to disease-specific survival.[20] Frustaci et al. also showed the contribution of CT to the survival of patients with high-risk soft tissue sarcomas and reported that sarcomas are chemosensitive tumors.[7] In the present study, only 34% of the patients received adjuvant CT. Those patients who received adjuvant CT had already undergone curative surgery. In addition, 8.3% of the patients who received adjuvant CT had tumor Stage 2 and below, while 91.7% had tumor Stage 3. These factors may have influenced the result. Similarly, only 25% of the patients in our study received radiotherapy, and 88.8% of these patients were in advanced stages. Therefore, no significant relationship was found between radiotherapy and patient survival.

Anthracycline-based CT regimen is the preferred first-line treatment of metastatic synovial sarcoma.[21] In the present study, 60% of the patients receiving first-line treatment for the metastatic disease had received CT regimens containing doxorubicin. The lowest mPFS was observed for the gemcitabine-docetaxel CT. Tansir et al. reported that the mPFS for synovial sarcoma patients receiving gemcitabine-docetaxel as the first-line treatment for the metastatic disease was 3 months; this duration was similar to that observed in our study.[22]

The present study has some limitations. The sample size was small, and the study was retrospective in nature. However, because synovial sarcoma is a rare tumor and our study was a single-center investigation, we believe that the findings of this study will contribute to the existing literature.

CONCLUSION

In the present study, tumor localization, curative surgery, and ECOG performance score were found to be the independent prognostic factors affecting the OS of patients with synovial sarcoma. The OS time of patients with tumor localization in the extremity was significantly longer. Curative surgery with negative surgical margins is critical for local control and prognosis of the disease.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or mem-

bers of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Doğan Bayram, Gökhan Uçar, Doğan Uncu;* ***Design:*** *Doğan Bayram, Serhat Sekmek;* ***Control/Supervision:*** *Gökhan Uçar, Öznur Bal;* ***Data Collection and/or Processing:*** *Doğan Bayram, İsmet Seven;* ***Analysis and/or Interpretation:*** *Emre Hafızoğlu, Efnan Algın;* ***Literature Review:*** *Doğan Bayram, Burak Civelek;* ***Writing the Article:*** *Doğan Bayram, Fahriye Tuğba Köş;* ***Critical Review:*** *Doğan Bayram, Doğan Uncu;* ***References and Fundings:*** *Doğan Bayram;* ***Materials:*** *Doğan Bayram.*

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