

# Clinical and strategic outcomes of metastatic synovial sarcoma on limb

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## Introduction

Synovial sarcoma (SS) is an aggressive mesenchymal neoplasm with distinct uniform cytopathological features.<sup>[1]</sup> It can occur almost anywhere and affects people of all ages, with a propensity to occur in adolescents and young adults.<sup>[2-4]</sup> SS accounts for 5–10% of soft-tissue sarcomas in adolescents and young adults.<sup>[2,5,6]</sup> Most cases occur at extra-articular sites in the extremities.<sup>[7]</sup> The treatment for local SS includes wide resection and adjuvant or neoadjuvant radiotherapy, which provides a satisfactory prognosis.<sup>[8]</sup> Although SS is moderately sensitive to chemotherapy,<sup>[9,10]</sup> the use of chemotherapy remains controversial.<sup>[11,12]</sup> SS is regarded as a high-grade sarcoma, characterized by local invasiveness and metastatic propensity.<sup>[13]</sup> The lung is the most common site of SS metastasis.<sup>[6]</sup> Patients usually have a poor prognosis if they developed metastatic disease.<sup>[7]</sup> Metastatic limb SS (LSS) is very rare, with no standard therapy. However, the demographic, prognostic, and outcomes data of metastatic LSS are poorly documented.

Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified all patients diagnosed with

## ABSTRACT

**Objective:** Synovial sarcoma (SS) is one of the most frequent malignant soft-tissue tumors, and nearly 65% arise in the lower extremities. Survival prediction and the risk factors of the patients are poorly understood. Thus, this study examined the survival and prognostic variables of metastatic limb SS (LSS).

**Methods:** Clinical data of LSS patients with metastasis at the presentation from 1975 to 2017 were obtained from the Surveillance, Epidemiology, and End Results database program database. Kaplan–Meier method was used to describe the survival curves. Univariate and multivariate Cox regression analysis were conducted to reveal the real prognostic predictors.

**Results:** Male predominance was observed in the metastatic LSS group from a total number of 217 patients. This population was composed of 49.8% not other specified subtype, 32.7% spindle cell subtype, 17.1% biphasic subtype, and 0.5% epithelioid cell subtype. The 3-year overall survival (OS) and cancer-specific survival (CSS) rates of the entire group were 27.2% and 28.3%, respectively. Tumor size <10 cm, surgery, radiotherapy, and chemotherapy were calculated as independent predictors of improved OS and CSS by multivariate analyses.

**Conclusion:** SS is still a disease with a poor prognosis. This can increase the survival rate and time by the well-planned treatment.

**Keywords:** Synovial sarcoma, limb, metastatic, clinical, strategic

LSS with metastasis at presentation from 1975 to 2016. This study first examined the clinical features of LSS patients with metastasis at presentation and confirmed the prognostic factors for this patient population, which should improve clinicians' understanding of this disease.

## Patients and Methods

### Study population

This study reviewed all patients diagnosed with LSS and metastasis at presentation between 1975 and 2016. The data of this cohort were extracted from the SEER database ([www.seer.cancer.gov](http://www.seer.cancer.gov)), which is available to the public. This database collects data from 18 registry areas in the United States and does not contain patient identification information. The study was approved by the local Institutional Review Board. LSS patients were selected based on the 3<sup>rd</sup> edition of the International Classification of Diseases for Oncology (ICD-O-3). ICD-O-3 code, 9040-9043, was used to indicate SS patients while primary site code, C40.0-C41.9, indicating extremity site. All patients were enrolled according to the

pathological confirmation, not clinical diagnosis or autopsy. Patients without survival data were also excluded. Clinical pathological characteristics obtained from the SEER database included age at diagnosis, gender, tumor grade, tumor type, tumor size, surgery, radiotherapy, chemotherapy, vital status, cause of death, and survival months. Surgery or radiotherapy in the present study refers to local treatment for tumors located in the primary sites. Age was divided into two groups: <40 years and ≥40 years. Tumor grade was divided into three categories: Low grade, high grade, and unknown. Low grade refers to ICD-O-3 Grade 1 (well differentiated) and Grade 2 (moderately differentiated). High grade refers to ICD-O-3 Grade 3 (poorly differentiated) and Grade 4 (undifferentiated anaplastic).

### Statistical analysis

We applied SPSS 24.0 software to conduct all statistical tests. According to the previous study,<sup>[14]</sup> we defined cancer-specific survival (CSS) as the time from diagnosis to death due specifically to cancer and overall survival (OS) as the time from diagnosis to death from any cause. Figure 1 shows plot survival curves find out by Kaplan–Meier method and predict survival rates.

To compare the survival curves, the log-rank test was used. To identify independent predictors of survival, univariate and multivariate Cox regression analyses were performed simultaneously. We also calculated hazard ratios (HRs) with corresponding 95% confidence intervals to reveal the effect of various predictors on survival.  $P < 0.05$  was two sided, and it was considered statistically significant.

## Results

### Patients’ characteristics

The present study included 217 eligible patients for prognostic analysis. Basic clinical characteristics of metastatic LSS patients are shown in Table 1.

One hundred and six (48.8%) patients were aged <40 years, and 111 (51.2%) patients were aged ≥40 years. Gender distribution was the female 37.8% and the male 62.2%. A total of 11 (5.1%), 104 (47.9%), and 102 (47.0%) of the patients had low, high, and unknown tumor grade, respectively. Almost half of the patients were diagnosed with SS, NOS (49.8%). Tumor size was available in 163 cases (75.1%), and nearly half of cases (47.0%) were with ≥10 cm nearly two-thirds of the patients (65.0%) underwent local surgery, 88 patients (40.6%) underwent radiotherapy, and 161 patients (74.2%) received chemotherapy. The 3-year OS and CSS rates of the population were 27.2% and 28.3%, respectively.

### Univariate analysis

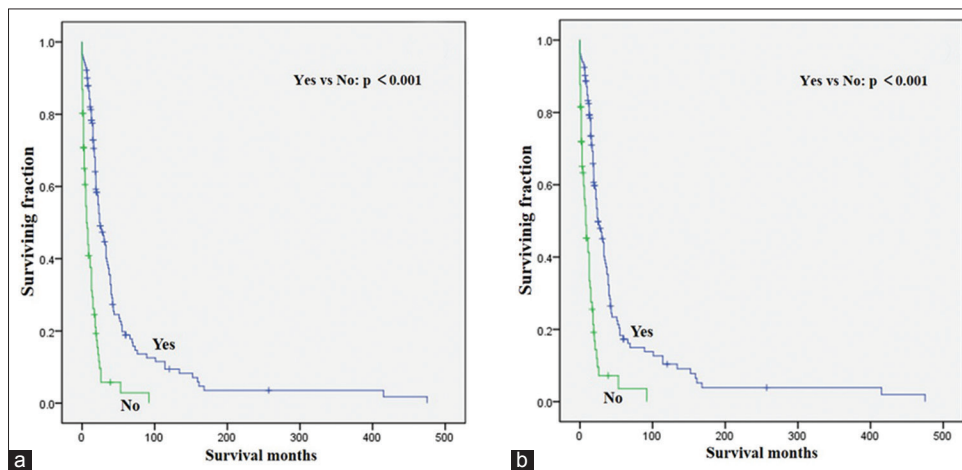
Median survival data of metastatic LSS patients are shown in Table 2.

Based on the univariate analysis [Table 3], age at diagnosis, gender, tumor grade, and tumor type was not significantly associated with either OS or CSS.

Radiotherapy and chemotherapy were associated with OS but not CSS. Patients who performed local surgery had significantly better outcomes than other patients [Figure 1a and b]. In addition, patients with tumor size <10 cm did not predict a better prognosis compared with patients with tumor size ≥10 cm.

### Multivariate analysis

We integrated variables with  $P < 0.1$  from univariate analysis into the multivariate analysis. Results of multivariate Cox regression analysis are shown in Table 4. Tumor size <10 cm, surgery, radiotherapy, and chemotherapy showed significant survival benefits.



**Figure 1:** Kaplan–Meier plot for estimating overall survival (a) and cancer-specific survival (b) among limb synovial sarcoma patients with metastasis at presentation stratified by surgery

**Table 1:** Characteristics of 217 patients with limb synovial sarcoma and metastasis at presentation

Category	Value
Age (years)	
<40	106 (48.8%)
≥40	111 (51.2%)
Gender	
Female	82 (37.8%)
Male	135 (62.2%)
Tumor grade	
Low	11 (5.1%)
High	104 (47.9%)
Unknown	102 (47.0%)
Tumor type	
Synovial sarcoma, NOS	108 (49.8%)
Synovial sarcoma, spindle cell	71 (32.7%)
Synovial sarcoma, biphasic	37 (17.1%)
Synovial sarcoma, epithelioid cell	1 (0.5%)
Tumor size	
<10 cm	61 (28.1%)
≥10 cm	102 (47.0%)
Unknown	54 (24.9%)
Surgery	
Yes	141 (65.0%)
No	76 (35.0%)
Radiation treatment	
Yes	88 (40.6%)
No	129 (59.4%)
Chemotherapy	
Yes	161 (74.2%)
No	56 (25.8%)
Dead	
Yes	179 (82.5%)
No	38 (17.5%)
3-year OS rate	27.20%
3-year CSS rate	28.30%
5-year OS rate	13.70%
5-year CSS rate	13.20%

NOS: Not other specified, OS: Overall survival, CSS: Cancer-specific survival

## Discussion

In this study, we included 217 metastatic LSS patients from the SEER database for survival analysis. There are very few cases of metastatic LSS and few studies have documented the findings. In addition, the standard treatment for metastatic LSS is poorly documented. Tumor patients' survival knowledge will help the clinicians in developing appropriate surgical procedures. This study is the first to reveal clinical features of metastatic LSS patients and ulteriorly explore independent predictors of survival using the public SEER database. The

**Table 2:** Median survival data (month) of patients with limb synovial sarcoma and metastasis at presentation

Category	OS	95% CI	CSS	95% CI
Overall	18.0±1.3	15.5–20.5	19.0±1.5	16.0–22.0
Age (years)				
<40	23.0±1.9	19.3–26.7	24.0±2.2	19.6–28.4
≥8	15.0±1.9	11.2–18.8	16.0±1.4	13.3–18.7
Gender				
Female	20.0±2.4	15.3–24.7	22.0±2.4	17.3–26.7
Male	18.0±1.3	15.4–20.6	19.0±1.3	16.5–21.5
Tumor grade				
Low	22.0±16.0	0.0–53.4	16.0±2.0	12.0–20.0
High	19.0±2.0	15.1–22.9	23.0±3.3	16.4–29.6
Tumor type				
Synovial sarcoma, NOS	16.0±1.9	12.3–19.7	16.0±2.0	12.0–20.0
Synovial sarcoma, spindle cell	22.0±3.4	15.3–28.7	23.0±3.3	16.4–29.6
Other	24.0±6.4	11.4±36.6	30.0±5.9	18.4–41.6
Tumor size				
<10 cm	29.0±5.2	18.8–39.2	33.0±4.3	24.7–41.3
≥1 cm	16.0±1.1	13.8–18.2	16.0±1.2	13.7–18.3
Surgery				
Yes	24.0±3.4	17.3–30.7	25.0±3.8	17.5–32.5
No	6.0±1.4	3.2–8.8	8.0±2.2	3.7–12.3
Radiotherapy				
Yes	22.0±2.0	18.0–26.0	22.0±2.8	16.6–27.4
No	17.0±1.7	13.7–20.3	18.0±1.6	14.9–21.1
Chemotherapy				
Yes	21.0±1.6	17.8±24.2	22.0±1.7	18.7±25.3
No	9.0±2.8	3.4±14.6	10.0±2.6	5.0±15.0

average and median age at diagnosis of this population was 40 years, which is almost similar to that reported by Krieg *et al.*,<sup>[15]</sup> that is, 35.4 years. Therefore, LSS is also prone to affect young people, similar to the overall SS.<sup>[8]</sup> Spurrell *et al.*<sup>[9]</sup> reported that there is a slight male predominance in advanced SS from the single-center study. Male predominance was also observed in the metastatic LSS group. Metastasis was common in LSS, and the most common site is lung.<sup>[8]</sup> Despite treatment, SS is associated with a high recurrence rate (24–29%) and metastatic rate (47–48%).<sup>[11,15,16]</sup> Further, SS patients with metastasis at diagnosis had significant poorer OS than those with late metastasis.<sup>[15]</sup> The 5-year OS rate of this metastatic cohort was 13.7%, which was worse than that reported by Krieg *et al.*<sup>[15]</sup> of 28%. Therefore, it is essential to single out such patients for prognostic analysis. On univariate analysis, age was not a significant potential predictor of OS or CSS. Okcu *et al.*<sup>[17]</sup> also found that age was not associated with survival in young SS patients. We have noted that neither gender nor tumor type was significantly related to survival time. In general, tumor grade was seen as a significant prognostic indicator of SS.<sup>[13,18]</sup> However, our univariate analysis showed no obvious difference

**Table 3:** Univariate Cox analysis of variables in patients with limb synovial sarcoma and metastasis at presentation

Category	OS		CSS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (years)				
<40	1		1	
≥40	1.223 (0.907–1.649)	0.188	1.225 (0.893–1.681)	0.208
Gender				
Female	1		1	
Male	1.139 (0.839–1.546)	0.402	1.136 (0.824–1.567)	0.435
Tumor grade				
Low	1		1	
High	1.416 (0.680–2.950)	0.353	1.588 (0.726–3.476)	0.247
Tumor type				
Synovial sarcoma, NOS	1		1	
Synovial sarcoma, spindle cell	0.780 (0.556–1.093)	0.149	0.789 (0.553–1.126)	0.192
Other	0.812 (0.542–1.215)	0.31	0.804 (0.522–1.236)	0.32
Tumor size				
<10 cm	1		1	
≥10 cm	1.581 (1.108–2.255)	0.012	1.752 (1.201–2.556)	0.004
Surgery				
Yes	1		1	
No	3.299 (2.376–4.582)	<0.001	3.176 (2.234–4.514)	<0.001
Radiotherapy				
Yes	1		1	
No	1.365 (1.010–1.843)	0.043	1.321 (0.963–1.813)	0.085
Chemotherapy				
Yes	1		1	
No	1.484 (1.056–2.087)	0.023	1.395 (0.963–2.201)	0.078

in either OS or CSS, based on tumor grade. Maybe metastatic LSS has its unique features. Tumor size is one of the most significant factors associated with the survival of SS.<sup>[8,17,19]</sup> Jacobs *et al.*<sup>[19]</sup> reported that the tumor size was an independent risk factor of survival for SS. Moreover, Spillane *et al.*<sup>[8]</sup> reported that the tumor size was associated with the tumor stage in SS patients and hence affected survival. However, they also found that smaller SSs had an unexpectedly poor prognosis. Pappo *et al.*<sup>[18]</sup> found a borderline significant relationship between OS and tumor size ( $P = 0.09$ ). The present study demonstrated that tumor size  $\geq 10$  cm could independently predict worse survival in metastatic LSS patients. Although surgical resection is regarded as the mainstream treatment for

**Table 4:** Multivariate Cox analysis for OS and CSS for patients with limb synovial sarcoma and metastasis at presentation

Category	OS		CSS	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Tumor size				
<10 cm	1		1	
≥mz cm	1.533 (1.064–2.208)	0.022	1.635 (1.103–2.425)	0.014
Surgery				
Yes	1		1	
No	3.308 (2.361–4.634)	<0.001	3.047 (2.121–4.376)	<0.001
Radiotherapy				
Yes	1		1	
No	1.455 (1.063–1.992)	0.019	1.458 (1.047–2.029)	0.025
Chemotherapy				
Yes	1		1	
No	1.573 (1.094–2.262)	0.014	1.478 (1.003–2.179)	0.048

LSS, evidence for the role of surgery among metastatic LSS patients still lack. Ferrari *et al.*<sup>[20]</sup> found that the surgery alone is sufficient therapy for patients with adequately resected  $\leq 5$  cm SS. We found that surgery was the most significant prognostic factor for both OS and CSS based on multivariate analysis. Spillane *et al.*<sup>[8]</sup> also thought that adequate local treatment might affect the survival of SS patients. Adjuvant radiotherapy is often employed in SS patients with tumor size  $\geq 5$  cm.<sup>[17]</sup> Ferrari *et al.*<sup>[21]</sup> thought that radiotherapy might improve the local control not only after wide resection but also after narrower resection. Al-Hussaini *et al.*<sup>[10]</sup> showed that surgery combined with radiotherapy could prolong the survival of patients with localized SS. This research first showed the role of radiotherapy to improve metastatic LSS survival. While SS is considered to be chemosensitive, there are still controversy about the use of chemotherapy in SS.<sup>[17]</sup> Some studies reported a survival benefit with chemotherapy among SS patients,<sup>[22–25]</sup> while others did not observe this evidence.<sup>[26–28]</sup> Despite considerable toxicity of high-dose ifosfamide, this regimen translated into a survival benefit among patients with metastatic SS.<sup>[29]</sup> In fact, Ferrari *et al.*<sup>[21]</sup> recommended that SS patients with tumor size  $> 5$  cm be the first to be considered for chemotherapy. This study preliminarily determined the effect of chemotherapy on prolonging the prognosis of metastatic LSS. There are some limitations to this study. First, details about local or distant recurrence after diagnosis were not documented in the SEER database, which may influence survival time. Second, some other clinical variables, such as surgical margin and chemoradiotherapy program, were not available in this database. Third, this study was a retrospective study with some bias. Despite these limitations, the SEER database is a very useful resource for studying rare tumors, such as LSS patients with metastasis at presentation.



## Conclusion

Therefore, this study revealed that LSS patients with metastasis at presentation had a very poor prognosis. Combination therapy of surgery, radiotherapy, and chemotherapy may be beneficial for prolonging their survival time.

## Authors' Declaration Statements

### Ethical approval

This manuscript and design plan were approved by the ethics committee of the General Hospital of Ningxia Medical University.

### Statement of informed consent

No consent was needed because the database is publicly available and does not include unique patient identifiers.

### Availability of data and materials

By reasonable request, the author will provide data.

### Funding

None.

### Interests of competing

None of the authors have competing interests.

## Authors' Contributions

SAJ and SAM carried out the studies; participated in collecting data SAJ, SJ, MMST, ZX, SSM, and SAM; conceived and designed the study SAJ, SJ, and SAM; SAJ and SAM wrote different parts of the manuscript; all authors participated complete data analysis; all authors revised the manuscript; all authors approved the final manuscript.

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