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Lung metastasis in soft tissue sarcomas: survival and risk factors using the SEER database

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Abstract

Aim: To investigate patients with soft tissue sarcoma (STS) and evaluate (1) factors associated with lung metastases at the time of diagnosis; (2) the impact these factors had on overall survival; and (3) the impact of the metastatic site on survival.

Methods: We utilized the SEER database to analyze data from 14,520 patients diagnosed with STS between 2010 and 2018. Inclusion criteria included histologically confirmed STS of the lower limb, upper limb, or pelvis. Demographic, oncologic, and survival data were extracted, including tumor size, histopathology, AJCC staging, and metastatic status. Univariable and multivariable analyses identified risk factors for lung metastasis and Kaplan-Meier survival analysis was used to assess disease-specific survival (DSS).

Results: Of the 13,372 patients with STS, 7.9% had lung metastases at diagnosis. Undifferentiated pleomorphic sarcoma, leiomyosarcoma, and rhabdomyosarcoma were the most common STS presenting with lung metastasis. Patients who present with STS of the lower extremity, higher grade, and either leiomyosarcoma, spindle cell, or synovial cell sarcoma were more likely to present with lung metastases. Patients with lung metastases had worse survival than patients without metastases. However, survival was better in patients with isolated lung metastases than in those with any combination of lung, bone, brain, and/or liver metastases.

Conclusion: Tumor location, grade, T score, and lymph node involvement were significant risk factors for lung

metastasis. A deeper understanding of risk factors for lung metastases presents a new opportunity for investigation in management. As expected, patients who present with lung metastases have worse overall survival.

Keywords: Soft tissue sarcoma, metastasis, lung, SEER

INTRODUCTION

Soft tissue sarcoma (STS) is a rare diagnosis, accounting for less than 1% of newly diagnosed malignancies[1]. Metastatic disease is crucial for prognosis and treatment planning in STS as survival rates vary significantly based on staging at diagnosis; a 20-year study reported a 5-year survival rate of 51% for high-risk, deep, high-grade extremity tumors larger than 10 cm[2]. Other studies show similar 5-year survival rates for STS, ranging from 48% to 56% over 25 years[3]. It is known that sarcoma most commonly metastasizes to the lungs, but factors that predict the risk of metastases on presentation are not well understood from a large population standpoint[4-6]. Furthermore, metastases to other locations in the body have a poorly understood risk profile and effect on outcome[5]. While metastatic STS carries a poorer prognosis, aggressive treatments like metastasectomy and stereotactic body radiation therapy (SBRT) can improve survival, which ranges from 26%[7] to 30%[8]. This literature varies as there is no consensus as to when metastasectomy or radiation therapy is most appropriate. As there is a need for a more unified understanding of indications for metastatic disease treatment, some authors discuss the introduction of staging for lung metastasectomy (LM) or other forms of metastatic treatment[9-11]. Further investigation is needed regarding the indication for LM, which is typically at the discretion of the surgeon. Histologic grade and tumor subtype are recognized as key prognostic factors, with Callegaro *et al.* demonstrating several nomograms predicting 5- and 10-year survival based on histologic subtype[12]. With over 70 histologic subtypes, prognosis and outcomes in STS remain highly variable[13].

Utilizing a large population-based registry to understand better the risk factors of lung metastases can help further the literature in evaluating patients with lung metastases and the appropriateness of metastasectomy in the light of their diagnosis and prognosis. To drive toward this goal, we focused on the factors associated with metastasis presentation to further understand management. Furthermore, relating the factors in common with lung metastases at presentation and statistically significant in disease specific survival to better characterize the factors involved. Beyond identifying metastatic factors, understanding lung metastatic disease versus other locations of metastases at diagnosis is crucial to the diagnostic and treatment process. While the lung is the most common site of STS metastasis, brain, bone, lymph node, and liver are reported. Identifying risk factors for lung metastasis and other locations of metastasis can aid clinicians in discussing population-based prognoses with patients.

Utilizing the Surveillance, Epidemiology, and End Result (SEER) database, we investigated (1) risk factors associated with lung metastases at diagnosis; (2) the impact of these factors on overall survival; and (3) the impact of various metastatic sites on survival.

METHODS

Utilizing the Surveillance, Epidemiology, and End Result (SEER) database, patient data were collected from 2010 to 2018. We utilized SEER Research Plus Data to include additional information on treatment and patient outcomes.

The inclusion criteria were: (1) histologically confirmed STS; (2) location in the lower limb, upper limb, or pelvis; and (3) classification as a primary malignancy. Our initial search retrieved 28,743 patients with STS

localized to the extremities or pelvis. A total of 14,223 patients (49.5%) were excluded due to missing metastatic data at diagnosis. Ultimately, 14,520 patients with STS were considered in the final analysis.

Patient demographics including age, sex, race, and age of diagnosis were collected. Oncologic information including primary tumor location, primary tumor size, histopathology, survival, cause of death, grade, tumor size, AJCC staging (8th edition), type of surgical intervention, and metastatic data were retrieved. For tumor grade, the 4-grading system described in the AJCC 7th edition was used. The 3-grade system implemented in the 8th edition was only available from 2017 onwards and would have significantly decreased the sample size of our target population. Due to database limitations, only metastatic disease at presentation can be assessed. Furthermore, assessment of metastatic location was restricted to the lung, bone, liver, brain, and distant lymph node (LN). Any additional sites were displayed in the database as "other sites".

Statistical analysis

Demographic and clinical characteristics were analyzed with descriptive statistics. For continuous variables with a non-normal distribution, median values and interquartile ranges (IQR) were displayed. The normality of data distribution was assessed using the Shapiro-Wilk test. Due to non-normal distribution, continuous variables were assessed using the Mann-Whitney U test if there were only two groups, and the Kruskal-Wallis test if there were three or more groups. For categorical variables, differences between groups were assessed using the chi-square test. Univariable logistic regression was performed to identify potential risk factors for metastatic disease at presentation. Multivariable (adjusted) analysis was additionally performed to correct the model for collinearity and confounding factors. Overall survival, 1-year, 2-year, and 5-year survival were calculated with Kaplan-Meier techniques. Differences in survival rates were compared using Log-rank analysis. Statistical analysis was performed using Stata software (StataCorp LLC, Texas, USA).

RESULTS

Baseline characteristics of STS patients with lung metastasis

We found that 7.9% (1,148/14,520) of patients with STS had lung metastases at diagnosis. Median age at diagnosis and sex distribution was similar between groups [Table 1]. Tumors were more frequently located in the pelvis in the metastatic group than in the non-metastatic group (27.5% *vs.* 16.6%; $P < 0.001$). Patients with lung metastases also had a higher rate of lymph node involvement (17.5%) compared to those without (3.8%). Median survival was 8 months among patients with lung metastasis, compared to 32 months for those without lung metastasis ($P < 0.001$).

The most common histologies that presented with lung metastasis were undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma, rhabdomyosarcoma, and synovial cell sarcoma [Figure 1A]. These tumors accounted for the highest absolute number of cases with lung metastasis at diagnosis, with the incidence order generally following this pattern, except that rhabdomyosarcoma had more cases with lung metastases than leiomyosarcoma. The demographic and clinical characteristics of the six most common histologic subtypes are presented in Table 2.

We performed a subanalysis assessing patients presenting with lung metastasis at diagnosis by tumor subtype [Figure 1B]. Alveolar soft part sarcoma (ASPS), small cell sarcoma, and desmoid small round cell tumor (DSRCT) all exhibited lung metastasis rates above 15%.

Table 1. Baseline characteristics of patients with STS by lung metastatic status

	No lung metastasis (*n* = 13,372)	Lung metastasis (*n* = 1,148)	*P*-value
Age [+]	60 (45, 72)	59.5 (41, 70)	0.006
Sex			0.16
Male	7400 (55.3%)	660 (57.5%)	
Female	5972 (44.7%)	488 (42.5%)	
Race			< 0.001
White	10509 (79.6%)	867 (75.7%)	
Black	1490 (11.3%)	180 (15.7%)	
Asian/Pacific Islander	1113 (8.4%)	94 (8.2%)	
American Indian/Alaska Native	93 (0.7%)	5 (0.4%)	
Location			< 0.001
Lower limb	8180 (61.2%)	675 (58.8%)	
Upper limb	2967 (22.2%)	157 (13.7%)	
Pelvis	2225 (16.6%)	316 (27.5%)	
T score			< 0.001
T1	3948 (32.8%)	102 (10.4%)	
T2	3795 (31.6%)	308 (31.5%)	
T3	2122 (17.7%)	272 (27.8%)	
T4	2154 (17.9%)	297 (30.3%)	
N score			< 0.001
N0	12200 (96.6%)	834 (82.5%)	
N1	427 (3.4%)	177 (17.5%)	
Histologic grade			< 0.001
1	1938 (21.1%)	10 (1.5%)	
2	1793 (19.5%)	58 (8.6%)	
3	2023 (22.0%)	196 (29.2%)	
4	3440 (37.4%)	407 (60.7%)	
Survival (months) [+]	32 (13, 62)	8 (3, 20)	< 0.001

[+]Values displayed in these rows refer to the median and interquartile range. STS: soft tissue sarcoma.

Risk factors for presenting lung metastasis at diagnosis

We conducted univariable and multivariable analyses to determine risk factors for presenting lung metastases at diagnosis. On univariable analysis, race, tumor location, grade, T score, N score, and tumor histology impacted the risk of presenting with lung metastasis at diagnosis [Table 3].

On multivariable analysis, the location of the primary tumor in the upper limb was a protective factor from being concurrently diagnosed with lung metastases (OR = 0.70, $P = 0.03$) [Table 3]. Higher histologic grade was associated with an increased risk of lung metastasis at diagnosis as well. Higher T scores were also associated with an increased risk of presenting with lung metastasis. Compared with a T1 score, the risk was 2.6 times greater for T2 ($P < 0.001$), 4.96 times for T3 ($P < 0.001$), and 6.06 times for T4 ($P < 0.001$). Patients with regional LN involvement (N1 score) had a 4.32 times higher risk of presenting lung metastasis at diagnosis ($P < 0.001$). Patients with leiomyosarcoma (OR = 0.15) and synovial sarcoma (OR = 0.44) were less likely to present with lung metastasis compared with undifferentiated pleomorphic sarcoma.

Survival by tumor histology

Disease-specific survival (DSS) was assessed in patients without metastatic disease and those with lung metastasis. In the absence of metastatic disease, two-year DSS for all tumor subtypes was near 75%

Table 2. Baseline characteristics of patients with STS presenting with lung metastasis by histologic subtype

	UPS (*n* = 241)	Leiomyosarcoma (*n* = 178)	Rhabdomyosarcoma (*n* = 102)	Synovial sarcoma (*n* = 99)	Spindle cell sarcoma (*n* = 84)	Liposarcoma (*n* = 57)	*P*-value
Age [+]	64 (54, 75)	65 (56, 73)	34.5 (12, 62)	39 (26, 56)	63.5 (53.5, 72)	62 (45, 75)	< 0.001
Sex							< 0.001
Male	152 (63.1%)	75 (42.1%)	66 (64.7%)	59 (59.6%)	42 (50.0%)	43 (75.4%)	
Female	89 (36.9%)	103 (57.9%)	36 (35.3%)	40 (40.4%)	42 (50.0%)	14 (24.6%)	
Race							0.10
White	189 (78.8%)	137 (77.0%)	76 (74.5%)	76 (76.8%)	66 (78.6%)	43 (75.4%)	
Black	37 (15.4%)	27 (15.2%)	19 (18.6%)	14 (14.1%)	11 (13.1%)	9 (15.8%)	
Asian/Pacific Islander	14 (5.8%)	13 (7.3%)	7 (6.9%)	8 (8.1%)	7 (8.3%)	5 (8.8%)	
American Indian/Alaska Native	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	
Location							< 0.001
Lower limb	165 (68.5%)	85 (47.8%)	41 (40.2%)	72 (72.7%)	43 (51.2%)	40 (70.2%)	
Upper limb	31 (12.9%)	15 (8.4%)	16 (15.7%)	15 (15.2%)	17 (20.2%)	7 (12.3%)	
Pelvis	45 (18.7%)	78 (43.8%)	45 (44.1%)	12 (12.1%)	24 (28.6%)	10 (17.5%)	
T score							< 0.001
T1	20 (9.4%)	19 (12.1%)	10 (12.2%)	7 (7.7%)	9 (13.2%)	3 (5.9%)	
T2	55 (25.9%)	46 (29.3%)	40 (48.8%)	26 (28.6%)	17 (25.0%)	11 (21.6%)	
T3	60 (28.3%)	45 (28.7%)	21 (25.6%)	31 (34.1%)	17 (25.0%)	10 (19.6%)	
T4	77 (36.3%)	47 (29.9%)	11 (13.4%)	27 (29.7%)	25 (36.8%)	27 (52.9%)	
N score							< 0.001
N0	185 (84.1%)	148 (88.1%)	53 (61.6%)	74 (83.1%)	64 (86.5%)	47 (92.2%)	
N1	35 (15.9%)	20 (11.9%)	33 (38.4%)	15 (16.9%)	10 (13.5%)	4 (7.8%)	
Histologic grade							< 0.001
1	1 (0.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	3 (8.8%)	
2	2 (1.1%)	18 (16.2%)	1 (3.3%)	5 (9.1%)	5 (8.9%)	1 (2.9%)	
3	32 (17.9%)	34 (30.6%)	8 (26.7%)	33 (60.0%)	21 (37.5%)	8 (23.5%)	
4	144 (80.4%)	58 (52.3%)	21 (70.0%)	17 (30.9%)	29 (51.8%)	22 (64.7%)	
Survival (months) [+]	7 (2, 17)	12 (5, 26)	11.5 (3, 20)	15 (5, 23)	7 (3, 18)	7 (2, 14)	< 0.001

[+]Values displayed in these rows refer to the median and interquartile range. STS: soft tissue sarcoma; UPS: undifferentiated pleomorphic sarcoma.

[Figure 2A]. In patients with metastatic lung disease, two-year DSS was slightly above 25% [Figure 2B]. Differences in outcomes were greater in the long term. Five-year survival was below 25% in all patients with lung metastasis, while 10-year survival for those without lung metastases ranged between 50 and 75%.

Table 3. Risk factors for presenting lung metastasis at diagnosis in patients with STS

	Univariable		Multivariable	
	OR (95%CI)	***P*-value**	**OR (95%CI)**	***P*-value**
Age ≥ 60 years	0.96 (0.85-1.08)	0.48	-	-
Female sex	0.92 (0.81-1.03)	0.16	-	-
Race				
Black	1.46 (1.24-1.73)	< 0.001	1.16 (0.84-1.59)	0.37
Asian/Pacific Islander	1.02 (0.82-1.28)	0.84	0.82 (0.53-1.26)	0.37
American Indian/Alaska Native	0.65 (0.26-1.61)	0.35	0.29 (0.04-2.22)	0.24
Location (BL: Lower limb)				
Upper limb	0.64 (0.54-0.77)	< 0.001	0.70 (0.50-0.97)	0.03
Pelvis	1.72 (1.49-1.98)	< 0.001	1.14 (0.86-1.5)	0.36
Histologic grade (BL: 1)				
2	6.27 (3.19-12.3)	< 0.001	4.77 (1.61-14.14)	0.01
3	18.78 (9.92-35.55)	< 0.001	13 (4.6-36.77)	< 0.001
4	22.93 (12.21-43.04)	< 0.001	16.16 (5.74-45.51)	< 0.001
T score (BL: T1)				
T2	3.14 (2.5-3.95)	< 0.001	2.60 (1.76-3.83)	< 0.001
T3	4.96 (3.93-6.27)	< 0.001	4.96 (3.35-7.36)	< 0.001
T4	5.34 (4.24-6.72)	< 0.001	6.06 (4.07-9.03)	< 0.001
N score (BL: N0)				
N1	6.06 (5.02-7.32)	< 0.001	4.34 (3.02-6.23)	< 0.001
First malignant tumor	0.9 (0.77-1.05)	0.18	-	-
Histologic type (BL: UPS)				
Leiomyosarcoma	1.19 (0.97-1.45)	0.10	0.15 (0.09-0.23)	< 0.001
Liposarcoma	0.18 (0.13-0.24)	< 0.001	0.66 (0.39-1.11)	0.12
Rhabdomyosarcoma	2.61 (2.02-3.36)	< 0.001	0.88 (0.59-1.31)	0.54
Spindle cell sarcoma	1.63 (1.25-2.13)	< 0.001	1.32 (0.88-1.98)	0.18
Synovial sarcoma	1.53 (1.19-1.96)	0.001	0.44 (0.33-0.59)	< 0.001

BL: baseline; CI: confidence interval; OR: odds ratio; UPS: undifferentiated pleomorphic sarcoma.

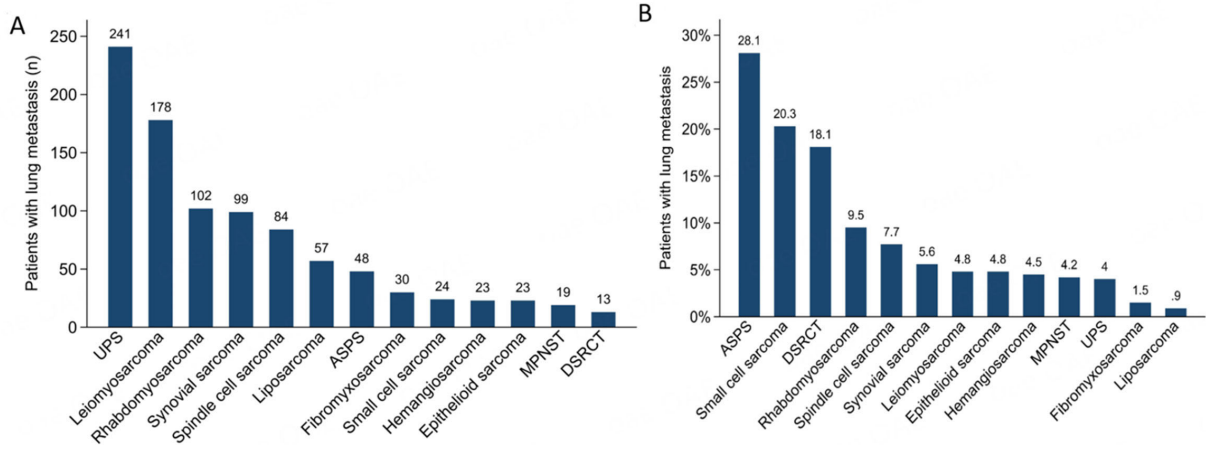

Figure 1. (A) Total count, and (B) percent of all patients with soft tissue sarcoma presenting with lung metastasis at diagnosis. ASPS: alveolar soft part sarcoma; DSRCT: desmoplastic small round cell tumor; MPNST: malignant peripheral nerve sheath tumor; UPS: undifferentiated pleomorphic sarcoma.

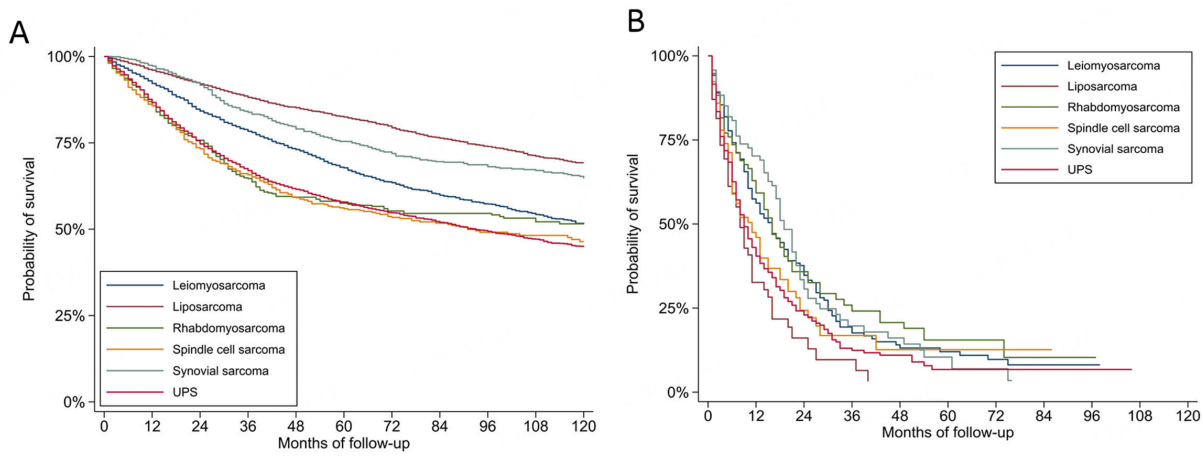

Figure 2. Disease-specific survival of patients with soft tissue sarcoma (A) without and (B) with lung metastasis at the time of diagnosis. UPS: undifferentiated pleomorphic sarcoma.

Survival by metastatic distribution

An analysis was also conducted evaluating the survival of patients with only lung metastasis and those with metastasis to the lung and other site(s). We additionally compared the impact of certain lung metastatic patterns on patient DSS. Our study showed that patients with only lung metastasis had higher DSS than those with metastasis to the lungs and other sites [Figure 3A]. Furthermore, we observed significant differences in survival between patients with only lung metastasis and those with metastases to the lungs and liver, lungs and bone, and lungs, liver, and bones [Figure 3B]. We performed a similar analysis for patients with a diagnosis of UPS [Figure 4A] and those with a diagnosis of leiomyosarcoma [Figure 4B].

DISCUSSION

The univariable and multivariable analyses highlighted the significance of primary tumors located in the upper extremity in relation to lung metastases. Although one study found that upper extremity STS had worse outcomes[14], our analysis suggests that an upper extremity location may actually reduce the risk of lung metastases. We hypothesize that the subcutaneous location of upper extremity STS enables earlier detection, which may confer a protective effect by preventing the progression to lung metastases. This would contrast with the above study, which captures the higher frequency of positive margins and less radiotherapy use.

As expected, a higher histologic grade at STS diagnosis was associated with poorer prognosis and an increased likelihood of lung metastases. With the implementation of the AJCC 8th edition in 2018, patients recorded in the database until 2017 were staged according to the AJCC 7th edition[15]. Under this staging, patients with grade III or IV disease showed a higher likelihood of lung metastases, with aggressive histologic features linked to increased metastatic risk. Welter *et al.* evaluated the prognostic effect of histologic grade in STS patients with lung metastases, finding that a higher metastatic volume (> 35 mm) correlated with histologic aggression and predicted poorer outcomes[16]. Additionally, the largest pulmonary metastasis diameter is recognized in multiple studies as a risk factor for poor prognosis[17,18]. The authors noted that histologic behavior correlated with risk of local recurrence[19] and incidence of pulmonary metastases[4]. Our findings support the relationship between more aggressive histology and worse outcomes and lung metastatic disease.

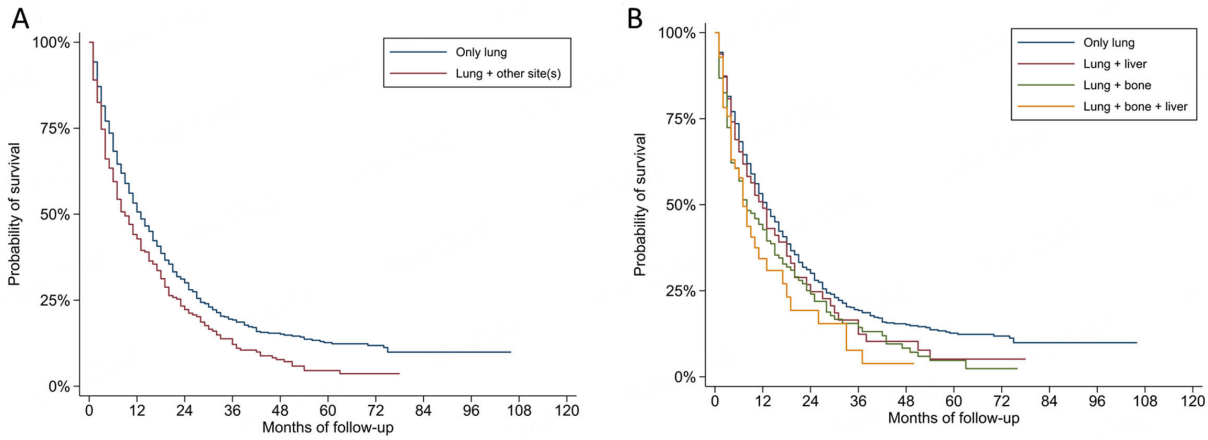

Figure 3. Disease-specific survival of patients with soft tissue sarcoma by (A) extent of metastatic involvement, and (B) metastatic pattern at the time of diagnosis.

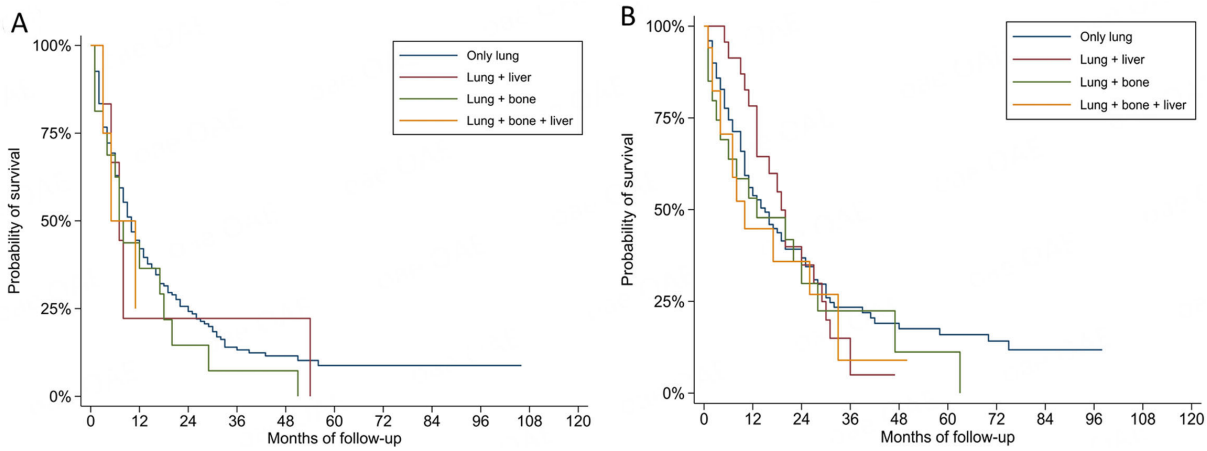

Figure 4. Disease-specific survival by metastatic pattern at the time of diagnosis in patients with (A) undifferentiated pleomorphic sarcoma, and (B) leiomyosarcoma.

With the AJCC 8th edition data, T scores from 2 to 4 were associated with a higher risk of metastatic disease, reflecting either a longer period from tumor growth to diagnosis or a more aggressive histology predisposing to metastatic spread. The N score was also separately evaluated in the 8th edition group, which, on multivariate analysis, showed a more than fourfold increase in risk for lung metastases. A study by Pfannschmidt *et al.* described 69 STS patients with lung metastases, which found that 23.2% had nodal involvement, illustrating the relationship between nodal and lung involvement[20]. Patients with N1 involvement had a mean survival of 32.7 months, while those with N0 had 63.9 months, highlighting that nodal involvement correlates with poorer prognosis and metastatic disease[20]. Additionally, a separate study found that while nodal disease worsened outcomes, lymphadenectomy did not improve survival, suggesting that histologic subtype or other factors influence prognosis than nodal lymphadectomy[21].

Histologically, the most common tumors metastasizing to the lung were UPS, leiomyosarcoma, rhabdomyosarcoma, and synovial sarcoma. In contrast, ADPS, small cell sarcoma, DSRCT, rhabdomyosarcoma, and spindle cell sarcoma were most likely to present with lung metastases, suggesting that histologic behavior contributes to the likelihood of lung metastases. While it is challenging to extract

detailed information beyond histologic diagnosis, such as microscopic infiltration or mitotic activity, Sawamura *et al.* found that patients with non-rhabdomyosarcoma histologies had better overall survival compared to those with rhabdomyosarcoma[21]. Additionally, a study by the French sarcoma group noted that survival outcomes have evolved with the advent of targeted therapies for different STS subtypes[22]. Nevertheless, survival rates still vary significantly by histologic subtype, with worse overall survival observed for UPS, MPNST, and rhabdomyosarcoma compared to leiomyosarcoma.

Metastatic burden and overall survival

We found that patients with isolated lung metastases had better overall survival compared to those with metastases to the lung and liver, lung and bone, or lung, bone, and liver. Since lung metastases are the most common site of spread in STS, metastases in other locations indicate more extensive disease. This aligns with the concept that less aggressive or earlier diagnosed and treated disease is associated with better survival. Several studies have shown that metastatic disease at diagnosis correlates with poorer survival[22-25]. Factors that improve survival in STS with metastatic disease include resection of metastases, a disease-free interval greater than 1 year, and fewer than four metastases[26-29].

With the understanding of the distribution of metastases based on histology, there appears to be a consideration for staging systems for lung metastases, initially introduced in 1998 by Pastorino *et al.*[9] and then further discussed in 2016[10] and 2021[11].

Limitations

Our study presented several limitations, primarily due to the nature of the SEER database. First, analysis of metastatic disease was restricted to metastases detected at diagnosis. As most metastases present in the course of the disease, our findings cannot be generalized to all patients with metastatic STS. Second, analysis of metastases by location was limited to the sites included in the database: lung, liver, brain, bone, and distant LN. Third, there was no available information on the chemotherapy and/or radiotherapy treatment plans and the intent (curative *vs.* palliative) of therapy. Fourth, as the variable "surgery at the distant site" did not specify the exact surgical location in patients with multiorgan metastatic disease, the site of surgery could not be confirmed.

CONCLUSIONS

In conclusion, our study identifies key factors influencing the likelihood of lung metastasis in soft tissue sarcoma (STS) and their impact on survival. Tumor location, histologic grade, and lymph node involvement were significant predictors of lung metastasis, with upper extremity tumors showing a protective effect. Aggressive histology and higher T and N scores correlated with a higher risk of lung metastasis and worse survival outcomes. Patients with isolated lung metastasis had better survival compared to those with metastases to multiple sites, highlighting the importance of metastatic burden in prognosis. These findings emphasize the value of early detection and personalized treatment strategies for metastatic STS. Additionally, the discussion of metastasis treatment is valuable, further suggesting the need for continued investigation into metastatic disease prognosis.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed review and editing: Lozano-Calderon SA

Made substantial contributions to the conception and design, performed data acquisition, as well as providing statistical and editing support, and manuscript writing: Gonzalez MR

Made substantial contributions to the conception and design, manuscript writing, and editing: Rizk PA, Hodo TW

Availability of data and materials

Data were all acquired from the SEER Database.

Financial support and sponsorship

None.

Conflicts of interest

Santiago A. Lozano-Calderon is a Junior Editorial Board member of Journal of Cancer Metastasis and Treatment. Santiago A. Lozano-Calderon was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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