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Clinical Features and Prognosis of Patients with Soft Tissue Sarcoma in Extremity and Synchronous Lung Metastasis: A SEER Analysis

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ABSTRACT

Purpose: The aim of this study was to elucidate the relationship between clinical characteristics and risk of synchronous lung metastasis (SLM) in patients with extremity soft tissue sarcomas (ESTSLM) at the time of diagnosis and their prognosis.

Methods: Cases from 1975-2018 were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database and demographic, treatments and survival outcomes were analysed.

Results: 533 of 7533 patients included in the analysis had SLM. Risk of lung metastasis was high with several variables including male gender, young age, white race, primary site in lower extremity or deep tissues, high differentiation grade, large tumor size, Ewing's sarcoma, rhabdomyosarcoma, and nodal metastasis. The 5-year cancer-specific survival (CSS) rate and median survival of ESTSLM patients was 22.4% and 14 months, respectively. Multivariate analysis showed that older adults, lack of primary site surgery and chemotherapy, and multi-site metastasis including the lungs, were risk factors ($p < 0.05$). Whereas chemotherapy improved short-term survival compared to survival without chemotherapy (2-year CSS rates of 36.2% vs 26.1%, $p < 0.001$), there were no survival benefits with metastasectomy (OS, $p = 0.286$; CSS, $p = 0.627$).

Conclusions: This is the first comprehensive study that unraveled lung risk factors and prognostic factors affecting metastasis in ESTSLM patients. The findings of this study may be useful for screening and management of patients with ESTSLM.

INTRODUCTION

Soft tissue sarcomas (STS) are a rare and histologically heterogeneous group of cancers with an overall malignancy incidence of 0.72% Siegel et al. (2019). Compared to other common cancers, STS originate from almost any anatomic site Mastrangelo et al. (2012), but are biased towards the extremities, which comprise ~ 40% of the overall primary sites Hui et al. (2016). Compared to viscera and retroperitoneum, the prognosis is good for localized extremity soft tissue sarcomas (ESTS) with a 5-year overall survival (OS) rate of 68% Stiller et al. (2013). Nonetheless, the occurrence of distant metastasis can reduce this to 15% Abaricia et al. (2019) and therefore, despite improvements in multi-modality treatments, distant metastasis remains the major determinant of mortality for ESTS Kane et al. (2002). The lung is the most common metastasis ESTS site initially presented by 20% of ESTS patients or who subsequently develop lung metastasis Gadd et al. (1993)

While there is a probability that ESTS patients have a degree of synchronous lung metastasis (SLM), current studies only focus on metachronous lung metastasis Ferguson et al. (2011). Screening and management of ESTS patients with SLM (ESTSLM) are fraught with inefficiencies Kane et al. (2002) and therefore, it is paramount to characterize the disease for designing better treatment regimens.

The Surveillance, Epidemiology, and End Results (SEER) database of survival data from population-based cancer registries encompass ~28% of the American population with recorded lung metastasis data since 2010. The aim of the current study was to identify the clinical features and prognosis of ESTSLM using SEER analysis to determine disease management and therapeutic approaches.

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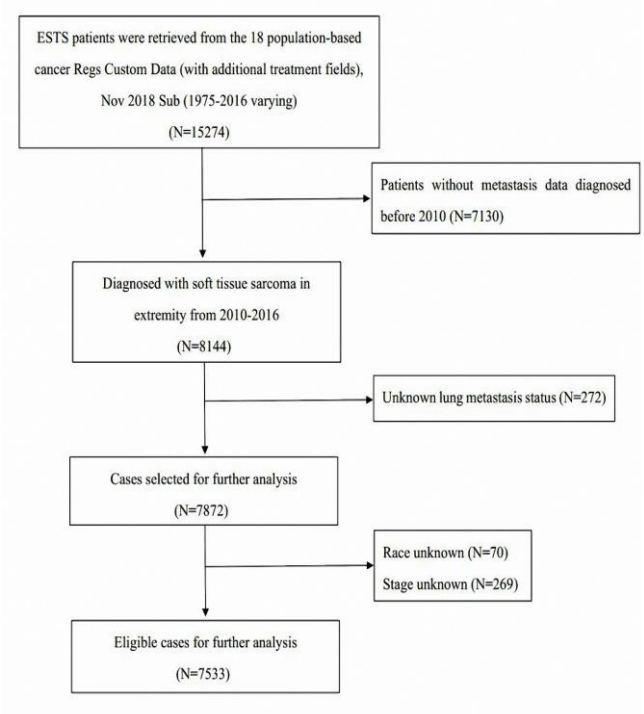
Keywords: Soft tissue sarcoma; synchronous lung metastasis; SEER database; prognosis

MATERIALS AND METHODS

Patient population

This population study used SEER-18 Dataset consisting of 18 cancer registries across the United States. Patients with mediastinal neoplasms diagnosed between 1975 and 2016 as of November 2018 were included in this study. Data were extracted using the SEER*Stat software (version 8.3.6) of National Cancer Institute. Queries were restricted to STS patients diagnosed between 2010 and 2015 because distant metastasis data were recorded during this period. Diagnosed cases were identified by the specific codes of the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) for the following (i) primary sites: C47.1(peripheral nerve and autonomic nerve system: upper limb, shoulder), C47.2(peripheral nerve and autonomic nerve system: lower limb, hip), C49.1(connective subcutaneous and other soft tissue: upper limb and shoulder) and C49.2(connective subcutaneous and other soft tissue: lower limb, hip shoulder); (ii) ICD-O-3 histology/behavior types labeled with sarcoma, not otherwise specified (8800/3), undifferentiated polymorphic sarcoma (8802/3, 8805/3, 8830/3), fibrosarcoma (8810-11/3, 8814-15/3, 8825/3, 8840/3), liposarcoma (8850/3-8858/3), leiomyosarcoma (8890-8891/3, 8893/3, 8896/3), rhabdomyosarcoma (8900-8902/3, 8910/3, 8912/3, 8920-8921/3), synovial sarcoma (9040-9043/3), clear cell sarcoma (9044/3), angiosarcoma (9120/3), osteosarcoma (9180-9181/3, 9186/3, 9192/3), chondrosarcoma (9240/3,9243/3),

Figure 1: Selection flowchart for ESTS patients.



Ewing sarcoma (9260/3), malignant peripheral nerve sheath tumor (9540/3, 9560-9561/3). Cases without confirmation of lung metastasis status, American Joint Committee on Cancer (AJCC, 7th edition) stage, and ethnicity were excluded (Figure 1). Other clinical characteristics abstracted in the study were ethnicity, age at diagnosis, sex, anatomic site, histologic type, histologic grade, AJCC Tumor-Nodes-Metastasis (TNM) 7th stage, tumor size, lymph node and distant metastasis (lung, bone, liver and brain) at the time of diagnosis, surgery, chemotherapy, radiation therapy, SEER cancer-specific death classification, and survival time. Age at diagnosis was categorized into three groups as previously described9: children (0-14 years old), adolescent and young adult (YAY, 15-39 years old), old adult (OA, ≥40 years old). Tumor size was categorized into four groups: ≦5 cm, 5-10 cm, 10-15 cm, >15cm. Anatomic depth was categorized into two groups, superficial and deep, according to the T stage.

Statistical analysis

Student's t test was used to compare continous variables and Chi-square test for categorical variables. Overall survival (OS) was the period from diagnosis to death or last follow-up, while cancer-specific survival (CSS) was the period between diagnosis and death due to STS or until the last follow-up. Death caused by sarcomas was defined as the event and death related to other causes was the censored observation. Log-rank test and Kaplan-Meier plots were implemented for determining the survival difference of variables. Cox proportional hazards model was used for identifying risk factors of prognosis and included univariate and multivariate analyses, with hazard ratio (HR) and 95% confidence intervals (CI). All statistical analyses were performed using SPSS version 23.0 (IBM Inc. Chicago, IL, USA). A two-tailed P value less than 0.05 was considered as statistically significant.

RESULTS

A total of 7,533 ESTS cases of which 728 (9.66%) had distant metastasis at the time of diagnosis was selected and analyzed. Among those with metastasis, 533 (7.1%) had lung metastasis, accounting for the largest proportion (73.2%). Liposarcoma was the most common sarcoma that accounted for 24.4% of the total ESTS, followed by undifferentiated pleomorphic sarcoma (UPS)/malignant fibrous histiocytoma (MFH) (21.7%), and fibrosarcoma (12.6%).

SLM reflected worse 5-year OS and CSS rates (Figure 2) with risk factors being male gender ($p = 0.003$), 0-14 years old ($p = 0.003$), Black/African-American ($p = 0.02$), primary site in lower extremity ($p < 0.001$), anatomically deep primary site ($p < 0.001$), high grade differentiation ($p < 0.001$), large tumor size ($p < 0.001$), and positive nodal metastasis ($p < 0.001$) (Table 1).

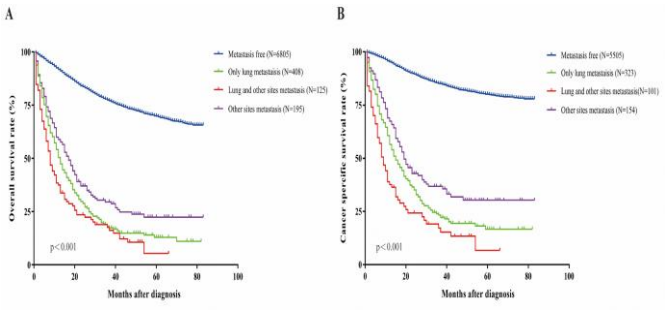
Table 1: Clinical characteristics and lung metastasis associated risk factors at the time of diagnosis of ESTS patients in SEER database.

Features	Non-lung metastasis N (%) 7000 (92.7)	Lung metastasis N (%) 533 (7.3)	All N (%) 7553 (100)	p
Gender	-	-	-	**0.003**
Male	3823(92.1)	326(7.9)	4149(55.1)	-
Female	3177(93.9)	207(6.1)	3384(44.9)	-
Age at diagnosis (years)	-	-	-	**0.003**
0-14	205(89.1)	25(10.9)	230(3.1)	-
15-39	1043(91.3)	100(8.7)	1143(15.2)	-
≥40	5752(93.4)	408(6.6)	6160(81.8)	-
Ethnicity	-	-	-	**0.02**
Caucasian	5668(93.4)	403(6.6)	6071(80.6)	-
African-American	727(90.0)	81(10.0)	808(10.7)	-
Asian	605(92.5)	49(7.5)	654(8.7)	-
Anatomic site	-	-	-	**<0.001**
Soft tissue, lower extremity	5205(92.6)	434(7.4)	5639(74.7)	-
Soft tissue, upper extremity	1795(95.1)	99(4.9)	1894(25.3)	-
Anatomic depth	-	-	-	**<0.001**
Superficial	1168(96.4)	43(3.6)	1211(16.1)	-
Deep	2988(90.2)	325(9.8)	3313(44.0)	-
Missing	2844(94.5)	165(5.5)	3009(39.9)	-
Histologic type	-	-	-	**<0.001**
Sarcoma, NOS	828(86.3)	131(13.7)	959(12.7)	-
UPS/MFH	1511(92.2)	127(7.8)	1638(21.7)	-
Fibrosarcoma	916(96.4)	34(3.6)	950(12.6)	-
Liposarcoma	1813(98.6)	25(1.4)	1838(24.4)	-
Leiomyosarcoma	792(92.4)	65(7.6)	857(11.4)	-
Rhabdomyosarcoma	169(84.9)	30(15.1)	199(2.6)	-
Synovial sarcoma	433(87.8)	60(12.2)	493(6.5)	-
Clear cell sarcoma	60(92.3)	5(7.7)	65(0.9)	-
Angiosarcoma	156(90.2)	17(9.8)	173(2.3)	-
Extra skeletal osteosarcoma	47(87.0)	7(13.0)	54(0.7)	-

Extra skeletal	15(100.0)	0	15(0.2)	-
Chrondrosarcoma	-	-	-	-
Ewing sarcoma	51(78.5)	14(21.5)	65(0.9)	-
MPNST	209(92.1)	18(7.9)	227(3.0)	-
Grade	-	-	-	**<0.001**
Well	1176(99.4)	7(0.6)	1183(15.7)	-
Moderate	1085(97.1)	32(2.9)	1117(14.8)	-
Poor	1240(90.9)	124(9.1)	1364(18.1)	-
Undifferentiated	2067(90.2)	225(9.8)	2292(30.4)	-
Unknown	1432(90.8)	145(9.2)	1577(20.9)	-
Tumor size (cm)	-	-	-	**<0.001**
0-5	2180(97.9)	46(2.1)	2226(29.5)	-
5-10	2024(93.8)	134(6.2)	2158(28.6)	-
10-15	1098(88.9)	137(11.1)	1235(16.4)	-
>15	1299(90.2)	141(9.8)	1440(19.1)	-
Unknown	399(84.2)	75(15.8)	474(6.3)	-
Nodal metastasis	-	-	-	**<0.001**
Yes	191(70.0)	82(30.0)	273(3.6)	-
No	6794(94.5)	394(5.5)	7188(95.4)	-
Unknown	15(0.2)	57(10.7)	72(1.0)	-
Bone metastasis	-	-	-	**<0.001**
Yes	86(50.3)	85(49.7)	171(2.2)	-
No	6913(94.2)	441(5.8)	7354(97.6)	-
Unknown	1(12.5)	7(87.5)	8(0.1)	-
Brain metastasis	-	-	-	-
Yes	7(50.0)	7(50.0)	14(0.2)	**<0.001**
No	6993(93.1)	518(6.9)	7511(99.7)	-
Unknown	0	8(100)	8(0.1)	-
Liver metastasis	-	-	-	**<0.001**
Yes	24(37.5)	40(62.5)	64(0.8)	-
No	6976(93.5)	486(6.5)	7462(99.1)	-
Unknown	0	7(1.3)	7(0.1)	-

MFH, malignant fibrous histocytomaUPS, undifferentiated pleomorphic sarcomaMPNST, malignant peripheral nerve sheath sarcoma

Figure 2: Kaplan-Meier analysis of OS and CSS of ESTS patients.



A 5-year OS rates of patients with metastasis free, only lung metastasis, lung with other sites metastasis, and other sites metastasis were 69.9%, 12.9%, 5.3% and 22.3%, respectively ($p < 0.001$). B 5-year CSS rates of patients with metastasis free, only lung metastasis, lung with other sites metastasis, and other sites metastasis were 80.1%, 16.7%, 6.7% and 30.3%, respectively ($p < 0.001$).

Whereas liposarcoma, the most common ESTS, had the lowest pulmonary metastasis rate (1.4%, $p < 0.001$), Ewing sarcoma showed the highest (21.5%, $p < 0.001$). The most common site of metastasis concurrent with pulmonary metastasis was the bone ($p < 0.001$). Whereas lung metastasis comprised 73.2% of ESTS patients with synchronous metastasis, lymph node metastasis accounted for only 3.6%, and among these positive cases, 30% showed lung metastasis. Concurrent lung metastasis developed in 48.6% of bone, 50% brain, and 62.5% liver metastasis patients.

The risk of lung metastasis with high-grade sarcoma was 15-fold higher than that of low-grade sarcoma and tumor size larger than 10 cm showed a 5-fold increased risk of lung metastasis than tumors measuring 0-5 cm. While 81.8% of ESTS patients were OA (≥ 40 years old), lung metastasis rates were higher in children (10.9%) and YAY (8.7%) than OA (6.6%). Lung metastasis rate in males (7.9%) was higher compared to females (6.1%) and African-American patients had the highest lung metastasis rate (10%). Increased blood supply indicate higher lung metastasis risk, which was 1.5-fold higher in lower limbs compared to upper limbs and ESTS in deep sites was 3-fold higher than in superficial sites.

Univariate analysis showed race, age, histologic type, anatomic site, depth, differentiation grade, size, nodal metastasis, distant metastasis, surgery, radiotherapy, and chemotherapy to have a significant ($p < 0.05$) influence on prognosis of ESTS (Table 2). Multivariate analysis identified several independent prognostic factors including ages 0-14 years (HR: 0.278, 95% CI: 0.190–0.405, $p < 0.001$), age 15-39 years (HR: 0.514, 95% CI: 0.431–0.614, $p < 0.001$), UPS/MFH (HR: 2.252, 95% CI: 1.786-2.839, $p < 0.001$), fibrosarcoma (HR: 1.511, 95% CI: 1.206-1.893, $p < 0.001$), leiomyosarcoma (HR: 1.411, 95% CI: 1.084-1.837, $p = 0.011$), rhabdomyosarcoma (HR: 2.621, 95% CI: 1.889-3.638, $p < 0.001$), synovial sarcoma (HR: 1.667, 95% CI: 1.253-2.218, $p = 0.001$), clear cell sarcoma (HR: 4.953, 95% CI: 3.034-8.088, $p < 0.001$), angiosarcoma (HR: 4.179, 95% CI: 3.027-5.770, $p < 0.001$), MPNST (HR:2.822, 95% CI: 2.048-3.888, $p < 0.001$), superficial sites (HR:0.667, 95% CI: 0.553-0.805, $p < 0.001$), moderate differentiation (HR: 6.279, 95% CI: 3.692-10.680, $p < 0.001$), poor differentiation (HR: 14.895, 95% CI: 8.915-24.886, $p < 0.001$), undifferentiated (HR: 13.612, 95% CI: 8.163-22.700, $p < 0.001$), tumor size 5-10 cm (HR: 1.651, 95% CI: 1.1.360-2.004, $p < 0.001$), tumor size 10-15 cm (HR:2.103, 95% CI: 1.703-2.596, $p < 0.001$), tumor size > 15 cm (HR: 3.242, 95% CI: 2.645-3.974, $p < 0.001$), nodal metastasis (HR:1.490, 95% CI: 1.220-1.820, $p < 0.001$), metastasis free (HR: 0.231, 95% CI: 0.194-0.275, $p < 0.001$), lung and other sites metastasis (HR: 1.367, 95% CI: 1.048-1.784, $p = 0.021$), surgery (HR:0.372, 95% CI: 0.315-0.440, $p < 0.001$), and chemotherapy (HR: 0.814, 95% CI: 0.708-0.936, $p = 0.004$).

The median CSS of ESTSLM patients was 14 months. Univariate analysis showed age, histologic types, metastasis to other sites, surgery, radiotherapy, and chemotherapy to have a significant ($p < 0.05$) influence on prognosis of ESTSLM. Mutivariate analysis identified several independent prognostic factors including age 0-14 years (HR: 0.275, 95% CI: 0.134-0.563, $p < 0.001$), age 15-39 years old (HR: 0.636, 95% CI: 0.471-0.860, $p < 0.003$), metastasis to sites besides lung (HR: 1.426, 95% CI: 1.076-1.889, $p = 0.013$), chemotherapy (HR: 0.549, 95% CI: 0.428-0.704, $p < 0.001$), and primary site surgery (HR: 0.517, 95% CI: 0.395-0.678, $p < 0.001$) (Table 3).

Analysis of the therapeutic value of specific interventions in ESTSLM patients using Kaplan-Meier survival curves showed a 5-year CSS rate of 18.7% for patients with primary site surgery, compared to 7.1% without surgery (Figure 3).

Figure 3: Survival analysis of certain interventions in STSLM patients.

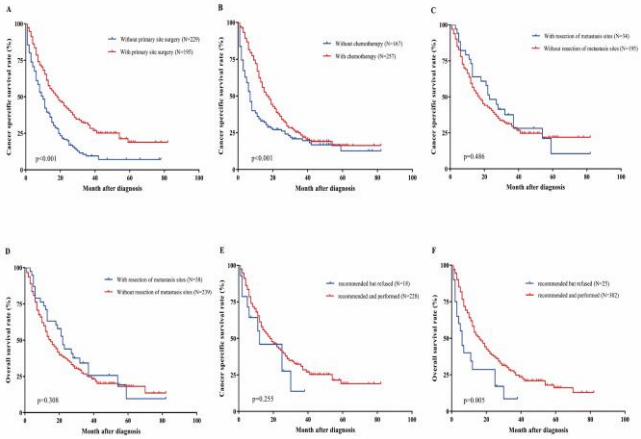


Table 2: Univariate and multivariate analysis of cancer-specific survival for total ESTS patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Gender	-	-	-	-
Female	Reference	-	-	-
Male	1.110(0.973-1.265)	0.119	-	-
Race	-	-	-	-
Asian	Reference	-	Reference	-
African-American	1.377(1.080-1.755)	**0.010**	1.079(0.843-1.380)	0.546
Caucasian	1.005(0.820-1.232)	0.961	1.002(0.816-1.230)	0.985
Age (years)	-	-	-	-
≥40	Reference	-	Reference	-
0-14	0.675(0.480-0.950)	**0.024**	0.278(0.190-0.405)	**<0.001**
15-39	0.702(0.597-0.824)	**<0.001**	0.514(0.431-0.614)	**<0.001**
Histologic type	-	-	-	-
Liposarcoma	Reference	-	Reference	-
UPS/MFH	4.708(3.797-5.837)	**<0.001**	2.252(1.786-2.839)	**<0.001**
Fibrosarcoma	3.555(2.896-4.365)	**<0.001**	1.511(1.206-1.893)	**<0.001**
Sarcoma, NOS	1.327(1.006-1.752)	**0.042**	1.136(0.852-1.514)	0.385
Leiomyosarcoma	2.284(1.781-2.928)	**<0.001**	1.411(1.084-1.837)	**0.011**
Rhabdomyosarcoma	6.873(5.167-9.142)	**<0.001**	2.621(1.889-3.638)	**<0.001**
Synovial sarcoma	2.655(2.038-3.46)	**<0.001**	1.667(1.253-2.218)	**<0.001**
Clear cell sarcoma	4.441(2.772-7.115)	**<0.001**	4.953(3.034-8.088)	**<0.001**
Hemangiosarcoma	8.056(5.917-10.969)	**<0.001**	4.179(3.027-5.770)	**<0.001**
Extra skeletal osteosarcoma	3.912(2.164-7.069)	**<0.001**	1.521(0.821-2.818)	0.183
Extra skeletal chrondrosarcoma	2.452(0.780-7.704)	0.117	1.623(0.511-5.150)	0.411
Ewing sarcoma	3.342(1.957-5.705)	**<0.001**	1.201(0.685-2.106)	0.523
MPNST	4.359(3.202-5.934)	**<0.001**	2.822(2.048-3.888)	**<0.001**
Anatomic Site	-	-	-	-
Upper limb	Reference	-	Reference	-
Lower limb	0.772(0.645-0.925)	**0.005**	1.058(0.916-1.222)	0.44
Anatomic depth	-	**-**	-	-
Deep	Reference	**-**	Reference	-

Superficial	0.396(0.331-0.472)	**<0.001**	0.667(0.553-0.805)	**<0.001**
Missing	NA	NA	NA	NA
Grade	-	-	-	-
Well	Reference	-	Reference	-
Moderate	6.154(3.671-10.316)	**<0.001**	6.279(3.692-10.680)	**<0.001**
Poor	20.751(12.741-33.797)	**<0.001**	14.895(8.915-24.886)	**<0.001**
Undifferentiated	20.427(12.598-33.121)	**<0.001**	13.612(8.163-22.700)	**<0.001**
Unknown	NA	NA	NA	NA
Tumor size(cm)	-	-	-	-
0-5	Reference	-	Reference	-
5-10	2.255(1.875-2.712)	**<0.001**	1.651(1.36-2.004)	**<0.001**
10-15	3.232(2.666-3.918)	**<0.001**	2.103(1.703-2.596)	**<0.001**
Above 15	3.927(3.270-4.715)	**<0.001**	3.242(2.645-3.974)	**<0.001**
Unknown	NA	NA	NA	NA
Nodal metastasis	-	-	-	-
No	Reference	-	Reference	-
Yes	4.813(4.016-5.768)	**<0.001**	1.490(1.220-1.820)	**<0.001**
Unknown	NA	NA	NA	NA
Distant metastasis	-	-	-	-
Lung metastasis	Reference	-	Reference	-
Metastasis free	0.107(0.092-0.124)	**<0.001**	0.231(0.194-0.275)	**<0.001**
Lung and other sites metastasis	1.526(1.186-1.964)	**0.001**	1.367(1.048-1.784)	**0.021**
Other sites metastasis	0.702(0.552-0.894)	**0.004**	0.889(0.686-1.153)	0.376
Primary site surgery	-	-	-	-
No	Reference	-	Reference	-
Resection	0.163(0.144-0.185)	**<0.001**	0.372(0.315-0.440)	**<0.001**
Radiotherapy	-	-	-	-
No	Reference	-	Reference	-
Yes	1.162(1.039-1.300)	**0.009**	0.904(0.789-1.036)	0.147
Chemotherapy	-	-	-	-
No/Unknown	Reference	-	Reference	-
Yes	2.603(2.322-2.918)	**<0.001**	0.838(0.728-0.963)	**0.013**

Table 3: Univariate and multivariate analysis of cancer-specific survival for ESTSLM patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Gender	-	-	-	-
Female	Reference	-	-	-
Male	0.900(0.718-1.128)	0.36	-	-
Race	-	-	-	-
Asian	Reference	-	-	-
African-American	1.077(0.678-1.710)	0.754	-	-
Caucasian	1.028(0.837-1.262)	0.892	-	-
Age (years)	-	-	-	-
≥40	Reference	-	Reference	-
0-14	0.297(0.157-0.560)	<0.001	0.275(0.134-0.563)	<0.001
15-39	0.678(0.518-0.887)	0.005	0.636(0.471-0.860)	0.003
Histologic type	-	-	-	-
MPNST	Reference	-	Reference	-
UPS/MFH	2.276(1.098-4.715)	0.027	0.991(0.456-2.156)	0.982
Fibrosarcoma	1.594(0.766-3.319)	0.212	0.947(0.404-2.221)	0.9
Sarcoma, NOS	1.563(0.692-3.531)	0.283	1.252(0.583-2.685)	0.564
Liposarcoma	2.521(1.054-6.029)	0.038	1.537(0.621-3.806)	0.352
Leiomyosarcoma	1.479(0.684-3.196)	0.32	0.703(0.308-1.609)	0.405
Rhabdomyosarcoma	1.733(0.767-3.917)	0.186	1.558(0.657-3.695)	0.315
Synovial sarcoma	1.387(0.648-2.971)	0.4	1.152(0.525-2.526)	0.725
Clear cell sarcoma	3.975(1.294-12.211)	0.016	2.055(0.642-6.578)	0.225
Angiosarcoma	2.229(0.911-5.455)	0.079	0.986(0.388-2.504)	0.976
Extra skeletal osteosarcoma	0.922(0.244-3.478)	0.905	0.643(0.167-2.478)	0.521
Extra skeletal chrondrosarcoma	NA	NA	-	-
Ewing sarcoma	0.873(0.316-2.409)	0.793	0.795(0.277-2.276)	0.668
Site	-	-	-	-
Upper limb	Reference	-	-	-
Lower limb	0.981(0.735-1.311)	0.898	-	-
Anatomic depth	-	-	-	-
Deep	Reference	-	-	-

Superficial	1.194(0.781-1.826)	0.412	-	-
Missing	NA	NA	-	-
Grade	-	-	-	-
Well	Reference	-	-	-
Moderate	1.63(0.486-5.472)	0.429	-	-
Poor	1.616(0.509-5.133)	0.416	-	-
Undifferentiated	1.574(0.500-4.956)	0.438	-	-
Unknown	NA	NA	-	-
Tumor size(cm)	-	-	-	-
0-5	Reference	-	-	-
5-10	0.973(0.618-1.532)	0.905	-	-
10-15	1.055(0.673-1.655)	0.815	-	-
Above 15	1.378(0.886-2.142)	0.154	-	-
Unknown	NA	NA	-	-
Nodal metastasis	-	-	-	-
No	Reference	-	-	-
Yes	1.296(0.961-1.747)	0.09	-	-
Unknown	NA	NA	-	-
With other sites metastasis	-	-	-	-
No	Reference	-	Reference	-
Yes	1.488(1.156-1.916)	0.002	1.426(1.076-1.889)	0.013
Primary site surgery	-	-	-	-
No	Reference	-	Reference	-
Resection	0.478(0.382-0.599)	<0.001	0.517(0.395-0.678)	<0.001
Primary site radiotherapy	-	-	-	-
No	Reference	-	Reference	-
Yes	0.580(0.447-0.751)	<0.001	0.789(0.585-1.066)	0.122
Primary site chemotherapy	-	-	-	-
No/Unknown	Reference	-	Reference	-
Yes	0.558(0.445-0.700)	<0.001	0.549(0.428-0.704)	<0.001

However, resection of metastasis sites had no significant effects on OS (p = 0.308) and CSS (p = 0.486) in ESTSLM patients with primary site surgery. While chemotherapy improved short-term survival there was no effect on the 5-year CSS rate. The median survival of ESTSLM patients without chemotherapy was 7 months, which extended to 17 months with chemotherapy.

Table 4: Survival outcomes of different histologic subtypes in ESTSLM patients.

	3-y OS			3-y CSS		
	R (95% CI)	**Number (%)**	**Median**	**R (95% CI)**	**Number (%)**	**Median**
Overall sarcomas	16.9(13.3-20.4)	533(100)	11	21.1(16.7-25.5)	424(100)	12
Sarcoma, NOS	12.5(6.1-18.6)	131(24.6)	6	14.6(6.6-22.5)	98(23.1)	8
UPS/MFH	12.7(5.9-19.6)	127(23.9)	10	21.3(11.8-30.8)	98(23.1)	12
Fibrosarcoma	18.2(5.0-31.4)	34(6.4)	13	19.2(4.1-34.4)	28(6.6)	14
Liposarcoma	0	25(4.7)	9	0	17(4.0)	11
Leiomyosarcoma	26.2(14.3-38.0)	65(12.2)	13	26.5(11.9-41.2)	48(11.3)	14
Rhabdomyosarcoma	20.0(4.9-35.2)	30(5.6)	14	22.1(5.8-38.4)	28(6.6)	12
Synovial sarcoma	19.2(8.2-30.3)	60(11.3)	18	20.0(10.5-36.2)	55(13.0)	19
Clear cell sarcoma	0	5(1.0)	4	0	5(1.2)	4
Angiosarcoma	11.8(-3.5-27.1)	17(3.2)	3	20.0(-0.2-40.2)	15(3.5)	3
Extra skeletal osteosarcoma	21.4(-13.4-56.3)	7(1.3)	12	30.0(-16.8-76.8)	5(1.2)	36
Extra skeletal chrondrosarcoma	NA	0	NA	NA	0	NA
Ewing sarcoma	NA	14(2.6)	17	NA	14(3.3)	14
MPNST	25.9(4.9-46.9)	18(3.4)	11	36.9(9.9-64.0)	13(3.1)	19

The 1-year CSS rate for chemotherapy was 62.4% and 32.5% without chemotherapy. The 2-year CSS rates were 36.2% and 27.1%, respectively, but there was no discrepancy in survival in the 3-year CSS rates.

Analysis of 12 histological subtypes showed a median OS of 11 months and CSS of 12 months, 3-year OS rate of 18% and 3-year CSS rate of 22.4%. The best prognosis with a 3-year CSS rate of 36.9 and median CSS of 19 months was noted with MPNST, whereas liposarcoma had the worst prognosis with a 3-year CSS rate of 0% (Table 4). Thus, pulmonary metastasis presented with poor prognosis irrespective of the histologic subgroup diagnosed.

DISCUSSION

Except for two small case studies Kane et al. (2002), Ferguson et al. (2011) the paucity of patients and studies has resulted in limited analysis of data to effectively treat and manage ESTSLM, whose risk is poorly characterized and disease characteristics and therapeutic regimens are non-specific von Mehren et al. (2018). To the best of our knowledge, this is the first SEER analysis of clinical features, SLM risk factors, and prognosis of ESTS.

Though lungs are the most common metastatic sites at diagnosis, bone, liver and brain are other metastasis sites. This was corroborated in our study, which showed that patients with lung metastasis showed a higher rate compared with other sites of metastasis, though in synchrony with lung metastasis. On the other hand, lymph node metastasis was rare for STS, accounting for 3.6% in the current study, which was in line with a previous study (2.6%) Fong et al. (1993).

Routine chest imaging guidelines proposed by the National Comprehensive Cancer Network (NCCN) is based on two variables — differentiation grade and tumor size — both of which influence lung metastasis Brownstein et al. (2020), and support our data showing higher risk of lung metastasis with high grade sarcoma and tumor size. However, Ferguson et al failed to identify the prognostic significance of tumor size and grade in STSLM patients Ferguson et al. (2011), which these authors speculated could be due to their limited cohort sample size of 112 patients Ferguson et al. (2011). Our results agreed with that of Ferguson et al. (2011) since both tumor size and grade lost their prognostic value in 533 ESTSLM patients.

Analyses of age, gender and race on rates of lung metastasis yielded interesting results. An increase in the incidence of ESTS with age was observed in our study. However, this did not translate to high rate of metastasis, indicating that chest CT scans may be more informative in younger patients. Males and African-American had the highest rate of lung metastasis in the SEER database. Our findings are the first to show gender and race predilection for lung metastasis. Primary site blood supply may have an important role in tumor formation. We found that ESTS was more frequent in sites with higher blood supply such as lower limbs than upper limbs since blood circulation in deep tissues of the extremities is more abundant than superficial tissues.

For the first time, we proposed varying lung metastasis rates for distinct histological subtypes of STS. Clinical and pathological behaviors of STS subtypes are diverse and heterogeneous, with varying tendencies for lung metastasis. Of the 50 histological subtypes Nakano et al. (2020), 12 most common subtypes were examined in our study and results obtained were in accordance with previous studies. For example, liposarcoma was the most common subtype, but showed the lowest lung metastasis rate. Liposarcoma comprises several subtypes presenting with specific lung metastasis propensity. Well-differentiated liposarcoma is the major liposarcoma subtypes in the extremity, which has little-to-no metastatic potential Lee et al. (2018).

In our study, high metastatic potential subtypes such as dedifferentiated liposarcoma were rare (7.9%) in the extremities. Small proportion of dedifferentiated liposarcoma was the major cause of low lung metastasis rate. Similarly, the low rate of lung metastasis (3.6%) in fibrosarcoma does not suggest that treatment modalities should de-emphasize the subtypes. Folpe et al recommended indefinite follow-up for fibrosarcoma patients because metastasis may develop more than 20 years after diagnosis Folpe et al. (2014). However, lung metastasis was high in younger patients in our analysis. Ewing sarcoma and rhabdomyosarcoma occurred at any age with a peak incidence in children and AYA. These two subtypes presented with the highest lung metastasis propensity of 21.5% and 15.1% for Ewing sarcoma and rhabdomyosarcoma, respectively.

Retrospective studies that examined prognostic factors of STS showed a significant effect of age, histological subtypes, anatomic depth, stages, surgery, and chemotherapy Gutierrez et al. (2007), which was similar to our findings. Our study examined, for the first time, a large population comprising 533 ESTSLM patients from the SEER database, and identified prognostic factors and found that OA (≥ 40 years old) had worst survival compared with children (0-14 years old) and AYA (15-39 years old). Previous studies only assessed patients who presented initially with localized burden and subsequently metastasized to new sites. For example, Billingsley et al analyzed 719 patients who developed or presented with pulmonary metastasis and identified that age >50 years correlated to poor prognosis Billingsley et al. (1999) and also found similar results in 230 patients who had metastasis after primary disease was cured Billingsley et al. (1999).

The strength of our study lies in its sample size, which was large enough to make comparisons between subtypes of synchronous pulmonary metastasis. While Billingsley et al. (1999) identified liposarcoma and MPNST as unfavorable prognosis factors, our multivariate analysis showed that these two subtypes lost their prognostic power. In contrast to Billingsley et al. (1999), the 3-year survival rate of liposarcoma in lung metastasis patients decreased to 0 and liposarcoma was significant in univariate test whereas the 3-year CSS rate of 38.5% and median survival of 19 months in MPNST patients were the highest. In fact, the 3-year OS and 3-year CSS rates of overall STS subtypes were similar and decreased to 30%. We found that though histological subtype is a critical prognostic factor in STS patients, its potential prognostic value in ESTSLM patients was negligible.

The rarity of ESTSLM has diminished the application of targeted therapies leading to the current use of empirical therapies. Multivariate analysis showed that primary site surgery was a prognostic factor with a median CSS of 18 months for surgery and 10 months without surgery. This analysis may have been subjected to selection bias since patients who were physically fit may have qualified for surgery compared to those that were not. Therefore, to overcome the bias that surgery, rather than physical state, was the leading contributing factor, patients who were recommended for surgery, but declined, were compared to those who underwent surgery and the OS rate was significantly different, but there was no difference in CSS rate, which may be attributed to the small sample size (n = 18) of patients who declined surgery.

Depending on ESTS patient health, recovery time is generally between three months to a year Davis et al. (2002). Our study revealed a median recovery time of 18 months, which indicate that patients who underwent surgery spent considerable post-operative time in recovery. Therefore, patient survival and quality of life can be prolonged through a comprehensive pre-operative assessment.

The benefits of metastasectomy in STS patients with synchronous metastasis remain a matter of debate. Whereas Ferguson et al. (2011) found improvement in OS rate with metastasectomy, Kane et al. (2002) found none, which was in agreement with our study. Since ESTSLM patients were considerably poor in physical

health, recovery was generally long. As extending survival of patients with synchronous disease who underwent surgery was not achievable, our findings suggest palliative care and improvement in quality of life of metastasectomy patients.

Our analyses were restricted to survival differences between patients who underwent chemotherapy and those who did not because different chemotherapy regimens were not documented in the SEER database. We found improvement in survival with short-term chemotherapy. There were no significant benefits with primary site radiotherapy, which was not unexpected because metastatic site progression could be the true determinant of survival. Nevertheless, radiotherapy may be advantageous for alleviation of symptoms such as pain, ischemia, and limits on physical activity.

This study is not without limitations. First, lack of certain clinicopathological data may have introduced interpretation bias. Second, not all ESTS patients in this retrospective study of SEER database patients may have had a routine chest CT scan, which may have undermined the actual rate of lung metastasis. Third, the SEER database lacked data on gene mutations that affect STS formation and development, which are essential for incorporating precision medicine into treatment regimens.

CONCLUSIONS

Our study was the first comprehensive study that unraveled lung risk factors and prognostic factors affecting metastasis in ESTSLM patients. The findings of this study may be useful for screening and management of patients with ESTSLM.

DECLARATIONS

Author contributions

Xudong Yang, Jie Tang, Kejia Zhao: Writing - Original Draft, Conceptualization, Methodology.

Manjun Chen, Yingsong Tian: Resources, Formal analysis, Investigation and Visualization.

Xiaobo Chen: Writing - Review & Editing, Supervision.

Declaration of Conflict of Interest

None.

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Data Availability Statement

We declare that our data comes from the SEER public database Nov 2018 sub (1975-2016 varying) and that the data is available.

Ethical Statement

This is a population study that involves no identifiable information for individuals throughout the analyses. Institutional Review Board at The First Affiliated Hospital of Kunming Medical University approved this study and gave ethics exemption because the study was deemed not to constitute human subject research.

REFERENCES

1.Siegel RL, Miller KD and Jemal A. 2019. Cancer statistics, 2019. CA Cancer J Clin. 69: 7-34.

2.Mastrangelo G, Coindre JM, Ducimetiere F, et al. 2012. Incidence of soft tissue sarcoma and beyond. Cancer. 118: 5339-48.

3.Hui JYC. 2016. Epidemiology and Etiology of Sarcomas. Surg Clin North Am. 96: 901-14.

4.Stiller CA, Trama A, Serraino D, et al. 2013. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer. 49: 684-95.

5.Abaricia S and Van Tine BA. 2019. Management of localized extremity and retroperitoneal soft tissue sarcoma. Curr Probl Cancer. 43: 273-82.

6.Kane JM, Finley JW, Driscoll D, et al. 2002. The treatment and outcome of patients with soft tissue sarcomas and synchronous metastases. Sarcoma. 6: 69-73.

7.Gadd MA, Casper ES, Woodruff JM, et al. 1993. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Ann Surg. 218: 705-12.

8.Ferguson PC, Deheshi BM, Chung P, et al. 2011. Soft tissue sarcoma presenting with metastatic disease: outcome with primary surgical resection. Cancer. 117: 372-79.

9.Papworth KE, Arroyo VM, Styring E, et al. 2019. Soft-tissue sarcoma in adolescents and young adults compared with older adults: A report among 5000 patients from the Scandinavian Sarcoma Group Central Register. Cancer. 125: 3595-02.

10.von Mehren M, Randall RL, Benjamin RS, et al. 2018. Soft Tissue Sarcoma, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 16: 536-63.

11.Fong Y, Coit DG, Woodruff JM, et al. 1993. lymph-node metastasis from soft-tissue sarcoma in adults - analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg. 217: 72-77.

12.Brownstein JM and DeLaney TF. 2020. Malignant Soft-Tissue Sarcomas. Hematol Oncol Clin North Am. 34: 161-175.

13.Nakano K and Takahashi S. 2020. Precision Medicine in Soft Tissue Sarcoma Treatment. Cancers (Basel). 12: 221.

14.Lee ATJ, Thway K, Huang Ph et al. 2018. Clinical and Molecular Spectrum of Liposarcoma. J Clin Oncol. 36: 151-59.

15.Folpe AL. 2014. Fibrosarcoma: a review and update. Histopathology. 64: 12-25.

16.Gutierrez JC, Perez EA, Franceschi D, et al. 2007. Outcomes for soft-tissue sarcoma in 8249 cases from a large state cancer registry. J Surg Res. 141: 105-14.

17.Billingsley KG, Burt ME, Jara E, et al. 1999. Pulmonary metastases from soft tissue sarcoma - Analysis of patterns of disease and post metastasis survival. Ann Surg. 229: 602-12.

18.Billingsley KG, Lewis JJ, Leung DHY, et al. 1999. Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer. 85: 389-95.

19.Davis AM, O'Sullivan B, Bell RS, et al. 2002. Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. J Clin Oncol. 20: 4472-77.

