

University of Groningen

Metastatic appendicular soft tissue sarcoma

Gonzalez, Marcos R.; Rizk, Paul; Hodo, Thomas W.; Bedi, Angad; Karczewski, Daniel; Lozano-Calderon, Santiago A.

Published in:
Journal of Cancer Metastasis and Treatment

DOI:
[10.20517/2394-4722.2022.138](https://doi.org/10.20517/2394-4722.2022.138)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gonzalez, M. R., Rizk, P., Hodo, T. W., Bedi, A., Karczewski, D., & Lozano-Calderon, S. A. (2023). Metastatic appendicular soft tissue sarcoma: treatment and survival outcomes of 2,553 patients from the SEER database. *Journal of Cancer Metastasis and Treatment*, 9, Article 24. <https://doi.org/10.20517/2394-4722.2022.138>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Original Article

Open Access



Metastatic appendicular soft tissue sarcoma: treatment and survival outcomes of 2,553 patients from the SEER database

Marcos R. Gonzalez¹, Paul Rizk² , Thomas W. Hodo³, Angad Bedi^{1,4} , Daniel Karczewski¹, Santiago A. Lozano-Calderon¹

¹Division of Orthopaedic Oncology, Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02144, USA.

²Department of Orthopaedic Surgery, University of Florida, Gainesville, FL 32608, USA.

³Department of Orthopaedic Surgery, Tulane University School of Medicine, New Orleans, LA 70112, USA.

⁴Department of Orthopaedic Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Correspondence to: Dr. Santiago A. Lozano-Calderon, Division of Orthopaedic Oncology, Department of Orthopaedic Surgery, Massachusetts General Hospital, Boston, MA 02144, USA, E-mail: slozanocalderon@mgh.harvard.edu

How to cite this article: Gonzalez MR, Rizk P, Hodo TW, Bedi A, Karczewski D, Lozano-Calderon SA. Metastatic appendicular soft tissue sarcoma: treatment and survival outcomes of 2,553 patients from the SEER database. *J Cancer Metastasis Treat* 2023;9:24. <https://dx.doi.org/10.20517/2394-4722.2022.138>

Received: 13 Dec 2022 **First Decision:** 21 Apr 2023 **Revised:** 5 May 2023 **Accepted:** 6 Jun 2023 **Published:** 16 Jun 2023

Academic Editors: Christos A. Papadimitriou, Giovanna Tosato, William P. Schiemann **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Introduction: Patients with soft tissue sarcoma (STS) that present with metastasis at diagnosis have a dire prognosis. Within this patient population, we sought to assess: (1) demographic and clinical characteristics, (2) metastatic patterns, (3) treatment strategies, and (4) disease-specific survival (DSS).

Materials and Methods: The SEER database was queried to identify patients with histologically confirmed STS of the pelvis or extremity. Univariate and multivariate analysis was performed using the Cox proportional hazards model. Disease-specific survival (DSS) was analyzed using the Kaplan-Meier method.

Results: A total of 22,683 patients were retrieved, out of which 2,553 (11.3%) had metastasis at diagnosis. Leiomyosarcoma, undifferentiated pleomorphic sarcoma (UPS), liposarcoma, synovial sarcoma, spindle cell sarcoma, and alveolar rhabdomyosarcoma (A-RMS) were the six most common STS presenting with metastasis. Among patients with metastasis, 53.7% and 33.2% of patients had primary tumors located in the lower limb and



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



pelvis, respectively. Lung was the most common site of metastasis in all subtypes except A-RMS, in which bone metastases and lymph node (LN) predominated (85.2% and 62.1%, respectively). Chemotherapy and radiotherapy were associated with higher DSS (HR = 0.788 and HR = 0.755, respectively). Five-year DSS was below 20% in all tumor histologies. Two-year DSS for patients with synchronous lung and liver metastases was 28%.

Conclusion: Although the lung was the most common site of metastasis, metastatic patterns are highly variable depending on tumor histology. Metastatic A-RMS is most commonly presented with regional LN and bone involvement. Disease-specific survival remained poor for patients with metastatic disease at presentation regardless of (neo)-adjuvant radiotherapy or chemotherapy.

Keywords: Soft tissue sarcoma, metastasis, treatment, survival

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal neoplasms representing 1% of the cancer burden in the US^[1]. Comprising more than 50 different histologic subtypes, each with a distinct behavior, treatment remains challenging^[2]. Recent advances have improved the treatment and diagnosis of STS to involve a multidisciplinary approach that combines surgery, chemotherapy (QT), radiation therapy (RT) and immunotherapy^[3]. Despite these advances, high-risk STS carry a 50% lifetime risk of developing metastases and 5-year overall survival of 55%^[4].

Guidelines currently recommend pulmonary imaging after STS diagnosis, either with chest radiographs or CT scan, to rule out lung metastases^[5]. Other potential sites of metastases, however, are not often screened and are typically detected when patients become symptomatic. Approximately 2.2% and 3.2% of patients with STS present with metastases to the skeletal system or liver, respectively^[6,7]. In the setting of a diverse array of histologic subtypes, metastatic patterns can differ between histologic subtypes and general guidelines might not always be applicable.

The optimal treatment of metastatic STS is a topic under debate. While anthracycline-based cytotoxic therapy is the standard of care in metastatic disease, response is poor and median overall survival is 14.3 months^[8]. Radiation therapy is also often utilized and recent studies have reported a high success rate for local control of the metastatic site^[9]. The role of surgery in the metastatic site is extremely restricted, with only resection of metachronous lung metastases in patients without extrapulmonary disease showing a clear survival benefit^[10]. Immunotherapy has shown promising results in the histologically-driven management of STS without many of the side effects of conventional cytotoxic treatment^[11].

Owing to the overall scarcity of data on metastatic patterns of STS, our study focused on the tumors that most commonly presented with metastasis at diagnosis. Within this population, our study sought to analyze (1) demographic and clinical characteristics; (2) metastatic patterns by tumor histology; (3) management strategies and impact of QT and RT on disease-specific survival (DSS); and (4) DSS by metastatic patterns and tumor histology.

MATERIALS AND METHODS

The Surveillance, Epidemiology and End Results (SEER) is a database elaborated by the National Cancer Institute, which compiles information from 18 population-based cancer registries covering approximately 28% of the US population. Along with the National Cancer Database, the SEER database is one of the most extensively used databases to study outcomes of patients with cancer and a valuable tool for studies in soft

tissue and bone sarcomas^[12-14].

Our study used the SEER Research Plus Data, an extension of the SEER database, which includes additional variables on treatment strategy and patient outcomes. Patients included in our analyses were diagnosed between 2000 and 2018, the latter being the last year available in the database. Variables regarding the location of metastases (bone, liver, brain and/or lung) were added in 2010 and most of our analysis was therefore restricted to the period following 2010. As a result, the demographic analysis contains a higher patient count than the analysis of metastatic patterns.

Data were accessed using the SEER*Stat 8.4.0.1 software. The following inclusion criteria were applied: (1) positive histological diagnosis of STS according to “Site recode ICD-O-3/WHO 2008”; (2) location in the upper limb, lower limb, or pelvis; (3) complete data on metastatic status at diagnosis; and (4) be classified as a primary malignancy by international rules. Out of the 95,449 cases initially retrieved from the SEER database, 28,743 patients were included. Patients were then selected by metastatic status for a total of 2,553 patients with metastasis at diagnosis. For analyses regarding metastasis location, the sample diminished to 1,503. The remaining 1,050 patients with metastasis at diagnosis were excluded due to missing data on the precise metastatic location.

The following demographic and clinical variables were included in our analysis: age, sex, sub-population, tumor location, tumor size, T and N scores (American Joint Committee on Cancer [AJCC] 8th Ed.), site of metastasis, histologic grade, and whether the tumor was the first malignancy of the patient. Treatment variables included surgery to the primary site, type of surgery (limb salvage or amputation), surgery to the distant site, chemotherapy (QT), and radiotherapy (RT).

It is important to note that the SEER database only considered metastases that were detected at diagnosis and did not include those that developed in the course of the disease. Furthermore, the only metastatic sites that can be individually assessed are lung, bone, liver, brain, distant lymph node (LN), and other sites. The latter included all anatomic sites different from the ones listed above. Regarding the lymph nodes, the SEER database distinguished between regional (N1) and distant (M1) LN involvement. Although a difference exists with regards to the relationship between the involved LN and the primary site of disease, the 8th edition of the AJCC edition considered both clinical scenarios as part of stage IV disease. Analysis of surgery to the distant site was limited since most patients with metastatic disease have multiple organ involvement and the variable does not specify on which organ the surgery was performed.

Statistical analysis

Demographic, clinical, and treatment characteristics were analyzed using descriptive statistics. Logistic regression with the Cox proportional hazards model was performed to determine the role of QT and RT on disease-specific survival. One-, two-, and five-year DSS were calculated using the Kaplan-Meier method. Differences in survival were compared using Log-rank analysis. A *P* value ≤ 0.05 was considered statistically significant. All statistical analyses were performed with Stata (StataCorp LLC, Texas, USA).

RESULTS

Patient demographic and clinical characteristics

We initially classified the tumors that most commonly presented with metastasis at diagnosis by histology [Figure 1A].

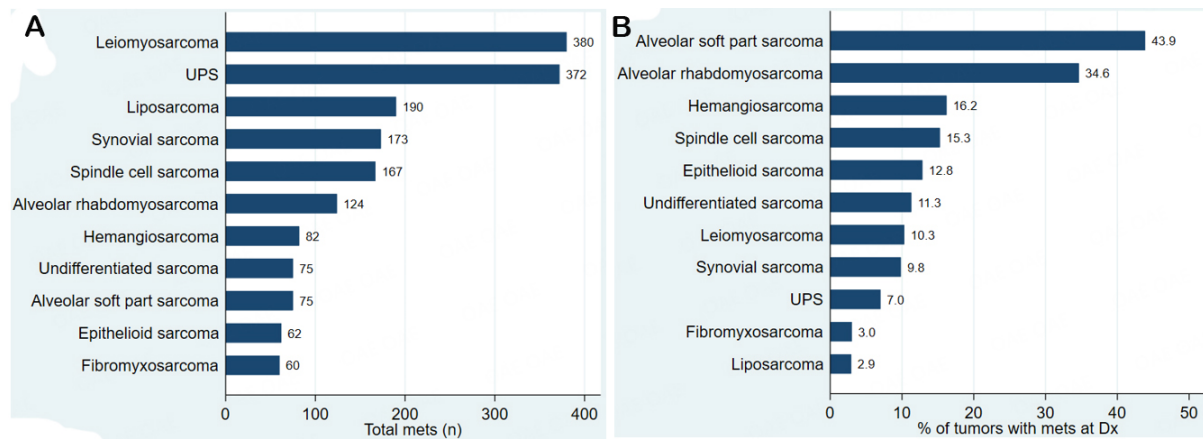


Figure 1. (A) Total number of patients with metastatic disease at presentation according to tumor histology. (B) Metastatic rate of each tumor histology. Dx: Diagnosis; UPS: undifferentiated pleomorphic sarcoma.

The six most common STS presenting with metastasis at diagnosis were leiomyosarcoma, undifferentiated pleomorphic sarcoma (UPS), liposarcoma, synovial sarcoma, spindle cell sarcoma, and alveolar rhabdomyosarcoma (A-RMS). We additionally analyzed the metastatic rates of these tumors by dividing the number of cases presenting with metastases by the total number of patients diagnosed with that STS histology. Alveolar soft part sarcoma and alveolar rhabdomyosarcoma had the highest metastatic rates, presenting with metastasis in 43.9% and 34.6% of cases, respectively [Figure 1B]. Leiomyosarcoma, which showed the highest number of metastases, had a metastatic rate of 10.3%.

For our demographic analysis, we compared patients with and without metastasis at presentation in the general STS population and for each of the six most common tumor subtypes. A total of 2,553 and 20,130 patients with and without metastasis at diagnosis were included. Sex distribution was similar in both groups, slightly favoring the male population ($P = 0.89$) [Table 1].

Sub-population patterns differed between the metastatic and non-metastatic groups. Afro-American patients accounted for only 11.1% of the non-metastatic group but 15.6% of the metastatic group ($P < 0.001$). The lower limb was the most common location in both groups and tumors located in the pelvis were more commonly in the metastatic (33.2%) than in the non-metastatic (16%) group ($P < 0.001$). Tumors in the metastatic group were significantly larger (median size: 111 mm) than those in the non-metastatic group (73 mm). Likewise, LN compromise was more common in patients with metastasis at diagnosis than in those without (21.9% and 2.3%, respectively). Median survival was 10 months for patients with metastatic STS and 48 months for those without metastasis ($P < 0.001$).

We conducted a separate analysis of demographic and clinical characteristics by histology to see if general trends remained stable across the most common tumor subtypes [Tables 2 and 3]

Leiomyosarcoma

A total of 380 patients with appendicular leiomyosarcoma presented with metastasis at diagnosis [Table 2]. A higher proportion of female patients was seen in the metastatic group (62.9%) than in the non-metastatic group (45.9%) ($P < 0.001$). Rates of Afro-American patients were significantly higher in the metastatic group ($P < 0.001$). Tumor location in the pelvis was more common in patients with metastatic disease (51.3%). In patients with metastasis, 51.3% had primary tumors in the pelvis. Lymph node involvement was present in

Table 1. Demographic and clinical characteristics of patients with soft tissue sarcoma with and without metastasis at diagnosis

	Total (n = 22,683)		P
	Non-metastatic (n = 20,130)	Metastatic (n = 2,553)	
Age*	59 (45-72)	58 (39-71)	< 0.001
Sex			0.89
Male	11,025 (54.8%)	1,402 (54.9%)	
Female	9,105 (45.2%)	1,151 (45.1%)	
Race			< 0.001
White	15,997 (80.4%)	1,936 (76.0%)	
Black	2,199 (11.1%)	397 (15.6%)	
Asian/Pacific Islander	1,568 (7.9%)	197 (7.7%)	
American Indian/Alaska Native	134 (0.7%)	19 (0.7%)	
Location			< 0.001
Lower limb	12,267 (60.9%)	1,372 (53.7%)	
Upper limb	4,646 (23.1%)	333 (13.0%)	
Pelvis	3,217 (16.0%)	848 (33.2%)	
Tumor size* (mm)	73 (40-128)	111 (76-165)	< 0.001
T score			< 0.001
T1	6,134 (34.5%)	256 (12.2%)	
T2	5,582 (31.4%)	677 (32.3%)	
T3	3,089 (17.4%)	560 (26.7%)	
T4	2,989 (16.8%)	606 (28.9%)	
N score			< 0.001
N0	18,868 (97.7%)	1,761 (78.1%)	
N1	454 (2.3%)	495 (21.9%)	
Histologic grade			< 0.001
Well-differentiated	3,127 (21.5%)	36 (2.4%)	
Moderately-differentiated	2,870 (19.7%)	142 (9.4%)	
Poorly-differentiated	3,208 (22.1%)	453 (29.9%)	
Undifferentiated	5,339 (36.7%)	886 (58.4%)	
First malignancy			0.008
No	3,178 (15.8%)	455 (17.8%)	
Yes	16,952 (84.2%)	2,098 (82.2%)	
Survival* (months)	48 (19-95)	10 (3-23)	< 0.001

UPS: Undifferentiated pleomorphic sarcoma; *Refers to median value and interquartile range between brackets.

12.9% of patients with metastasis at diagnosis. Median DSS in patients with and without metastasis was 13 months and 49 months, respectively.

Undifferentiated pleomorphic sarcoma

A total of 372 patients with UPS presented with metastasis at diagnosis [Table 2]. A higher rate of Afro-American patients was seen in the metastatic group ($P < 0.001$). Tumors were located in the pelvis in 19.6% and 8.3% of patients with and without metastasis. In 15.9% of patients with metastasis at diagnosis, LN involvement was detected. Median DSS was 7 and 39 months for patients with UPS with and without metastasis, respectively.

Table 2. Demographic and clinical characteristics of patients with soft tissue sarcoma with (M1) and without (M0) metastasis at diagnosis according to histology

	Leiomyosarcoma (n = 2,901)			UPS (n = 3,938)			Liposarcoma (n = 5,198)		
	M0 (n = 2,521)	M1 (n = 380)	P	M0 (n = 3,566)	M1 (n = 372)	P	M0 (n = 5,008)	M1 (n = 190)	P
Age*	63 (51-73)	65 (55-74)	0.04	67 (55-78)	65.5 (56-76)	0.42	59 (47-70)	59 (44-70)	0.82
Sex			< 0.001			0.9			0.013
Male	1,363 (54.1%)	141 (37.1%)		1,944 (54.5%)	204 (54.8%)		3,005 (60.0%)	131 (68.9%)	
Female	1,158 (45.9%)	239 (62.9%)		1,622 (45.5%)	168 (45.2%)		2,003 (40.0%)	59 (31.1%)	
Race			0.001			< 0.001			0.12
White	2,084 (83.6%)	286 (75.3%)		2,925 (82.6%)	286 (77.1%)		4,008 (81.0%)	147 (77.8%)	
Black	252 (10.1%)	60 (15.8%)		314 (8.9%)	60 (16.2%)		492 (9.9%)	28 (14.8%)	
Asian/Pacific Islander	140 (5.6%)	30 (7.9%)		277 (7.8%)	24 (6.5%)		419 (8.5%)	14 (7.4%)	
American Indian/Alaska Native	16 (0.6%)	4 (1.1%)		24 (0.7%)	1 (0.3%)		27 (0.5%)	0 (0.0%)	
Location			< 0.001			< 0.001			0.07
Lower limb	1,301 (51.6%)	155 (40.8%)		2,352 (66.0%)	241 (64.8%)		3,513 (70.1%)	132 (69.5%)	
Upper limb	580 (23.0%)	30 (7.9%)		918 (25.7%)	58 (15.6%)		554 (11.1%)	13 (6.8%)	
Pelvis	640 (25.4%)	195 (51.3%)		296 (8.3%)	73 (19.6%)		941 (18.8%)	45 (23.7%)	
Tumor size* (mm)	50 (25-90)	110 (72-160)	< 0.001	70 (42-120)	118 (76-170)	< 0.001	120 (72-180)	150 (100-200)	< 0.001
T score			< 0.001			< 0.001			< 0.001
T1	1,141 (52.7%)	41 (13.2%)		1,086 (33.7%)	41 (12.8%)		646 (14.0%)	11 (6.5%)	
T2	581 (26.8%)	97 (31.2%)		1,113 (34.5%)	98 (30.6%)		1,274 (27.6%)	36 (21.2%)	
T3	256 (11.8%)	86 (27.7%)		581 (18.0%)	73 (22.8%)		1,106 (24.0%)	39 (22.9%)	
T4	189 (8.7%)	87 (28.0%)		442 (13.7%)	108 (33.8%)		1,587 (34.4%)	84 (49.4%)	
N score			< 0.001			< 0.001			< 0.001
N0	2,385 (98.8%)	297 (87.1%)		3,404 (98.1%)	287 (84.7%)		4,819 (99.4%)	150 (89.8%)	
N1	28 (1.2%)	44 (12.9%)		67 (1.9%)	52 (15.3%)		30 (0.6%)	17 (10.2%)	
Histologic grade			< 0.001			0.001			< 0.001
Well-differentiated	241 (14.0%)	8 (3.3%)		30 (1.1%)	2 (0.7%)		2,322 (55.8%)	12 (9.8%)	
Moderately-differentiated	514 (29.9%)	38 (15.8%)		208 (7.3%)	5 (1.8%)		740 (17.8%)	20 (16.4%)	
Poorly-differentiated	431 (25.1%)	77 (32.1%)		687 (24.1%)	58 (20.9%)		520 (12.5%)	37 (30.3%)	
Undifferentiated	534 (31.0%)	117 (48.8%)		1,924 (67.5%)	212 (76.5%)		577 (13.9%)	53 (43.4%)	
First malignancy			0.65			0.23			0.52
No	462 (18.3%)	66 (17.4%)		703 (19.7%)	83 (22.3%)		683 (13.6%)	29 (15.3%)	
Yes	2,059	314		2,863	289		4,325	161	

	(81.7%)	(82.6%)		(80.3%)	(77.7%)		(86.4%)	(84.7%)	
Survival* (months)	49 (20-92)	13 (5-28)	< 0.001	39 (15-91)	7 (3-18)	< 0.001	59.5 (27-105)	11 (4-31)	< 0.001

UPS: Undifferentiated Pleomorphic Sarcoma; *Refers to median value and interquartile range between brackets.

Liposarcoma

Liposarcoma was the most common STS overall ($n = 5,198$) and third highest by number of patients with metastasis [Table 2]. Males were most often affected in both non-metastatic (60%) and metastatic (68.9%) groups. Patients affected were most often of European descent and the lower limb was the most common location in both groups. No differences in sex distribution or tumor location were found between groups. Lymph node involvement occurred in 10.2% of patients with metastasis at diagnosis. Median DSS was 11 months and 59.5 months for metastatic and non-metastatic patients, respectively.

Synovial sarcoma

173 patients with synovial sarcoma presented with metastasis at diagnosis [Table 3]. Male patients were significantly more involved in the metastatic group (61.8%) than the non-metastatic group (49.6%) ($P = 0.003$). The primary tumor was located in the pelvis in 15% and 6.5% of cases with and without metastasis at diagnosis ($P < 0.001$). Among patients with metastases, 15.5% had LN compromise. Median DSS was 15 months and 57 months for patients with and without metastasis at presentation, respectively.

Spindle cell sarcoma

A total of 167 patients (18.2%) with spindle cell sarcoma presented with metastasis at diagnosis. No differences in sex distribution were seen between patients with and without metastasis at diagnosis in spindle cell sarcoma [Table 3]. The primary tumor was located in the pelvis in 32.3% and 15.1% of cases with and without metastasis at diagnosis ($P < 0.001$). Lymph node involvement was present in 17% of cases with metastatic disease. Diagnosis of spindle cell sarcoma as first malignancy was more common in patients without metastasis ($P = 0.002$). Median DSS was 30 months in patients without metastasis and 6 months in those with metastasis ($P < 0.001$).

Alveolar rhabdomyosarcoma

Alveolar rhabdomyosarcoma presented with metastasis in 124 cases (47.5%) [Table 3]. The median age at diagnosis was 14 years in patients with metastasis and 10 years in those without ($P < 0.001$). The primary tumor was located in the pelvis in 37.9% and 24.1% of cases with and without metastasis at diagnosis, respectively ($P < 0.001$). Lymph node compromise was present in 67.5% of patients with metastatic disease at presentation. The median DSS was 43 months in patients without metastasis and 18.5 months in patients with metastasis ($P < 0.001$).

Metastatic patterns of the most common STS

In the entire cohort, lung was the most common site of metastases (77%), followed by bone (29.7%), distant LNs (17.8%), and liver (14.5%) [Table 4]. Metastases to other sites, which included any location other than the lung, bone, liver, brain, and distant LNs, occurred in 26.2% of cases.

Different metastatic patterns were seen when patients were stratified by histology. In alveolar rhabdomyosarcoma, only 45.9% of patients with metastasis at diagnosis had lung compromise ($P < 0.001$). Instead, patients with this tumor presented with bone metastases in 85.2% of cases; in all other histologic subtypes, this incidence ranged between 14.4% and 30.2% [Table 4]. Liver metastases ranged from 3.3% in alveolar rhabdomyosarcoma to 30.2% in leiomyosarcoma. Brain metastases were rare, with a frequency below 5 percent across all histologies.

Table 3. Demographic and clinical characteristics of patients with soft tissue sarcoma with (M1) and without (M0) metastasis at diagnosis according to histology

	Synovial sarcoma (n = 1,363)			Spindle cell sarcoma (n = 917)			Alveolar rhabdomyosarcoma (n = 261)		
	M0 (n = 1,190)	M1 (n = 173)	P	M0 (n = 750)	M1 (n = 167)	P	M0 (n = 137)	M1 (n = 124)	P
Age*	35 (23-50)	42 (27-56)	0.004	61 (47-75)	64 (54-74)	0.28	10 (4-17)	14 (10-17.5)	< 0.001
Sex			0.003			0.91			0.47
Male	590 (49.6%)	107 (61.8%)		387 (51.6%)	87 (52.1%)		69 (50.4%)	68 (54.8%)	
Female	600 (50.4%)	66 (38.2%)		363 (48.4%)	80 (47.9%)		68 (49.6%)	56 (45.2%)	
Race			0.41			0.64			0.23
White	936 (79.6%)	133 (76.9%)		598 (80.7%)	129 (77.2%)		101 (74.8%)	85 (68.5%)	
Black	128 (10.9%)	26 (15.0%)		82 (11.1%)	23 (13.8%)		24 (17.8%)	23 (18.5%)	
Asian/Pacific Islander	100 (8.5%)	13 (7.5%)		53 (7.2%)	14 (8.4%)		10 (7.4%)	13 (10.5%)	
American Indian/Alaska Native	12 (1.0%)	1 (0.6%)		8 (1.1%)	1 (0.6%)		0 (0.0%)	3 (2.4%)	
Location			< 0.001			< 0.001			0.022
Lower limb	808 (67.9%)	125 (72.3%)		422 (56.3%)	84 (50.3%)		53 (38.7%)	47 (37.9%)	
Upper limb	305 (25.6%)	22 (12.7%)		215 (28.7%)	29 (17.4%)		51 (37.2%)	30 (24.2%)	
Pelvis	77 (6.5%)	26 (15.0%)		113 (15.1%)	54 (32.3%)		33 (24.1%)	47 (37.9%)	
Tumor size* (mm)	59 (34-93)	120 (81-160)	< 0.001	75 (40-117)	123 (82-172)	< 0.001	58 (42-80)	81 (57.5-106.5)	< 0.001
T score			< 0.001			< 0.001			< 0.001
T1	457 (43.4%)	14 (9.3%)		224 (34.3%)	17 (13.0%)		44 (37.0%)	19 (19.0%)	
T2	385 (36.5%)	48 (31.8%)		207 (31.7%)	32 (24.4%)		62 (52.1%)	50 (50.0%)	
T3	148 (14.0%)	43 (28.5%)		140 (21.4%)	36 (27.5%)		10 (8.4%)	27 (27.0%)	
T4	64 (6.1%)	46 (30.5%)		82 (12.6%)	46 (35.1%)		3 (2.5%)	4 (4.0%)	
N score			< 0.001			< 0.001			< 0.001
N0	1,128 (97.8%)	131 (84.5%)		698 (97.1%)	117 (83.0%)		83 (62.4%)	37 (32.5%)	
N1	25 (2.2%)	24 (15.5%)		21 (2.9%)	24 (17.0%)		50 (37.6%)	77 (67.5%)	
Histologic grade			< 0.001			0.002			0.18
Well-differentiated	13 (1.9%)	0 (0.0%)		32 (5.7%)	2 (1.8%)		2 (6%)	0 (0%)	
Moderately-differentiated	175 (25.9%)	6 (6.4%)		139 (25.0%)	12 (10.9%)		0 (0%)	0 (0%)	
Poorly-differentiated	279 (41.3%)	51 (54.3%)		147 (26.4%)	34 (30.9%)		10 (30%)	11 (52%)	
Undifferentiated	208 (30.8%)	37 (39.4%)		239 (42.9%)	62 (56.4%)		21 (64%)	10 (48%)	
First malignancy			0.87			0.002			0.6
No	72 (6.1%)	11 (6.4%)		137 (18.3%)	48 (28.7%)		3 (2.2%)	4 (3.2%)	

Yes	1,118 (93.9%)	162 (93.6%)		613 (81.7%)	119 (71.3%)		134 (97.8%)	120 (96.8%)	
Survival* (months)	57 (25-107)	15 (5-24)	< 0.001	30 (12-70)	6 (2-17)	< 0.001	43 (24-107)	18.5 (12-32.5)	< 0.001

*Refers to median value and interquartile range between brackets.

Table 4. Associated metastases at the time of diagnosis in patients with metastatic soft tissue sarcoma

	Total (n = 1,503)	Leiomyosarcoma (n = 229)	UPS (n = 215)	Liposarcoma (n = 117)	Synovial sarcoma (n = 106)	Spindle cell sarcoma (n = 101)	Alveolar rhabdomyosarcoma (n = 61)	P
Regional LN								< 0.001
No	1,070 (80.1%)	185 (87.3%)	171 (85.9%)	98 (90.7%)	80 (83.3%)	78 (85.7%)	22 (37.9%)	
Yes	266 (19.9%)	27 (12.7%)	28 (14.1%)	10 (9.3%)	16 (16.7%)	13 (14.3%)	36 (62.1%)	
Lung mets								< 0.001
No	342 (23.0%)	45 (20.2%)	24 (11.2%)	59 (50.9%)	6 (5.7%)	16 (16.0%)	33 (54.1%)	
Yes	1,148 (77.0%)	178 (79.8%)	191 (88.8%)	57 (49.1%)	99 (94.3%)	84 (84.0%)	28 (45.9%)	
Bone mets								< 0.001
No	1,039 (70.3%)	157 (69.8%)	177 (83.5%)	72 (62.1%)	87 (83.7%)	73 (74.5%)	9 (14.8%)	
Yes	439 (29.7%)	68 (30.2%)	35 (16.5%)	44 (37.9%)	17 (16.3%)	25 (25.5%)	52 (85.2%)	
Liver mets								< 0.001
No	1,261 (85.5%)	156 (70.0%)	193 (91.5%)	94 (81.0%)	100 (96.2%)	89 (89.9%)	59 (96.7%)	
Yes	214 (14.5%)	67 (30.0%)	18 (8.5%)	22 (19.0%)	4 (3.8%)	10 (10.1%)	2 (3.3%)	
Brain mets								0.42
No	1,422 (96.4%)	216 (97.3%)	206 (97.2%)	111 (95.7%)	104 (100.0%)	95 (96.0%)	57 (95.0%)	
Yes	53 (3.6%)	6 (2.7%)	6 (2.8%)	5 (4.3%)	0 (0.0%)	4 (4.0%)	3 (5.0%)	
Distant LN mets								0.032
No	502 (82.2%)	84 (91%)	68 (83%)	49 (83%)	28 (82%)	37 (88%)	14 (67%)	
Yes	109 (17.8%)	8 (9%)	14 (17%)	10 (17%)	6 (18%)	5 (12%)	7 (33%)	
Mets to other sites								< 0.001
No	450 (73.8%)	71 (78%)	62 (74%)	35 (60%)	31 (94%)	32 (76%)	8 (38%)	
Yes	160 (26.2%)	20 (22%)	22 (26%)	23 (40%)	2 (6%)	10 (24%)	13 (62%)	

LN: Lymph node; UPS: undifferentiated pleomorphic sarcoma.

Treatment outcomes in patients with and without metastatic STS

Surgery at the primary site was performed in 42% and 88.9% of patients with and without metastatic disease, respectively [Table 5]. Amputation was performed in 14% of patients with metastasis at diagnosis and 5.9% of those without ($P < 0.001$). Chemotherapy was administered in 60.4% and 19.5% of patients with and without metastasis at diagnosis ($P < 0.001$). Radiotherapy was given in 42.4% of patients with metastasis and 47% of those without ($P < 0.001$).

A regression analysis was performed to assess whether radiotherapy and chemotherapy were associated with improved disease-specific survival [Table 6]. On multivariate analysis, radiotherapy (HR = 0.788) and chemotherapy (HR = 0.755) were both associated with increased survival.

We compared DSS in patients with metastasis at diagnosis treated with radiotherapy or chemotherapy, in addition to surgery. Patients treated with surgery, RT and chemotherapy had a higher DSS than those treated with only surgery and chemotherapy [Figure 2A, $P < 0.001$]. The addition of chemotherapy to RT and surgery only showed a survival benefit at the 12- and 24-month marks [Figure 2B, $P < 0.001$]. No difference in survival between groups was seen at the 5- and 10-year follow-up marks.

Disease-specific survival according to metastatic patterns and histologic subtypes

Disease-specific survival by STS histology and metastatic pattern were additionally analyzed [Table 7].

Patients with alveolar rhabdomyosarcoma had a higher DSS than other STS subtypes [Figure 3] ($P < 0.05$).

Patients with metastatic UPS showed the worst survival pattern of all histologic subtypes. Five-year DSS for all histologic subtypes was less than 20%.

An additional analysis of the most common metastatic patterns was conducted. Five-year DSS was considerably lower in patients with metastasis to ≥ 2 organs. Five-year DSS was 5.6% for patients with metastases to the bone and lung and 7.2% for those with metastases to the liver and lung [Table 7]. A trend towards better DSS in patients with only liver metastasis was detected [Figure 4]; this was not significant in log-rank analysis.

DISCUSSION

Effective management of metastatic soft tissue sarcomas (STS) in the extremities and pelvis remains challenging, despite the abundance of available literature. This is due to the significant variability in behaviors between histologies, which makes a “one-size-fits-all” treatment model difficult to implement. Our study demonstrated that metastatic patterns differ substantially between histologies, underscoring the need for tailored treatment strategies. Despite the ample use of neo-adjuvant treatment, metastatic STS is still associated with a dismal prognosis. This study sought to provide a comprehensive overview of the metastatic patterns of STS and their clinical course and help pave the way for the development of more effective histology-based staging and surveillance guidelines.

Patient demographic characteristics

Our study found that 8.9% of patients diagnosed with STS of the extremities and pelvis presented with metastasis at diagnosis. This is consistent with the 7% to 12% rate reported in the literature^[15,16]. Alveolar soft part sarcoma (ASPS) showed the highest rate of metastatic disease at presentation among all tumors. Although extremely rare, accounting for less than 1% of all STS, this tumor is extremely aggressive and 15% of patients with disseminated disease develop brain metastases^[17]. This was in contrast with liposarcoma, the

Table 5. Treatment modalities in patients with soft tissue sarcoma according to metastatic status

	STS without mets (n = 27,240)	STS with mets (n = 1,503)	P
Qx to primary site			< 0.001
No	3,023 (11.1%)	871 (58.0%)	
Yes	24,134 (88.9%)	630 (42.0%)	
Type of Qx			< 0.001
Limb-salvage	22,326 (94.1%)	529 (86.0%)	
Amputation	1,403 (5.9%)	86 (14.0%)	
Qx to distant site			< 0.001
No	22,889 (97.9%)	1,325 (88.3%)	
Yes	483 (2.1%)	176 (11.7%)	
QT			< 0.001
No	21,929 (80.5%)	595 (39.6%)	
Yes	5,311 (19.5%)	908 (60.4%)	
RT			< 0.001
No	14,231 (53.0%)	851 (57.6%)	
Yes	12,635 (47.0%)	627 (42.4%)	

QT: Chemotherapy; Qx: surgery; RT: radiotherapy; STS: soft tissue sarcoma.

Table 6. Multivariate regression analysis for risk factors for disease-specific death in patients with metastatic soft tissue sarcoma. Model was adjusted for age, sex, tumor size, grade, T and N score, and histologic subtype

	HR (95%CI)	P
Age	1.014 (1.007-1.021)	< 0.001
QT	0.788 (0.628-0.988)	0.039
RT	0.755 (0.616-0.925)	0.007
N score		
NO	1	-
N1	1.434 (1.071-1.92)	0.016

HR: Hazard ratio; QT: chemotherapy; Qx: surgery.

second most common STS in our cohort, which displayed the lowest rate of metastasis at diagnosis (2.9%). However, due to the high frequency of this histology, metastases caused by liposarcoma ranked third in absolute incidence. The metastatic rate of liposarcoma found by our study was lower than in previous studies^[18]. In a long-term cohort of 133 patients with liposarcoma, Knebel *et al.* found that 22.6% developed metastases in the course of the disease^[18]. We consider that the lower rate found in our study is due to the SEER database only capturing metastatic events at diagnosis.

Age distribution favored patients in their late fifth decade of life for most STS subtypes. The exception was rhabdomyosarcoma, which is the most common STS in children and accounts for half of all STS and 3.5% of all tumors diagnosed in children^[19]. Interestingly, we found that patients with alveolar rhabdomyosarcoma presenting with metastases were significantly older than those without. Literature on alveolar rhabdomyosarcoma has reported that adults generally fare worse than pediatric patients^[20,21]. Within the pediatric population, a cohort study of 2,343 patients with A-RMS by Joshi *et al.* found that adolescents (≥ 10 years) had lower failure-free survival than children aged 1-9 years^[21]. In light of our

Table 7. Median survival and one-, two- and five-year disease-specific survival in patients with metastatic soft tissue sarcoma according to histologic subtype and metastatic pattern

	Median (months)	1-year (95%CI)	2-year (95%CI)	5-year (95%CI)
Histologic subtype				
Alveolar rhabdomyosarcoma	18.5 (12-32.5)	84.6% (76.7-90)	52.3% (42.5-61.1)	17.4% (10.7-25.6)
Liposarcoma	11 (4-31)	59.2% (51.4-66.2)	42.4% (34.5-50)	20.8% (14.2-28.2)
Leiomyosarcoma	13 (5-28)	64.6% (59.3-69.3)	45.2% (39.7-50.5)	16.2% (12-20.9)
Spindle cell sarcoma	6 (2-17)	50.4% (41.8-58.3)	28% (20.2-36.3)	14.6% (8.4-22.5)
Synovial sarcoma	15 (5-24)	70.4% (62.6-76.9)	38.3% (30.3-46.2)	13.4% (8-20.1)
UPS	7 (3-18)	48.4% (42.8-53.8)	29.1% (23.8-34.5)	13% (9-17.8)
Metastatic pattern				
Bone + Lung	6 (2-17)	49.6% (40.9-57.8)	28.2% (20.3-36.7)	5.6% (2-12)
Bone only	11 (4-21)	65.5% (57.5-72.4)	38.1% (29.8-46.4)	17.9% (11-26.1)
Liver + Lung	7 (2-18)	56.9% (43.2-68.5)	36% (22.9-49.3)	7.2% (1.7-18.5)
Liver only	10 (3-25)	64.8% (50.6-75.9)	44.4% (30.1-57.7)	22.2% (10.4-36.7)
Lung only	9 (3-21)	59.1% (55.3-62.6)	36.3% (32.5-40.2)	16.1% (12.9-19.7)

CI: Confidence interval; UPS: undifferentiated pleomorphic sarcoma.

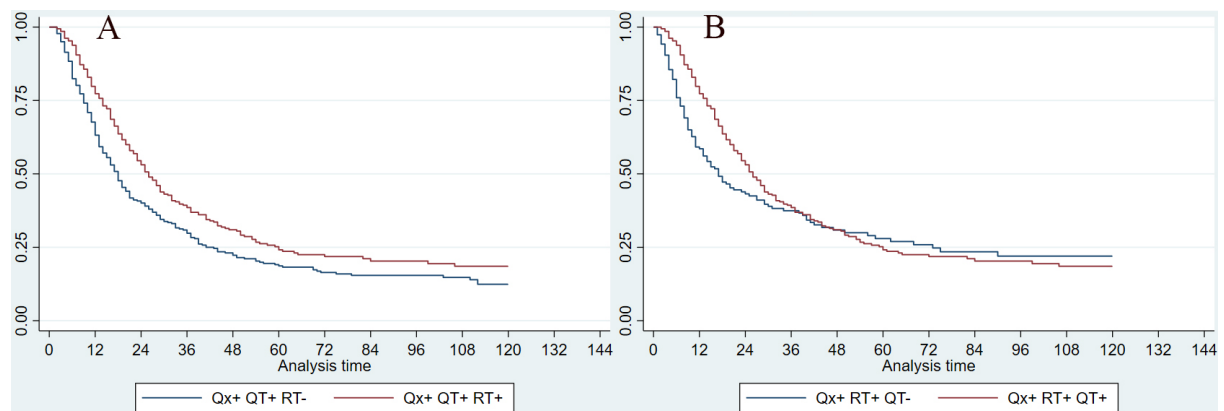


Figure 2. Kaplan-Meier disease-specific survival for patients with metastatic soft tissue sarcoma according to (A) radiotherapy and (B) chemotherapy treatment. Differences were significant for both curves (Log-rank test: $P < 0.001$). QT: Chemotherapy, RT: radiotherapy.

findings, we consider this survival difference might be partially explained by a higher rate of metastasis in teenagers and adolescents.

Soft tissue sarcomas most commonly affect patients of European descent. However, we found that the frequency of Afro-American patients increased in the metastatic cohort. On histologic sub-analysis, differences in sub-population distribution patterns were seen in patients with leiomyosarcoma and UPS. Similar racial disparities in metastatic status have been reported in primary breast, colorectal, and prostate cancer^[22]. Although the underlying causes of racial disparities remain unclear, differences in socioeconomic background and access to healthcare have been reported to be important factors^[23].

Across all STS histologies, the lower limb was the most common location for patients without metastatic disease. Moreover, STS located in the pelvis increased in frequency in patients with metastasis at diagnosis. Pelvic sarcomas have already been recognized for their larger size at presentation, early involvement of adjacent structures and difficulty obtaining wide margins due to anatomic location^[24]. We consider that these factors might explain the higher rates of metastatic disease seen in pelvic tumors at presentation^[25].

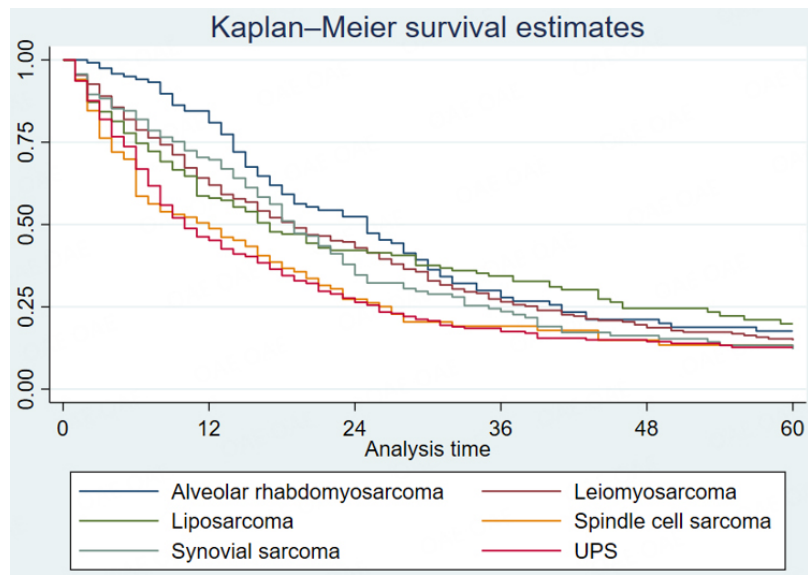


Figure 3. Kaplan-Meier disease-specific survival for patients with metastatic soft tissue sarcoma according to tumor histology. UPS: Undifferentiated pleomorphic sarcoma.

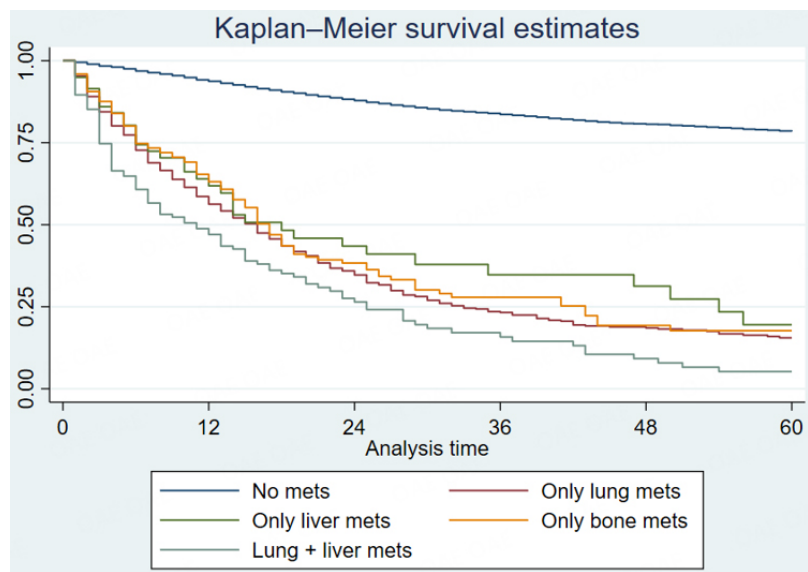


Figure 4. Kaplan-Meier disease-specific survival for patients with metastatic soft tissue sarcoma according to metastatic pattern.

Metastatic patterns of the most common STS

Metastatic soft tissue sarcomas (STS) typically affect the lungs as the first site of metastasis, accounting for about 70% of cases^[26]. However, some STS subtypes exhibit different metastatic patterns. For example, myxoid liposarcoma is known to present with extrapulmonary metastases in 85% of cases, while alveolar soft part sarcoma (ASPS) often metastasizes to the brain^[3,27]. In our study, only 45.9% of patients with metastatic STS showed lung involvement, while involvement of the bones and regional LNs was seen in 85.2% and 62.1% of cases, respectively. The extensive variability in metastatic patterns between STS subtypes reflects the group heterogeneity, especially with regards to molecular profile^[28]. Indeed, unlike other neoplasms such as carcinomas, soft tissue sarcomas encompass a varied array of tumors derived from a

mesenchymal progenitor. Although current STS staging guidelines recommend chest imaging at diagnosis to rule out pulmonary metastases^[5], these guidelines are based on the most common STS types and may not capture the unique metastatic patterns of rarer subtypes. Thus, additional imaging studies tailored to each tumor's specific metastatic patterns should be considered after a histopathological diagnosis is made.

While much of the literature on metastatic STS focuses on lung metastasis, liver metastases also represent a significant concern. In our study, 14.5% of patients presenting with metastatic STS will present with liver metastases. This figure was even higher in leiomyosarcoma, where 30% of metastatic patients showed liver involvement. Furthermore, a study by Jaques *et al.* found that in 65 patients with STS with metastatic disease, 85% of those with liver metastases had leiomyosarcoma as primary tumor^[29]. While retroperitoneal and/or visceral leiomyosarcomas are commonly studied in metastatic STS, it is worth noting that appendicular leiomyosarcomas also frequently metastasize to the liver^[30]. In the setting of STS that tend to metastasize to the liver such as leiomyosarcoma, early detection of liver metastases is paramount due to the reported survival benefit of hepatic metastasectomy in soft tissue sarcomas^[31]. Although retrospective in nature, this nationwide study by Grimme *et al.* reported a 53.9% 3-year overall survival after hepatic metastasectomy^[31]. However, further prospective studies are required to compare surgical resection of hepatic metastases with available chemotherapy regimens.

Patients with alveolar rhabdomyosarcoma differed from all other tumor subtypes as they were more likely to present with bone metastases (85.2%) rather than lung metastases (45.9%). A study from the Intergroup Rhabdomyosarcoma Study group reported lung (47%), bone marrow (38%), bone (34%), and distant LN (26%) as the most common metastatic sites in this tumor^[32]. Furthermore, they found that patients with bone metastasis had a lower 3-year event-free survival (14%) than those with lung metastases (24% for combined lung and extrapulmonary metastasis). Although our study did not identify a survival difference between patients with isolated bone or lung metastases, our analysis was restricted to metastasis at the time of diagnosis and may not represent the course of all patients who develop bone metastasis.

Treatment outcomes in patients with and without metastatic STS

Limb-sparing surgery has been widely adopted as the standard treatment for localized, appendicular STS^[33]. In metastatic STS, however, surgery to the primary site is not often performed and treatment usually takes a palliative approach. This is reflected in our findings, with only 42% of patients with metastatic disease at presentation having surgery at the primary site. Likewise, surgery to the distant site is rare in this population as a clear survival benefit has only been demonstrated in patients with metachronous lung metastasis^[34]. In our study, we found that only 11.7% of patients with metastatic disease at diagnosis had surgery at the distant site. Of 1,503 patients with metastatic disease, 77% presented with lung metastasis and only 11.7% underwent surgery at this distant site.

Radiotherapy was used in 42.4% of patients with metastatic disease and was associated with longer survival (HR = 0.755). Although the use of radiation was almost as common in patients with metastases as in those without, we consider that the scope of treatment was different. Neo-adjuvant radiotherapy in localized appendicular STS is an effective technique to optimize tumor control in the primary site^[9]. In metastatic disease, however, radiation therapy is often used for palliative reasons or local control of metastasis in patients not suitable for surgery^[35]. Our analysis was restricted to the assessment of treatment patterns and due to the retrospective nature of the database, no cause-effect conclusions can be inferred.

Our study also reported that long-term DSS was low for patients with metastatic STS regardless of the use of chemotherapy [Figure 2B]. Although higher 1-year and 2-year survival rates were seen in patients receiving

chemotherapy, 10-year DSS remained below 25% in both groups. Our findings emphasize how, unlike in other malignancies such as breast carcinoma, systemic treatment falls short of achieving more reliable disease remission or cure^[36]. This can be partially explained by the lack of major breakthroughs in systemic treatment, which has relied on the combination of doxorubicin and ifosfamide for the last 30 years^[8].

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 the majority of 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

Extensive heterogeneity in rates of metastatic disease at presentation and organ involvement patterns exists between different STS histologies. Although most STSs present with metastasis involving the lung, alveolar rhabdomyosarcoma most commonly affects the bones and lymph nodes. Disease-specific survival remained poor for patients with metastatic disease at presentation regardless of (neo)-adjuvant radiotherapy or chemotherapy.

DECLARATIONS

Authors' contributions

Conceptualization: Lozano-Calderon SA

Methodology: Gonzalez MR, Lozano-Calderon SA

Formal analysis: Gonzalez MR

Writing - original draft: Gonzalez MR, Rizk P, Hodo TW, Bedi A, Karczewski D

Writing - review & editing: All authors

Supervision: Lozano-Calderon SA

Project administration: Gonzalez MR

Availability of data and materials

Data used in this manuscript were obtained from the SEER database. Access to data can be obtained after proper registration at seer.cancer.gov

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

No ethical approval was required in accordance with the SEER Research Data User Agreement.

Consent for publication

No consent for publication was required since our manuscript adhered to the SEER Research Data User Agreement.

Copyright

© The Author(s) 2023.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43-66. DOI PubMed
2. Gamboa AC, Gronchi A, Cardona K. Soft-tissue sarcoma in adults: an update on the current state of histiotype-specific management in an era of personalized medicine. *CA Cancer J Clin* 2020;70:200-29. DOI
3. Gonzalez MR, Bryce-Alberti M, Leon-Abarca JA, Pretell-Mazzini J. Brain metastases in patients with soft-tissue sarcomas: management and survival-a SEER population-based cohort study. *J Am Acad Orthop Surg Glob Res Rev* 2021;5:1-10. DOI PubMed PMC
4. Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res* 2016;6:20. DOI PubMed PMC
5. Von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue sarcoma, version 2.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16:536-63. DOI
6. Kawai Y, Matsuoka M, Onodera T, et al. Liver metastasis in soft tissue sarcoma at initial presentation. *J Surg Oncol* 2022;126:1074-9. DOI
7. Younis MH, Summers S, Pretell-Mazzini J. Bone metastasis in extremity soft tissue sarcomas: risk factors and survival analysis using the SEER registry. *Musculoskelet Surg* 2022;106:59-68. DOI PubMed
8. Frezza AM, Stacchiotti S, Gronchi A. Systemic treatment in advanced soft tissue sarcoma: what is standard, what is new. *BMC Med* 2017;15:109. DOI PubMed PMC
9. Shah NK, Yegya-Raman N, Jones JA, Shabason JE. Radiation therapy in metastatic soft tissue sarcoma: from palliation to ablation. *Cancers* 2021;13:4775. DOI PubMed PMC
10. Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018;29:iv51-67. DOI
11. Haddox CL, Riedel RF. Individualizing systemic therapy for advanced soft tissue sarcomas based on tumor histology and biology. *Expert Rev Anticancer Ther* 2020;20:5-8. DOI PubMed
12. Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the surveillance, epidemiology, and end results (SEER) program. *Oncologist* 2003;8:541-52. DOI PubMed
13. Gonzalez MR, Bryce-Alberti M, Portmann-Baracco A, Inchaustegui ML, Castillo-Flores S, Pretell-Mazzini J. Appendicular dedifferentiated chondrosarcoma: a management and survival study from the SEER database. *J Bone Oncol* 2022;37:100456. DOI PubMed PMC
14. Gonzalez MR, Bryce-Alberti M, Portmann-Baracco A, Castillo-Flores S, Pretell-Mazzini J. Treatment and survival outcomes in metastatic Merkel cell carcinoma: analysis of 2010 patients from the SEER database. *Cancer Treat Res Commun* 2022;33:100665. DOI PubMed
15. Ferguson PC, Deheshi BM, Chung P, et al. Soft tissue sarcoma presenting with metastatic disease: outcome with primary surgical resection. *Cancer* 2011;117:372-9. DOI
16. Krishnan CK, Kim HS, Park JW, Han I. Outcome after surgery for extremity soft tissue sarcoma in patients presenting with metastasis at diagnosis. *Am J Clin Oncol* 2018;41:681-6. DOI PubMed
17. Tao X, Hou Z, Wu Z, Hao S, Liu B. Brain metastatic alveolar soft-part sarcoma: clinicopathological profiles, management and outcomes. *Oncol Lett* 2017;14:5779-84. DOI PubMed PMC
18. Knebel C, Lenze U, Pohlrig F, et al. Prognostic factors and outcome of Liposarcoma patients: a retrospective evaluation over 15 years. *BMC Cancer* 2017;17:410. DOI PubMed PMC
19. Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. *Nat Rev Dis Primers* 2019;5:1. DOI PubMed PMC
20. Van Gaal JC, Van Der Graaf WTA, Rikhof B, et al. The impact of age on outcome of embryonal and alveolar rhabdomyosarcoma patients. A multicenter study. *Anticancer Res* 2012;32:4485-98. PubMed
21. Joshi D, Anderson JR, Paidas C, Breneman J, Parham DM, Crist W. Age is an independent prognostic factor in rhabdomyosarcoma: a report from the soft tissue sarcoma committee of the children's oncology group. *Pediatr Blood Cancer* 2004;42:64-73. DOI PubMed
22. Akinyemiju T, Sakhuja S, Waterbor J, Pisu M, Altekruze SF. Racial/ethnic disparities in de novo metastases sites and survival outcomes for patients with primary breast, colorectal, and prostate cancer. *Cancer Med* 2018;7:1183-93. DOI PubMed PMC
23. Akinyemiju TF, Vin-Raviv N, Chavez-Yenter D, Zhao X, Budhwani H. Race/ethnicity and socio-economic differences in breast cancer surgery outcomes. *Cancer Epidemiol* 2015;39:745-51. DOI
24. Lewis SJ, Wunder JS, Couture J, et al. Soft tissue sarcomas involving the pelvis. *J Surg Oncol* 2001;77:8-14; discussion 15. DOI
25. Keyzer-Dekker CM, Houtkamp RG, Peterse JL, Van Coevorden F. Adult pelvic sarcomas: a heterogeneous collection of sarcomas? *Sarcoma* 2004;8:19-24. DOI PubMed PMC
26. Brennan MF, Antonescu CR, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. *Ann Surg* 2014;260:416-21; discussion 421-2. DOI PubMed PMC
27. Smith HG, Memos N, Thomas JM, Smith MJ, Strauss DC, Hayes AJ. Patterns of disease relapse in primary extremity soft-tissue sarcoma. *Br J Surg* 2016;103:1487-96. DOI PubMed

28. Jain S, Xu R, Prieto VG, Lee P. Molecular classification of soft tissue sarcomas and its clinical applications. *Int J Clin Exp Pathol* 2010;3:416-28. [PubMed](#) [PMC](#)
29. Jaques DP, Coit DG, Casper ES, Brennan MF. Hepatic metastases from soft-tissue sarcoma. *Ann Surg* 1995;221:392-7. [DOI](#) [PubMed](#) [PMC](#)
30. Smolle MA, Leithner A, Bernhardt GA. Abdominal metastases of primary extremity soft tissue sarcoma: a systematic review. *World J Clin Oncol* 2020;11:74-82. [DOI](#) [PubMed](#) [PMC](#)
31. Grimme FAB, Seesing MFJ, van Hillegersberg R, et al. Liver resection for hepatic metastases from soft tissue sarcoma: a nationwide study. *Dig Surg* 2019;36:479-86. [DOI](#) [PubMed](#) [PMC](#)
32. Oberlin O, Rey A, Lyden E, et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. *J Clin Oncol* 2008;26:2384-9. [DOI](#) [PubMed](#) [PMC](#)
33. Smith HG, Thomas JM, Smith MJF, Hayes AJ, Strauss DC. Major amputations for extremity soft-tissue sarcoma. *Ann Surg Oncol* 2018;25:387-93. [DOI](#) [PubMed](#)
34. Lindsay AD, Haupt EE, Chan CM, et al. Treatment of sarcoma lung metastases with stereotactic body radiotherapy. *Sarcoma* 2018;2018:9132359. [DOI](#) [PubMed](#) [PMC](#)
35. Loi M, Duijm M, Baker S, et al. Stereotactic body radiotherapy for oligometastatic soft tissue sarcoma. *Radiol Med* 2018;123:871-8. [DOI](#)
36. Wiltink LM, Haas RLM, Gelderblom H, van de Sande MAJ. Treatment strategies for metastatic soft tissue sarcomas. *Cancers* 2021;13:1722. [DOI](#) [PubMed](#) [PMC](#)