Survival analysis and treatment strategies for limb liposarcoma patients with metastasis at presentation

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Abstract

Limited data exist on patients with limb liposarcoma (LLS) with metastasis at presentation Moreover, the potential prognostic factors of this patient population are poorly documented because of its rarity. Therefore, we conducted this study to evaluate the clinicopathologic characteristics and prognostic factors for patients with metastatic LLS.

All patients with LLS with metastasis at presentation from 1975 to 2016 were identified by using the Surveillance, Epidemiology, and End Results (SEER) database. The following clinical data were derived from this clinical database: age, sex, histologic grade, subtype, size of tumor, surgery, radiotherapy, chemotherapy, vital status, cause of death, and survival duration. The Kaplan-Meier method was performed to calculate median survival time and draw survivorship curves. Cox-proportional hazards regression model was used to reveal the statistical independence between various variables.

The present study collected 184 cases from SEER database for survival analysis. Mean age was 57.8 years with 63.6% (n = 117) men. The 3-year overall survival (OS) and cancer-specific survival (CSS) rates of this population were 27.8% and 30.1%, respectively. Univariate analysis revealed that age, tumor grade, and surgery were significantly correlated with survival. Sex and tumor size did not reach significant predictor status of survival. Multivariate analysis revealed that age at diagnosis <60, low tumor grade, and local surgery were significantly correlated with improved OS and CSS.

Patients with LLS with metastasis at diagnosis experienced quite poor prognosis. Currently, surgery for the primary tumor significantly prolonged the survival of those patients, whereas chemotherapy and radiotherapy need to be further confirmed.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, ICD-O-3 = 3rd edition of International Classification of Diseases for Oncology, LLS = limb liposarcoma, LS = liposarcoma, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results.

Keywords: limb liposarcoma, metastasis, prognosis, treatment

1. Introduction

Liposarcoma (LS) is a malignant mesenchymal neoplasm, originating from the adipose tissue. It is the most common subtype of soft tissue sarcoma (accounts for 20%).[1] It predominantly occurs in adults older than 50 years, with a slight male predilection.[2] It can occur at almost any site and most cases occur in the limbs and retroperitoneum, especially the upper legs.[3,4] Treatment for limb liposarcoma (LLS) includes surgical resection, radiotherapy, and chemotherapy. However, there is still no standard treatment strategies for those patients especially patients with metastatic LLS.[5] LS obtains local invasiveness and metastatic propensity with high mortality rate.[6] The lung is the most common site of metastasis for LS. Patients usually experience an adverse prognosis if they developed metastatic disease. Although radiotherapy can provide local control and reduce risk of local recurrence,[7] the role of radiotherapy in prolonging survival time of patients with LLS with metastasis at presentation remains unknown. For patients with metastatic LS, chemotherapy is usually required.[2] But whether it can provide a satisfactory prognosis also remains unknown.

We performed this study and analyzed the prognosis of patients with LLS with metastasis at presentation from 1975 to 2016, based on Surveillance, Epidemiology, and End Results (SEER) database. This research is aimed to reveal demographic and prognostic information for patients with LLS with metastasis at presentation, which is helpful for an improved understanding of this cohort.

2. Methods

2.1. Study cohort

Patients with LLS with metastasis at presentation diagnosed from 1975 to 2016 were retrospectively identified by searching SEER

program database. They were enrolled consecutively from the SEER 18 registries in the United States. The database collects tumor information from 20 geographic areas, covering 28% of the US population (https://seer.cancer.gov/). This study does not require informed consent of patients as it is a public database and contains no identifiable data. The study was approved by the Institutional Review Board of Ningbo No. 6 Hospital.

We followed the International Classification of Diseases for Oncology, third edition (ICD-O-3) codes[8] to select LLS cases (9040–9043). We also defined the primary site ICD-O-3 codes (C40.0–C41.9). All patients had a positive histological diagnosis, based on specimen from the biopsy or the surgery. Only patients with metastatic LLS met the requirements of this study. Patients with missing survival information or diagnosed based on autopsy were excluded. The following clinical data were derived from this clinical database: age, sex, histologic grade, subtype, size of tumor, surgery, radiotherapy, chemotherapy, vital status, death causes, and survival duration. Radiotherapy or surgical resection analyzed in this study was performed for primary tumors not metastasis.[8]

2.2. Statistical methods

All statistical analyses were conducted using IBM SPSS Statistics 20.0. We defined cancer-specific survival (CSS)[8] as the duration from initial diagnosis to death resulting from LS. Kaplan–Meier method was employed to evaluate the relationship between variables and survival and generate median survival time. Then we used the Cox regression model to confirm the independent predictors of survival by univariate and multivariate analyses. We simultaneously calculated hazard ratios and 95% confidence interval to show the impact of covariates on survival. Bilateral $P < .05$ was statistically significant.

3. Results

3.1. Patients' characteristics

The present study included a total of 184 eligible patients with LLS with metastasis at presentation for survival analysis. Clinicopathological characteristics of the patients with metastatic LLS are presented in Table 1. We divided age into 2 categories: <60 years and ≥60 years. Mean age was 57.8 years with 63.6% (n=117) men. Grade distribution was low grade 17.9%, high grade 50.0%, and unknown 32.1%. About one third of patients were diagnosed with myxoid liposarcoma (34.8%). A total of 41 (22.3%), 118 (64.1%), and 25 (13.6%) patients had ≤10 cm, >10 cm, and unknown size, respectively. A total of 69.6% of patients received local surgical treatment, 51.6% received radiation treatment, and 60.3% received chemotherapy.

3.2. Survival and prognostic factors

The 3- and 5-year overall survival (OS) rates of metastatic LLS patients were 27.8% and 18.8%, respectively (Table 1). Table 2 summarizes median survival time of this population, including median survival data stratified by various factors.

Univariate analysis (Table 3) revealed that age, tumor grade, and surgery were significantly correlated with both OS and CSS. Sex and tumor size did not reach significant predictor status of survival. A significant increase in survival was seen in patients who received local surgery. OS and CSS were well stratified according to surgery (Fig. 1A and B). Patients receiving

Table 1

Clinical and pathological features of 184 patients with metastatic limb liposarcoma.

Variable	Value
Age at diagnosis (yr)	
<60	97 (52.7%)
≥60	87 (47.3%)
Sex	
Female	67 (36.4%)
Male	117 (63.6%)
Histological grade	
Low (grade 1–2)	33 (17.9%)
High (grade 3–4)	92 (50.0%)
Unknown	59 (32.1%)
Subtype	
Liposarcoma, NOS	20 (10.9%)
Liposarcoma, well differentiated	9 (4.9%)
Myxoid liposarcoma	64 (34.8%)
Round cell liposarcoma	22 (12.0%)
Pleomorphic liposarcoma	40 (21.7%)
Mixed liposarcoma	12 (6.5%)
Dedifferentiated liposarcoma	17 (9.2%)
Tumor size	
≤10 cm	41 (22.3%)
>10 cm	118 (64.1%)
Unknown	25 (13.6%)
Surgery	
Yes	128 (69.6%)
No	56 (30.4%)
Radiation treatment	
Yes	95 (51.6%)
No	89 (48.4%)
Chemotherapy	
Yes	111 (60.3%)
No	73 (39.7%)
Dead	
Yes	144 (78.3%)
No	40 (21.7%)
OS rate (3-yr)	27.8%
OS rate (5-yr)	18.8%
CSS rate (3-yr)	30.1%
CSS rate (5-yr)	19.0%

CSS = cancer-specific survival, NOS = not otherwise specified, OS = overall survival.

radiotherapy or chemotherapy, however, demonstrated no survival benefit ($P < .05$) in univariate Cox analysis.

We integrated significant variables from univariate analysis into the multivariate analysis. On multivariate analysis (Table 4), age ≥60, high tumor grade, and surgery were identified as significant adverse prognostic predictors.

4. Discussion

We retrospectively identified a total of 184 eligible patients with LLS with metastasis at presentation diagnosed between 1975 and 2016 from the SEER database. Many previous studies described the clinicopathologic characteristics and explored the prognostic factors of primary LS. Due to the rarity of metastatic LS, little is known about the clinicopathologic features and survival outcomes of them. In addition, the benefits of various treatment strategies for patients with metastatic LLS are rarely explored. Notably, this is the first and largest study to investigate the clinicopathologic characteristics and prognostic factors of

Table 2

Median survival time of 184 patients with metastatic limb liposarcoma.

Variable	OS (mo)	95% CI	CSS (mo)	95% CI
Overall	15.0 ± 3.1	8.9–21.1	20.0 ± 3.1	14.0–26.0
Age at diagnosis (yr)				
<60	23.0 ± 3.9	15.3–30.7	24.0 ± 3.7	16.8–31.2
≥60	10.0 ± 1.6	6.9–13.1	11.0 ± 1.7	7.6–14.4
Sex				
Female	16.0 ± 2.8	10.6–21.4	19.0 ± 3.9	11.4–26.6
Male	14.0 ± 2.9	8.4–19.6	20.0 ± 5.1	10.0–30.0
Histological grade				
Low (grade 1–2)	37.0 ± 15.6	6.4–67.6	40.0 ± 29.9	0.0–98.7
High (grade 3–4)	11.0 ± 1.4	8.3–13.7	11.0 ± 1.8	7.6–14.4
Tumor size				
≤10 cm	14.0 ± 3.7	6.7–21.3	21.0 ± 10.7	0.0–42.0
>10 cm	15.0 ± 3.1	9.0–21.0	19.0 ± 2.9	13.4–24.6
Surgery				
Yes	19.0 ± 3.3	12.6–25.4	22.0 ± 2.7	16.7–27.3
No	11.0 ± 1.8	7.5–14.5	11.0 ± 2.6	5.9–16.1
Radiotherapy				
Yes	17.0 ± 4.8	7.6–26.4	22.0 ± 3.1	16.0–28.0
No	13.0 ± 2.6	8.0–18.0	16.0 ± 4.6	6.9–25.1
Chemotherapy				
Yes	21.0 ± 3.3	14.6–27.4	24.0 ± 2.8	18.5–29.5
No	11.0 ± 2.0	7.2–14.8	11.0 ± 3.9	3.4–18.6

CI = confidence interval, CSS = cancer-specific survival, OS = overall survival.

patients with LLS with metastasis at presentation, which is beneficial for clinicians to treat patients with LS with metastasis more efficiently.

The mean age at diagnosis of metastatic LLS patients was 57.8 years, which is similar to that of all LS.[9,10] Male predominance (63.6%) was observed in metastatic LLS cohort, and as was consistent with previous studies.[11–13] Patients with metastasis usually had significantly poorer OS than those without metastasis. A recent study showed that the 5-year OS rate of 181 patients with LS of the extremity and truncal wall was 93.3%, whereas this study reported a very poor prognosis (5-year OS rate, 18.8%) among patients with metastatic LLS.[14] The

Table 3

Univariate analysis of variables in 184 patients with metastatic limb liposarcoma.

Variable	OS		CSS	
	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis (yr)				
<60	1		1	
≥60	1.711 (1.232–2.377)	.001	1.738 (1.178–2.564)	.005
Sex				
Female	1		1	
Male	0.954 (0.682–1.335)	.786	0.941 (0.635–1.394)	.762
Histological grade				
Low (grade 1–2)	1		1	
High (grade 3–4)	2.117 (1.305–3.435)	.002	2.379 (1.345–4.208)	.003
Unknown	1.478 (0.874–2.500)	.145	1.588 (0.859–2.934)	.140
Tumor size				
≤10 cm	1		1	
>10 cm	1.165 (0.775–1.751)	.463	1.200 (0.753–1.912)	.444
Unknown	1.009 (0.579–1.756)	.976	1.110 (0.582–2.117)	.752
Surgery				
Yes	1		1	
No	1.545 (1.074–2.224)	.019	1.629 (1.076–2.466)	.021
Radiotherapy				
Yes	1		1	
No	1.066 (0.765–1.486)	.704	1.057 (0.720–1.551)	.778
Chemotherapy				
Yes	1		1	
No	1.338 (0.955–1.874)	.091	1.340 (0.900–1.994)	.150

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival.
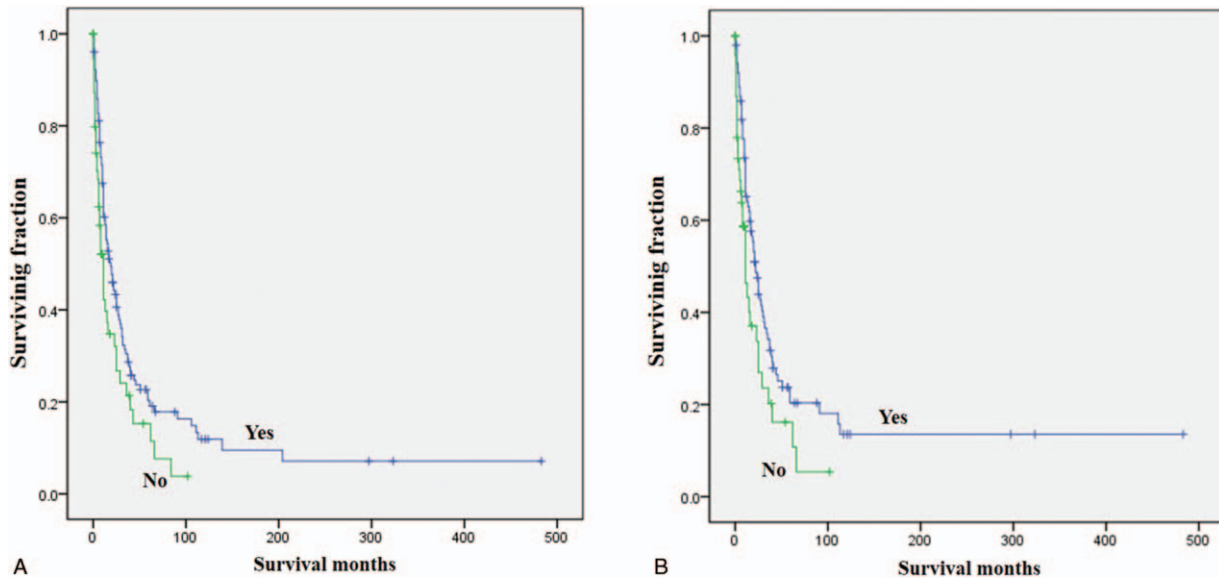
Figure 1. Kaplan-Meier overall (A) and cancer-specific (B) survival curves of patients with metastatic LLS stratified by surgery.

median OS from in this special cohort was 15.0 ± 3.1 months, which is similar to results reported from inoperable or metastatic LS.[13] Treatments for patients with metastatic LLS are, however, rarely reported and remain unknown. Thus, how to treat such patients and find effective prognostic factors is the urgent task at present.

This study found that age at diagnosis was a significant independent predictor of survival. Greto et al,[15] confirmed that age older than 65 years was an adverse independent predictor of recurrence and OS among patients with operable LS. Maybe elderly patients obtain specific genomic alterations and present with larger tumors at diagnosis.[15–17] Langman et al,[13] however, reported that age at diagnosis of advanced disease was not associated with OS based on univariate analysis. We noted that sex was not a prognostic predictor, which was congruent with many previous studies.[2,13,15] Survival benefits were usually pronounced in patients with LS with low tumor grade.[14,15] Our multivariate analysis also showed tumor grade was independently correlated with OS and CSS among metastatic patients with LLS. Tumor size is one of the common predictors of survival among patients with LS.[18,19] However, some studies

failed to find that tumor size was associated with survival among patients with LS.[2,14,20] Similar survival outcomes were found in metastatic patients with LLS. Interestingly, previous studies also reported the lack of a size effect on metastases, which was an important event for survival time.[21–23] However, this departure from the expected relationship between tumor size and survival has not been well explained. Thus, further studies are needed to confirm the relationship between tumor size and survival among specific patients with LS.

Although surgical resection is the mainstream treatment for patients with local LLS, little is known of the role of surgery among patients with metastatic LLS. This study first confirmed the positive role of local surgery for primary tumor in prolonging survival among patients with metastatic LLS. Radiotherapy provided local control in patients with LS after surgical resection but not significantly reduced the rate of metastasis or improved survival.[24,25] We did not observe a survival benefit with radiotherapy among patients with metastatic LLS. Simultaneously, we demonstrated that patients with metastatic LLS who received chemotherapy did not benefit from survival. Maybe chemotherapy resistance is common among metastatic LS.[26]

Table 4

Multivariate analysis of variables in 184 patients with metastatic limb liposarcoma.

Variable	OS		CSS	
	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis (yr)				
<60	1		1	
≥60	1.774 (1.270–2.477)	.001	1.727 (1.164–2.560)	.007
Histological grade				
Low (grade 1–2)	1		1	
High (grade 3–4)	2.471 (1.504–4.060)	<.001	2.623 (1.470–4.678)	.001
Unknown	1.668 (0.977–2.848)	.061	1.694 (0.910–3.155)	.096
Surgery				
Yes	1		1	.011
No	1.748 (1.200–2.544)	.004	1.732 (1.135–2.644)	

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival.

This study initially delineated therapeutic management of metastatic LLS, and more studies are needed in the future.

Although this study provided survival information for metastatic LLS, it has several limitations: it was a retrospective study with certain bias; information about local or distant recurrence during follow-up were not documented in the SEER database, which might affect the outcome; other clinical factors, such as surgical margin and detailed systemic chemotherapy regimen, were not available in the SEER database. Despite these defects, the SEER database is a very important clinical research tool for rare tumor populations, such as patients with LLS with metastasis at presentation.

5. Conclusion

The present study revealed that patients with LLS with metastasis at presentation experienced quite poor prognosis. Surgery for the primary tumor may be beneficial for prolonging survival time, whereas combination therapies such as chemotherapy and/or radiotherapy need to be further explored.

Author contributions

Conceptualization: Jing Ling.
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