Lung metastases pattern in limb osteosarcoma
A population-based study from 2010 to 2018
Binbin Liu, MM∗, Liyuan Tang, MMb

Abstract
Osteosarcoma (OS) is one of the most prevalent malignant bone tumors. The proportion of limb OS is relatively high, and lung metastases (LM) are one of the most prevalent metastatic types. A total of 1694 new cases of limb OS were identified in the surveillance, epidemiology and end results (SEER) database from 2010 to 2018. Cox regression analyze was performed to identify prognostic factors for limb OS with LM, and univariate and multivariate logistic regression analyses were used to assess risk factors for LM. Kaplan–Meier analysis was performed to calculate overall survival for LM, and a log-rank test was used for comparison. A total of 287 patients (16.94%) were diagnosed with limb OS with LM. 25 to 59 years old (odds ratio, OR 0.68; 95% confidence interval, CI: 0.46–0.99), larger than 100mm tumors (OR 3.65, 95% CI: 1.54–8.64), telangiectatic osteosarcoma type (OR 0.24, 95% CI: 0.07–0.81), central osteosarcoma type (OR 0.44, 95% CI: 0.19–0.99), T2 stage (OR 2.59, 95% CI: 1.18–5.69), N1 stage (OR 7.79, 95% CI: 3.90–15.56), presence of bone metastases (OR 4.58, 95% CI: 2.43–8.63) and surgical treatments of primary site (OR 0.22, 95% CI: 0.14–0.33) were significant correlations with lung metastases. Elderly age, black race and absence of surgery were harmful for survival. Age between 25 and 59 years, telangiectatic osteosarcoma and central osteosarcoma were identified as high-risk factors in limb OS patients with LM, and surgical treatment of the primary site significantly increased the survival rate of LM in these patients.

Abbreviations: CI = confidence interval, LM = lung metastases, OR = odds ratio, OS = osteosarcoma, SEER = the surveillance, epidemiology and end results.

Keywords: lung metastases, osteosarcoma, prognosis, risk factor, SEER program

1. Introduction
Osteosarcoma (OS) is one of the most prevalent bone tumors and occurs mostly in young people.1 It is mostly derived from the terminus of the limb, including the humerus, distal femur and proximal.2,3 The most common organ with metastasis is the lungs which accounts for 80% of all metastatic cases. OS occurred more frequently in men than in women. Following treatment, 30% to 40% of individuals still experience recurrence, and <20% of patients survive after recurrence.4 The median time for lung metastases (LM) is 10 months.5 Treasure and Macbeth found that surgery was an effective way to treat OS, and patients with high recurrence rates and low survival rates after treatment lacked efficient early screening models for disease. Limb OS is relatively high in the proportion of OS, and it is one of the most harmful bone malignant bone cancers with a poor prognosis. Patients with limb OS may benefit from early screening, diagnosis and treatment effective.6,7

The surveillance, epidemiology, and end results (SEER) database is a publicly accessible database that collects data on approximately 30% of the United States population. It provides risk data and prognostic data were collected from 18 established cancer registries in the United States.

The data from this study is publicly available in the national cancer institute’s SEER database at https://seer.cancer.gov/data/access.html. There are about 18 forms in SEER*Stat’s, the official software recommended by the SEER database, with a total of more than 80 variables. Including the patient’s registration code, primary tumor location, tumor size, tumor histological type (Histologic Type ICD-3), treatment plan and cause of death. The SEER database has a very large sample size and contains a variety of rare cancers, and it is very convenient to obtain data, and the data can be downloaded in excel format and analyzed...
using software such as SPSS software. We analyzed information from the SEER database to investigate the prevalence and risk factors of limb OS with LM. In addition, survival analysis was performed for limb OS with LM to assess the prognostic factors.

2. Material and Methods

2.1. Ethical statement

The study is based on Helsinki Declaration and subsequent amendments.

2.2. Study population

Data were collected from the SEER Database, and SEER Stat 8.3.9 software was used to collect case listings. Detailed information on limb OS metastasis was not available prior to 2010. Therefore we chose to study OS between 2010 and 2018. The histological types of OS were limited to 9180/3, 9181/3, 9182/3, 9183/3, 9184/3, 9185/3, 9186/3, 9187/3, 9192/3, 9193/3, and 9194/3 according to the International Classification of Diseases for Oncology-3 (ICD-O-3).[8] 9180/3, 9181/3, 9182/3, 9183/3, 9184/3, 9185/3, 9186/3, 9187/3, 9192/3, 9193/3, and 9194/3 represented osteosarcoma NOS, chondroblastic osteosarcoma, fibroblastic osteosarcoma, telangiectatic osteosarcoma, osteosarcoma in Paget disease of bone, small cell osteosarcoma, central osteosarcoma, intratissue well differentiated osteosarcoma, parosteal osteosarcoma, periosseal osteosarcoma and high grade surface osteosarcoma respectively. Limb OS was limited to c40.0, c40.1, c40.2, c40.3, c40.8, c40.9, c49.1, and c49.2 according to the primary situation. c40.0, c40.1, c40.2, c40.3, c40.8, c40.9, c49.1, and c49.2 represented long bones of the upper limb, short bones of the upper limb, long bones of the lower limb, short bones of the lower limb, cartilage of the limbs, bone of the limb, soft tissue of the upper limb, and soft tissue of the lower limb, respectively. The exclusion criteria were as follows: patients from the SEER database outside of January 1, 2010, to December 31, 2018; limb OS was not the primary disease of the patient; and all blank options and unknown options for limb OS patients with LM.[9] From this database, 1694 patients were identified as having limb OS and 287 patients were diagnosed with limb OS with LM.

2.3. Statistical analysis

The demographic and clinical characteristics of patients with limb OS were divided into:

- Age (≤24, 25–59 and ≥ 60 years);
- Sex (female and male);
- Race (White, Black, American Indian/Alaska Native, Asian or Pacific Islander and unknown);
- Tumor size (<50, 50–100, >100 mm and unknown);
- T stage (T1, T2, T3, T4, and unknown);
- N stage (N0, N1, and unknown);
- M stage (M0, M1, and unknown);
- Tumor differentiation grade (I, II, III, IV, and unknown);
- Histological types (9180/3, 9181/3, 9182/3, 9183/3, 9184/3, 9185/3, 9186/3, 9187/3, 9192/3, 9193/3, and 9194/3); absence or presence of bone, brain, liver metastases, and surgery. Differences in the prevalence of LM were analyzed using Pearson chi-square test.[10] The patients’ risk factors were first determined by univariate logistic regression, and multivariate analysis was performed for statistically significant risk factors (P < .05). The K-M curve and log-rank test were used to analyze survival difference in limb OS patients with LM. Multivariate Cox proportional risk regression was performed according to the above factors, and statistical significance was set at P < .05 was considered as significant.[10] All statistical analyses were performed using the social science statistical software package (SPSS) 25.0 (IBM, Armonk, NY), and all survival charts were analyzed using GraphPad Prism 9 (GraphPad, Inc.). Statistical significance was defined as a two-tailed P < .05.

3. Results

3.1. Prevalence of lung metastases

A total of 1694 limb OS were included in this study. The incidence of LM was 16.94% in the 287 patients with limb OS and LM (Table 1). Among the 1694 limb OS patients, 3.10% (N = 52), 0.18% (N = 3), and 0.12% (N = 2) of patients had metastases to the liver, brain, or bones, respectively. LM alone accounted for 82.90 percent of all metastatic cases (N = 257). Patients under 24 years of age comprised the majority of the overall number of patients with limb OS and LM. Patients older than 60 years had a significantly higher rate of LM than younger patients (χ² = 9.62; P = .008). Males were more likely than females to develop lung metastases (18.55 % versus 14.86 %), and male patients experienced a considerably higher rate of LM than female patients (χ² = 4.03; P = .045). The prevalence of LM was not significantly different between racial and ethnic groups. Additional clinical and pathological information is included in Table 1.

3.2. Risk factors for developing lung metastases

According to univariate logistic analysis, multiple characteristics were significantly related to lung metastases. These factors include age 25 to 59 years (odds ratio [OR] = 0.63, 95% CI: 0.45–0.88, P = .007), gender as female (OR = 0.77, 95% CI: 0.59–0.99, P = .045), primary tumor size 50 to 100 mm (OR = 2.30, 95% CI: 1.13–4.69, P = .022), primary tumor size larger than 100 mm (OR = 5.04, 95% CI: 2.51–10.11, P < .001), primary tumor T2 stage (OR = 2.23, 95% CI: 1.59–3.12, P < .001); T3 stage (OR = 5.89, 95% CI: 3.14–11.04, P < .001); regional lymph node N1 stage (OR = 9.90, 95% CI: 5.28–18.58, P < .001); histological types include telangiectatic osteosarcoma (OR = 0.225, 95% CI: 0.07–0.73, P = .013); central osteosarcoma (OR = 0.40, 95% CI: 0.18–0.88, P = .022) and parosteal osteosarcoma (OR = 0.05, 95% CI: 0.01–0.34, P = .002); tumor differentiated Grade: Grade III (OR = 14.96, 95% CI: 2.04–109.60, P = .008); Grade IV (OR = 12.71, 95% CI: 1.74–92.57, P = .012). Bone metastases (OR = 7.44, 95% CI: 4.22–13.10, P < .001) and primary site surgery (OR = 0.20, 95% CI: 0.14–0.28, P < .001).

Multivariate logistic analysis showed that multiple factors were significantly associated with LM. These items are: 25–59 years old (OR = 0.68, 95% CI: 0.46–0.99, P = .049); primary tumor larger than 100 mm (OR = 3.65, 95% CI: 1.54–8.64, P = .003); histological type: telangiectatic osteosarcoma (OR = 0.24, 95% CI: 0.07–0.81, P = .022), central osteosarcoma (OR = 0.44, 95% CI: 0.19–0.99, P = .048); primary tumor T stage: T3 stage (OR = 2.59, 95% CI: 1.18–5.69, P = .018); regional lymph node N1 stage (OR = 7.79, 95% CI: 3.90–15.56, P < .001); bone metastases (OR = 4.58, 95% CI: 2.43–8.63, P < .001) and primary site surgery (OR = 0.22, 95% CI: 0.14–0.33, P < .001) (Table 1).

3.3. Survival time and prognostic factors for LM

In the end, 60.63% of limb OS patients with LM died, the median overall survival for limb OS patients with LM was 21.00 months (95% CI: 17.94–24.06 months, Fig. 1A, GraphPad Prism 9, Graphpad, Inc.). K-M analysis of overall survival showed that the patients aged 25 to 59 years old (OR = 0.46–0.99, P = .049); primary tumor larger than 100 mm (OR = 3.65, 95% CI: 1.54–8.64, P = .003); histological type: telangiectatic osteosarcoma (OR = 0.24, 95% CI: 0.07–0.81, P = .022), central osteosarcoma (OR = 0.44, 95% CI: 0.19–0.99, P = .048); primary tumor T stage: T3 stage (OR = 2.59, 95% CI: 1.18–5.69, P = .018); regional lymph node N1 stage (OR = 7.79, 95% CI: 3.90–15.56, P < .001); bone metastases (OR = 4.58, 95% CI: 2.43–8.63, P < .001) and primary site surgery (OR = 0.22, 95% CI: 0.14–0.33, P < .001) (Table 1).
In the multivariable Cox regression model, the overall survival rate of elderly patients, (25–59 years, hazard ratio, HR = 1.77, 95% CI: 1.17–2.67, \( P = .007 \); ≥60 years, hazard ratio, HR = 3.92, 95% CI: 2.44–6.31, \( P < .001 \); black race (HR = 1.66; 95% CI: 1.12–2.46; \( P = .012 \) were worse than those of younger patients, and the median survival times were 12 and 5 months, respectively. The results showed that patients undergoing primary site surgery (HR = 0.40; 95% CI: 0.27–0.58; \( P < .001 \) had better overall survival than no surgical treatments, a median survival time 29 months (Table 2).

### 4. Discussion

This study aimed to evaluate the risk and prognosis factors associated with limb OS in patients with LM. Currently, there are a few reports of osteosarcoma that have spread to the lungs; however, research on limb OS with LM is uncommon. Treasure and Macbeth found that 81% of 202 patients with bone sarcoma had LM, and 62% had LM only.\(^7\) In this study, we discovered that 16.94% of limb OS patients had LM, 14.94% had LM only, 60.63% (\( N = 174 \)) and LM had a significant effect on the survival of patients with limb OS. To forecast and intervene in disease progression and survival rate in advance, we propose that these risk factors be identified early by medical researchers and that physicians use these risk factors to tailor treatment regimens and follow-up tactics for patients.\(^{12–14}\)

### Table 1

Multivariable logistic regression analysis of characteristics of limb osteosarcoma patients (diagnosed between 2010 and 2018).

| Subject characteristics                          | With LM (n, %) | Without LM (n, %) | OR (95% CI) | \( P \) value |
|--------------------------------------------------|---------------|------------------|------------|--------------|
| n                                                | 287 (16.94)   | 1407 (83.06)     |            |              |
| Age, in yr                                        |               |                  |            |              |
| 24≤                                              | 201 (17.98)   | 917 (82.02)      | 1 (Reference) | 1.00          |
| 25–59                                            | 48 (12.12)    | 348 (87.88)      | 0.68 (0.46–0.99) | .049          |
| ≥60                                               | 38 (21.11)    | 142 (78.89)      | 0.84 (0.52–1.34) | .451          |
| Tumor size (mm)                                   |               |                  |            |              |
| <50                                               | 9 (5.59)      | 152 (94.41)      | 1 (Reference) | 1.00          |
| 50–100                                            | 80 (11.99)    | 567 (88.01)      | 1.80 (1.19–2.68) | .018          |
| >100                                              | 154 (22.99)   | 516 (77.01)      | 3.65 (1.54–8.64) | .003          |
| Unknown                                           | 44 (22.45)    | 152 (77.55)      | NA         |              |
| Histological type                                 |               |                  |            |              |
| Osteosarcoma and NOS                              | 224 (19.21)   | 942 (80.79)      | 1 (Reference) | 1.00          |
| Chondroblastic osteosarcoma                       | 39 (19.31)    | 163 (80.69)      | 0.95 (0.63–1.43) | .792          |
| Fibroblastic osteosarcoma                         | 5 (11.11)     | 40 (88.89)       | 0.59 (0.22–1.62) | .307          |
| Telangiectatic osteosarcoma                       | 3 (6.08)      | 56 (94.92)       | 0.24 (0.07–0.81) | .022          |
| Osteosarcoma in Paget disease of bone             | 1 (6.67)      | 5 (93.33)        | 0.22 (0.02–3.14) | .266          |
| Small cell osteosarcoma                           | 5 (20.83)     | 21 (79.17)       | 1.81 (0.63–5.76) | .342          |
| Central osteosarcoma                              | 7 (8.64)      | 64 (91.36)       | 0.44 (0.19–0.99) | .048          |
| Intraosseous well differentiated osteosarcoma      | 0 (0.00)      | 2 (100.00)       | 0.00 (0.00–NA) | 1.000          |
| Parosteal osteosarcoma                            | 1 (1.10)      | 9 (98.90)        | 0.16 (0.02–1.22) | .076          |
| Periosteal osteosarcoma                           | 1 (0.25)      | 18 (94.74)       | 0.20 (0.02–2.05) | .173          |
| High grade surface osteosarcoma                    | 1 (10.00)     | 9 (90.00)        | 0.60 (0.07–5.37) | .649          |
| T stage                                           |               |                  |            |              |
| T1                                                | 49 (9.33)     | 476 (90.67)      | 1 (Reference) | 1.00          |
| T2                                                | 177 (18.65)   | 772 (81.35)      | 2.59 (1.19–5.69) | .018          |
| T3                                                | 20 (7.74)     | 33 (62.62)       | 0.00 (0.00–NA) | .999          |
| T4                                                | 0 (0.00)      | 3 (100.00)       | 1.23 (0.54–2.78) | .622          |
| Unknown                                           | 41 (25.00)    | 123 (75.00)      | NA         |              |
| N stage                                           |               |                  |            |              |
| N0                                                | 237 (15.02)   | 1341 (84.98)     | 1 (Reference) | 1.00          |
| N1                                                | 28 (63.64)    | 16 (36.36)       | 7.79 (3.90–15.56) | <.001          |
| Unknown                                           | 22 (32.95)    | 50 (69.44)       | NA         |              |
| Grade                                             |               |                  |            |              |
| Grade I                                           | 1 (1.59)      | 62 (98.41)       | 1 (Reference) | 1.00          |
| Grade II                                          | 5 (6.41)      | 73 (93.59)       | 3.60 (0.38–34.46) | .266          |
| Grade III                                         | 76 (19.44)    | 315 (80.56)      | 5.84 (0.73–46.83) | .096          |
| Grade IV                                          | 116 (17.01)   | 566 (82.99)      | 5.01 (0.63–39.83) | .128          |
| Unknown                                           | 89 (18.54)    | 391 (81.46)      | NA         |              |
| Bone metastases                                   |               |                  |            |              |
| None                                              | 254 (15.50)   | 1385 (84.50)     | 1 (Reference) | 1.00          |
| Yes                                               | 30 (57.69)    | 22 (42.31)       | 4.58 (2.43–8.63) | <.001          |
| Unknown                                           | 3 (100.00)    | 0 (00.00)        | NA         |              |
| Surg                                              |               |                  |            |              |
| None                                              | 74 (44.58)    | 92 (55.42)       | 1 (Reference) | 1.00          |
| Yes                                               | 211 (13.96)   | 1301 (86.04)     | 0.22 (0.14–0.33) | <.001          |
| Unknown                                           | 2 (12.50)     | 14 (87.50)       | NA         |              |

\( \text{AI} = \text{American Indian/Alaska Native}, \ \text{API} = \text{Asian or Pacific Islander}, \ \text{LM} = \text{lung metastases}, \ \text{NA} = \text{not available}, \ \text{OR} = \text{odds ratio}, \ \text{Surg, surgical treatments of the primary site.} \)
It is not surprising that age >60 years of age, larger initial tumor size, and higher T and N stages were found to be risk factors for LM limb OS. Age 25 to 59 years was detected in this study as a risk factor for limb OS in patients with LM, and this difference may be explained by the earlier onset of cancer due to stress at work and in daily life.\(^{[14,15]}\) Other studies simply separated it into osteosarcoma NOS and others, based on its pathological nature.\(^{[11]}\) Osteosarcoma NOS was one of the 11 subtypes included in this study that examined disease risk factors. LM is highly linked to telangiectatic and central osteosarcoma. Patients with the two aforementioned pathological categories of limb OS without lung metastases will be the focus of follow-up in the future.

According to a retrospective study, surgery can improve survival in patients with OS and LM. In this study, surgery increased survival in patients with limb OS with and without lung metastases. In terms of prognostic factors, 73.52% of patients with LM underwent surgery compared to 92.47% of patients without surgery.

**Table 2**

| Subject characteristics | No. of bone sarcoma patients | Overall | Deceased (n, %) | Survival, median (IQR), mo | HR (95% CI) | P value |
|-------------------------|-------------------------------|---------|----------------|---------------------------|-------------|---------|
| n                       | 287                           | 174 (60.63) |                |                           |             |         |
| Age, in yr              |                               |         |                |                           |             |         |
| 24≤                    | 201                           | 106 (52.74) | 31.00 (23.80–38.20) | 1 (Reference) | 1.00      |         |
| 25–59                   | 48                            | 34 (70.83) | 12.00 (6.13–17.87) | 1.77 (1.17–2.67) | .007     |         |
| ≥60                     | 38                            | 34 (89.47) | 5.00 (3.70–6.30) | 3.75 (2.30–6.12) | <.001    |         |
| Race                    |                               |         |                |                           |             |         |
| White                   | 210                           | 127 (60.48) | 21.00 (17.02–24.98) | 1 (Reference) | 1.00      |         |
| Black                   | 50                            | 36 (72.00) | 15.00 (7.84–22.16) | 1.66 (1.12–2.46) | .012     |         |
| AI                      | 4                             | 2 (50.00) | 20.00 (2.40–37.60) | 0.49 (0.12–2.09) | .337     |         |
| API                     | 23                            | 9 (39.13) | 40.00 (32.42–47.58) | 0.62 (0.31–1.22) | .164     |         |
| Surg                    |                               |         |                |                           |             |         |
| None                    | 74                            | 60 (81.08) | 8.00 (6.22–9.78) | 1 (Reference) | 1.00      |         |
| Yes                     | 211                           | 113 (53.55) | 29.00 (22.39–35.62) | 0.40 (0.27–0.58) | <.001    |         |

AI = American Indian/Alaska Native, API = Asian or Pacific Islander, NA = not available, Surg = surgical treatments of the primary site.
Patients who underwent surgery, whether they had LM or not, had better outcomes than those who did not. Patients should receive surgical treatment as soon as possible.\cite{16,17}

This study has some limitations. First, there is no further description of surgical information in the SEER database, including details of surgical type, operative time, intraoperative blood loss etc. Second, among limb OS patients with LM, the SEER database did not record symptomless patients or patients who developed advanced LM.\cite{18} The actual incidence of LM in patients with limb OS may have been underestimated. Finally, a large number of other studies are required to verify these results.\cite{19}

5. Conclusion
Age between 25 and 59 years, telangiectatic osteosarcoma and central osteosarcoma were identified as high-risk factors in patients with limb OS and LM, and surgical treatment of the primary site significantly increased the survival rate of LM in these patients.

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Author contributions
Conceptualization: Binbin Liu.
Data curation: Binbin Liu, Liyuan Tang.
Formal analysis: Binbin Liu, Liyuan Tang.
Investigation: Binbin Liu.
Methodology: Binbin Liu, Liyuan Tang.
Project administration: Binbin Liu.
Resources: Binbin Liu, Liyuan Tang.
Software: Binbin Liu, Liyuan Tang.
Supervision: Binbin Liu.
Validation: Binbin Liu.
Visualization: Binbin Liu.
Writing – original draft: Binbin Liu.
Writing – review & editing: Binbin Liu.

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