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Research Paper

Risk and clinicopathological features of osteosarcoma metastasis to the lung: A population-based study

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A B S T R A C T

Background: Osteosarcoma is the most common primary sarcoma of the bone.
Lung osteosarcoma metastases at diagnosis have a significantly poor prognosis, even when surgery plus chemotherapy are performed. Our goal was to analyze clinical and sarcoma characteristics that could help identify factors related to an increased rate of lung metastasis and to identify different modes of treatment and its correlation with survival.

Materials and Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify all osteosarcoma patients diagnosed from 2010 to 2015. Patient characteristics such as age, sex, ethnicity, marital status, tumor location, histologic grade, surgery, chemotherapy, radiation therapy, SEER cause-specific death classification, survival, and lung metastasis were collected. These factors were analyzed using Univariate and multivariate regression models in survival analyses.

Results: A total of 1057 osteosarcoma patients diagnosed from 2010 to 2015 were included, of which 176 were patients with lung metastasis. Substantial disparities in the rate of lung metastasis existed when osteosarcoma patients were stratified according to tumor location ($P = 0.0002$) and tumor size ($P < .001$). Using a Multivariate Cox regression model, being older than 30 years (vs. younger than 30, HR = 2.171, 95% CI = 1.623–2.905, $P < .0001$), having a tumor >5–10 cm (vs. <5 cm, HR = 2.046, 95% CI = 1.153–3.632, $P = 0.0014$) and >10 cm (vs. <5 cm, HR = 3.610, 95% CI = 2.066–6.310, $P < .0001$) were related to an increased HR for all-cause death. The HR decreased in patients with surgery (vs. no surgery, HR = 0.189, 95% CI = 0.138–0.260, $P < 0.0001$) and osteosarcoma. As for osteosarcoma patients with lung metastases, Multivariate Cox regressions revealed that an increased HR was associated with being older than 30 years (vs. younger than 30 years, HR = 2.142, 95% CI = 1.273–3.605, $P = .0041$) and married (vs. no marriage, HR = 2.418, 95% CI = 1.400–4.176, $P = .0015$), while a decreased HR was related to having had surgery (vs. no surgery, HR = 0.282, 95% CI = 0.171–0.464, $P < .0001$) and chemotherapy (vs. no chemotherapy, HR = 0.107, 95% CI = 0.050–0.229, $P < .0001$).

Conclusions: Advanced age (older than 30 years) and large tumors were related to a higher risk of lung metastases in osteosarcoma patients. Therefore, patients who were diagnosed at advanced age or had large tumors should receive comprehensive chest CT scans. Surgery and chemotherapy can significantly improve the survival of metastatic patients, while radiotherapy did not improve survival in these patients.

1. Introduction

Osteosarcoma is the most common primary malignancy of the bones. Its incidence follows a bimodal age distribution, with two dominant peaks in adolescent and elderly patients [1]. According to previous studies, osteosarcoma is more likely to occur in the metaphyseal portion of long bones [2]. Since the introduction of chemotherapy in the 1980s, the overall survival rate of non-metastatic osteosarcoma patients has improved from 20% to over 70% [3]. However, the prognosis for osteosarcoma distant metastasis cases remains poor.

Lung metastases are of particular poor prognosis among patients with osteosarcoma. It is assumed that approximately 20% of the sarcoma patients have detectable metastasis at diagnosis [4]. In fact, the 5-year overall survival for osteosarcoma patients with lung metastases is approximately 30%, compared to 70% of those without metastasis [5]. The current treatment for osteosarcoma patients with lung metastasis is complete surgical resection, followed by the same chemotherapy regimen prescribed to patients with localized high-grade osteosarcoma [6]. However, the prognosis for metastatic disease remains poor and more than half of the cases relapse, even when combined treatments are used. At present, the best treatment strategy to manage osteosarcoma

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patients with lung metastasis is still not clear.

A better understanding of the risk and the clinicopathological features of osteosarcoma patients with lung metastases can help identify patients with high-risk factors and improve prognosis. The aim of the present study was to analyze clinical and sarcoma characteristics to identify factors related to an increased rate of lung metastasis.

2. Materials and methods

2.1. Patient data

Patient data were obtained from the 18 population-based cancer Registries Custom Data (with additional treatment fields), Nov 2017 Sub (1973–2015 varying) of the Surveillance, Epidemiology, and End Results (SEER) database, which covers cancer incidence and survival data of approximately 28% of the population of the United States. Using SEER *Stat (version 8.3.5 National Cancer Institute, Bethesda, MD), we chose a cohort as follows: Site recode: ICD-O-3/WHO 2008 = "Bones and Joints"; Histologic Type: ICD-O-3 = "9180–9187,9192–9195". Because SEER only included information on the location of metastases between 2010 and 2015, we only identified patients who were diagnosed during these years. A total of 1057 patients with osteosarcoma were identified. Patients' and treatment characteristics of interest included: age, sex, ethnicity, marital status, tumor location, histologic grade, surgery, chemotherapy, radiation therapy, SEER cause-specific death classification, survival time, and lung metastasis. Surgery and radiation therapy were considered for the primary site. Ethnicity was characterized as white, black, or other. Marital status was characterized as married, not married, and unknown. Not married included single (never married), widowed, divorced, separated and unmarried or domestic partner. Tumor location was classified as in extremity, axial, and other. Tumor size was characterized as ≤ 5 cm, >5–10 cm and >10 cm. We excluded a total of 484 patients from those diagnosed with osteosarcoma in the SEER database (n = 1541) because of unknown histologic grade (n = 390), unknown stage (n = 79), unknown ethnicity (n = 6) or unknown metastatic site (n = 9). Finally, a total of 1057 osteosarcoma patients were included in the analysis (Fig. 1).

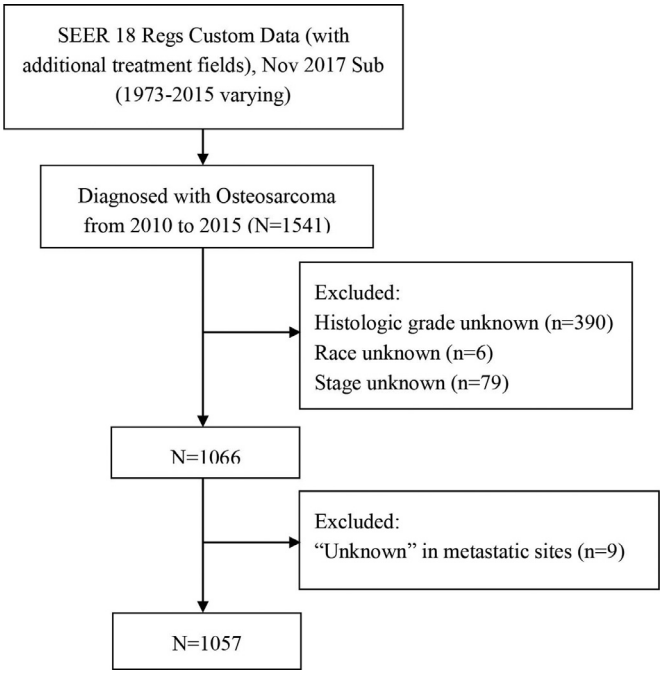

Fig. 1. A flowchart of patient selection from the SEER database.

2.2. Statistical analysis

Categorical variables of clinical characteristics of patients were analyzed by Chi-square test and rank-sum test. Cancer specific survival (CSS) was defined as the period from diagnosis to death as a result of osteosarcoma. The hazard ratio (HR), and its corresponding 95% confidence interval (95% CI), was obtained using a proportional hazard regression model. Multivariate analysis was applied to calculate HR for sex, age, histologic grade, tumor location, tumor size, surgery, and radiation. All P values were two-tailed and a P <.05 was considered statistically significant. SAS software (version 9.3; SAS Institute, Cary, CA) and SPSS (version 19.0 IBM Corporation, Armonk, NY) were used to conduct the statistical analyses.

3. Results

3.1. Characteristics of the patients with osteosarcoma

A total of 1057 patients with osteosarcoma diagnosed from 2010 to 2015 were included. Among these patients, 176 had lung metastasis. The characteristics of osteosarcoma patients with lung metastasis is shown in Table 1. The overall rate of osteosarcoma patients with lung metastasis at presentation was 16.65%. There was a peak in the incidence of lung metastasis in osteosarcoma patients according to their age at diagnosis. The age distribution of the whole cohort and the percentage of patients with lung metastasis at presentation according to age at diagnosis are shown in Fig. 2. To further clarify the proportion of lung metastasis at diagnosis among osteosarcoma patients, we performed a detailed classification of the histologic subtypes, which revealed that patients with fibroblastic osteosarcoma (9.09%), telangiectatic osteosarcoma (7.41%), intraosseous well-differentiated osteosarcoma (0%), parosteal osteosarcoma (3.51%), periosteal osteosarcoma (0%) and high-grade surface osteosarcoma (0%) were less likely to have lung metastasis (Table 2). While the subtype of osteosarcoma (19.62%), osteosarcoma in Paget's disease of bone (33.33%) and small cell osteosarcoma (36.36%) were more likely to have lung metastasis (Table 2).

3.2. Survival outcomes of osteosarcoma patients

Because the survival rate of patients with osteosarcoma is over 50%, the median overall survival time could not be calculated. We then conducted Univariate Cox regression analysis to evaluate which clinical characteristics are associated with osteosarcoma's prognosis. The HR for all-cause mortality according to all variables in the univariate Cox regression model is shown in Table 3. Increased HR of all-cause mortality was associated with male (vs. female, HR = 1.611, 95% CI = 1.211–2.143, P = .0011), age group older than 30 years (vs. younger than 30 years, HR = 1.812, 95% CI = 1.378–2.384, P < .0001), poor-grade (vs. moderately grade, HR = 3.952, 95% CI = 1.601–9.760, P = .0029), undifferentiated grade (vs. moderately grade, HR = 3.675, 95% CI = 1.503–8.986, P = .0043), other tumor location (vs. extremity location, HR = 2.882, 95% CI = 1.645–5.049, P = .0002), >5–10 cm (vs. < 5 cm, HR = 2.135, 95% CI = 1.203–3.788, P = .0095), >10 cm (vs. < 5 cm, HR = 3.769, 95% CI = 2.158–6.584, P < .0001), radiation (vs. no/unknown radiation, HR = 1.472–3.099, P < .0001) and marriage (vs. no marriage, HR = 1.627, 95% CI = 1.207–2.193, P = .0014). Conversely, resection (vs. no surgery, HR = 0.147, 95% CI = 0.105–0.205, P < .0001) and amputation (vs. no surgery, HR = 0.273, 95% CI = 0.186–0.402, P < .0001) were associated with decreased all-cause death in osteosarcoma patients. The percent of 1-year and 2-year cause-specific deaths were calculated (Table 3). In Multivariate Cox regression analysis, the age group older than 30 years (vs. younger than 30, HR = 2.114, 95% CI = 1.556–2.871, P < .0001), poor-grade (vs. well-grade, HR = 3.133, 95% CI = 1.231–7.972, P = .0166),

Table 1
Clinical characteristics of osteosarcoma patients.

Item	Non-metastasis	Lung metastasis	All	Statistics	*P* value
Sex				$\chi^2 = 2.03$	0.1546
Male (%)	469 (53.23)	104 (59.09)	573 (54.21)		
Female (%)	412 (46.77)	72 (40.91)	484 (45.79)		
Age				$\chi^2 = 0.83$	0.3624
≤30	119(67.61)	564(64.02)	683(64.62)		
>30	57(32.39)	317(35.98)	374(35.38)		
Race				$\chi^2 = 1.27$	0.5310
White (%)	655 (74.35)	126 (71.59)	781 (73.89)		
Black (%)	140 (15.89)	34 (19.32)	174 (16.46)		
Other (%)	86 (9.76)	16 (9.09)	102 (9.65)		
Location				$\chi^2 = 16.59$	0.0002
axial (%)	133 (15.10)	8 (4.55)	141 (13.34)		
extremity (%)	652 (74.01)	139 (78.98)	791 (74.83)		
other (%)	96 (10.90)	29 (16.48)	125 (11.83)		
Marriage				$\chi^2 = 1.66$	0.1979
No or UK (%)	666 (75.60)	141 (80.11)	807 (76.35)		
Yes (%)	215 (24.40)	35 (19.89)	250 (23.65)		
Grade				$Z = 1.96$	0.0503
Well (%)	53 (6.02)	1 (0.57)	54 (5.11)		
Moderately (%)	73 (8.29)	4 (2.27)	77 (7.28)		
Poorly (%)	271 (30.76)	68 (38.64)	339 (32.07)		
Undifferentiated (%)	484 (54.94)	103 (58.52)	587 (55.53)		
tumor size				$Z = 8.10$	<0.0001
0–5 (%)	160 (18.16)	8 (4.55)	168 (15.89)		
5–10 (%)	387 (43.93)	53 (30.11)	440 (41.63)		
10- (%)	316 (35.87)	85 (48.30)	401 (37.94)		
UK (%)	18 (2.04)	30 (17.05)	48 (4.54)		

UK: Unknown.

undifferentiated grade, (vs. low-grade, HR = 2.866, 95% CI = 1.139–7.209, $P = .0253$), >5–10 cm (vs. <5 cm, HR = 1.861, 95% CI = 1.036–3.342, $P = .0375$) and >10 cm (vs. <5 cm, HR = 3.519, 95% CI = 1.972–6.280, $P < .0001$) were related to an increased HR for all-cause death. The HR was decreased in resection (vs. no surgery, HR = 0.192, 95% CI = 0.135–0.272, $P < .0001$) and amputation (vs. no surgery, HR = 0.295, 95% CI = 0.198–0.439, $P < .0001$) in osteosarcoma patients (Table 3). It can be seen from the results that surgery can improve the survival rate of osteosarcoma, and radiotherapy cannot improve the survival rate of osteosarcoma.

3.3. Survival outcomes of patients with lung metastasis

The median overall survival time in osteosarcoma patients with lung metastasis was 25 months (Fig. 3). Univariate Cox regression analysis was used to evaluate the HR of factors related to prognosis in

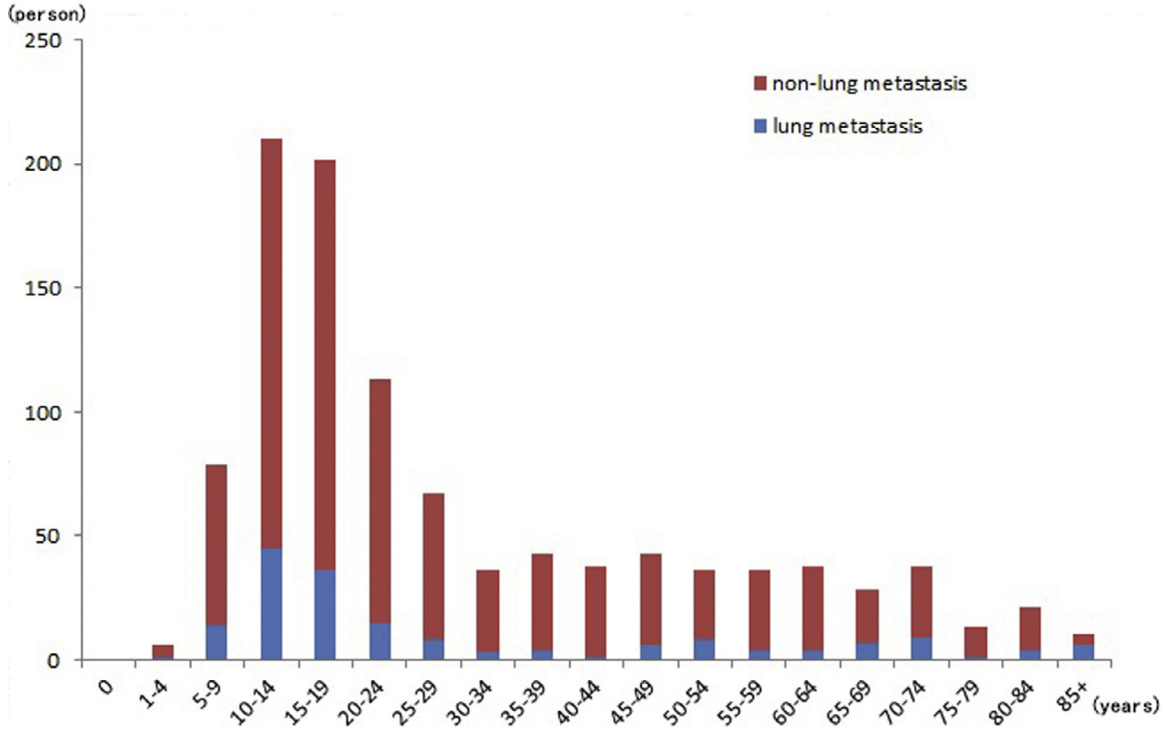

Fig. 2. Age distribution of patients with osteosarcoma.

Table 2
Histologic subtype of osteosarcoma and lung metastasis.

Histologic subtype	No.	Lung metastasis (%)
Total	1057	176 (16.65)
Osteosarcoma	693	136 (19.62)
Chondroblastic osteosarcoma	165	22 (13.33)
Fibroblastic osteosarcoma	33	3 (9.09)
Telangiectatic osteosarcoma	27	2 (7.41)
Osteosarcoma in Paget's disease of bone	3	1 (33.33)
Small cell osteosarcoma	11	4 (36.36)
Central osteosarcoma	49	5 (10.20)
Intraosseous well differentiated ostersarcoma	2	0 (0)
Parosteal osteosarcoma	57	2 (3.51)
Periosteal osteosarcoma	11	0 (0)
High grade surface osteosarcoma	6	0 (0)
Intracortical osteosarcoma	0	0 (-)

osteosarcoma patients. Age group older than 30 years (vs. younger than 30 years, HR = 3.575, 95% CI = 2.278–5.612, $P < .0001$) and marriage (vs. no marriage, HR = 3.489, 95% CI = 2.090–5.827, $P < .0001$) were associated with increased all-cause death of osteosarcoma patients with lung metastasis. Resection (vs. no surgery, HR = 0.237, 95% CI = 0.143–0.394, $P < .0001$), amputation (vs. no surgery, HR = 0.397, 95% CI = 0.223–0.708, $P = .0017$) and chemotherapy (vs. no chemotherapy, HR = 0.037, 95% CI = 0.035–0.152, $P < .0001$) were associated with decreased all-cause death of osteosarcoma patients with lung metastasis. The survival curve of osteosarcoma patients with lung metastasis stratified by chemotherapy is shown in Fig. 4. In Multivariate Cox regression analysis, an increased HR was associated with the age group older than 30 years (vs. younger than 30 years, HR = 2.482, 95% CI = 1.460–4.219, $P = .0008$), while a decreased HR was related to resection (vs. no surgery, HR = 0.313, 95% CI = 0.183–0.534, $P < .0001$) and chemotherapy (vs. no chemotherapy, HR = 0.169, 95% CI = 0.078–0.367, $P < .0001$) (Table 4).

4. Discussion

To our knowledge, this is the first population-based study of osteosarcoma lung metastasis at presentation. In this study, among the 1057 patients with osteosarcoma, there were 176 patients with lung metastasis, leading to an incidence of lung metastases of 16.7%. We found that osteosarcomas with lung metastasis were associated with axial location of the tumor. As for the histologic subtypes, the lung metastasis in osteosarcoma's grade in Paget's disease of bone and small cell osteosarcoma was higher than in the overall osteosarcoma patient sample. Furthermore, other factors that are related to prognosis in osteosarcoma patients were evaluated. In osteosarcoma patients with lung metastasis, multivariate Cox analysis revealed that being a man older than 30 years was associated with poor prognosis, while having had surgery (resection, amputation) and chemotherapy was related to a better prognosis.

Previous studies report that, depending on their age, 10%−47% of osteosarcoma patients have lung metastasis at diagnosis [7,8]. Bielack et al. reported on the prognostic factors of high-grade osteosarcoma patients from 1980 to 1998 [9]. They found that the incidence proportion of lung metastasis was 10.75% (183/1702). Likewise, Kaste et al. estimated that the incidence of lung metastases among patients with osteosarcoma was 15% [5]. Munajat et al. assessed the association between presentation of lung metastasis and tumor volume in a cohort of 70 patients with osteosarcoma [10]. They found that 33 patients (47%) had evidence of lung metastasis. Furthermore, they concluded that a larger tumor volume is more likely to be associated with lung metastasis at diagnosis. We found that the incidence of lung metastasis was 16.7%, which is in accordance with previous studies.

Patients with lung metastasis have a dismal prognosis [11]. Besides, patients with osteosarcoma lung metastasis at diagnosis are more likely to recur than those without [12]. Therefore, detection of lung metastasis at diagnosis has a significant impact on prognosis in osteosarcoma patients. Lung metastases in patients with osteosarcoma are usually found by chest CT scanning [13]. However, their accuracy for detecting lung metastasis needs to be improved, since up to about 14% of lung lesions are atypical [14] and therefore, difficult to detect. Thus, identifying patients with osteosarcoma at high risk of lung metastasis and conducting comprehensive chest CT scans are effective approaches to improve the survival rate of osteosarcoma patients. Of note, substantial disparities in tumor location and tumor size of lung metastasis were observed. Axial osteosarcomas with a tumor diameter larger than 5 cm were related to a higher risk of lung metastasis at diagnosis. Previous studies indicate that osteosarcoma patients with higher-grade tumors, monocyte ratio >1 and neutrophil/lymphocyte ratio (NLR) >1 were more likely to metastasize [15]. Taken together, this suggests that osteosarcoma patients with large tumor sizes, axial location, high monocyte ratio >1 and NLR >1 should receive thorough chest CT scannings.

In multivariate analysis, age >30 years and tumor size >5 cm were associated with poor prognosis, whereas surgery (both resection and amputation) and chemotherapy were associated with preferable prognoses. As for the subgroup of lung metastasis, the survival analysis revealed that male sex and age >30 years were related to poor prognosis. Age may be a significant factor that impacts survival rates of patients with osteosarcoma. Joo et al. conducted a retrospective study in osteosarcoma patients over the age of 40 years in Eastern Asian populations [16]. They found that the 5-year overall survival in this age group was 60.3%. Hung et al. identified prognostic factors in pediatric osteosarcoma patients in Taiwan and found that the 5-year overall survival and progression-free survival were 77 and 70%, respectively [17]. Kager et al. found that the patient's age was significantly related to survival in primary metastatic osteosarcoma [18]. These previous results and our study reveal that elderly patients with osteosarcoma have a poorer prognosis.

Surgery and chemotherapy were associated with better prognosis. Surgery is the mainstay management and current standard treatment includes surgery plus chemotherapy [19]. For osteosarcoma patients with lung metastasis, the survival rate remains low even when aggressive surgical strategies are applied [20]. There is increasing evidence that thoracotomy of pulmonary metastases is beneficial for prolonging the survival of osteosarcoma patients [21,22]. Carter et al. found that osteosarcoma patients undergoing resection of pulmonary metastases may have a longer survival than those not undergoing thoracotomy [23]. Our survival analysis suggested that surgery is beneficial for both the whole cohort and the lung metastasis subgroup. However, due to the limited data in the SEER database, we could not evaluate whether thoracotomy is an independent prognostic factor for osteosarcoma patients with lung metastasis.

Although it has been controversial since the 1970s, chemotherapy has significantly increased survival of osteosarcoma patients [24]. Currently, commonly used agents for treating osteosarcoma include methotrexate (MTX), doxorubicin, cisplatin and ifosfamide [25,26]. High-dose chemotherapy is being applied to metastatic patients, but their side effects also increase [6,27,28]. Therefore, the dose of chemotherapy for treating metastatic patients should be carefully considered. Our study supports the notion that chemotherapy is beneficial for all the osteosarcoma patients. However, defining the best chemotherapy strategy for metastatic patients remains controversial.

Our study also revealed that radiation did not improve the prognosis of osteosarcoma patients with lung metastasis. Generally, osteosarcoma is considered radioresistant and radiation is not a common option for treating osteosarcoma patients. Accordingly, radiotherapy did not contribute to prolonging the survival of osteosarcoma patients with lung metastases. However, some previous studies show that radiation can achieve a local control of the disease in some cases. Machak et al. evaluated the effectiveness of radiation for local control after induction

Table 3
Survival analysis for all osteosarcoma patients.

	Univariate analysis				Multivariate analysis	
	Hazard Ratio (95% CI)	P[a]	1-y CSS* (%)	2-y CSS* (%)	Hazard Ratio (95% CI)	P[b]
Sex						
Male	1.611 (1.211, 2.143)	0.0011	11.81(8.91,14.71)	23.34(19.24,27.45)	0.695(0.521,0.928)	0.0135
Female	Ref		6.73(4.31,9.15)	15.44(11.55,19.32)	Ref	
Age						
≤30	Ref		6.09(4.13,8.06)	17.07(13.71,20.43)	Ref	
>30	1.812 (1.378, 2.384)	<0.0001	16.29(12.11,20.48)	25.09(19.78,30.40)	2.114(1.556,2.871)	<0.0001
Race						
White	Ref		10.06(7.74,12.38)	20.74(17.34,24.14)		
Black	0.976 (0.674, 1.413)	0.8965	7.19(3.08,11.31)	17.86(11.1,24.62)		
Other	0.798 (0.477, 1.334)	0.3889	9.15(3.05,15.25)	15.96(7.38,24.54)		
Grade						
Well	NA	NA	NA	NA	NA	NA
Moderately	Ref		5.04(0.00,10.65)	6.98(0.32,13.64)	Ref	
Poorly	3.952 (1.601, 9.760)	0.0029	10.88(7.23,14.52)	22.36(17.08,27.65)	3.133(1.231,7.972)	0.0166
Undifferentiated	3.675 (1.503, 8.986)	0.0043	10.18(7.51,12.84)	21.97(17.93,26.01)	2.866(1.139,7.209)	0.0253
Location						
Extremity	Ref		7.36(2.7,12.02)	12.12(5.78,18.47)		
Axial	1.388 (0.861, 2.236)	0.1779	8.89(6.73,11.05)	18.75(15.54,21.96)		
Other[#]	2.882 (1.645, 5.049)	0.0002	16.31(8.86,23.77)	36.7(25.76,47.63)		
Tumor Size						
< 5 cm	Ref		1.43(0.00,3.40)	5.26(1.12,9.40)	Ref	
> 5–10 cm	2.135 (1.203, 3.788)	0.0095	7.76(5.03,10.5)	15.89(11.79,20)	1.861(1.036,3.342)	0.0375
>10 cm	3.769 (2.158, 6.584)	<0.0001	12.32(8.81,15.84)	27.71(22.51,32.91)	3.519(1.972,6.280)	<0.0001
Unknown	7.010 (3.450, 14.244)	<0.0001	31.73(16.53,46.94)	39.64(22.66,56.62)	5.368(2.579,11.173)	<0.0001
Lung metastasis						
No	Ref		5.23 (3.6, 6.85)	12.84 (10.19, 15.5)		
Yes	5.693 (4.296, 7.544)	<0.0001	31.81 (24.15, 39.347)	57.45 (48.16, 66.74)		
Surgery						
No	Ref					
Destruction	NA	NA	44.05(33.64,54.46)	65.47(54.18,76.77)		
Resection	0.147(0.105,0.205)	<0.0001	NA	NA		
Amputation	0.273(0.186,0.402)	<0.0001	3.97(2.4,5.54)	12.08(9.19,14.98)		
Unknown type	0.390(0.122,1.248)	0.1126	31.82(1.71,61.93)	31.82(1.71,61.93)		
Regional lymph nodes removed						
No	Ref		9.56(7.49,11.64)	19.88(16.8,22.96)		
Yes	0.910(0.590,1.404)	0.6693	9.88(4.04,15.73)	20.59(12.23,28.96)		
Unknown	1.842(0.588,5.772)	0.2943	NA	NA		
Surgery on distant site						
No	Ref		9.53(7.52,11.53)	18.86(15.97,21.76)	Ref	
Yes	2.183(1.389,3.430)	0.0007	9.57(1.56,17.57)	37.39(21.75,53.03)		
unknown	NA	NA	0(0,0)	NA		
Chemotherapy						
Yes	1.396 (0.926, 2.105)	0.1114	8.69(6.62,10.75)	20.66(17.43,23.9)		
No/Unknown	Ref		13.14(7.95,18.33)	14.86(9.25,20.47)		
Radiation						
Yes	2.136 (1.472, 3.099)	<0.0001	16.33(8.44,24.22)	39.22(27.41,51.03)		
No/Unknown	Ref		8.79(6.82,10.76)	17.86(14.96,20.75)		
Radiation sequence with surgery						
After	Ref		5.65(−0.59,11.9)	28.5(14.6,42.4)		
Prior	1.866(0.429,8.123)	0.4060	33.33(−4.39,71.05)	33.33(−4.39,71.05)		
none	0.744(0.447,1.239)	0.2558	9.61(7.59,11.62)	19.2(16.27,22.13)		
Marriage						
Yes	1.627 (1.207, 2.193)	0.0014	15.37(10.32,20.43)	25.24(18.63,31.85)		
No	Ref		7.83(5.81,9.84)	18.27(15.1,21.44)		

P^a: P value for hazard ratio in Univariate analysis; P^b: P value for hazard ratio in Multivariate analysis; *1-y CSS: The percentage of cause-specific death classification in 1 year; 2-y CSS: The percentage of cause-specific death classification in 2 years Ref: Reference; #Other: tumor location in both extremity and axial.

chemotherapy and found that it achieved local control and preserved limb function [29]. Lee et al. performed radiotherapy using a median dose of 50.0 Gy along with gemcitabine-docetaxel in six children and adolescents with osteosarcoma [30]. They reported that radiotherapy and gemcitabine-docetaxel chemotherapy improved unresectable, recurrent, or refractory osteosarcoma outcomes. The sample size of this study was small and therefore the efficacy of radiotherapy in this setting still needs to be validated.

Other factors, such as marriage status, were evaluated by Cox analysis. Although the Univariate Cox analysis revealed that marriage was associated with increased overall death of osteosarcoma patients with lung metastasis, this result may be affected by age and socioeconomic status. Therefore, the association between marital status and survival in osteosarcoma patients remains unclear.

Our study had also some limitations. Firstly, all the data were collected using the SEER database, leading to an inherent bias, which could not be avoided in retrospective studies. Secondly, the incidence of lung metastases might be underestimated, since subsequent lung metastases during disease progression were not included in the database. Thirdly, some of the data were unavailable in the SEER, such as dose and agent of chemotherapy, which might be confounding factors affecting the result of the survival analysis. Fourthly, the chemotherapy and radiation data in the current SEER database may be highly specific [31].

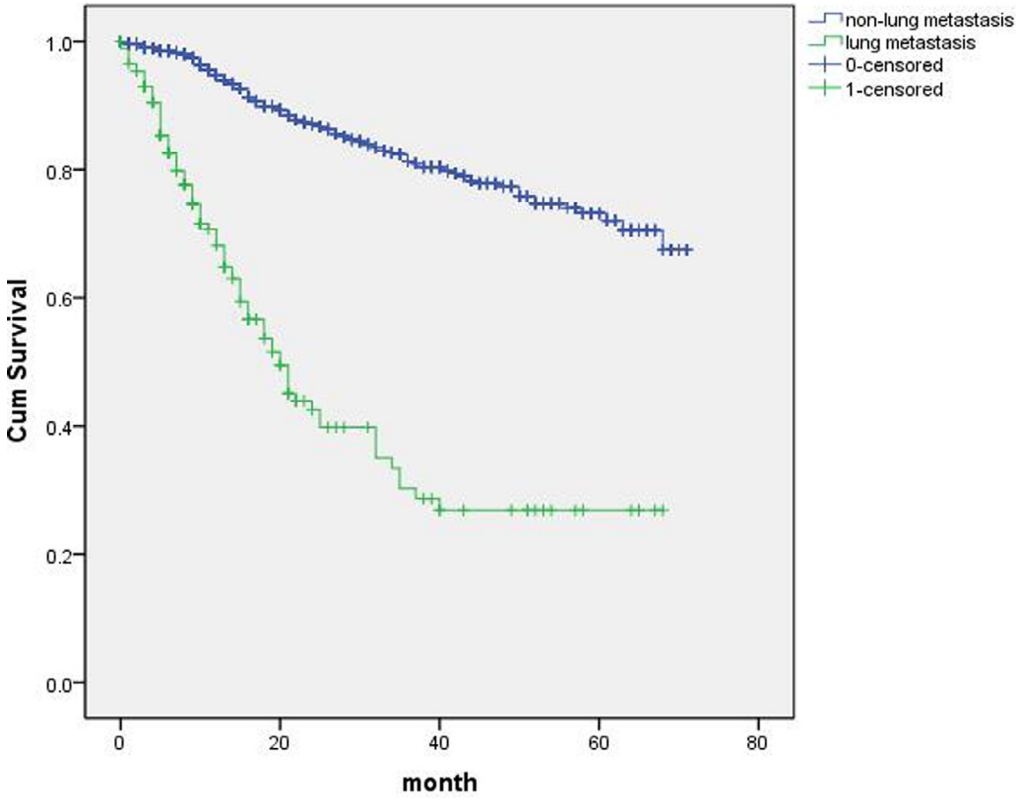

Fig. 3. The survival curve of patients with osteosarcoma.

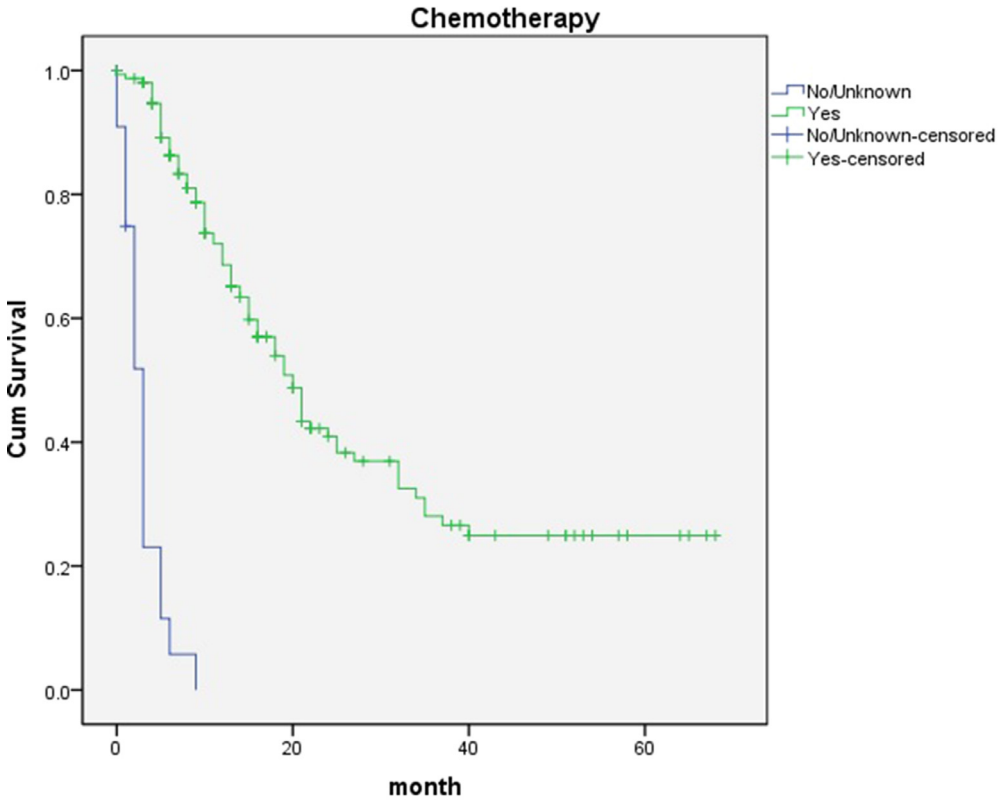

Fig. 4. The survival curve of osteosarcoma patients with lung metastasis stratified by chemotherapy.

Table 4
Survival analysis for osteosarcoma patients with lung metastasis.

		Univariate analysis				Multivariate analysis	
	Median OS	Hazard Ratio (95% CI)	P_a	1-y CSS* (%)	2-y CSS* (%)	Hazard Ratio (95% CI)	P_b
Sex							
Male	19 (13, 24)	1.290 (0.818, 2.034)	0.2731	36.34(26.29,46.39)	61.67(50.33,73.02)		
Female	22 (16, 35)	Ref		24.13(12.91,35.36)	50.24(34.34,66.14)		
Age							
≤30	25 (20, 37)	Ref		20.47(12.58,28.37)	48.12(36.87,59.37)	Ref	
>30	9 (5, 13)	3.575 (2.278, 5.612)	<0.0001	61.32(45.68,76.96)	82.81(69.13,96.49)	2.482(1.460,4.219)	0.0008
Race							
White	19 (14, 22)	Ref		32.43(23.29,41.57)	63.84(53.03,74.64)		
Black	35	0.685 (0.369, 1.270)	0.2293	27.9(11.11,44.69)	38.31(18.65,57.98)		
Other	35	0.771 (0.353, 1.688)	0.5158	34.34(9.46,59.23)	43.72(16.43,71.01)		
Grade							
Well	NA	NA	NA	NA	NA		
Moderately	12 (3, 25)	Ref		75(32.56,117.44)	75(32.56,117.44)		
Poorly	21 (13, 32)	0.434 (0.153, 1.233)	0.1173	29.4(17.45,41.35)	57.1(42,72.19)		
Undifferentiated	20 (15, 34)	0.407 (0.146, 1.135)	0.0857	31.17(21.25,41.1)	57.08(44.84,69.33)		
Location							
Extremity	16	Ref		42.86(6.2,79.52)	71.43(27.79,100.00)		
Axial	21 (18, 34)	0.509 (0.184, 1.405)	0.1922	28.9(20.71,37.09)	53.39(43.2,63.58)		
Other#	13 (5, 16)	1.422 (0.466, 4.336)	0.5363	47.67(23.12,72.22)	88.37(67.89,100.00)		
Tumor Size							
<5 cm	21	Ref		33.33(−4.39,71.05)	55.56(12,99.11)		
> 5–10 cm	21	1.214 (0.360, 4.093)	0.754	28.33(14.5,42.16)	51.86(34.73,68.98)		
>10 cm	19 (14, 25)	1.626 (0.505, 5.236)	0.4154	30.13(19.69,40.58)	59.12(46.37,71.86)		
Unknown	16	1.959 (0.557, 6.888)	0.2946	44.97(23.1,66.83)	62.26(37.19,87.34)		
Surgery							
No	9(7,12)	Ref		69.75(54.67,84.84)	86.39(74.43,98.35)	Ref	
Destruction	NA	NA	NA	NA	NA	NA	NA
Resection	34(22,40)	0.237(0.143,0.394)	<0.0001	10.8(3.7,17.91)	38.47(24.63,52.3)	0.313(0.183,0.534)	<0.0001
Amputation	18(13,32)	0.397(0.223,0.708)	0.0017	27.93(12.11,43.75)	63.83(44.26,83.41)	0.550(0.301,1.006)	0.0523
Unknown type	8(6,10)	1.821(0.433,7.660)	0.4136	NA	NA	3.956(0.898,17.423)	0.0690
Regional lymph nodes removed							
No	20(16,25)	Ref		33.5(25.25,41.75)	58.56(48.87,68.25)		
Yes	NA	0.738(0.320,1.699)	0.4748	19.23(0.00,38.84)	44.62(17.12,72.11)		
Unknown	NA	NA	NA	NA	NA		
Surgery on distant site							
No	18(14,24)	Ref		36.94(28.07,45.81)	61.49(51.3,71.68)		
Yes	NA	0.608(0.336,1.100)	0.1000	10.84(−0.82,22.49)	41.08(19.65,62.51)		
Chemotherapy							
Yes	21 (18, 32)	0.037 (0.035, 0.152)	<0.0001	26.47 (18.84, 34.10)	54.12 (44.30, 63.94)	0.169(0.078,0.367)	<0.0001
No/Unknown	3 (2, 6)	Ref		100	100	Ref	
Radiation							
Yes	21 (16, 32)	1.523 (0.892, 2.600)	0.1233	41.29(21.18,61.39)	75.6(55.78,95.42)		
No/Unknown	13 (10, 24)	Ref		29.84(21.64,38.04)	53.43(43.28,63.59)		
Radiation sequence with surgery							
After	NA	Ref		9.09(−7.9,26.08)	67.53(31.75,103.32)		
Prior	NA	4.527(0.861,23.806)	0.0746	NA	NA		
None	21(15,32)	1.230(0.497,3.043)	0.6544	32.67(24.59,40.76)	56.02(46.41,65.62)		
Marriage							
Yes	8 (5, 12)	3.489 (2.090, 5.827)	<0.0001	75.81(56.68,94.95)	81.86(64.22,99.5)		
No	21 (19, 35)	Ref		23.6(16,31.2)	53.06(42.67,63.46)		

P^a: P value for hazard ratio in Univariate analysis; P^b: P value for hazard ratio in Multivariate analysis; *1-y CSS: The percentage of cause-specific death classification in 1 year; 2-y CSS: The percentage of cause-specific death classification in 2 years Ref: Reference; #Other: tumor location in both extremity and axial.

In conclusion, advanced age and large tumor size were related to a higher risk of lung metastases in osteosarcoma patients. The results of the survival analysis revealed that advanced age, high-grade and large tumor size were associated with a poor prognosis in the cohort of osteosarcoma patients studied. Patients who were diagnosed at advanced age or with large tumor size should receive comprehensive chest CT scans. As for patients with lung metastases, advanced age was correlated with a poor prognosis. Finally, surgery and chemotherapy significantly improve the survival of patients with metastatic lung osteosarcoma.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2019.100230.

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