Regional lymph node involvement is associated with poorer survivorship in patients with upper extremity osteosarcoma than with lower extremity osteosarcoma: a SEER analysis

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Background: Although the upper limb is the second most common site of osteosarcoma, investigations into clinical manifestation differences between upper and lower limb patients are still sporadic. We retrospectively investigated the characteristics of these patients to gain a better understanding of the differences between upper and lower limb osteosarcoma patients.

Methods: This retrospective study involved patients diagnosed with extremity osteosarcoma between 1997 and 2016 collected from the Surveillance, Epidemiology, and End Results (SEER) database. Patient characteristics were analyzed with *t*-tests, rank sum tests and chi-square tests. Log-rank tests were applied to evaluate univariate significance, and Cox hazards models were performed in multivariate analysis. A binary logistics regression model was used to screen the risk factors related to lymph node involvement.

Results: In total, 1,882 patients, 1,588 (84.4%) with lower limb lesions and 294 (15.6%) with upper limb lesions were enrolled in our study. The patients with upper limb osteosarcoma exhibited poorer 5-year overall survival (OS) than patients with lower limb osteosarcoma (54.8% *vs.* 63.2%, P=0.02). The upper limb patients had more lymph node involvement (5.6% *vs.* 2.7%, P=0.03), which was found to be an independent prognostic factor (P=0.000). Tumors located in the upper limbs and the presence of distal metastasis were risk factors related to lymph node involvement in the extremity (P<0.05). The upper limb patients were tended to suffer greater risk of being affected by both metastasis and lymph node involvement (15.7% *vs.* 9.4%, P=0.18).

Conclusions: Upper limb osteosarcoma patients are characterized by more lymph node involvement than lower limb patients, leading to poorer OS. In addition, upper limb patients are at greater risk for both lymph node involvement and distal metastasis. Our results suggest that upper limb patients should be screened more thoroughly for regional lymph node involvement.

Keywords: Extremity osteosarcoma; lymph node involvement; upper limb; Surveillance, Epidemiology, and End Results database (SEER database); survival

Introduction

Osteosarcoma is the most common type of primary bone sarcoma. Current treatment for osteosarcoma consists of surgery and chemotherapy, and the goal of surgery is to complete remove the tumor and preserve as much function as possible (1,2).

The most frequent sites are the metaphyseal areas of the long bones in the extremities, which account for 85% of all primary sites (3,4). Although the upper limb is the second most common site of osteosarcoma, these lesions are still thought to show similar characteristics to other extremity lesions and thus are rarely reported separately from lower limb patients (4-7). Some studies have reported that the upper limb tumor is more proximal and led to more distal metastasis than the lower limb patients and upper limb patients showed poorer survival than lower limb patients (8-10). These findings indicate that additional research is needed to determine which characteristics are predictors of survival in upper and lower limb osteosarcoma patients in order to provide a systematic understanding of the differences between upper and lower limb osteosarcoma patients and to avoid inadvertently compromising patient outcomes.

One aspect of the different clinical manifestation between upper and lower limb patients was reflect on the different distal metastasis rate and it was associated with poorer survival in osteosarcoma patients (8). Osteosarcoma progressed primarily hematogenously and also sometimes lymphogenously (11). Regional lymph node involvement in upper limb was mainly reported in case report but the prevalence of lymph involvement has not been well defined and their clinical manifestation has not been systematically evaluated and compared with other extremity patients (*Figure 1*).

Currently, population-based databases have become increasingly relevant for studying clinical manifestation and tumor outcome in bone sarcoma research (12). The Surveillance, Epidemiology, and End Results (SEER) database, covering 28% of US population, is one of the most often used large national cancer databases (13). The main purpose of this study was to systematically evaluated and compared the clinical manifestation and tumor outcome between the upper and lower limbs osteosarcoma patients based on large dataset in SEER database, thereby refining the regional lymph node involvement prevalence in upper and lower limb patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2187).

Methods

Patient population

This retrospective study included data from extremity osteosarcoma patients extracted from the National Cancer Institute's SEER database from 1997 to 2016 (13). The cases met the following inclusion criteria: (I) patients diagnosed with osteosarcoma with positive histological confirmation (ICD-O-3 histologic type: 9180-9187, 9192-9195); (II) high-grade osteosarcoma, which is poorly differentiated and anaplastic; (III) the primary site of the tumor is C40.2-Long bones of lower limb and associated joints or C40.0-Long bones: upper limb, scapula, and associated joints with site record of "bones and joints"; and (IV) the year of diagnosis was between 1997 and 2016. Patients were collected and included in our study. The exclusion criteria were as follows: (I) follow-up data were missing, or survival did not exceed 0 day; (II) histological confirmation was obtained from autopsy and the death certificate only; (III) osteosarcoma was not the first primary tumor; and (IV) patients with multiple tumor. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patient data were extracted from the database using SEER*Stat version 8.3.6 software (National Cancer Institute, Bethesda, MD, USA) (13). We extracted age, sex, race, primary site, histological type, tumor size, lymph node involvement, distal metastasis, AJCC stage, treatment protocols, and survival time until death or the last follow-up for each patient in the study. The AJCC stage was evaluated with the *The AJCC 8th edition staging system for soft tissue sarcoma* (14). Age was categorized into youth, adult and elderly patient groups, with cut-off points at 18 and 40 years old (15).

The lymph node involvement is based on "Derived AJCC N, 6th ed. (2004–2015)", "Derived AJCC N, 6th ed. (2004–2015)", "Derived SEER Combined N (2016+)", "Derived SEER Combined N Src (2016+)", "N value—based on AJCC 3rd (1988–2003)", "Regional nodes positive (1988+)", "CS lymph nodes (2004–2015)", "CS Reg Node Eval (2004–2015)" and the lost message is recode as "NX". And patients with localized extend of disease are also enrolled in the no lymph node involvement patients.
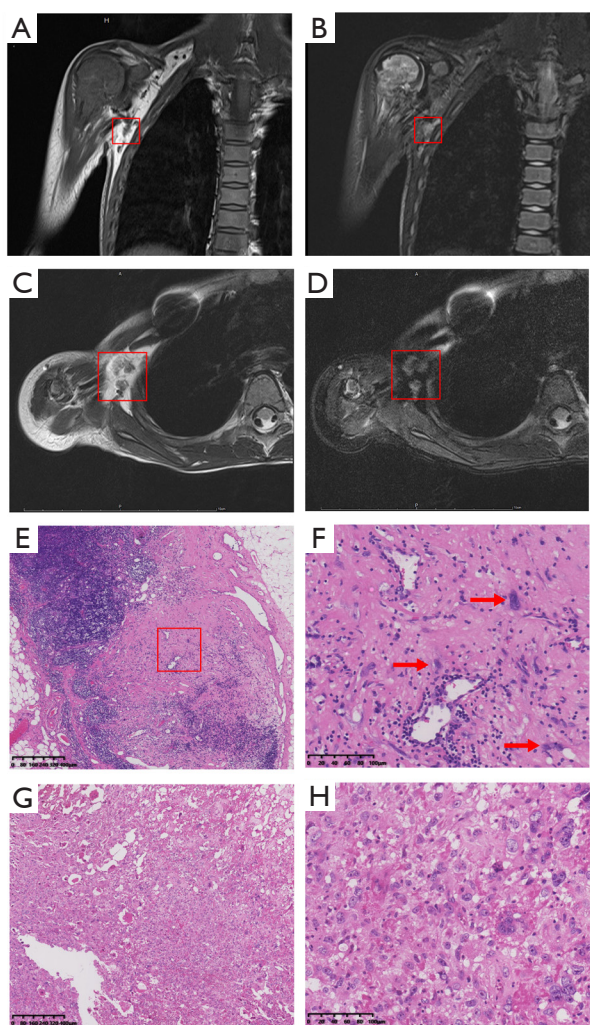
Figure 1 MRI images for axillary node involved osteosarcoma patient. (A) For coronal T1-weighted image for a proximal humeral osteosarcoma patient with axillary lymph node involvement (showed in red box); (B) for coronal T2-weighted image for a proximal humeral osteosarcoma patient with axillary lymph node involvement (showed in red box); (C) for transversal T1-weighted image for a proximal humeral osteosarcoma patient with axillary lymph node involvement (showed in red box); (D) for transversal T2-weighted image (fat suppressed) for a proximal humeral osteosarcoma patient with axillary lymph node involvement (showed in red box); (E) for HE staining (×80 scale) of lymph node specimen; (F) for HE staining (×400 scale) showing the osteosarcoma cell infiltrated in the lymph node specimen (showed with red arrow); (G) HE staining (×80 scale) of primary tumor specimen; (H) HE staining (×400 scale) of primary tumor specimen.

Statistical analyses

The demographic and clinical characteristics of enrolled patients were compared using the chi-square test for categorical variables, rank sum tests for grade variables and *t*-tests for continuous variables to determine the baseline differences between the upper and lower limb groups. In the survival analysis, overall survival (OS) was defined as the time from diagnosis to death for patients. Year of diagnosis was dichotomized using optimal cut-off values that were achieved from the time-dependent receiver operating characteristic (t-ROC) curve of the years of diagnosis and patient status at the predicted time (16).

Log-rank tests were applied to evaluate the potential differences between groups in the univariate analysis using the Kaplan-Meier (KM) method. Significant variables (P<0.10) were included in the multivariate survival analysis using Cox proportional hazards models. The binary logistics regression method was used to evaluate the risk factors related to regional lymph node involvement.

Data were analyzed using SPSS Statistics (version 24.0; IBM, USA), and a t-ROC curve was performed in R 3.6.2 with the "survival ROC" package with a prediction time of 60 months.

Results

Demographic and clinical characteristics

The SEER database contained 2,096 patients who were diagnosed with extremity osteosarcoma and had positive histological confirmation between 1997 and 2016. We excluded 214 patients, and 1,882 patients were ultimately included in our study. The enrolled patients were followed for a median of 45.5 (range: 1–239) months. Among the surviving patients, the median follow-up time was 86 (range: 1–239) months. The flowchart of the patient selection process is reported in *Figure 2*.

Among the eligible patients, 1,588 (84.4%) had lower limb lesions, and 294 (15.6%) had upper limb lesions. Patient characteristics are shown in *Table 1* according to the tumor location in the upper and lower limbs. Primary upper limb patients showed similar clinical characteristics with regard to sex, age, race, histologic subtype, tumor size, and distal metastasis (P>0.05 for all comparisons). However, the upper limb showed more lymph node involvement than the lower limb (5.6% *vs.* 2.7%, P=0.03).
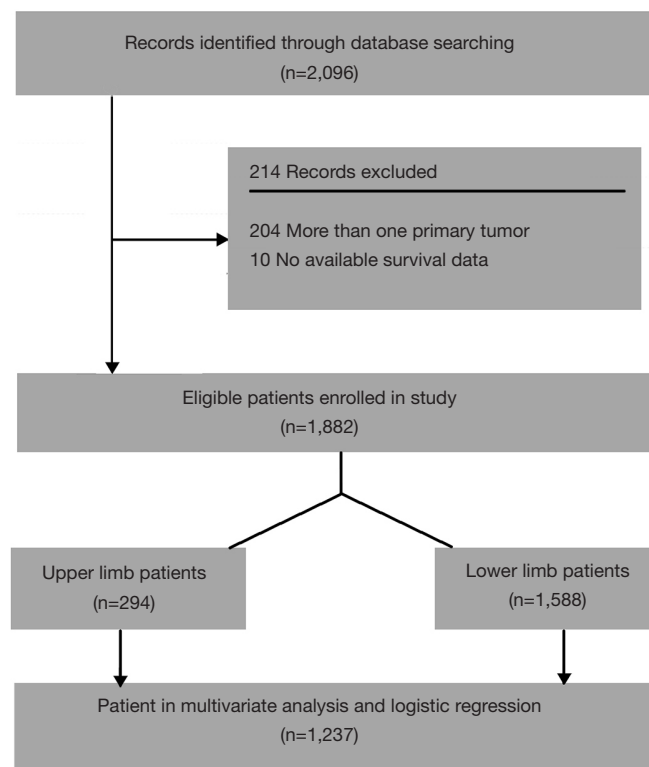
Figure 2 The flowchart describes the study procedure from collect cases from SEER database to statistical analysis. SEER, Surveillance, Epidemiology, and End Results.

The median year of diagnosis was 2009. The upper limb patients were in comparable years of diagnosis with the lower limb patients (median 2008 *vs.* 2008, P=0.07). The t-ROC curve is shown in Figure S1. The Youden index reached its peak in 2011 at 0.037. However, the AUC for the model was 0.49, showing that patient survival was not statistically related to the year of diagnosis during 1997–2016. The KM curves also showed that patient survival remained relatively comparable during this time period (P=0.77, Figure S2).

The KM curves of upper and lower limb patients is shown in *Figure 3*. By the end of follow-up, 683 (36.3%) of the enrolled patients had died. The 5-year OS rates of the upper and lower limb groups were 54.8% and 63.2%, respectively (P=0.02).

Univariate and multivariate analyses of the prognostic factors

The results of univariate and multivariate analyses are

shown in *Table 2*. In the univariate analysis, older age, male sex, specific histologic subtype, larger tumor size, more regional lymph node involvement, distal metastasis and disease stage higher than stage I were associated with a worse prognosis (P<0.05). These prognostic factors were evaluated using Cox proportional hazards models. A total of 1,237 patients with complete data, 1,038 with lesions of the lower limb and 199 with lesions of the upper limb, were enrolled in the multivariate survival analysis. The Cox analysis showed that age >18, tumor size >5 cm, lymph node involvement and distal metastasis were statistically independent variables affecting patients' 5-year OS (P<0.05). Their respective KM curves are shown in *Figure 4*.

Upper limb lesions and distal metastasis were risk factors for lymph node involvement

The results of the binary logistic regression model of risk factors for lymph node involvement is shown in *Table 3*. Upper limb lesions and distal metastasis were independent

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Table 1 Characteristics of 1,882 patients with osteosarcoma according to present in upper and lower limbs

Characteristics	Upper limbs (n=294), n (%)	Lower limbs (n=1,588), n (%)	P value
Gender			0.98
Female	121 (41.2)	655 (41.2)	
Male	173 (58.8)	933 (58.8)	
Age			0.43
<18	165 (56.1)	905 (57.0)	
18–40	82 (27.9)	460 (29.0)	
>40	47 (16.0)	223 (14.0)	
Race			0.64
White	207 (70.6)	1,158 (73.2)	
Black	55 (18.8)	266 (16.8)	
Other	31 (10.6)	157 (9.9)	
Year of diagnosis	Median 2008	Median 2008	0.07
Histology type			0.96
Osteosarcoma, NOS[†]	210 (71.4)	1,096 (69.0)	
Chondroblastic osteosarcoma	30 (10.2)	226 (14.2)	
Fibroblastic osteosarcoma	16 (5.4)	84 (5.3)	
Telangiectatic osteosarcoma	18 (6.1)	60 (3.8)	
Osteosarcoma in Paget disease	2 (0.7)	8 (0.5)	
Small cell osteosarcoma	5 (1.7)	13 (0.8)	
Central osteosarcoma	12 (4.1)	49 (3.1)	
Parostreal osteosarcoma	1 (0.3)	22 (1.4)	
Periosteal osteosarcoma	0 (0.0)	27 (1.1)	
High grade surface osteosarcoma	0 (0.0)	13 (0.8)	
AJCC stage[‡]			0.27
II	19 (6.3)	92 (7.9)	
III	128 (56.9)	722 (62.1)	
IV	78 (34.7)	348 (29.9)	
T stage (tumor size)[§]			0.09
I (≤5 cm)	29 (11.7)	155 (11.7)	
II (5–10 cm)	94 (37.9)	621 (46.7)	
III (10–15 cm)	88 (35.5)	354 (26.6)	
IV (>15 cm)	37 (14.9)	199 (15.0)	
N stage (lymph involvement)[¶]			0.03*
0 (non-involved)	202 (94.4)	1,098 (97.3)	
I (involved)	12 (5.6)	31 (2.7)	
M stage (distal metastasis)[¶]			0.13
0 (non-metastasis)	214 (74.3)	1,231 (78.4)	
I (metastasis)	74 (25.7)	340 (21.6)	

[†], NOS is stand for "not otherwise specified" in SEER database; [‡], AJCC stage is evaluated with *The AJCC 8th edition staging system for soft tissue sarcoma*; [§], tumor size is measured as the maximum diameter of the primary tumor (cm); [¶], lymph involvement and distal metastasis is diagnosed clinically or pathologically; *, $P<0.05$. NOS, not otherwise specified; SEER, Surveillance, Epidemiology, and End Results.
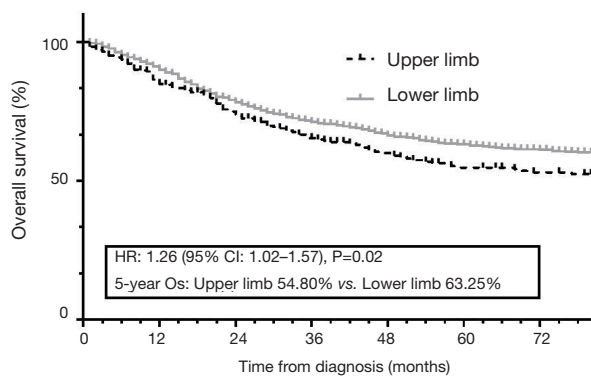
Figure 3 KM curves showed the survival difference between upper and lower limb patients. KM, Kaplan-Meier; OS, overall survival.

risk factors leading to lymph node involvement (P<0.05), but large tumor size or factors such as age, sex, and histologic type were less related to lymph node involvement (P>0.10). Although the lymph node-involved histologic subtype remained statistically comparable to no lymph node-involved patients (P=0.20), fibroblastic osteosarcoma, small cell osteosarcoma, parosteal osteosarcoma, periosteal osteosarcoma and high-grade surface osteosarcoma did not exhibit lymph node involvement (0.0%).

A total of 72.1% (31/43) of lymph node-involved patients also presented with distal metastasis (P=0.000). Among the metastatic patients, upper limb lesions showed a higher risk of simultaneous lymph and distal involvement, but this difference was not statistically significant (15.7% *vs.* 9.4%, P=0.18). *Figure 5* shows the KM curves for subtype analysis among the lymph node-involved and distal metastatic patients. In these progressed patients, the lymph node-involved patients showed a similar 5-year survival to the metastatic patients (22.9% *vs.* 35.8%, P=0.48). The patients who were affected with both lymph and distal lesions showed much poorer survival than other progressed patients (5.8% *vs.* 35.2%, P=0.000).

Discussion

The results of this study showed that patients with upper limb lesions, which comprise 15.6% (294/1,882) of the total, had a worse 5-year OS than those with lower limb osteosarcoma (54.8% *vs.* 63.2%, P=0.02). This finding is consistent with the results of other studies reporting that upper limb lesions had an unfavorable effect on patient survival compared with other extremity lesions, especially for tumors in the proximal humerus (4,5). However, among

existing studies, we found only sporadic investigations into the differences in the clinical manifestation of upper versus lower limb osteosarcoma patients (1,3,4,8,15,17). We found that upper limb patients showed more lymph node involvement (5.6% *vs.* 2.7%, P=0.03) than lower limb patients. The prevalence of lymph node involvement is consistent with the present epidemiological study in osteosarcoma (18).

As demonstrated in a previous study, lymph node involvement is an infrequent event in the natural history of osteosarcoma, but it is a highly adverse factor in osteosarcoma patient survival (18-21). We identified that tumors located in the upper limb and distal metastasis are risk factors leading to lymph node involvement in extremity osteosarcoma patients (P<0.05). It is consistent that some studies have reported that risk location, large tumor size, distal metastasis, high-grade and extraskeletal tumor are important factors to lymph involvement in patients with bone malignance (18,21-24).

Previous studies demonstrated that osteosarcoma could progress not only hematogenously but also lymphogenously in case series (11). Our studies found lymph involvement is often occurred with combination of distal metastasis (72.1%). It is consistently with previous studies that many case report series observed that lymph node involvement and distal metastasis were occurred simultaneously in extremity osteosarcoma patients (19-21,25). And the result showed the lymph involved patients had no statistical difference in 5-year OS to the metastasis patients (35.8% *vs.* 22.9%, P=0.48). It was also reported that regional lymph node-involved patients showed a similarly poor survival like in other metastatic osteosarcoma patients (21). Thus, we postulated that the lymph node involvement presents in a lymphogenous phenotype of distal metastasis and that the difference in lymph node involvement is attributed to the anatomical difference between the regional lymph node network in upper and lower limbs. It can be interpreted as follows: upper limb lesions are most commonly located in the proximal humerus, close to neighboring axial nodes and vessels (26), while lower limb lesions are located near the knee joint, close to popliteal vessels but separated by muscle and interosseous membrane from the lymph network (27).

Our results showed that lymph node involvement is an important prognostic variable that differentiate the tumor outcomes between upper and lower limb osteosarcoma. In patients with no lymph node involvement, the survival differences between upper and lower limb osteosarcoma patients were eliminated (70.5% *vs.* 73.1%, P=0.20). This

Table 2 Univariate and multivariate analyses of clinical characteristics on survival stratified with upper and lower limb

Characteristics	5-year OS	Univariate	Multivariate[†]	
		P value	Hazard ratio (95% CI)	P value
Age		<0.001***		<0.001***
<18	67.4		Reference	
18–40	63.6		0.25 (0.19–0.32)	<0.001***
>40	36.3		0.43 (0.33–0.57)	<0.001***
Gender		0.001***		
Male	58.7		Reference	
Female	66.5		0.97 (0.79–1.20)	0.80
Race		0.70		
White	62.3			
Black	58.8			
Other	63.6			
Histology type		<0.001***		0.17
Osteosarcoma, NOS	60.0	–	Reference	
Chondroblastic osteosarcoma	63.5	0.45	1.71 (0.42–6.90)	0.45
Fibroblastic osteosarcoma	72.7	0.03*	1.80 (0.44–7.40)	0.42
Telangiectatic osteosarcoma	61.2	0.61	1.17 (0.27–5.07)	0.84
Osteosarcoma in Paget disease	24.0	<0.001***	1.43 (0.32–6.31)	0.64
Small cell osteosarcoma	63.0	0.86	3.63 (0.69–19.09)	0.13
Central osteosarcoma	56.2	0.46	1.93 (0.37–10.06)	0.42
Parostreal osteosarcoma	62.4	0.38	1.14 (0.25–5.08)	0.87
Peristreal osteosarcoma	83.9	0.03*	1.04 (0.19–5.66)	0.97
High grade surface osteosarcoma	76.6	0.26	0.25 (0.02–2.77)	0.26
AJCC stage[‡]		<0.001***		
I				
II	85.6[‡]			
III	70.1			
IV	32.8			
T stage (tumor size)		<0.001***		0.001***
I (≤5 cm)	74.1		Reference	
II (5–10 cm)	65.7		0.39 (0.24–0.63)	<0.001***
III (10–15 cm)	57.4		0.73 (0.55–0.96)	0.02*
IV (>15 cm)	51.2		0.83 (0.63–1.11)	0.20
N stage (lymph involved)		<0.001***		
0 (non-involved)	64.2		Reference	
I (involved)	10.8		0.34 (0.22–0.51)	<0.001***
M stage (metastasis)		<0.001***		
0 (non-metastasis)	70.5		Reference	
I (metastasis)	33.1		0.29 (0.23–0.36)	<0.001***

[†], multivariate analysis includes 1,237 cases with complete data, 199 from upper limbs patients and 1,038 from lower limb patients; [‡], AJCC stage was a composite assessment of tumor size, lymph involved and metastasis and was not included in Cox analysis; *, P<0.05; ***, P<0.001. OS, overall survival; NOS, not otherwise specified.
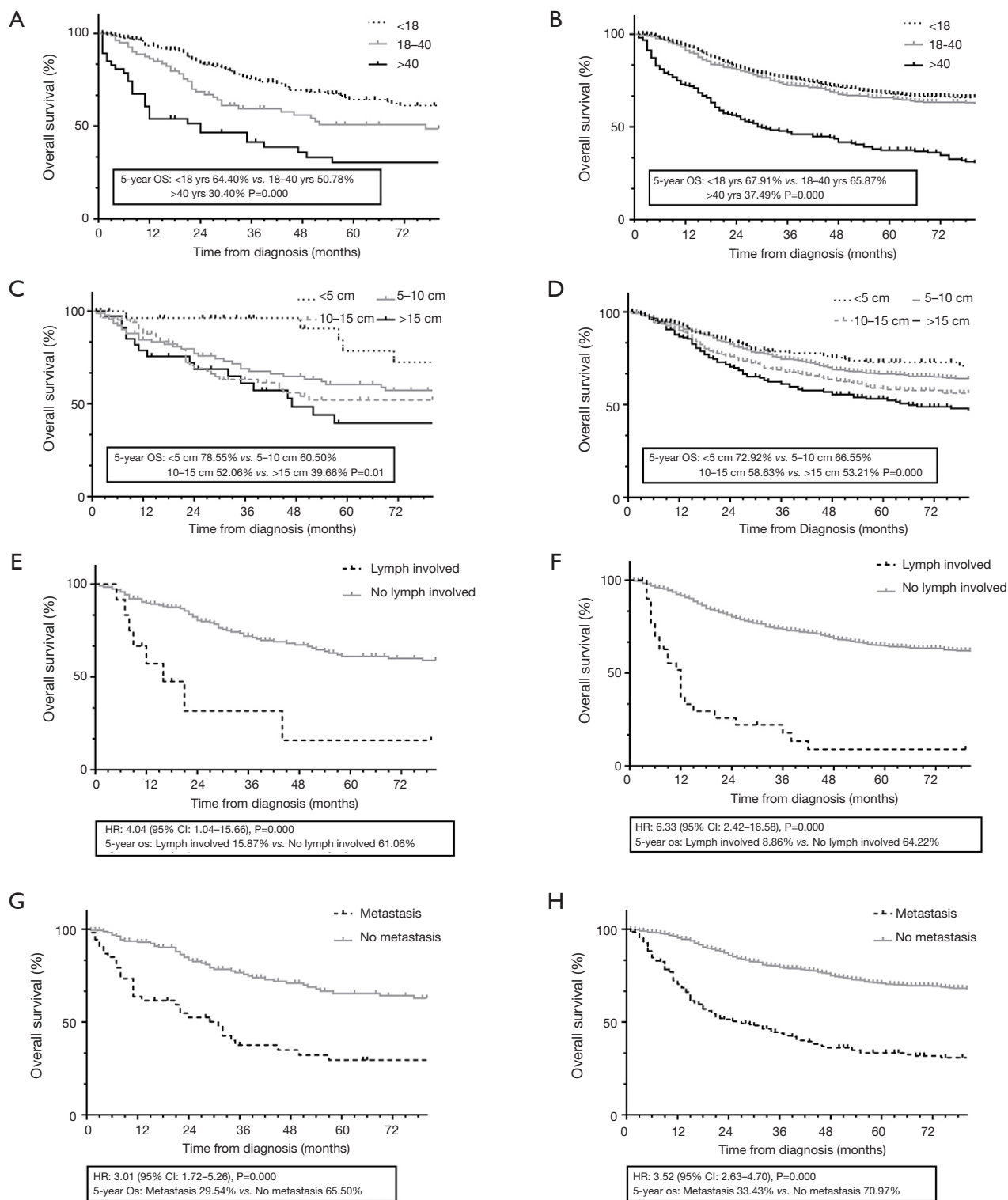
Figure 4 Subgroup KM curves for the prognostic characteristic in upper and lower limb patients. (A) For age subgroup in upper limb patients; (B) for age subgroup in lower limb patients; (C) for tumor size subgroup in lower limb patients; (D) for lymph involvement subgroup in upper limb patients; (E) for lymph involvement subgroup in lower limb patients; (F) for metastasis subgroup in upper limb patients; (G) for metastasis subgroup in lower limb patients; (H) for metastasis subgroup in upper limb patients. KM, Kaplan-Meier; OS, overall survival.

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Table 3 Binary logistics regression of risk factors related to lymph involvement in extremity osteosarcoma

Characteristics	No lymph involved, n (%)	Lymph involved, n (%)	Binary logistics regression[†]	
			HR (95% CI)	P value
Age				0.16
<18	756 (58.2)	22 (51.2)	Reference	
18–40	357 (27.5)	11 (25.6)	0.44 (0.19–1.02)	0.06
>40	187 (14.4)	10 (23.3)	0.52 (0.19–1.41)	0.20
Gender				
Male	754 (58.0)	27 (62.8)	Reference	
Female	546 (42.0)	16 (37.2)	0.95 (0.47–1.92)	0.88
Race				0.28
White	968 (74.8)	30 (69.8)	Reference	
Black	206 (15.9)	287 (15.8)	0.93 (0.27–3.26)	0.91
Other	120 (9.3)	169 (9.3)	1.41 (0.35–5.68)	0.63
Histology type[‡]				0.78
Osteosarcoma, NOS	902 (69.4)	33 (76.7)	Reference	
Chondroblastic osteosarcoma	168 (12.9)	7 (16.3)	1.83 (0.23–14.49)	0.57
Fibroblastic osteosarcoma	60 (4.6)	0 (0.0)	–	–
Telangiectatic osteosarcoma	59 (4.5)	1 (2.3)	2.25 (0.25–20.56)	0.47
Osteosarcoma in Paget disease	6 (0.5)	1 (2.3)	1.46 (0.08–25.77)	0.80
Small cell osteosarcoma	13 (1.0)	0 (0.0)	–	–
Central osteosarcoma	49 (3.8)	1 (2.3)	7.36 (0.29–187.65)	0.23
Parostreal osteosarcoma	17 (1.3)	0 (0.0)	–	–
Periosteal osteosarcoma	15 (1.2)	0 (0.0)	–	–
High grade surface osteosarcoma	11 (0.8)	0 (0.0)	–	–
Tumor location				
Upper limb	17 (27.9)	286 (15.6)	Reference	
Lower limb	44 (72.1)	1,546 (84.4)	2.14 (1.01–4.55)	0.048*
T stage (tumor size)				0.45
I (≤5 cm)	116 (9.7)	5 (13.2)	Reference	
II (5–10 cm)	549 (45.8)	11 (28.9)	1.64 (0.48–5.57)	0.43
III (10–15 cm)	356 (29.7)	13 (34.2)	0.65 (0.25–1.68)	0.37
IV (>15 cm)	178 (14.8)	9 (23.7)	0.93 (0.37–2.32)	0.87
M stage (metastasis)				
0 (non-metastasis)	1,032 (79.6)	12 (27.9)	Reference	
I (metastasis)	265 (20.4)	31 (72.1)	0.12 (0.06–0.25)	<0.001***

[†], binary logistics regression model includes 1,123 cases with complete data, 38 from lymph involved patients and 1,085 from no lymph involved patients; [‡], the fibroblastic, small cell, parostreal, periosteal, high grade surface osteosarcoma patients were found no lymph involvement and are not included in the logistics regression for the hazard ratio cannot be evaluated; *, P<0.05; ***, P<0.001. NOS, not otherwise specified.
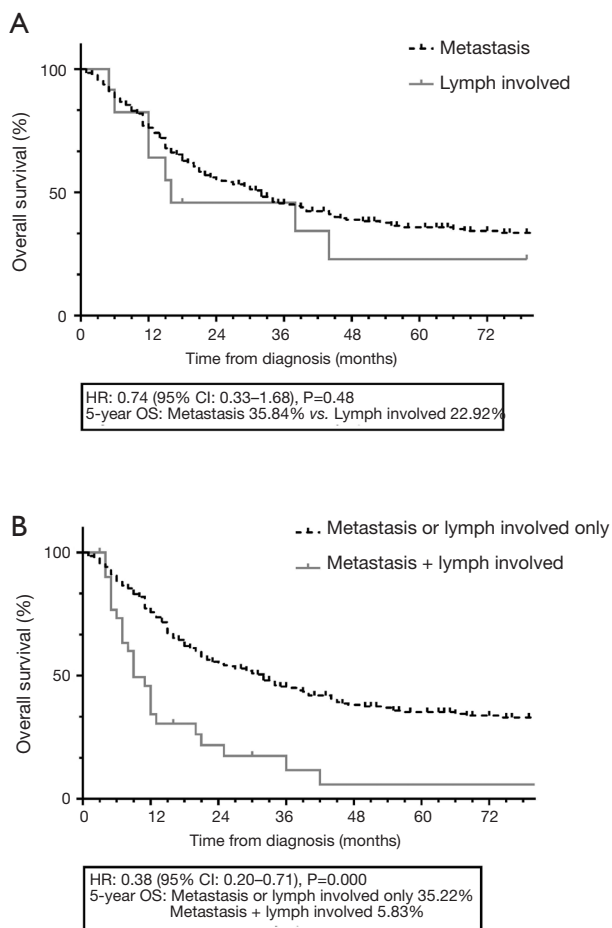
A

HR: 0.74 (95% CI: 0.33–1.68), P=0.48
5-year OS: Metastasis 35.84% *vs.* Lymph involved 22.92%

B

HR: 0.38 (95% CI: 0.20–0.71), P=0.000
5-year OS: Metastasis or lymph involved only 35.22%
Metastasis + lymph involved 5.83%

Figure 5 KM curves among the lymph involved and distal metastasis patients. (A) shows similar surviving in lymph involved and distal metastasis patients; (B) shows poorer surviving in patients simultaneously affected with lymph involved and distal metastasis to the lymph involved or distal metastasis only patients. KM, Kaplan-Meier; OS, overall survival.

finding emphasizes the notion that lymph node involvement acts as an independent factor leading to unfavorable survival, especially for upper limb patients. Present diagnostic strategy for lymph node involvement is thorough imaging examinations, including PET-CT and bone scans (28-30). Axillary lymphadenectomy is not primarily recommended to prevent lymph involvement in upper limb osteosarcoma patients for the low prevalence of lymph involvement (30). It suggests that additional work is needed in the future in terms of screening the lymph node status of upper limb osteosarcoma patients.

Nevertheless, our study is limited due to its retrospective nature. First, the SEER database provides trans-sectional data, and thus, we cannot obtain the time axis of patient treatment and disease progression, such as the time of surgery, local recurrence and distal metastasis. These data are useful when considering the time sequence and the causal relation between lymph node involvement and metastasis in the disease. Second, SEER provides lymph node involvement data based on a composite of histologically confirmed regional nodes, clinical and radiographic data and the database has not clarified the diagnosed procedure method in determining lymph node involvement. And the tumor imaging was not available and we are unable to reconfirm the exact regional presentation of the lymph involved osteosarcoma.

Nonetheless, our findings can help physicians better understand extremity osteosarcoma: patients with upper limb lesions tend to have a poorer OS and should be screened more thoroughly to determine regional lymph node involvement like screening the distal metastasis.

Conclusions

The results of our study demonstrated that upper limb osteosarcoma patients have a worse OS than lower limb osteosarcoma patients. Compared with lower limb patients, upper limb patients are characterized by more lymph node involvement, which is a negative prognostic factor. Upper limb patients have a higher risk of not only lymph node involvement but also distal metastasis. These lymph node-involved patients have similar survival to distal metastatic patients, and a large proportion of lymph node-involved patients are affected by distal metastasis. Our results suggest that upper limb patients should be screened more thoroughly for regional lymph node involvement.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2187). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This article does not contain any studies with human participants or animals performed by any of the authors.

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