International Orthopaedics (2019) 43:1983–1991
https://doi.org/10.1007/s00264-019-04348-4

ORIGINAL PAPER

Survival analysis of patients with metastatic osteosarcoma: a Surveillance, Epidemiology, and End Results population-based study

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Received: 16 September 2018 / Accepted: 14 May 2019 / Published online: 24 May 2019

Abstract

Purpose The present study is aimed at investigating whether (1) primary tumour surgery confers an improved survival on patients with metastatic osteosarcoma and (2) primary tumour surgery influences survival of patients with metastatic osteosarcoma differently according to primary tumour site.

Methods We retrospectively identified 517 patients with high-grade, metastatic osteosarcoma in the Surveillance, Epidemiology, and End Results (SEER) database between 1994 and 2013. The effect of primary tumour surgery on survival was assessed using Kaplan-Meier analyses, log-rank tests, and multivariate Cox proportional hazard regression modeling.

Results Of those 517 patients with metastatic osteosarcoma in the cohort, 351 patients (68%) underwent primary surgery, and 166 patients (32%) did not undergo surgery. Primary tumour surgery was associated with increased overall survival (hazard ratio (HR) = 0.457, 95% CI 0.354–0.590, $p < 0.001$) and cancer-specific survival (HR = 0.422, 95% CI 0.325–0.550, $p < 0.001$). When we focused on different primary tumour sites, receipt of primary tumour surgery significantly prolonged the survival of patients with extremity osteosarcoma ($p < 0.05$ for overall and cancer-specific survival). However, for patients with pelvis/spine osteosarcoma, both univariate and multivariate analyses indicated that primary tumour surgery might not be associated with improved survival ($p > 0.05$ for overall and cancer-specific survival).

Conclusions Our study is the first population-based analysis to provide evidence of a favourable prognostic impact of primary tumour surgery on metastatic extremity osteosarcoma patients but not metastatic axial (pelvis/spine) osteosarcoma patients. Moreover, we found that surgery type (resection of the primary tumor without amputation vs. amputation) did not influence survival in patients with metastatic osteosarcoma.

Keywords Osteosarcoma · Metastatic · Surgery · Survival

Kehan Song, Jian Song and Kaiyuan Lin contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00264-019-04348-4) contains supplementary material, which is available to authorized users.

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Introduction

Osteosarcoma is the most common primary bone cancer, with an estimated incidence of four to five cases per million people per year [1–4]. Surgical removal of primary tumour has been well accepted for the treatment of osteosarcoma patients with distant metastasis at diagnosis [5–9]. Nevertheless, up to our knowledge, evidence which justifies resection of the primary tumour in patients with osteosarcoma with metastases at presentation is still limited. In addition, the effect of primary tumour surgery on survival according to different primary tumour sites has never been investigated in metastatic osteosarcoma.

The Surveillance, Epidemiology, and End Results (SEER) database is the largest publicly available dataset, which collects data from 18 cancer registries and represents 28% of the

US population [10]. In this study, we used population-based data from the SEER database to answer the following: (1) Does primary tumour surgery improve survival in patients with metastatic osteosarcoma? (2) Does the effect of primary tumour surgery differ according to primary tumour site? (3) Does surgery type influence survival in patients who underwent primary tumour surgery?

Materials and methods

Database and study population

The data source was the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute (NCI). The SEER database is the largest publicly available dataset covering 28% of the US population [10]. The inclusion criteria were listed as follows: (1) high-grade osteosarcoma patients with distant metastasis at initial presentation; (2) osteosarcoma as the first primary cancer; (3) diagnosed between 1994 and 2013 to ensure at least two year follow-up; (4) being scheduled for chemotherapy; (5) diagnosis confirmed by histology; and (6) primary tumour site limited to the extremity, pelvis, or spine.

Clinicopathological factors and outcomes

Demographic factors included age, race, gender, and year of diagnosis. Age was classified into three groups (< 18 years, 18–40 years, > 40 years). Race was categorized as Caucasian, African-American, or other.

Tumour-specific factors included primary tumour site, histologic subtype, node involvement, and tumour size. Since the anatomic tumour location is relatively non-specific in the SEER database, as has been previously reported [11, 12], primary tumour site was categorized as lower extremity, upper extremity, or pelvis/spine. Histologic subtype was classified according to the "International Classification of Disease for Oncology, 3rd Edition (ICD-O-3)" [13]. Tumor size was divided into four groups (≤ 5 cm, > 5–10 cm, > 10 cm, unknown).

Primary tumour surgery referred to resection of the primary tumour. Resection of the primary tumour was confirmed by "site-specific surgery codes" in the SEER database [10]. Based on whether or not patients had undergone primary tumour surgery, eligible osteosarcoma patients were divided into two groups. The primary outcomes of interest in this study were overall survival (OS) and cancer-specific survival (CSS). Duration of OS was defined as the time from diagnosis to the date of death from all possible causes or last follow-up. Duration of CSS was defined as the time from diagnosis to the date of death attributed to osteosarcoma or last follow-up.

Patient cohort

In the present study, 517 osteosarcoma patients with distant metastasis at diagnosis were included (Fig. 1). Overall, primary tumour surgery was performed in 351 patients (68%), while 166 patients (32%) did not undergo primary tumour surgery. Of the 517 patients in the cohort, 359 patients (69%) had primary osteosarcoma in the lower extremity, 82 patients (16%) had primary osteosarcoma in the upper extremity, and 76 patients (15%) had primary osteosarcoma in the pelvis or spine. Five hundred nine patients (98%) and 487 patients (94%) in the cohort had complete follow-up for at least one year and two years, respectively. The median survival was 26 months (range 1–241 months) for surgery and ten months (range 1–197 months) for non-surgery.

Patient characteristics between surgery and non-surgery groups were outlined in Table 1. These factors including age, race, gender, year of diagnosis, primary tumour site, histologic subtype, node involvement, and tumour size were compared between surgery and non-surgery groups by the Pearson chi-square test. Based on the results of chi-square tests, we found that patients who had surgery were more likely to be younger and to have a tumor located in the appendicular skeleton and were less likely to have regional node involvement (Table 1).

Statistical analysis

The effect of primary tumor surgery on survival was assessed using Kaplan-Meier analysis, log-rank test, and multivariate Cox regression modeling. In the multivariate Cox analyses, confounding variables including age, race, gender, year of diagnosis, primary tumour site, histologic subtype, node involvement, and tumour size were controlled for.

The Pearson chi-square test, log-rank test, and multivariate Cox regression modeling were performed by IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The Kaplan-Meier analysis was conducted by using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). The SEER database was accessed using SEER*Stat software 8.3.4 (National Cancer Institute, Bethesda, MD, USA). A two-sided $p < 0.05$ indicated statistical significance.

Results

Primary tumour surgery in the overall cohort

Primary tumour surgery was found to be associated with improved survival in the overall cohort. Kaplan-Meier curves for patients with or without surgery in the overall

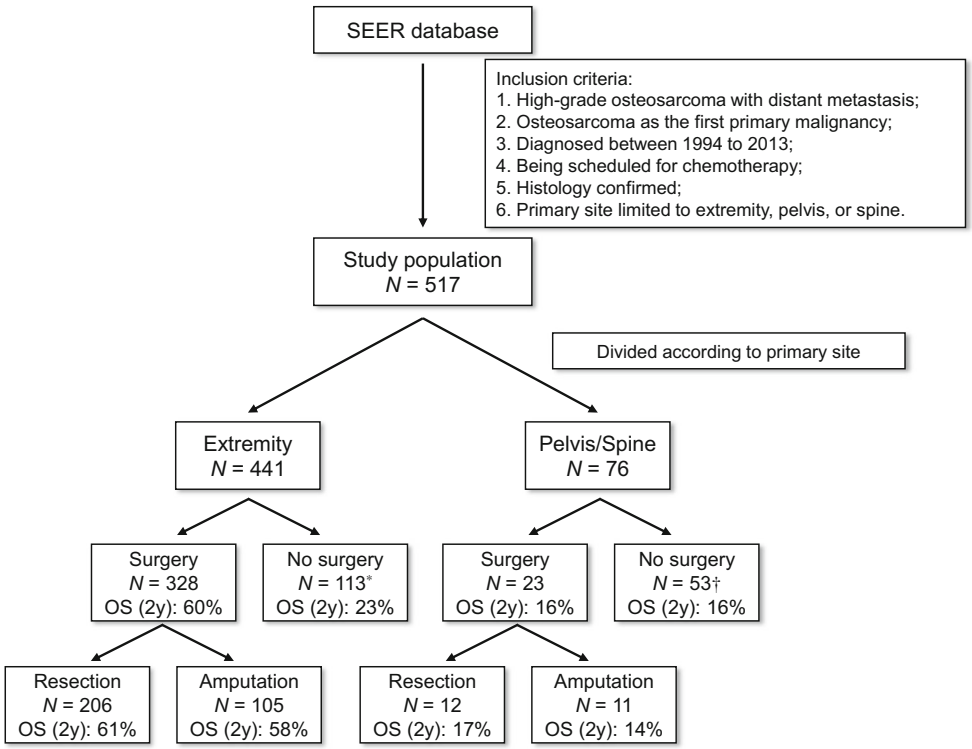

Fig. 1 The process of collecting patients. Based on the inclusion criteria, 517 patients were collected from the SEER database

* 27 patients had radiation therapy while 86 patients did not.
†23 patients had radiation therapy while 30 patients did not.

cohort demonstrated that undergoing primary tumour surgery was predictive of increased survival (log-rank $p < 0.001$ for OS; $p < 0.001$ for CSS) (Fig. 2). After controlling for other confounding variables, primary tumour surgery remained a significant prognostic factor for both OS (hazard ratio (HR) for death 0.457, 95% confidence interval (CI) 0.354–0.590, $p < 0.001$) and CSS (HR 0.422, 95% CI 0.325–0.550, $p < 0.001$) (Table 2).

Primary tumour surgery in different primary tumor sites

Effect of primary tumour surgery was further evaluated in different primary tumour sites. A favourable prognostic impact of primary tumour surgery was found in metastatic extremity osteosarcoma patients but not in metastatic axial (pelvis/spine) osteosarcoma patients. Kaplan-Meier curves showed primary tumour surgery was associated with increased survival in patients with primary osteosarcoma in the extremity (log-rank $p < 0.001$ for OS; $p < 0.001$ for CSS) (Fig. 3). However, primary tumour surgery conferred no survival advantage on patients with primary osteosarcoma in the pelvis or spine (log-rank $p = 0.782$ for OS; $p = 0.898$ for CSS).

Multivariate Cox analyses controlling for other confounding variables revealed similar results. Primary tumour surgery was a significant prognostic factor for patients with primary osteosarcoma in the extremity (HR 0.423, 95% CI 0.320–0.559, $p < 0.001$ for OS; HR 0.394, 95% CI 0.296–0.525, $p < 0.001$ for CSS) (Table 3). However, in patients with primary osteosarcoma in the pelvis or spine, no significant difference was observed between surgery and non-surgery groups (HR 0.763, 95% CI 0.399–1.461, $p = 0.414$ for OS; HR 0.649, 95% CI 0.327–1.289, $p = 0.217$ for CSS) (Supplementary Table 1).

Surgery type in different primary tumour sites

We further investigated whether surgery type (resection of the primary tumour without amputation vs. amputation) influenced survival in patients with metastatic osteosarcoma. We found that there was no association between surgery type and survival in patients with appendicular osteosarcoma. Among patients with appendicular osteosarcoma, 206 patients underwent resection of the primary tumour (without amputation) and 105 patients underwent amputation. The Kaplan-Meier and log-rank analyses suggested there was no association between surgery type and survival (log-rank $p = 0.168$ for OS; $p = 0.238$ for CSS). After controlling for confounding variables, amputation was not associated with improved survival compared with those who underwent primary tumour resection only (OS: HR = 1.205, 95% CI, 0.894–1.624, $p = 0.221$; CSS: HR = 1.170, 95% CI, 0.856–1.600, $p = 0.325$).

Table 1 Baseline characteristics of metastatic osteosarcoma patients at diagnosis

Characteristic	Total $N = 517$	Primary tumour surgery $N = 351$	No primary tumour surgery $N = 166$	p value[a]
Age				< 0.001
< 18	283 (54.7)	224 (63.8)	59 (35.5)	
18–40	139 (26.9)	84 (23.9)	55 (33.1)	
> 40	95 (18.4)	43 (12.3)	52 (31.3)	
Median (range)	17 (3–85)	15 (4–85)	21 (3–85)	
Race				0.480
Caucasian	393 (76.0)	261 (74.4)	132 (79.5)	
African-American	77 (14.9)	56 (16.0)	21 (12.7)	
Other	47 (9.1)	34 (9.7)	13 (7.8)	
Gender				0.770
Male	326 (63.1)	223 (63.5)	103 (62.0)	
Female	191 (36.9)	128 (36.5)	63 (38.0)	
Year of diagnosis				0.845
1994 to 2003	187 (36.2)	126 (35.9)	61 (36.7)	
2004 to 2013	330 (63.8)	225 (64.1)	105 (63.3)	
Primary tumour site				< 0.001
Lower extremity	359 (69.4)	269 (76.6)	90 (54.2)	
Upper extremity	82 (15.9)	59 (16.8)	23 (13.9)	
Pelvis/spine	76 (14.7)	23 (6.6)	53 (31.9)	
Histologic subtype				0.223
Osteosarcoma, NOS	407 (78.7)	277 (78.9)	130 (78.3)	
Chondroblastic	61 (11.8)	39 (11.1)	22 (13.3)	
Fibroblastic	19 (3.7)	14 (4.0)	5 (3.0)	
Telangiectatic	16 (3.1)	14 (4.0)	2 (1.2)	
Paget	8 (1.5)	3 (0.9)	5 (3.0)	
Small cell	6 (1.2)	4 (1.1)	2 (1.2)	
Node involvement				0.001
No	331 (64.0)	237 (67.5)	94 (56.6)	
Yes	39 (7.5)	16 (4.6)	23 (13.9)	
Unknown	147 (28.4)	98 (27.9)	49 (29.5)	
Tumour size (cm)				< 0.001
≤ 5 cm	34 (6.6)	25 (7.1)	9 (5.4)	
> 5 to 10 cm	129 (25.0)	93 (26.5)	36 (21.7)	
> 10 cm	195 (37.7)	150 (42.7)	45 (27.1)	
Unknown	159 (30.8)	83 (23.6)	76 (45.8)	
Median (range)[b]	11.0 (0.2–82.0)	11.0 (0.2–82.0)	10.2 (1.0–27.0)	

[a] The p value compares the percentage of patients undergoing primary tumor surgery in each subgroup by the Pearson chi-square test

[b] 159 patients were excluded because of missing data

Likewise, no association between surgery type and survival was found in patients with pelvic osteosarcoma. Among patients with pelvic osteosarcoma, 12 patients underwent resection of the primary tumour (without amputation) and 11 patients underwent amputation. The Kaplan-Meier and log-rank analyses suggested there was no association between surgery type and survival (log-rank $p = 0.497$ for OS; $p = 0.806$ for CSS). Due to the rarity of metastatic, pelvic osteosarcoma patients, we did not further perform a multivariate analysis to validate our findings.

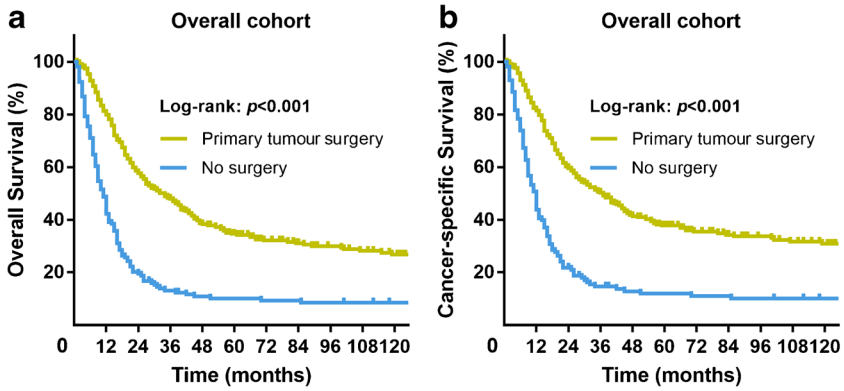

Fig. 2 Kaplan-Meier curves of (a) overall and (b) cancer-specific survival according to whether or not patients underwent primary tumour surgery in the overall cohort

Table 2 Multivariate analysis of prognostic factors for overall and cancer-specific survival in the overall cohort ($n = 517$)

Characteristic	Overall survival		Cancer-specific survival	
	HR (95%CI)	*p* value[a]	HR (95%CI)	*p* value
Primary tumor surgery				
No	Reference[b]		Reference	
Yes	0.457 (0.354–0.590)	< 0.001	0.422 (0.325–0.550)	< 0.001
Age				
< 18	Reference		Reference	
18–40	1.486 (1.154–1.913)	0.002	1.462 (1.124–1.902)	0.005
> 40	2.977 (2.219–3.995)	< 0.001	2.993 (2.211–4.051)	< 0.001
Race				
Caucasian	Reference		Reference	
African-American	0.975 (0.719–1.322)	0.871	0.936 (0.680–1.289)	0.685
Other	1.382 (0.967–1.976)	0.076	1.512 (1.056–2.166)	0.024
Gender				
Male	Reference		Reference	
Female	0.824 (0.659–1.032)	0.092	0.800 (0.633–1.011)	0.062
Year of diagnosis				
1994 to 2003	Reference		Reference	
2004 to 2013	1.232 (0.964–1.574)	0.096	1.198 (0.930–1.545)	0.162
Primary tumor site				
Lower extremity	Reference		Reference	
Upper extremity	0.894 (0.666–1.200)	0.456	0.828 (0.606–1.132)	0.237
Pelvis/spine	1.257 (0.919–1.720)	0.152	1.093 (0.787–1.518)	0.594
Histologic subtype				
Osteosarcoma, NOS	Reference		Reference	
Chondroblastic	0.865 (0.623–1.210)	0.386	0.955 (0.686–1.329)	0.785
Fibroblastic	0.911 (0.516–1.610)	0.749	0.870 (0.482–1.571)	0.645
Telangiectatic	1.124 (0.635–1.988)	0.689	1.041 (0.561–1.931)	0.898
Paget	2.406 (1.144–5.060)	0.021	1.880 (0.806–4.386)	0.144
Small cell	3.175 (1.336–7.543)	0.009	3.890 (1.632–9.271)	0.002
Node involvement				
No	Reference		Reference	
Yes	1.879 (1.289–2.738)	0.001	1.935 (1.314–2.848)	0.001
Unknown	1.101 (0.844–1.437)	0.476	1.139 (0.865–1.500)	0.354
Tumour size (cm)				
≤ 5 cm	Reference		Reference	
> 5 to 10 cm	1.088 (0.683–1.735)	0.722	0.991 (0.619–1.588)	0.970
> 10 cm	1.295 (0.829–2.023)	0.257	1.220 (0.779–1.910)	0.386
Unknown	1.144 (0.716–1.827)	0.574	0.958 (0.596–1.541)	0.860

[a] The *p* value compares the hazard of death between two subgroups by multivariate Cox analysis

[b] The reference stands for taking the hazard of death in this specific subgroup as the standard reference (hazard ratio = 1)

HR, hazard ratio; *CI*, confidence interval

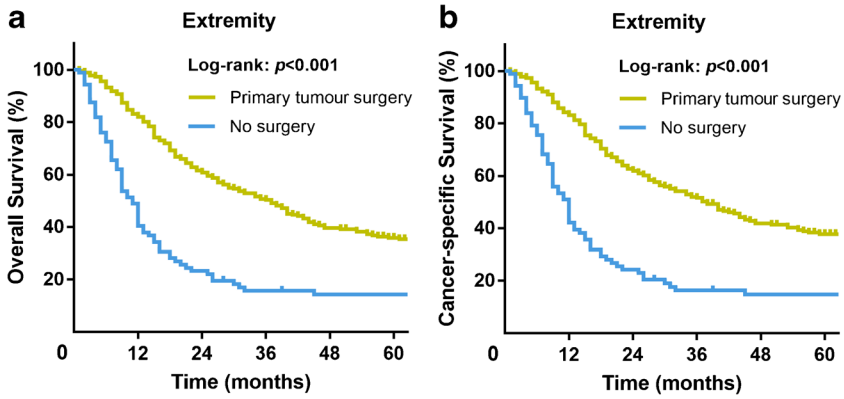

Fig. 3 Kaplan-Meier curves of (a) overall and (b) cancer-specific survival according to whether or not patients underwent primary tumor surgery in extremity osteosarcoma

Table 3 Multivariate analysis of prognostic factors for overall and cancer-specific survival in patients with extremity osteosarcoma ($n = 441$)

Characteristic	Overall survival		Cancer-specific survival	
	HR (95%CI)	*p* value[a]	HR (95%CI)	*p* value
Primary tumour surgery				
No	Reference[b]		Reference	
Yes	0.423 (0.320–0.559)	< 0.001	0.394 (0.296–0.525)	< 0.001
Age				
< 18	Reference		Reference	
18–40	1.383 (1.047–1.825)	0.022	1.339 (1.002–1.789)	0.048
> 40	2.781 (1.978–3.909)	< 0.001	2.765 (1.951–3.920)	< 0.001
Race				
Caucasian	Reference		Reference	
African-American	1.024 (0.737–1.422)	0.889	0.990 (0.703–1.395)	0.955
Other	1.347 (0.897–2.022)	0.151	1.442 (0.959–2.168)	0.079
Gender				
Male	Reference		Reference	
Female	0.788 (0.615–1.011)	0.061	0.758 (0.586–0.981)	0.035
Year of diagnosis				
1994 to 2003	Reference		Reference	
2004 to 2013	1.148 (0.874–1.508)	0.321	1.112 (0.840–1.473)	0.458
Histologic subtype				
Osteosarcoma, NOS	Reference		Reference	
Chondroblastic	0.950 (0.650–1.388)	0.792	1.034 (0.706–1.515)	0.864
Fibroblastic	0.866 (0.477–1.571)	0.636	0.817 (0.439–1.517)	0.521
Telangiectatic	1.121 (0.602–2.089)	0.719	0.991 (0.500–1.965)	0.980
Paget	2.113 (0.818–5.458)	0.122	2.144 (0.827–5.557)	0.117
Small cell	7.855 (2.437–25.318)	0.001	8.590 (2.659–27.752)	< 0.001
Node involvement				
No	Reference		Reference	
Yes	2.040 (1.342–3.099)	0.001	2.075 (1.354–3.180)	0.001
Unknown	1.091 (0.814–1.462)	0.561	1.107 (0.819–1.496)	0.510
Tumour size (cm)				
≤ 5 cm	Reference		Reference	
> 5 to 10 cm	1.195 (0.697–2.048)	0.517	1.140 (0.663–1.962)	0.635
> 10 cm	1.394 (0.832–2.334)	0.207	1.320 (0.786–2.217)	0.294
Unknown	1.227 (0.714–2.107)	0.458	1.079 (0.625–1.863)	0.786

[a] The *p* value compares the hazard of death between two subgroups by multivariate Cox analysis

[b] The reference stands for taking the hazard of death in this specific subgroup as the standard reference (hazard ratio = 1)

HR, hazard ratio; *CI*, confidence interval

Discussion

Neoadjuvant chemotherapy followed by surgical removal of the primary tumour along with metastatic site is the current management strategy for metastatic osteosarcoma [7–9, 14, 15]. However, up to our knowledge, limited evidence is available to justify primary tumour surgery in osteosarcoma patients with distant metastasis [7, 9, 16]. Table 4 lists the previously published studies of several treatment approaches in osteosarcoma patients. The present study provides a clear evidence of a favourable prognostic impact of primary tumour surgery on metastatic osteosarcoma patients.

Since the beneficial effect of primary tumour surgery on survival has been confirmed in many cancers, accumulating studies have been reported to support resection of primary tumour for patients with metastatic cancer. In fact, the justification for primary tumour surgery is based on several biologic rationales. Norton proposed a "cancer self-seeding" theory that tumour cells of the primary

Table 4 Review of the literature: the outcome for each treatment approach and site of tumour

Author	Journal, date of publication[a]	Treatment approach	Site	Outcome
Goorin et al. [17]	JCO, 2003	Presurgical chemotherapy vs. immediate surgery + chemotherapy for nonmetastatic osteosarcoma	Extremity	At 5 years, event-free survival (EFS) was 61% for presurgical chemotherapy and 69% for immediate surgery ($p = 0.8$). There was no advantage in EFS for patients given presurgical chemotherapy.
Bacci et al. [18]	JSO, 2008	Complete resection of pulmonary lesions vs. incomplete resection of pulmonary lesions for osteosarcoma with lung metastases	Extremity	5-year EFS was 27.4% for 91 patients who had complete resection of pulmonary lesions and none for 9 patients who had incomplete lung nodule resection.
Poudel et al. [19]	IJO, 2014	Limb salvage vs. amputation for nonmetastatic osteosarcoma	Extremity	The mean tumor volume in the group without local recurrence was 406.7 cc compared with 195.8 cc in the group with local recurrence ($p = 1.403$). The authors concluded that patients with high tumor volume should not be denied limb salvage.
Nataraj et al. [20]	CTO, 2015	Delaying metastasectomy to completion of chemotherapy vs. performing metastasectomy along with local site surgery for metastatic osteosarcoma	Extremity	The authors concluded that their survival (delaying metastasectomy to completion of chemotherapy) was comparable with data from other studies (performing metastasectomy along with local site surgery).

[a] *JCO*, Journal of Clinical Oncology; *JSO*, Journal of Surgical Oncology; *IJO*, Indian Journal of Orthopaedics; *CTO*, Clinical & Translational Oncology

tumour would recirculate and seed the primary tumour site; thus resection of the primary tumour could reduce tumour self-seeding [21]. Khan reported that the primary tumour could lead to metastatic spread, while alleviating the tumour burden could reduce the possibility of metastatic spread [22]. Shi et al. hypothesized that removal of the primary tumour is likely to lower the risk of infection caused by tumour ulceration or compromised immunity, and such tumour-caused infection is considered to be an important reason of cancer death [23]. Some scholars suggested that reducing tumour load might decrease or delay the occurrence of severe complications including hypoproteinemia and cachexia, thus lowering the corresponding risk of cancer death [24]. Reduction of the tumour volume could increase the effect of chemotherapy and lower the risk of local recurrence [25]. In addition, Poudel et al. pointed out that limb salvage should not be denied to patients merely by the assessment of tumour volume [19]. These theories all reveal the possible mechanism of the improved survival and support surgical resection of the primary tumour.

We also assess the prognostic significance of primary tumour surgery according to different primary tumour sites. Previous studies have reported that axial tumours consistently portend a poorer prognosis compared with appendicular tumours in osteosarcoma [4, 13, 26, 27]. Duchman et al. reported that patients with axial osteosarcoma had significantly decreased cancer-specific survival at ten years ($p < 0.001$) [13]. In an analysis of 1702 osteosarcoma patients, Laux et al. revealed that axial osteosarcoma patients had poorer event-free survival and overall survival after controlling for confounding variables [4]. In the current study, we determine that primary tumour surgery confers improved survival only on metastatic extremity osteosarcoma patients but not metastatic axial osteosarcoma patients even after controlling for confounding variables. Therefore, early surgery should be considered for patients with appendicular osteosarcoma. For patients with axial osteosarcoma, however, they would probably benefit more from conservative treatment rather than surgical resection. The inferior prognosis in these surgery-treated cases can be partially explained by the difficulty in achieving adequate local control.

The study has several limitations. First, the design of our study is retrospective by nature; thus long-term prospective studies are expected to validate our findings. Second, extent and location of distant metastasis is only recorded between 2010 and 2013. To include adequate patients in the study, we did not adjust for such variable in the multivariate analysis. Third, due to the limitations of the SEER database, we did not know the exact site of tumour (primary tumour site was categorized as lower extremity, upper extremity, or pelvis/spine). To address this issue, we

performed Kaplan-Meier analyses, multivariate analyses, and further subgroup analyses to reduce potential confounding. Finally, the record of response to chemotherapy was lacking in the SEER database. Therefore, we did not specifically divide the patients according to whether they responded to chemotherapy or not. Since the current study is the first population-based study to exploringly investigate the effect of surgery on metastatic osteosarcoma patients, further studies are expected to focus on metastatic osteosarcoma patients not responsive to neoadjuvant chemotherapy specifically.

In summary, this population-based study for the first time provides a clear evidence of a favourable prognostic impact of primary tumour surgery on metastatic osteosarcoma patients. Specifically, primary tumour surgery confers improved survival on metastatic extremity osteosarcoma patients but not metastatic axial osteosarcoma patients. Although long-term prospective studies are expected, currently available evidence should be discussed with metastatic osteosarcoma patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Because we obtain data from the SEER database with open access, we did not need to acquire patient consent or an ethical review committee statement, but we were required to sign a Data Use Agreement for the SEER 1973–2014 Research Data File to gain access to the SEER database.

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