

Prognostic factors to survival of patients with chondroblastic osteosarcoma

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Abstract

This study was aimed to reveal the changes in survival rates and prognostic factors to survival of chondroblastic osteosarcoma (COS).

Patients from the Surveillance, Epidemiology, and End Results (SEER) database were retrieved. Kaplan–Meier survival analysis and Cox proportional hazard model were used during analysis.

There were significant differences on overall survival between subtypes of osteosarcoma ($P < .001^*$). Overall survival of COS did not change significantly during last forty years ($P = .610$), and cancer-specific survival increased to a plateau in 1980s and then remained stable ($P = .058$). Younger onset age, patients of white race, well and moderately differentiated tumors, and surgery independently predicted better overall (Hazard ratio [HR]: 1.034, $P < .001^*$; HR: 0.538, $P = .004^*$; HR: 0.240, $P = .020^*$ and HR: 0.350, $P < .001^*$, respectively) and cancer-specific (HR: 1.031, $P = .002^*$; HR: 0.592, $P = .036^*$; HR: 0.098, $P = .027^*$ and HR: 0.253, $P < .001^*$, respectively) survival. Metastasis at diagnosis independently predicted worse overall (HR: 3.108, $P < .001^*$) and cancer-specific (HR: 4.26, $P < .001^*$) survival compared to no metastasis.

Younger onset age, white race, well and moderately differentiated tumors, no metastasis at diagnosis and surgical resection can independently predict better overall and cancer-specific survival of COS.

Abbreviations: CI = confidence interval, COS = chondroblastic osteosarcoma, HR = hazard ratio, SEER = the Surveillance, Epidemiology, and End Results.

Keywords: cancer-specific survival, chondroblastic osteosarcoma, overall survival, prognostic factors

1. Introduction

Chondroblastic osteosarcoma (COS) is a rare tumor, and is a common subtype of osteosarcoma with percentage of 11% to 50%. The age at diagnosis of COS appears to be variable in various studies, mainly with a peak at about twenty years old.^[1–6] It is characterized by predominant presence of chondroid matrix, which tends to exhibit a high degree of hyaline cartilage and is

intimately associated with the non-chondroid element (osteoid or bone matrix).^[7]

It is important to distinguish the COS from other subtypes, as gene expression, chemotherapy response and prognosis of the subtypes of osteosarcoma are different from each other.^[3,8–11] There have been rare case reports describing diagnosis, treatment strategies and prognosis of COS.^[3,7,12–16] However, its clinical characteristics have never been described due to low incidence. Although features of osteosarcoma have been frequently reported, there is controversial evidence as to whether there is prognostic differentiation among its subtypes. One study revealed that patients with COS had a higher survival rate when compared to patients with the osteoblastic osteosarcoma,^[17] while another study declared that the 5-year overall survival was significantly higher in patients with fibroblastic and telangiectatic tumors than in those with osteoblastic tumors and COS.^[9] Surprisingly, Mirabello et al reported that patients with COS presented similar 5-year survival rates than patients with fibroblastic and telangiectatic tumors in age group of 0 to 24, while they presented lower 5-year survival rates than patients with fibroblastic and telangiectatic tumors in age group of 25 to 59 and higher 5-year survival rates than patients with fibroblastic tumors in age group of 60+.^[6] Besides, the subtypes of osteosarcoma presented different signal distributions on MRI.^[18] These findings indicate that significant heterogeneity exists among the subtypes of osteosarcoma, thereby COS should be investigated separately.

However, it is difficult to study this disease by 1 single institute due to the very low incidence. In the present study, we revealed the changes in survival and prognostic factors to survival rates of

Editor: Meixia Lu.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We signed the Data-Use Agreement for the SEER 1973 to 2014 Research Data File and had the permission to use the database for research.

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The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:39(e12636)

Received: 3 April 2018 / Accepted: 9 September 2018

<http://dx.doi.org/10.1097/MD.0000000000012636>

such distal disease in patients from the Surveillance, Epidemiology, and End Results (SEER) database.

2. Methods

2.1. The SEER database and related codes

The SEER database contains information on cancer epidemiology among the United States population.^[19] All patients with osteosarcoma listed in the SEER database from 1973 to 2014 were identified. We used code number “011” under the North American Association of Central Cancer Registries item “CS Schema v0204+” as the first filter, which helped find all bone malignancies. Subtypes of osteosarcoma were coded as 9180 to 9187 and 9192 to 9194, and COS was coded as 9181 according to the International Classification of Diseases for Oncology (ICD-O-3 edition). Clinical factors, including age, gender, race, marital status, year of diagnosis, primary site, histology grade, metastasis at diagnosis, tumor size (largest dimension), treatment strategies, follow-up time and survival status were retrieved for this research. All data were extracted using Perl language. We signed the Data-Use Agreement for the SEER 1973 to 2014 Research Data File and had the permission to use the database for research.

2.2. Statistics

Demographic characteristics of patients and tumors were described with number and percentage. Changes in survival of COS were analyzed using Kaplan–Meier survival analysis for all

cohort. To avoid bias produced by incomplete data over such a long period (1973–2014), only patients diagnosed between 2004 and 2014 were further enrolled to determine the prognostic factors to survival via Cox proportional hazard model. Patients with unknown treatment strategies (code number 8 and 9) were excluded when investigating the influence of clinical factors on survival. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. The significance level for all tests was 2-sided at 5%. All data were analyzed using SPSS Statistics software (V.24; IBM Corporation). Survival time for patients who died during follow up was calculated from the date of diagnosis to the date of death and survival time for patients who were still alive at last follow up was calculated from the date of diagnosis to the date of the last follow-up.

3. Results

3.1. Demographic characteristics

Totally 5950 patients were diagnosed with osteosarcoma in SEER database between 1973 and 2014. Pathology of osteosarcoma was classified as “NOS” (not otherwise specified) for 70.1% (n=4172) of cases; otherwise, COS was the most common subtypes (12.2%, n=724), followed by fibroblastic (5.1%, n=304), parosteal (4.7%, n=277), telangiectatic (2.7%, n=162), central (1.7%, n=102), osteosarcoma in Paget disease (1.4%, n=86), periosteal (0.9%, n=54), small cell (0.8%, n=46), high grade surface (0.3%, n=16) and instrosseous well differentiated (0.1%, n=7). The incidence rates of osteosarcoma

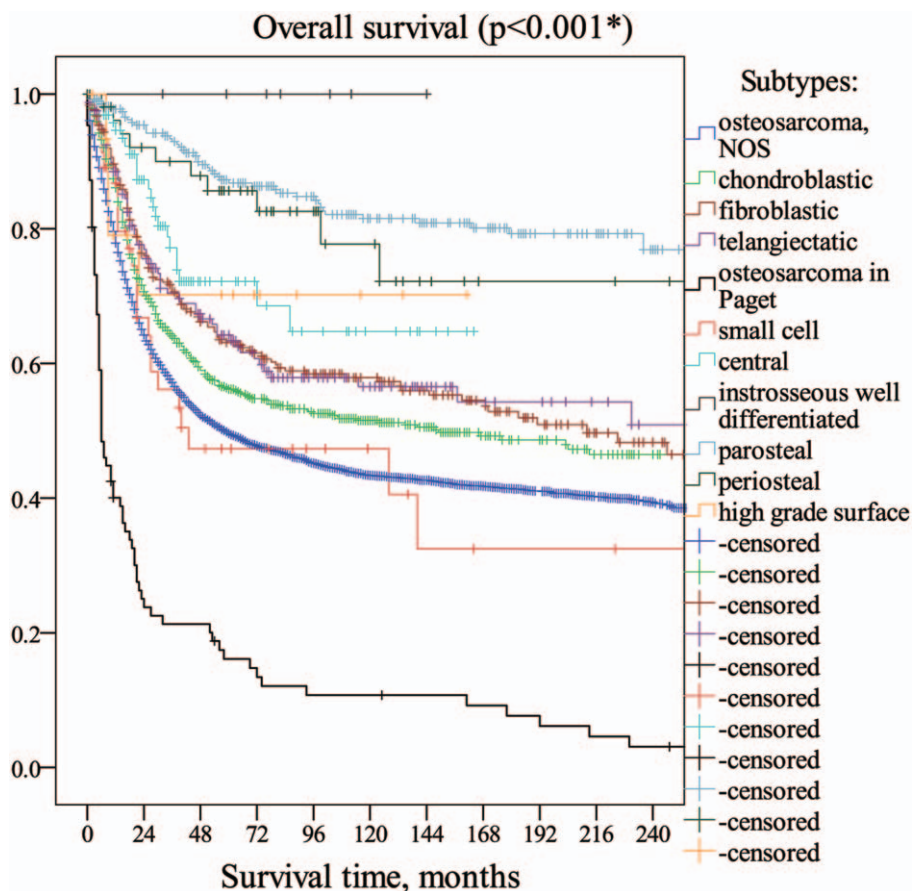


Figure 1. There were significant differences between subtypes of osteosarcoma ($P < .001^*$).

and COS were 0.3 and 0.03 per 100,000 and was age-adjusted to the 2000 US Standard Population, respectively. The mean follows up time was 83.8 months. There were significant differences in overall survival among different subtypes of osteosarcoma ($P < .001^*$, Fig. 1).

Totally 724 patients were diagnosed with COS in SEER database from 1973 to 2014. Characteristics of the enrolled cases were summarized in Table 1.

Table 1
Characteristics of patients with COS.

	Number	%
Patients	724	100
Onset age, mean (SD, years old)	27.4 (18.8)	
Follow up time, median (IQR, months)	29 (16–117)	
Year of diagnosis		
1976–1984	22	3.0
1985–1994	80	11.0
1995–2004	261	36.0
2005–2014	361	49.9
Gender		
Male	408	56.4
Female	316	43.6
Race		
White	538	74.3
Black	123	17.0
American Indian/Alaska Native	7	1.0
Asian or Pacific Islander	52	7.2
Unspecified	4	0.6
Marital status		
Single	507	70.0
Married	157	21.7
Others	60	8.3
Primary site		
Long bones of lower limbs	377	52.1
Pelvic bones and sacrum	97	13.4
Skull and face bones	70	9.7
Long bones of upper limbs and scapula	59	8.1
Mandible	58	8.0
Others	63	8.7
Distant metastasis at diagnosis		
No	321	44.3
Yes	63	8.7
Unrecorded	340	47.0
Tumor size, mean (SD, mm)	231.5 (317.8)	
Number of tumor entities		
1	603	83.3
2	98	13.5
>2	23	3.2
Surgery		
Yes	612	84.5
No	106	14.7
Unspecified	6	0.8
Radiation		
Yes	89	12.3
No / Unknown	635	87.7
Chemotherapy		
Yes	602	83.1
No / Unknown	122	16.9
Survival status		
Alive	405	55.9
Dead	319	44.1

Data were presented as number (%) unless special instructions in the row; COS=chondroblastic osteosarcoma, IQR=interquartile range, SD=standard deviation.

3.2. Overall survival during last forty years

1-year, 3-year, 5-year, and 10-year overall survival of all cohort were 86.1%, 64.1%, 56.2%, and 51.5%, respectively. The overall survival didn't change significantly over last 40 years ($P = .610$, Fig. 2A).

2772 patients were diagnosed with osteosarcoma between 2004 and 2014, 14.1% ($n=391$) patients were COS. 140 (35.8%) patients with COS were dead at last follow up, and 251 (64.2%) were still alive at last follow up.

In multivariate model ($n=391$, Table 2), younger onset age (HR: 1.034, 95% CI: 1.019–1.049, $P < .001^*$), patients of white race (HR: 0.538, 95% CI: 0.354–0.818, $P = .004^*$, Fig. 3A), well and moderately differentiated tumors (HR: 0.240, 95% CI: 0.072–0.799, $P = .020^*$, Fig. 3B), and surgery (HR: 0.350, 95% CI: 0.207–0.592, $P < .001^*$, Fig. 3C) independently predicted better overall survival, while metastasis at diagnosis independently predicted a worse overall survival compared to no metastasis (HR: 3.108, 95% CI: 1.972–4.898, $P < .001^*$, Fig. 3D).

3.3. Cancer-specific survival analysis during last forty years

Totally 127 patients died due to other reasons instead of COS, thus the remaining 597 cases were included to analyze cancer-specific survival. 1-year, 3-year, 5-year and 10 year cancer-specific survival were 90.2%, 68.8%, 61.8%, and 58.2%, respectively. Cancer-specific survival increased to a plateau in 1980s and then remained stable ($P = .058$, Fig. 2B).

In multivariate model ($n=332$, Table 3), younger onset age (HR: 1.031, 95% CI: 1.011–1.051, $P = .002^*$), patients of white race (HR: 0.592, 95% CI: 0.363–0.966, $P = .036^*$, Fig. 4A), well and moderately differentiated tumors (HR: 0.098, 95% CI: 0.013–0.770, $P = .027^*$, Fig. 4B), and surgery (HR: 0.253 95% CI: 0.128–0.500, $P < .001^*$, Fig. 4C) independently predicted better cancer-specific survival, while metastasis at diagnosis independently predicted a worse cancer-specific survival compared to no metastasis (HR: 4.26, 95% CI: 2.640–7.421, $P < .001^*$, Fig. 4D).

3.4. Variations in survival in different age groups

Patients were divided into 4 subgroups based on the age at diagnosis, which varied between 3 to 86 years old: 3 to 19, 20 to 39, 40 to 59 and 60 to 86. Almost half of the total patients were diagnosed between 3 to 19 years old. Patients older than 60 had lowest overall and cancer-specific survival rates than other age groups (Table 4, Fig. 5).

4. Discussion

As 1 of the most common subtypes of osteosarcoma, COS has never been well described due to low incidence. In the present study, all patients with osteosarcoma were reviewed from SEER database. We found that overall survival differed among different subtypes of osteosarcoma. Overall survival of COS did not change significantly during last forty years, and cancer-specific survival increased to a plateau in 1980s and then remained stable. Younger age and no metastasis at diagnosis, white race, well and moderately differentiated tumors, as well as surgical resection, can independently predict better overall and cancer-specific survival of COS.

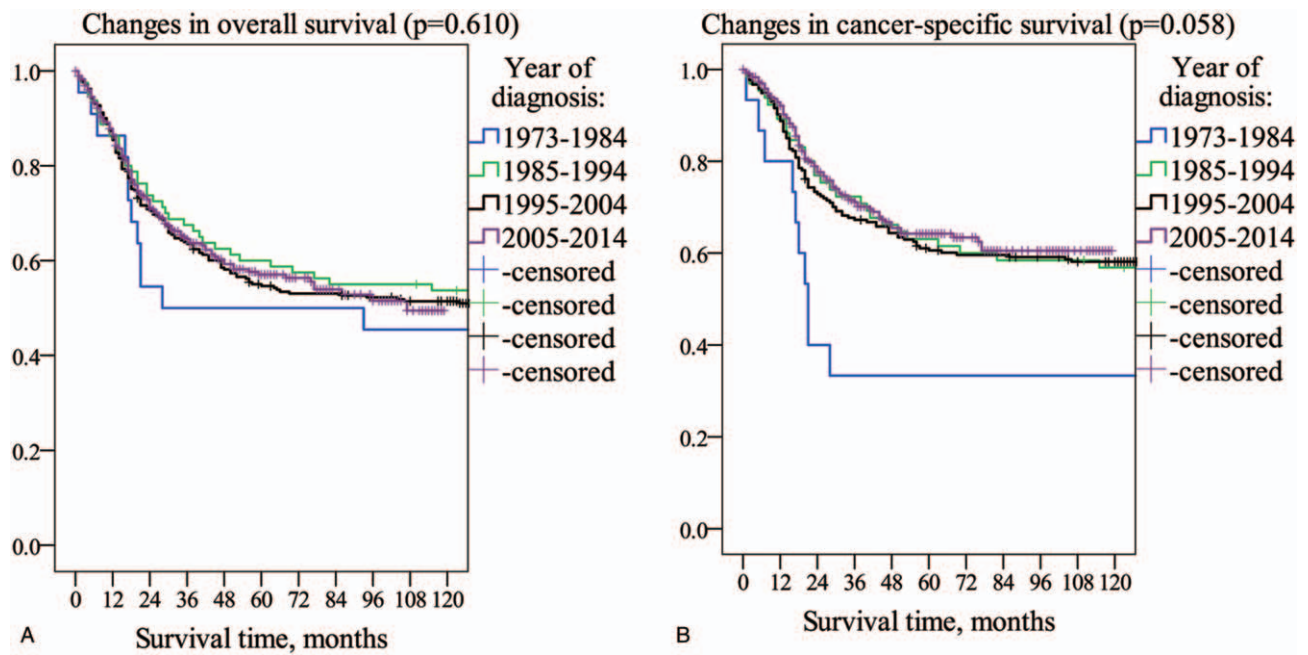


Figure 2. A: The overall survival did not change significantly over last 40 years ($P = .610$). B: Cancer-specific survival increased to a plateau in 1980s and then remained stable ($P = .058$).

Table 2

Prognostic factors to overall survival of COS: Cox proportional hazards analysis.

Variable	Univariate			Multivariate (final model)		
	HR	95% CI	P value	HR	95% CI	P value
Male (vs female)	0.964	0.690–1.346	.828	—	—	—
Onset age	1.031	1.022–1.039	<.001*	1.034	1.019–1.049	<.001*
White race (vs others)	0.704	0.488–1.016	.061	0.538	0.354–0.818	.004*
Single (vs others)	0.546	0.389–0.767	<.001*	—	—	—
Tumor size	1.001	1.000–1.002	.131	—	—	—
Long bones (vs other bones)	0.644	0.462–0.896	.009*	—	—	—
Metastasis (vs no metastasis)	3.448	2.390–4.973	<.001*	3.108	1.972–4.898	<.001*
One tumor entity (vs others)	0.366	0.247–0.542	<.001*	—	—	—
Highly differentiated* (vs others)	0.354	0.131–0.957	.041*	0.240	0.072–0.799	.020*
Surgery (vs no surgery)	0.199	0.134–0.294	<.001*	0.350	0.207–0.592	<.001*
Radiation (vs no/unknown radiation)	2.023	1.320–3.101	.001*	—	—	—
Chemotherapy (vs no/unknown chemotherapy)	0.586	0.383–0.897	.014*	—	—	—

CI = confidence interval, COS = chondroblastic osteosarcoma, HR = hazard ratio, SD = standard deviation.

* Highly differentiated means well and moderately differentiated.

Some studies described a second peak of incidence in patients older than 60 years old. However, we did not observe a second peak for the COS. An institution reported that the 5-year overall survival rate of COS was 60% ($n = 132$).^[9] In the present study, the 5-year overall survival rates were 56.2%, which was lower than the previous outcomes but still comparable.

Prognostic factors to survival of osteosarcoma varied in many studies. One study reported that tumor volume, age and histological subtypes were associated with disease free survival via multivariate analyses,^[11] while another study revealed that primary metastasis, tumor necrosis after chemotherapy, tumor site, surgical margins, extremity tumor, tumor volume, and location within the limb had prognostic significance via multivariate analyses.^[20] In the present study, we demonstrated

that different subtypes of osteosarcoma had different overall survival, supporting our decision to investigate the survival of COS separately, and it is consistent with the previously reported results.^[11] Moreover, we found that onset age and no metastasis at diagnosis, white race, tumor grade as well as surgical resection were associated with survival of COS, while tumor size and tumor location of long bones cannot independently predict survival rates.

Although different gene expression features and prognosis have been reported among subtypes of osteosarcoma, currently, there is no difference on the treatment strategies between COS and the other subtypes. The resection with tumor-free margins and systemic chemotherapy are the standard treatment option.^[3,7,21,22] Osteosarcoma is quite resistant to radiotherapy.

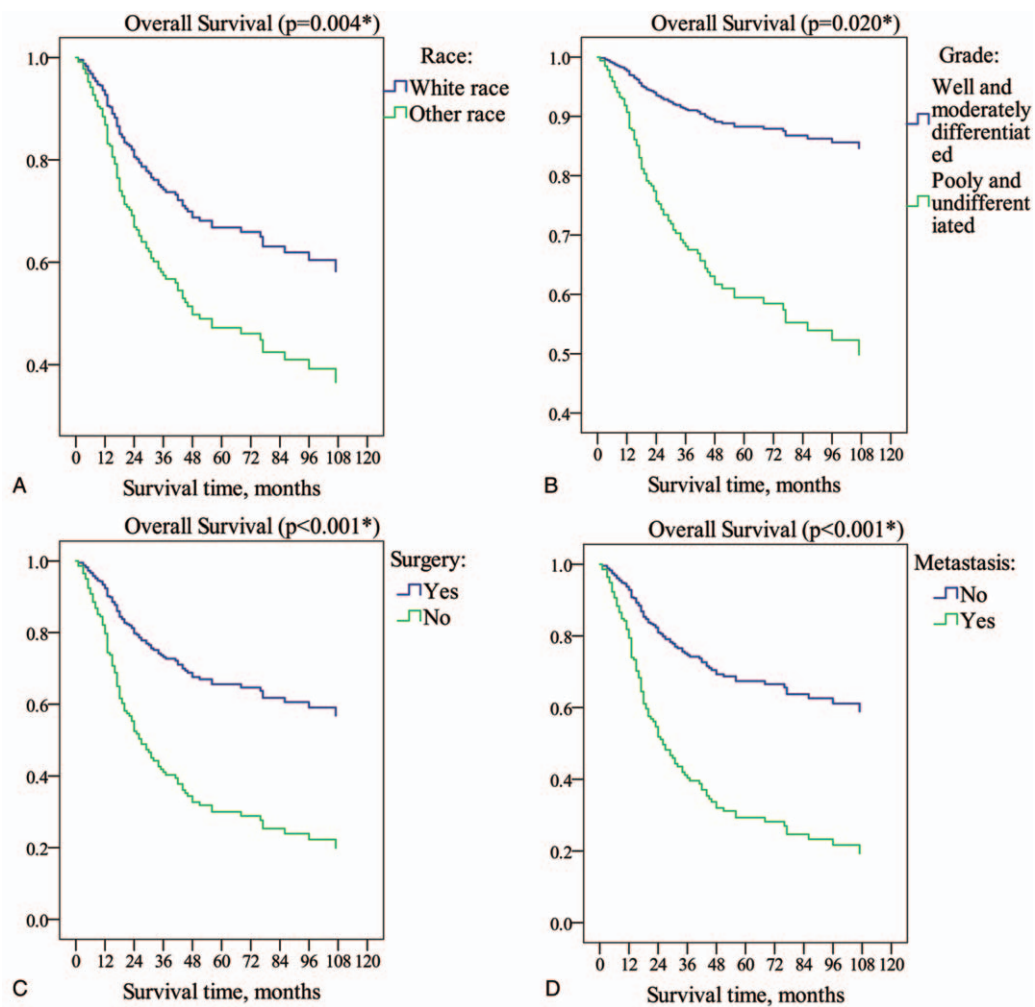


Figure 3. Overall survival curves for prognostic factors of race, tumor grade, metastasis at diagnosis and surgery in multivariate analysis.

However, in special locations where surgery is not feasible or for cases of bone metastases or in multifocal osteosarcoma, radiotherapy can prolong survival, and decrease pain intensity.^[23] However, radiotherapy predicted worse survival rates in our study. This has to be interpreted with caution because only unresectable tumors were included in their study, while both

resectable and unresectable tumors were included in our study. Many patients did not receive radiation but underwent tumor resection, thereby presenting better overall survival in this study. Our outcomes may be interpreted as those patients eligible for radiation presented relatively worse overall survival in all patients with COS.

Table 3
Prognostic factors to cancer-specific survival of COS: Cox proportional hazards analysis.

Variable	Univariate			Multivariate (final model)		
	HR	95% CI	P value	HR	95% CI	P value
Male (vs female)	1.075	0.717–1.610	.727	—		
Onset age	1.019	1.007–1.031	.002*	1.031	1.011–1.051	.002*
White race (vs others)	0.667	0.432–1.030	.068	0.592	0.363–0.966	.036*
Single (vs others)	0.798	0.509–1.250	.324	—		
Tumor size	1.001	1.000–1.002	.120	—		
Long bones (vs other bones)	0.716	0.480–1.068	.102	—		
Metastasis (vs no metastasis)	4.246	2.773–6.500	<.001*	4.426	2.640–7.421	<.001*
One tumor entity (vs others)	21.084	0.120–3720.0	.248	—		
Highly differentiated* (vs others)	0.257	0.063–1.041	.057	0.098	0.013–0.770	.027*
Surgery (vs no surgery)	0.189	0.115–0.309	<.001*	0.253	0.128–0.500	<.001*
Radiation (vs no/unknown radiation)	1.929	1.127–3.299	.016*	—		
Chemotherapy (vs no/unknown chemotherapy)	0.865	0.472–1.583	.637	—		

CI=confidence interval, COS=chondroblastic osteosarcoma, HR=hazard ratio.
*Highly differentiated means well and moderately differentiated.

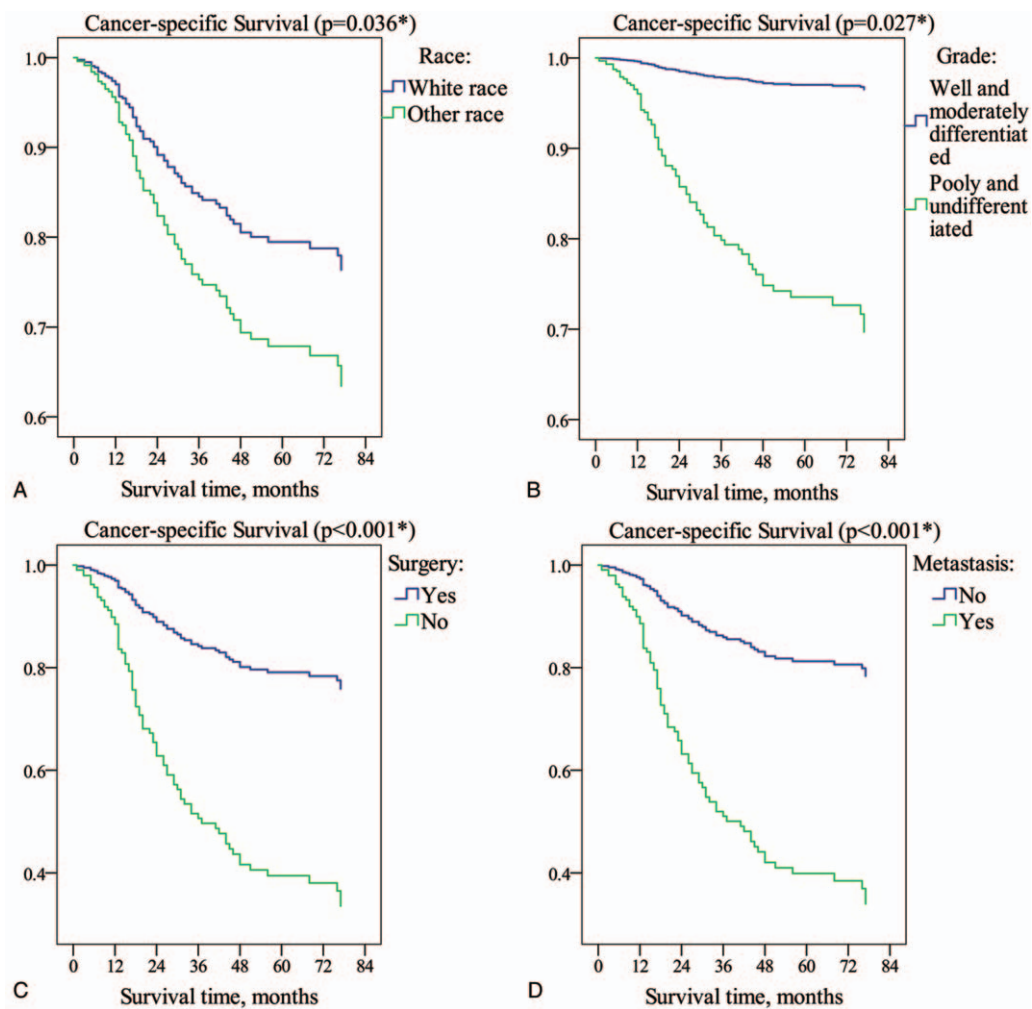


Figure 4. Cancer-specific survival curves for prognostic factors of race, tumor grade, metastasis at diagnosis and surgery in multivariate analysis.

Chemotherapeutic options depend on the institutions. The European Osteosarcoma Intergroup established a protocol which consists of cycles of cisplatin and doxorubicin, and the Brazilian Protocol for Metastatic and No Metastatic Osteosarcoma also made a protocol with cycles of cisplatin, ifosfamide and doxorubicin.^[24] The Cooperative Osteosarcoma Study group of Germany, Austria, and Switzerland reported a combination regimen of Methotrexate (12 g/m² per course), Adriamycin (60–90 mg/m² per course), Cisplatin (90–150 mg/m² per course), Ifosfamide (6–10 g/m² per course), and Bleomycin, Cyclophosphamide and Dactinomycin used in varying combinations.^[20] However, whether a combination chemotherapy may prolong survival remains controversial. There was no survival benefit

with a multi-agent regimen compared with a 2-drug regimen.^[25,26] Some other studies also revealed that intensification of chemotherapy did not improve the overall survival.^[27–30] Unfortunately, only the information of whether the patients were treated by chemotherapy or not was recorded, there was no information about which chemotherapeutic regimens were used in the SEER database (incomplete data).

5. Conclusion

In this retrospective study, we found that there were significant differences in overall survival between subtypes of osteosarcoma, and the overall and cancer-specific survival did not change

Table 4

Survival rates in different age subgroups.

Subgroups	Number of cases	Overall survival, %				Cancer-specific survival, %				
		1 year	3 year	5 year	10 year	Number of cases	1 year	3 year	5 year	10 year
3–19	195	94.5	72.5	65.3	59.1	187	94.8	72.8	66.1	64.7
20–39	113	87.5	67.5	62.1	58.6	94	90.8	74.2	69.6	65.7
40–59	44	90.2	64.7	47.6	33.3	37	91.1	64.9	54.8	47.0
60–86	39	45.3	22.7	22.7	—	14	53.8	38.5	38.5	—

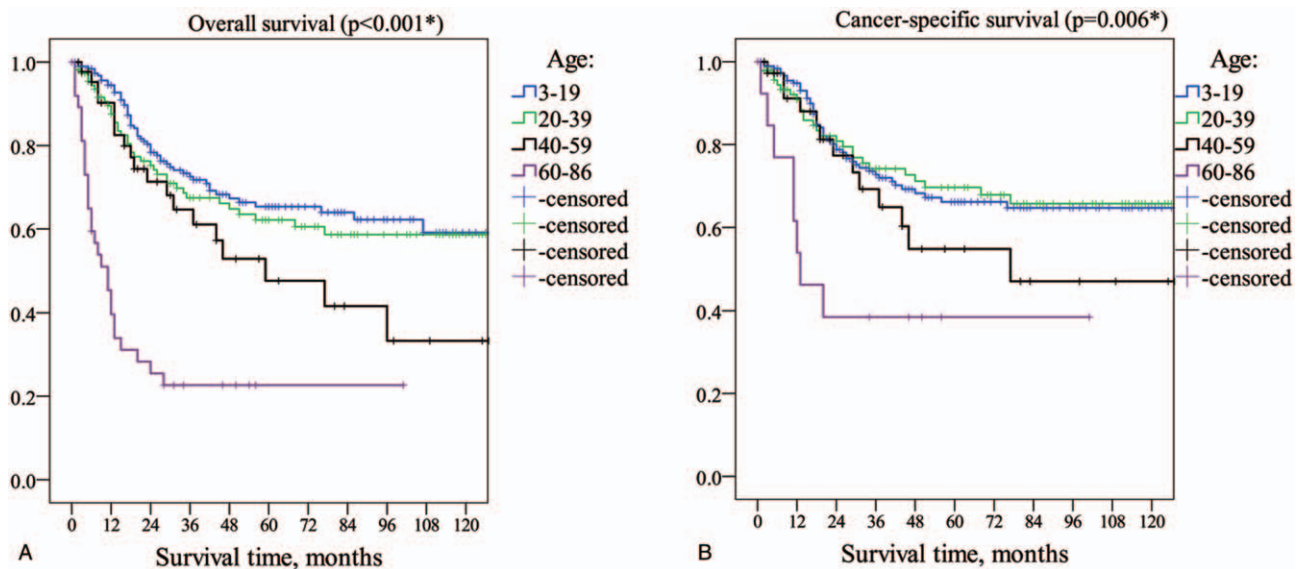


Figure 5. Comparison of survival rates in different age groups.

significantly during last few decades. Younger onset age, white race, well and moderately differentiated tumors, no metastasis at diagnosis and surgical resection can independently predict better overall and cancer-specific survival of COS.

We acknowledge some limitations existing in this study. First of all, the retrieved data partly relies on accuracy of written records of individuals. Second, although chemotherapy plays an important role in managing patients with COS, the chemotherapeutic regimens were unknown in SEER database. Third, the surgical margin status was unknown in this study. Despite these deficiencies, to the best of our knowledge, this is the largest scale study investigating survival of COS.

Author contributions

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Supervision: Kai-Jin Guo.

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