



Characteristics and prognosis of telangiectatic osteosarcoma: a population-based study using the Surveillance, Epidemiology and End Results (SEER) database

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Background: Telangiectatic osteosarcoma (TOS) is a rare type of osteosarcoma for which limited clinical data is available. Furthermore, the clinical characteristics and prognosis of TOS remain unclear.

Methods: A large population-based cohort analysis was conducted using the Surveillance, Epidemiology and End Results (SEER) registry. The data of TOS and conventional osteosarcoma (COS) patients from 2000 to 2017 were collected. The categorical variables were assessed by Chi-squared tests. Kaplan-Meier curves and log-rank (Mantel-Cox) tests were used to examine the survival outcomes between the groups. Cox proportional hazard models were used for univariate and multivariate analyses of TOS patient survival-related variables.

Results: A total of 141 TOS patients and 2961 COS patients were included in this analysis, and the mean age at diagnosis was 23.5 and 29.4 years, respectively. Compared to COS patients, TOS patients were more likely to be under 20 years old (61.7% vs. 51.7%, $P=0.022$), and without a second peak of incidence after 60 years of age. The median overall survival (mOS) of TOS patients was not reached compared to a median survival of 84 months for COS patients (hazard ratio 0.75, 95% confidence interval 0.59 to 0.95, $P=0.0175$). After adjusting these data for age at diagnosis, stage, and surgery at the primary site, no significant differences in mOS were observed between the two groups. In univariate analyses, being under 20 years of age, having localized or regional stage disease, and having undergone surgery were associated with a decreased risk of death. Subsequent multivariate analysis indicated that age at diagnosis, stage, and surgery at the primary site were all independent predictors of prognosis in TOS patients.

Conclusions: Patients with TOS were younger than patients with COS and did not show a second peak after 60 years of age. Age, summary stage at diagnosis, and surgery at the primary site were independent predictors of survival for TOS patients.

Keywords: Telangiectatic osteosarcoma (TOS); clinical characteristics; SEER; prognosis; median overall survival (mOS)

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Introduction

Osteosarcoma is among the most prevalent forms of non-hematopoietic primary malignant bone cancer (1). Approximately 90% of osteosarcomas are of the common types including osteoblastoma, fibroblastoma, and chondroblastoma. Numerous independent osteosarcoma histological types that have been differentiated from conventional osteosarcomas (COS) based upon their behaviors and characteristics upon X-ray analysis, including telangiectatic osteosarcoma (TOS), small cell osteosarcoma, intraosseous well-differentiated osteosarcoma, high-grade surface osteosarcoma, periosteal osteosarcoma, parosteal osteosarcoma, osteosarcoma in Paget's disease of the bone, and central osteosarcoma (2-5).

TOS is a rare osteosarcoma subtype that accounts for less than 4% of all cases (6), and was first described in 1854 by Paget. There were no significant differences in common symptoms and signs between TOS and COS, including recent local pain, soft tissue mass, or both. TOS consists of multiple characteristic dilated aneurysmal cavities containing blood, with highly malignant sarcoma cells being present at the peripheral margins and septations surrounding these cavities (7). As this is a very rare form of cancer, no large-scale clinical studies of TOS have been conducted to date, and case reports (8-10) and animal studies (11-13) thus account for the bulk of research related to this condition. Given these limitations, the clinical characteristics and prognosis of TOS remain poorly understood. Previously, TOS was presumed to be associated with a poorer prognosis compared to COS (14). However, some researchers have found TOS to be associated with no significant survival differences or with mildly improved survival as compared to patients with conventional high-grade intramedullary osteosarcoma (15,16).

Owing to the rarity of this condition and the discrepancies in the pertinent prognostic data available, the present study evaluated the clinical characteristics and prognosis of TOS using the Surveillance, Epidemiology, and End Result (SEER) database maintained by the National Cancer Institute.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-8001>).

Methods

Study population

The SEER database provides clinical information on many tumors, which is very useful for clinical analysis of rare

tumors (17-19). Through the SEER database (<http://seer.cancer.gov/>) all patients from 2000–2017 who had been diagnosed with TOS (IDC, 9183/3) were identified. Patients diagnosed with osteosarcoma that was not otherwise specified (NOS; IDC, 9180/3), were defined as COS patients in this present study, based upon the ICD-0-3/WHO 2008 criteria. The SEER*Stat 8.3.6.1 software platform was used for case identification. A total of 145 TOS and 3,115 COS patients were identified for this study. Patients were excluded from this analysis if they: (I) lacked a pathologically confirmed diagnosis; (II) were diagnosed upon death or via autopsy; (III) had uncertain overall survival outcomes; or (IV) had a history of other tumors. Based on these criteria, a final cohort of 141 TOS patients and 2,961 COS patients were included in this present analysis.

Statistical analysis

Categorical data were presented as numbers with percentages and was compared via chi-squared tests, while continuous data were presented as means or medians with corresponding ranges. Patient median overall survival (mOS) was measured as the time between diagnosis and the most recent follow-up or all-cause mortality. Survival outcomes were compared between groups using Kaplan-Meier curves and log-rank (Mantel-Cox) tests. In models assessing patient survival outcomes, age at diagnosis, gender, race, year of diagnosis, grade, primary site (laterality), summary stage, and surgery at the primary site were included as variables. Cox proportional hazard models were used for univariate and multivariate analyses of TOS patient survival-related variables. A two-sided P value <0.05 was used as the significance threshold in this analysis, and SPSS v23 (IBM Corp, NY, USA) was used for all statistical analyses.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As cancer is considered a reportable disease in the United States, no patient consent was necessary for the use of the SEER database.

Results

Patient characteristics

By reviewing the SEER database, we identified 4,630 patients who had been diagnosed with osteosarcoma between

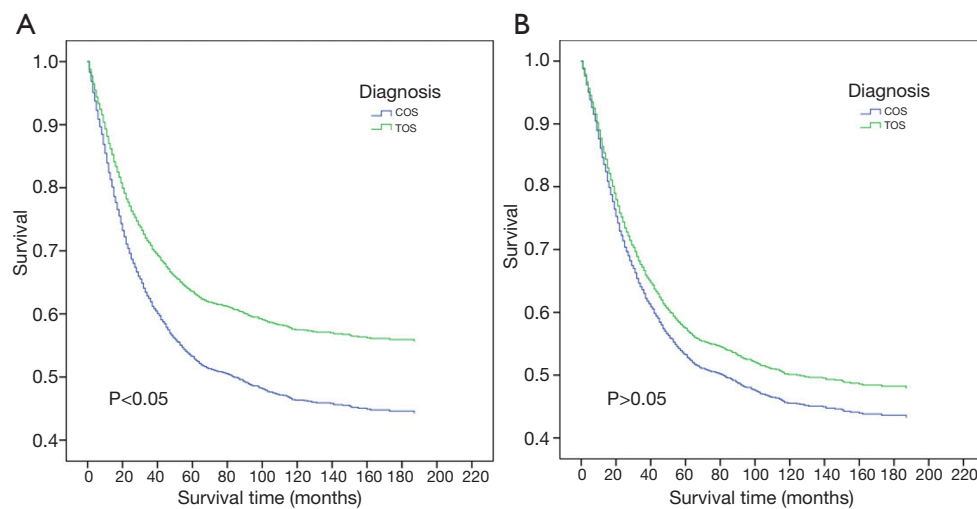


Figure 1 Kaplan-Meier survival curves of COS and TOS patients. (A) Kaplan-Meier curves indicated that TOS patients survived significantly longer than COS patients (not reached *vs.* 84 months; HR 0.75, 95% CI: 0.59 to 0.95, $P=0.0175$); (B) Kaplan-Meier curves indicated that the mOS of TOS patients did not differ significantly from that of COS patients after adjusting for age at diagnosis, stage, and surgery at primary site. TOS, telangiectatic osteosarcoma; HR, hazard ratio; CI, confidence interval; COS, conventional osteosarcoma; mOS, median overall survival.

2000 and 2017, including 3,115 COS patients and 145 TOS patients. TOS patients accounted for just 3.1% of the total osteosarcoma cases. Based upon the exclusion criteria, 2,961 COS patients and 141 TOS patients were finally included in the present study. These TOS and COS patients had a mean age at diagnosis of 23.5 and 29.4 years, respectively. Overall clinical and demographic data pertaining to these two patient cohorts have been compiled in *Table 1*.

Survival analysis

Significant differences were detected between the COS and TOS patient cohorts with respect to age at diagnosis, surgery at the primary site, and mOS. However, after these data were adjusted for age at diagnosis, tumor stage, and surgery at the primary site, no significant differences in mOS were observed between these groups. In addition, no significant differences were detected between these two patient cohorts with respect to patient gender, race, year of diagnosis, grade, laterality, or summary stage.

The survival of TOS and COS patients were compared (*Figure 1A*). The mOS of TOS patients was not reached as more than 50% of these patients are still alive (range, 1–209 months), while the mOS of COS patients was 84 months (range, 1–215 months). There was a significant

difference between these patient cohorts, with hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.59 to 0.95, and $P=0.0175$. However, no significant differences in mOS were detected between the two groups after adjusting for age at diagnosis, stage, and surgery at the primary site (*Figure 1B*).

The survival outcomes of TOS patients as a function of age at diagnosis were examined (*Figure 2*). Kaplan-Meier curves revealed that patients less than 20 years old at the time of diagnosis had significantly better survival outcomes compared to other patients (not reached *vs.* 49 months, HR 0.32, 95% CI: 0.18 to 0.58, $P<0.0001$), with patients less than 10 years old showing the best prognosis. TOS patient survival was also compared as a function of patient gender, race, grade, and laterality, but none of these factors were associated with survival ($P>0.05$) (*Figure 3*). In addition, TOS patient survival was compared as a function of summary stage and surgery of the primary site (*Figure 4*). Patients with localized or regional disease had significantly better survival outcomes compared to patients with advanced disease (not reached *vs.* 29.5 months, HR 0.13, 95% CI: 0.06 to 0.29, $P<0.0001$). Similarly, patients who underwent surgical tumor resection showed significantly improved survival compared to patients who did not undergo surgery (not reached *vs.* 100 months, HR 0.27,

Table 1 Demographic and clinic characteristics of patients diagnosed with TOS and COS between 2000 and 2017 in the SEER database

Diagnosis	TOS (%)	COS (%)	P value
N	141	2,961	
Age at diagnosis			0.022
<20	87 (61.7)	1,532 (51.7)	
20–39	30 (21.3)	571 (19.3)	
40–59	13 (9.2)	435 (14.7)	
≥60	11 (7.8)	423 (14.3)	
Race			0.496
White	111 (78.7)	2,218 (74.9)	
Black	20 (14.2)	452 (15.3)	
Other	10 (7.1)	291 (9.8)	
Gender			0.219
Female	56 (39.7)	1,332 (45.0)	
Male	85 (60.3)	1,629 (55.0)	
Year of diagnosis			0.551
2000–2004	43 (30.5)	793 (26.8)	
2005–2009	43 (30.5)	832 (28.1)	
2010–2014	34 (24.1)	812 (27.4)	
2015–2017	21 (14.9)	524 (17.7)	
Laterality			0.001
Left	78 (55.3)	1263 (42.7)	
Right	56 (39.7)	1,238 (41.8)	
Other	7 (5.0)	460 (15.5)	
Grade			0.134
I–II	3 (2.1)	185 (6.2)	
III–IV	99 (70.2)	1,983 (67.0)	
Unknown	39 (27.7)	793 (26.8)	
Stage			0.155
Localized	49 (34.8)	811 (27.4)	
Regional	51 (36.2)	1,046 (35.3)	
Distant	24 (17.0)	611 (20.6)	
Unknown	17 (12.1)	493 (16.6)	
Status			0.053
Alive	88 (62.4)	1,602 (54.1)	
Deceased	53 (37.6)	1,359 (45.9)	

Table 1 (continued)**Table 1** (continued)

Diagnosis	TOS (%)	COS (%)	P value
T staging			0.182
T1	25 (17.7)	430 (14.5)	
T2	31 (22.0)	511 (17.3)	
T3	3 (2.1)	39 (1.3)	
Unknown	82 (66.5)	1,981 (66.9)	
N staging			0.172
N0	62 (44.0)	1,092 (36.9)	
N1	2 (1.4)	26 (0.9)	
Unknown	77 (54.6)	1,843 (62.2)	
M staging			0.070
M0	58 (41.1)	967 (32.7)	
M1	7 (5.0)	243 (8.2)	
Unknown	76 (53.9)	1,751 (59.1)	
Surgery			0.017
No	15 (10.6)	549 (18.5)	
Yes	126 (89.4)	2,412 (81.5)	

TOS, telangiectatic osteosarcoma; COS, conventional osteosarcoma.

95% CI: 0.09 to 0.79, $P < 0.05$).

The overall 5- and 10-year survival rates of TOS patients were 48.2% ($n=68$) and 20.6% ($n=29$), respectively. Patients who were diagnosed at a younger age had better outcomes, with patients less than 20 years-old showing a 5-year survival rate of 59.8%, compared to rates of just 36.7%, 30.8%, and 9.1% in patients aged 20–39, 40–59, and greater than 60 years old, respectively. However, there were no significant differences in the 10-year survival among patients aged less than 20, 20–39, and 40–59 years (*Table 2*).

Lastly, univariate and multivariate analyses were conducted to evaluate the relationships between key clinical variables and patient mOS. In univariate analyses, an age of less than 20 years old was associated with a better prognosis. Patients who had localized or regional disease and patients who underwent surgery also showed better survival outcomes in univariate analysis (HR 0.41; 95% CI: 0.19 to 0.88; $P < 0.05$). Tumor grade, however, was not significantly associated with patient survival (*Table 3*). Age, summary stage, and surgery at the primary site were included as

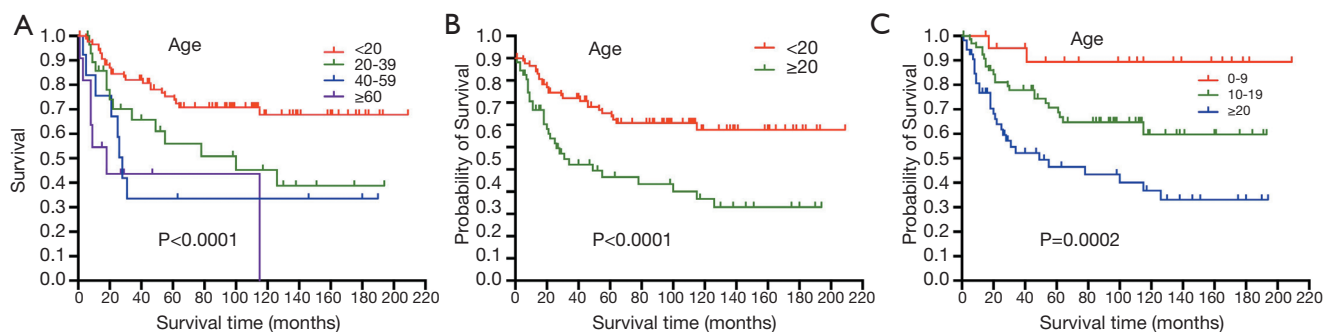


Figure 2 Kaplan-Meier curves revealed that TOS patients less than 20 years old survived significantly longer than other patients (not reached *vs.* 49 months, HR 0.32, 95% CI: 0.18 to 0.58, $P < 0.0001$), with patients less than 10 years old exhibiting the best prognosis. TOS, telangiectatic osteosarcoma; HR, hazard ratio; CI, confidence interval.

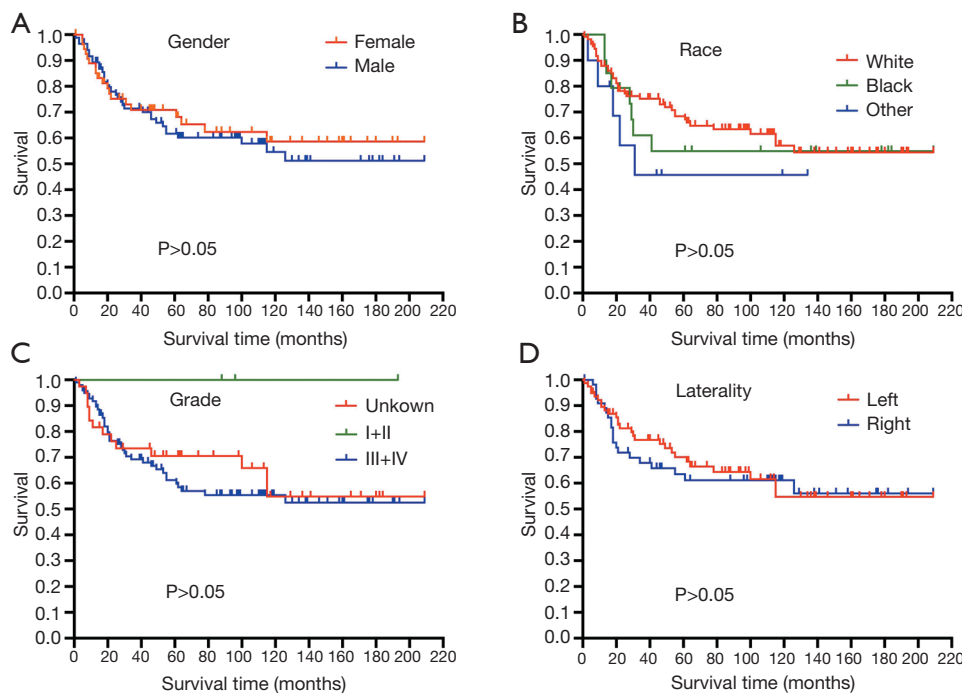


Figure 3 Kaplan-Meier curves revealed that TOS patient survival did not differ significantly as a function of gender, race, grade, laterality, or summary stage ($P > 0.05$). TOS, telangiectatic osteosarcoma.

covariates in a subsequent multivariate analysis, which revealed that patients less than 20 years old had significantly better outcomes, and this was consistent with our univariate analysis. In addition, the multivariate analysis revealed that localized or regional disease and having undergone surgery were independently associated with the prognosis of TOS patients (HR 0.53; 95% CI: 0.24 to 1.17; $P = 0.116$).

Discussion

TOS is a form of high-grade osteosarcoma that accounts for approximately 6.8% of all such osteosarcoma cases (6,20). In line with these prior reports, we found that TOS accounted for 3.1% of osteosarcoma cases in the SEER database. No large-scale clinical studies of TOS have been conducted to date, and as such animal studies and case reports are the

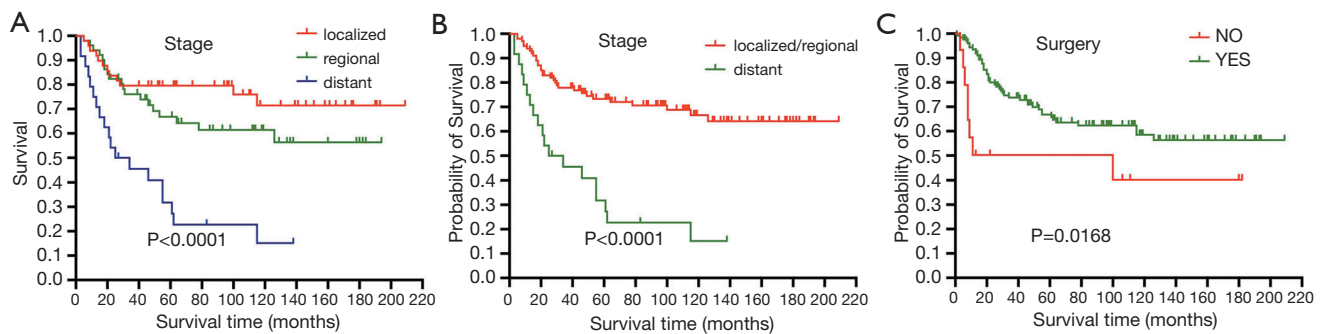


Figure 4 Kaplan-Meier survival curves of TOS patients according to tumor stage and surgery. (A,B) Kaplan-Meier curves revealed that early-stage disease was associated with better prognosis in TOS patients ($P < 0.0001$); (C) Kaplan-Meier curves showed that TOS patients who underwent surgery at the primary site survived for significantly longer than patients who did not undergo surgery (not reached *vs.* 100 months, HR 0.27, 95% CI: 0.09 to 0.79, $P < 0.05$). TOS, telangiectatic osteosarcoma; HR, hazard ratio; CI, confidence interval.

Table 2 The 5- and 10-year survival rates of TOS patients

Age	5-year	10-year
Overall population	48.2% (68/141)	20.6% (29/141)
<20	59.8% (52/87)	21.8% (19/87)
20–39	36.7% (11/30)	23.3% (7/30)
40–59	30.8% (4/13)	23.1% (3/13)
≥60	9.1% (1/11)	0% (0/11)

TOS, telangiectatic osteosarcoma.

primary sources of information pertaining to this disease. To better understand the characteristics of this condition, a comprehensive analysis of TOS cases in the SEER database was conducted.

In previous studies, TOS patients have been shown to exhibit symptoms, lesion locations, and demographics consistent with those of COS patients (21). In agreement with these findings, no significant differences were detected in gender, race, year of diagnosis, grade, or summary stage when comparing the TOS and COS patient cohorts in the SEER database. Consistent with our findings, osteosarcoma primarily affects children and young adults (7,22). Indeed, the relative prevalence of TOS among persons under 20 years of age was even higher than that of COS (61.7% *vs.* 51.7%). In addition, TOS patients had a lower mean age compared to COS patients (23.5 *vs.* 29 years). Unlike COS, a second peak of incidence was not detected for TOS patients over the age of 60 years. The male-female ratio in this study was 1.2:1, which contrasts with prior investigations reporting that this disease is more commonly detected in males with a male-

female ratio of 2.1:1 (7).

As relatively few TOS cases have been reported to date, the prognosis of this condition remains poorly understood. In a previous study, Matsuno *et al.* demonstrated that TOS patients had a poorer prognosis compared to COS patients (14), whereas other researchers have observed no differences in survival between these two disease types, and in fact, some reports have even found that TOS showed a mildly improved prognosis relative to conventional high-grade intramedullary osteosarcoma (15,16). We consider that the limited number of cases account for the contradictory results. In line with these latter findings, we determined that TOS was associated with a significantly longer mOS compared to COS (not reached *vs.* 84 months; HR 0.75, 95% CI: 0.59 to 0.95, $P = 0.0175$), although this difference was not significant once it had been adjusted for age, stage, or surgical treatment. The small sample sizes of TOS might involve in the causes of no significant differences between two groups.

Studies in the literature (23–26) have demonstrated that age at diagnosis, tumor grade, and stage are associated with the prognosis of COS. Consistent with these results, we found that TOS patients under that age of 20 had a better prognosis, with the best prognosis being observed in patients under the age of 10 years. However, no significant differences in the prognosis of TOS patients over the age of 20 were observed.

The primary treatment for osteosarcoma is surgical resection. Consistent with this, TOS patients without metastatic disease at the time of diagnosis and patients who underwent surgical treatment were shown to have a better prognosis than patients with metastatic disease and patients

Table 3 Univariate and multivariate analyses of the median overall survival of TOS patients

Variables	n	Univariate analysis		Multivariable analysis*	
		HR (95% CI)	P value	HR (95% CI)	P value
N	141	–	–	–	–
Age at diagnosis					
<20	87	1			
20–39	30	2.099 (1.084–4.064)	0.028	1.838 (0.943–3.584)	0.074
40–59	13	3.195 (1.431–7.135)	0.005	3.003 (1.291–6.986)	0.012
≥60	11	5.136 (2.185–12.075)	<0.001	4.461 (1.863–10.681)	0.001
Gender					
Female	56	1			
Male	85	1.134 (0.646–1.989)	0.661		
Race					
White	111	1			
Black	20	0.555 (0.218–1.140)	0.216		
Other	10	0.635 (0.207–1.943)	0.426		
Year of diagnosis					
2000–2004	43				
2005–2009	43	0.598 (0.317–1.129)	0.113		
2010–2014	34	0.339 (0.137–0.838)	0.019		
2015–2017	21	1.727 (0.710–4.201)	0.228		
Laterality					
Right	56	1			
Left	78	0.902 (0.510–1.596)	0.723		
Other	7	3.033 (1.139–8.073)	0.026		
Stage					
Localized	49	1			
Regional	51	1.639 (0.795–3.379)	0.18	1.716 (0.831–3.546)	0.144
Distant	24	5.033 (0.427–10.437)	<0.0001	5.275 (2.506–11.102)	<0.0001
Unknown	17	2.190 (0.610–7.862)	0.229	1.862 (0.500–6.938)	0.354
Surgery					
No	15				
Yes	126	0.411 (0.193–0.876)	0.021	0.398 (0.175–0.905)	0.028

*, adjusted for age at diagnosis, summary stage, and surgery at primary site. TOS, telangiectatic osteosarcoma; HR, hazard ratio; CI, confidence interval.

who did not undergo surgery.

Through univariate and multivariate analyses, age at diagnosis, stage, and surgery at the primary site were all determined to be independent predictors of TOS patient survival. Patients less than 20 years old, patients with localized or regional disease, and patients who underwent surgery showed the best prognosis. As there were no significant differences in tumor stage distributions in the TOS and COS patient cohorts, we speculated that a younger age and higher surgical resection rates were related to the improved prognosis of TOS patients in this cohort. TOS patients who underwent surgery showed improved mOS, suggesting that surgical resection is an effective treatment for this type of osteosarcoma.

No significant differences were observed in the mOS of TOS patients as a function of patient gender, race, or laterality. Unexpectedly, TOS grade was not associated with patient prognosis. However, this may be a consequence of the fact that grade data were unavailable for many patients, with only three patients in the TOS cohort having been diagnosed with grade I/II disease.

It is important to differentiate between TOS and aneurysmal bone cysts, given that they exhibit similar radiological and pathological phenotypes (27,28). Invasive growth pattern is occasionally accompanied by matrix mineralization, multiple fluid filled cavities of different sizes, surrounded by thick peripheral, septal and nodular tissue, which are helpful for the correct diagnosis of TOS (29). TOS lesions exhibit characteristic imaging findings that can guide the accurate preoperative diagnosis thereof including infiltrative growth, intermittent matrix mineralization, thickening of the peripheral tissue, the presence of multiple irregularly sized fluid-filled cavities, and the presence of septal tissue with surrounding nodule patterns. However, a pathological diagnosis is the gold standard and is necessary to formally confirm a diagnosis of TOS.

Through this study, we can have a better understanding of clinical characteristics and diagnosis of TOS. We will also further test the patient's gene and PD-L1 by Next-generation sequencing technology to further understand the disease and explore more advanced treatment option, such as target therapy and immune checkpoint inhibitors.

This study has several limitations. First, being a retrospective study, it was thus susceptible to selection bias. In addition, as the SEER database does not include gene expression data, we were not able to assess the relationship between gene expression patterns and patient survival outcomes. This database also does not include

details pertaining to patient comorbidities, drug usage, surgical treatments, or radiotherapy doses, and therefore we were not able to evaluate the relationship between these parameters and patient outcomes. Time- and site-specific differences in data entry into this SEER database may also contribute to significant heterogeneity among these results. Despite these limitations, this study offers new insights that will help to guide future research pertaining to this rare disease.

In conclusion, in the present population-based study we evaluated and summarized the clinical characteristics of TOS to improve current awareness and diagnosis of this disease. TOS was most often detected in patients under 20 years of age, without a second peak of incidence after 60 years of age. There was a slightly higher incidence in males compared to females. Age at diagnosis, summary stage, and surgery at the primary site were identified as independent predictors of prognosis in TOS patients. The mOS of TOS patients was longer than that of COS patients, which may be due to the younger age of the patients and the higher surgical resection rate in TOS patients. The latter suggested that surgical resection is an effective treatment for patients with this disease.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-8001>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-8001>). 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).

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