Characteristics and Prognostic Factors of Osteosarcoma of the Jaws
A Retrospective Cohort Study

Robert J. Lee, BS; Armin Arshi, BS; Harry C. Schwartz, DMD, MD; Russell E. Christensen, DDS, MS

IMPORTANCE Osteosarcoma of the jaws is rare and clinically distinct from osteosarcoma of the long bones of the body with different treatment and outcomes. The literature on these tumors is limited to case reports and small case series mostly from single institutions. We used data from the population-based national Surveillance, Epidemiology and End Results (SEER) cancer registry to determine the epidemiology and prognostic factors associated with osteosarcoma of the jaws.

OBJECTIVE To investigate the epidemiologic characteristics and prognostic factors for survival in patients diagnosed with osteosarcoma of the jaws.

DESIGN, SETTING, AND PARTICIPANTS A retrospective, population-based cohort study of 541 patients in the SEER tumor registry diagnosed with osteosarcoma of the jaws from 1973 through 2011 were reviewed.

EXPOSURES Patients had been treated with surgery, radiation, both, or neither.

MAIN OUTCOMES AND MEASURES Overall and disease-specific survival.

RESULTS A total of 541 patients diagnosed with osteosarcoma of the jaws were identified (49.9% male and 50.1% female, with a mean age of 41.3 years). Kaplan-Meier analysis demonstrated an overall survival (OS) and disease-specific survival (DSS) of 53% and 62%, respectively, at 5 years and 35% and 54%, respectively, at 10 years. Multivariate Cox regression analysis revealed that independent predictors of OS and DSS included age at diagnosis (hazard ratio [HR], 1.03; 95% CI, 1.02-1.04 [P < .001] for OS; and HR, 1.03; 95% CI, 1.02-1.05 [P < .001] for DSS); stage at presentation (HR, 1.37; 95% CI, 1.10-1.71 [P = .006] for OS; and HR, 1.34; 95% CI, 1.01-1.76 [P = .04] for DSS); and surgical resection (HR, 0.31; 95% CI, 0.16-0.60 [P < .001] for OS; and HR, 0.22; 95% CI, 0.09-0.56 [P = .001] for DSS). Tumor size was not significant for OS (HR, 1.00; 95% CI, 1.00-1.01 [P = .11]) but significant for DSS (HR, 1.01; 95% CI, 1.00-1.01 [P = .003]).

CONCLUSIONS AND RELEVANCE To our knowledge, this is the largest study to date investigating prognostic factors for survival in patients diagnosed with osteosarcoma of the jaws. Determinants of survival include age at diagnosis, stage at presentation, tumor size, and surgical therapy. Radiation therapy was not associated with improved survival, reflecting the controversy surrounding its use in clinical literature.
Osteosarcoma is a primary malignant bone tumor, which typically affects the metaphyseal growth plates in the femur, tibia, and humerus. Osteosarcoma occurring in the jaws is rare, constituting only 6% to 7% of all osteosarcomas.1,4 The biological behavior of jaw osteosarcoma (JOS) differs from osteosarcomas involving long bones. In JOS, the average age of onset is 10 to 20 years later, distant metastases occur less frequently, the histopathologic variables are more favorable, and the survival rates are higher.3-5 The clinical presentation of osteosarcomas in the jaws and long bones is also different. Swelling is the most common complaint in patients with JOS, while bone pain during activity is characteristic of long bone osteosarcoma.4,6 Despite the biological and clinical differences, JOS and osteosarcomas of the long bones are treated similarly, which may be owing to the difficulty in assessing unique prognostic factors from the small number of JOS cases.7

The most significant prognostic factor and primary treatment modality of JOS is complete surgical resection, which is more difficult to achieve in the jaws than the long bones because of complicated and delicate anatomy.2,8,9 While multimodal treatment of patients with osteosarcoma in long bones is well established, it is still controversial in JOS.10-18 There have been conflicting results between 2 meta-analyses for the use of chemotherapy in patients with JOS, with one reporting no advantage for adjuvant chemotherapy and the other finding significantly improved disease-free and overall survival to be significantly improved by chemotherapy.19-21 In addition, the role of radiation therapy for the treatment of JOS is unclear because some studies have reported significant improvement in survival with radiation therapy in patients with positive or uncertain margins, while others report no significant improvement for patients with positive or negative margins.1,3,11,15,19-24

A large population-based study of JOS could help clarify the roles of multimodal therapy in JOS treatment.

While there are several single and multicenter studies reported, population data are scarce and controversial.1,4,8,9,15,25-32 The objective of the present study was to determine the incidence and survival of patients with JOS in a larger population. We used data from the population-based US Surveillance, Epidemiology and End Results (SEER) cancer registry to analyze the patient and disease-related characteristics of 541 patients with JOS, to our knowledge, the largest population-based study of JOS to date, to determine factors affecting both overall survival (OS) and disease-specific survival (DSS) after diagnosis. Application of the SEER database for clinical outcomes research has been previously validated for both osteosarcomas and the head and neck separately.33-42

Methods
Data Collection
A population-based cohort analysis for patients diagnosed with JOS was performed using the SEER tumor registry (National Cancer Institute). Specifically, the SEER 18 registry was used, which represents approximately 27.8% of the US population, including 40% of Hispanics and 23% of African Americans. Geographic regions covered include Alaska, metropolitan Atlanta, California, Connecticut, Detroit, Georgia, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, rural Georgia, San Francisco-Oakland, San Jose-Monterey, Seattle, and Utah. Institutional review board approval was not required in this study because the SEER database uses publicly available information with no personal identifiers.

Patients diagnosed with JOS from 1973 through 2011 were identified using the primary site label C41.0 and C41.1. Site-specific codes were used to confirm that the tumor originated in the mandible or skull/facial bones. Histologic International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes 9180 to 9187 and 9192 to 9195 were used to include osteosarcoma, not otherwise specified (NOS); chondroblastic osteosarcoma; fibroblastic osteosarcoma; telangiectatic osteosarcoma; osteosarcoma in Paget disease; small cell osteosarcoma; central osteosarcoma; intraosseous well-differentiated osteosarcoma; parosteal osteosarcoma; periosteal osteosarcoma; high-grade surface osteosarcoma, and intracortical osteosarcoma. The primary data extracted from the SEER database for analysis include the following: age at diagnosis, race, sex, histologic subtype, tumor extent and tumor size from both collaborative stage and extent of disease coding methods, tumor grade, tumor stage, treatment with surgery and/or radiation therapy, and OS and DSS in months. In the SEER database, grade is recorded on a scale from I to IV, and for the purposes of this study, grades I and II were defined to be low-grade tumors, while grades III and IV were defined to be high-grade tumors. T, N, and M stage was recorded in this database for patients receiving a diagnosis after 2003. For cases prior to 2003, T, N, and M stage was retroactively determined when possible using collaborative stage and extent of disease staging codes for tumor size, extent, and lymph node involvement following classification determined by the American Joint Committee on Cancer (AJCC). Following determination of TNM staging and grade classification, stage at presentation was determined and used for analysis.

Statistical Analysis
Overall survival, the time in months from diagnosis to death from any cause, and DSS, the time in months from diagnosis to death directly caused by the primary malignant tumor as reported in the SEER database, were defined as the primary outcomes. The Kaplan-Meier method was used to calculate the OS and DSS rates and median survival time. The log-rank test was used to formally test the differences. For certain analyses, median survival could not be calculated and was listed as undefined because the event did not occur in over 50% of the analysis. Covariates were evaluated for predictive performance with univariate and multivariate Cox proportional hazards regression models with regard to OS and DSS. \( P < .05 \) was set as the statistically significant threshold in comparison between groups. Covariates were chosen for multivariate analysis based on factors identified in the univariate analysis to be statistically significant. This method minimizes the total number of covariates leading to improved generalizability of the findings and minimized instability in the model. Age and sex were included in all multivariate models as a default. By using this method, there were no fewer than 10 events per covari-
ate. SPSS 21 software (IBM Corp) was used to perform statistical analyses. This method of statistical analysis has been previously validated.40,41

Results

A total of 541 patients diagnosed with JOS from 1973 through 2011 were extracted from the SEER database. Of these patients, 49.9% were male and 50.1% were female (Table 1). The mean age at diagnosis was 41.3 years, ranging from 0 to 91 years, and 74.9% of patients were white, 16.8% were African American, and 8.2% were of other races. Patients presented with various histological subtypes of osteosarcoma. The most common histologic subtypes were osteosarcoma, NOS (68.8% of cases) and chondroblastic osteosarcoma (18.9% of cases). Other less common but notable histological categories included fibroblastic osteosarcoma (6.1%), telangiectatic osteosarcoma (0.4%), osteosarcoma with Paget disease (2.0%), small cell osteosarcoma (0.6%), central osteosarcoma (0.7%), intrasosseous well-differentiated osteosarcoma, parosteal osteosarcoma (1.8%), and periosteal osteosarcoma (0.6%). Distribution of JOS was 55.6% in the skull/facial bones and 44.4% in the mandible. At presentation, 40.9% of all tumors were known to be high grade (III-IV), 19.6% were known to be low grade (I-II), and 39.5% were of unknown grade. Regarding tumor stage, 18.5% of patients had stage IA disease; 0.7%, stage IB; 24.4%, stage IIA; 10.7%, stage III, stage IVA, or stage IVB (advanced disease); and 43.5%, unknown stage. Therapeutically, 83.9% of patients were treated surgically and 26.8% underwent radiation therapy: 59.1% of patients received only surgery; 3.7%, only radiation therapy; 22.6%, both surgery and radiation therapy; 10.7%, no therapy; and 3.9%, unknown therapy.

Factors Predicting Survival

In Kaplan-Meier analysis, the 5-year OS and DSS for JOS were 53% and 62%, respectively, and the 10-year OS and DSS were 35% and 54%, respectively, and the median OS was 8.0 years (Figure and Table 2). Median OS and DSS survival and Kaplan-Meier curves were determined for ranges of age at diagnosis as well as each histological subtype of JOS that had 10 or more documented cases (Figure and Table 2). Median OS and DSS survival and Kaplan-Meier curves were determined for ranges of age at diagnosis as well as each histological subtype of JOS that had 10 or more documented cases (Figure and Table 2). Of note, fibroblastic (OS, 21.0 years) and chondroblastic osteosarcoma (OS, 25.4 years) had the best prognosis of histological subtypes, while osteosarcoma in Paget disease had a particularly poor outcome (OS, 0.6 years; and DSS, 0.6 years). In addition, median OS and DSS survival were calculated for treatment modality type and by primary site (Table 2). In this calculation, the median survival for osteosarcoma of the mandible was associated with longer survival (OS, 10.4 years) than in cases with osteosarcoma of the skull/facial bones, including the maxilla (OS, 6.3 years; and DSS, 18.8 years).

Univariate analysis of the entire cohort revealed age (P < .001), histologic subtype (P < .001), tumor grade (P = .001), surgery (P < .001), radiation therapy (P = .002), and stage at presentation (P < .001) as independent predictors of OS. Age (P < .001), histologic subtype (P < .001), tumor grade (P = .01), surgery (P < .001), radiation therapy (P < .001), and stage at presentation (P < .001) were independent predictors of DSS (Table 3).
On our multivariate analysis model (Table 4), age (hazard ratio [HR], 1.03; 95% CI, 1.02-1.04 [P < .001]), surgery (HR, 0.31; 95% CI, 0.16-0.60 [P < .001]), and stage at presentation (HR, 1.37; 95% CI, 1.10-1.71 [P = .006]) were found to be independent predictors of OS. Tumor size was above the cutoff for statistical significance (HR, 1.00; 95% CI, 1.00-1.01 [P = .11]) for OS. For DSS, age (HR, 1.03; 95% CI, 1.02-1.05 [P < .001]), surgery (HR, 0.22; 95% CI, 0.09-0.56 [P = .001]), tumor size (HR, 1.01; 95% CI, 1.00-
Jaw osteosarcoma is a rare malignant condition, representing approximately 6% to 7% of osteosarcomas and 1% of all head and neck malignant neoplasms. Because of the rarity of these tumors, knowledge of JOS is limited to small single or multi-institutional studies, leading to uncertainty in the optimal treatment of JOS. Application of the SEER database allows for the assessment of treatment and outcomes of rare tumors with a greater statistical power. This database has been validated in previous studies to have the capability of finding determinants of survival in several types of malignant conditions. This study represents, to our knowledge, the largest population-based study analyzing prognostic factors for survival in patients diagnosed with JOS.

There are innate limitations to studies using this database because it lacks information on administration of chemotherapy, extent of surgical resection, margin status, and patient comorbidities. Also, miscategorization is possible because there is no centralized pathologic review. While the utility of chemotherapy for treatment of JOS is still debated in the literature, it is currently recommended by the National Comprehensive Cancer Network guidelines for relapsing or refractory disease and has been well studied. It is highly likely that some of the patients with JOS in this study received chemotherapy, which could potentially skew the results because it was not accounted for in our statistical analysis. This database had trouble classifying the histological subtype of JOS and does not document osteoblastic osteosarcoma. The majority of cases (68.8%) were reported as osteosarcoma, NOS. However, it is likely that the bulk of these NOS cases should have been recorded as osteoblastic osteosarcoma, a common JOS histologic subtype that has been reported to have a prevalence as high as 77%. In addition, while the SEER database specifically classifies the mandible, the maxilla had to be extrapolated from the classification bones of the skull and face associated joints; therefore, it is likely that some of the cases analyzed in this study were located in other craniofacial sites. The SEER database also has trouble identifying AJCC stage III and distinguishing between stage IVA and IVB. Because stage III tumors have been shown to have a poor prognosis more similar to stage IV than stage II, this study grouped stage III, IVA, and IVB together.

The large sample size in our study allowed us to compare survival between several histologic subtypes of JOS. However, because of the rarity of some of the histologic subtypes and insufficient numbers for statistical power, median survival was only calculated for subtypes with 10 or more documented cases. Chondroblastic, fibroblastic, and parosteal osteosarcomas were all found to have a good prognosis, which is consistent with several reports. We postulate that the majority of cases classified as osteosarcoma, NOS, are osteoblastic, which is consistent with the osteosarcoma, NOS, median survival determined in this study as well as in previous studies reporting that the osteoblastic subtype has a worse prognosis compared with the chondroblastic subtype.

The high occurrence rate of chondroblastic osteosarcomas in the jaws compared with their occurrence rate in long bones, which report a higher percentage of osteoblastic osteosarcomas, may be a factor for the better overall prognosis of JOS. In addition, our findings indicate a poor prognosis for JOS in Paget disease, which is consistent with previous studies that have reported a low 5-year survival rate of 5%.
were reinforced in our univariate analysis finding that histologic subtype is a predictor of OS and DSS.

Univariate analysis revealed a statistically significant difference in both OS and DSS for age at diagnosis, histologic subtype, tumor grade, tumor size, stage at presentation, surgery, and radiation therapy. No significant differences were found in sex, race, or primary site. Advanced age, high-grade tumors, tumor size, and higher stage at presentation were identified to be independent predictors of worse survival, which is consistent with several other studies. Kaplan-Meier analysis also found significant age cutoffs for decreased survival, which include ages 29, 49, and 59 years. Among these cohorts studied, there was no critical age cutoff where there was observed to be a precipitous drop off in survival. However, some studies have reported that advanced age and grade are not significant determinants of survival, demonstrating the current controversy over the prognostic factors of JOS. Surgical resection was found to improve survival, which is consistent with the established role of primary surgical resection in the management of JOS. Patients with JOS who are not candidates for surgical resection because of advanced disease or notable comorbidities at presentation may bias the survival advantage seen in this cohort. Radiation therapy was also found to improve survival, which is consistent with some studies. The use of radiation therapy for the treatment of JOS patients is still controversial and not well defined but should be considered in the case of positive margins or high-grade tumors. It should be noted that complete surgical resection of JOS, which is now possible owing to the advent of reconstruction using free bone flaps, may not have been feasible in the past. These older cases that may have been considered nonresectable at the time may have been treated with radiation therapy, which may bias the results found in radiation therapy. At present, the National Comprehensive Cancer Network guidelines recommend the use of radiation therapy only for palliation in unresectable cases and in relapsed disease using samarium-153 ethylene diamine tetramethylene phosphonate. However, one study did find that females diagnosed with JOS may have a worse prognosis. In addition, sex distribution of JOS is a controversial issue, with multiple studies finding that males are more commonly affected owing to a longer period of skeletal growth and additional volume of bone in males.

The data from our present study, to our knowledge the largest JOS study to date show that JOS occurs equally in men and women. Primary site between mandible and skull/facial bones was another factor that was found not to have a significant effect on survival, which is consistent with several studies. However, while significance was not found for primary site, slight differences in survival were found, with JOS in the mandible having increased OS and DSS median survival compared with JOS in the skull/facial bones. This may be because of the complex anatomy of the maxilla, which makes it technically difficult to achieve clear margins.

Multivariate analysis demonstrated that age, surgery, and stage at presentation are important independent determinants of OS. For DSS, age, surgery, stage at presentation, and tumor size were found to be statistically significant. These data are in accordance with previous studies and our univariate analysis. Advanced age may decrease the survival rate owing to an age-dependent T-lymphocyte depletion, an intolerance to the cytotoxic effects of chemotherapy, a higher propensity to development of metastatic disease, or differences in management based on age. However, in contrast with the univariate analysis, the multivariate analysis found that grade and radiation therapy were not considered to be significant determinants of OS or DSS. The discrepancy in grade may be due to the high percentage of cases defined to be unknown. The inconsistency for radiation therapy is consistent with its controversial use for the treatment of patients with JOS.

Table 4. Multivariate Cox Regression Analysis of Factors Affecting OS and DSS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OS HR (95% CI)</th>
<th>P Value</th>
<th>DSS HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02-1.04)</td>
<td>&lt;.001</td>
<td>1.03 (1.02-1.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.02 (0.67-1.54)</td>
<td>.94</td>
<td>0.99 (0.57-1.74)</td>
<td>.98</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>1.00 (0.89-1.11)</td>
<td>.95</td>
<td>1.04 (0.92-1.17)</td>
<td>.57</td>
</tr>
<tr>
<td>Primary site</td>
<td>1.01 (0.66-1.57)</td>
<td>.95</td>
<td>0.97 (0.56-1.68)</td>
<td>.91</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>0.76 (0.42-1.36)</td>
<td>.35</td>
<td>0.99 (0.47-2.10)</td>
<td>.98</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.00 (1.00-1.01)</td>
<td>.11</td>
<td>1.01 (1.00-1.01)</td>
<td>.003</td>
</tr>
<tr>
<td>Stage at presentation</td>
<td>1.37 (1.10-1.71)</td>
<td>.006</td>
<td>1.34 (1.01-1.76)</td>
<td>.04</td>
</tr>
<tr>
<td>Surgery performed</td>
<td>0.31 (0.16-0.60)</td>
<td>&lt;.001</td>
<td>0.22 (0.09-0.56)</td>
<td>.001</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>0.83 (0.53-1.32)</td>
<td>.44</td>
<td>0.94 (0.54-1.64)</td>
<td>.82</td>
</tr>
</tbody>
</table>

**Abbreviations:** DSS, disease-specific survival; HR, hazard ratio; OS, overall survival.

Conclusions

The rarity of JOS has led to controversy over several of the determinants of survival. We report herein the largest study to date, to our knowledge, in which we demonstrated that the determinants of survival for both OS and DSS include age at diagnosis, stage at presentation, tumor size, and surgical therapy. In addition, we found that radiation therapy has a controversial therapeutic role, as reported in clinical literature.
Cancer correlations.
Courtney RM, Crissman JD. Osteosarcomas and sarcoma of the jaws: factors influencing prognosis.

REFERENCES