Research Paper

Prognostic nomograms for predicting overall and cancer-specific survival of high-grade osteosarcoma patients

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A B S T R A C T

\begin{itemize}
  \item \textbf{Aim:} The present study aimed to develop nomograms estimating survival for patients with high-grade osteosarcoma.
  \item \textbf{Methods:} 1990 patients with high-grade osteosarcoma between 1994 and 2013 were retrospectively retrieved from the Surveillance, Epidemiology, and End Results (SEER) database. Data from 12 cancer registries (n = 1460) were used to conduct multivariate Cox analysis to identify independent prognostic factors. Nomograms which estimate 3- and 5-year overall survival (OS) and cancer-specific survival (CSS) were constructed. The nomograms were internally validated for calibration and were also externally validated with an independent patient cohort from 1 cancer registry (n = 530).
  \item \textbf{Results:} Age, primary site, tumor size, use of surgery, and extent of disease were found to be independently associated with OS and CSS (p < 0.05). The nomograms estimating 3- and 5-year OS and CSS were developed based on these prognostic factors. The concordance indices were high in internal validation (0.726 for OS and 0.731 for CSS) and external validation (0.716 for OS and 0.724 for CSS). Internal and external calibration plots demonstrated a good agreement between nomogram prediction and actual observation.
  \item \textbf{Conclusions:} We constructed nomograms that accurately predict OS and CSS of high-grade osteosarcoma patients. The nomograms can be used for counseling patients and establishing risk stratification.
\end{itemize}

1. Introduction

Among all primary malignant bone tumors, osteosarcoma accounts for 35%, which is the most common form of bone cancer [1,2]. Neoadjuvant chemotherapy followed by surgical removal of the primary tumor has been established as the standard treatment for newly diagnosed osteosarcoma [3]. With the establishment of multidisciplinary treatments, 5-year survival rate of non-metastatic patients is reported to be above 60% [4–7]. However, metastatic osteosarcoma still results in much poorer prognosis [4,5,8–10].

Various prognostic factors influence the survival outcomes of osteosarcoma patients. Tumor site [5,11], tumor size [12], tumor grade [12], patient age [4,13], presence of node involvement [14], and presence of distant metastasis [4,5,9,15] have been identified as independent prognostic factors for patients with osteosarcoma. Moreover, other clinicopathological factors, such as pathologic fracture [16], surgical margins [17,18] have also been reported to be correlated with survival of osteosarcoma patients. Since survival is multifactorial, influenced by many such factors, no single factor can accurately predict survival outcomes for patients with osteosarcoma. Therefore, it would be desirable to establish a statistical prediction model which can integrate all individual prognostic factors to precisely predict the survival of osteosarcoma patients.

Nomogram is a statistical prediction tool that can incorporate all prognostic factors to estimate the survival outcome for individual patient, as has been widely demonstrated in other cancers including lung cancer, prostate cancer, breast cancer, and rectal cancer [19–23]. Since osteosarcoma still cause a substantial number of deaths despite the recent improvement in survival [4,5,8–10], accurate prediction of medium- and long-term survival outcome and identification of subgroups with different levels of risk for patients with high-grade osteosarcoma is highly important. Nomogram serves as a useful tool to potentially address these issues. Ogura et al. have constructed a prognostic nomogram for non-metastatic osteosarcoma patients only [24], however, patients with metastatic osteosarcoma at presentation or patients treated non-surgically were not included in the study, and the

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calibration plots did not suggest a good predictive ability (the C-indices were less than 0.70). To our knowledge, nomogram which makes full use of available prognostic factors to predict survival of osteosarcoma patients has not been reported yet.

Established in 1973, the Surveillance, Epidemiology, and End Results (SEER) database collects data from 18 cancer registries and covers 28% of US population [25]. Using the SEER database, we can collect a nationwide, population-based cohort to answer: (1) which clinicopathological characteristics are independently associated with survival of high-grade osteosarcoma patients? (2) Can we precisely predict 3- and 5-year overall and cancer-specific survival of individual osteosarcoma patient?

Fig. 1. (A)–(C) The graphs show defining the optimal cutoff values of tumor size via X-tile analysis. (A) The black dot indicates that optimal cutoff values of tumor size have been identified. (B) A histogram and (C) Kaplan–Meier were constructed based on the identified cutoff values. Optimal cutoff values of tumor size were identified as 8.0 cm and 13.1 cm based on overall survival.

Fig. 2. The flow diagram indicates the process of collecting patients. Based on the inclusion and exclusion criteria, 1990 patients were collected from the SEER database. 1460 patients from 12 cancer registries and 530 patients from 1 cancer registry were assigned into the training and validation cohorts, respectively.

2. Methods

2.1. Data source and inclusion criteria

All the data were collected from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database comprises 18 population-based cancer registries and represents 28% of US population [25].

The inclusion criteria were as follows: (1) diagnosed with high-grade osteosarcoma as primary malignancy; (2) diagnosed between 1994 and 2013 to ensure a minimal follow-up length of three years; (3) site limited to a bone only; (4) being scheduled for chemotherapy; (5) known survival months and cause of death; (6) complete follow-up. The
2.2. Prognostic variables

Data on patient age, sex, race, year of diagnosis, primary site, tumor size, use of surgery, extent of disease, and survival time until death or the time of last follow-up were collected from the SEER database. Patient age was categorized into three groups, which were less than 18 years old, between 18 to 40 years old, and over 40 years old. Because the SEER database did not record the exact location of the bone (e.g., femur, tibia, and fibula were recorded as long bones of the lower extremities without distinction), primary sites were stratified into three groups, which were extremities (including long and short bones of the upper and lower extremities), pelvis/spine, and skull. Tumor size was divided into three groups using the X-tile program (Yale University, New Haven, CT, USA) to achieve the highest chi-square among groups [26]. The optimal cut-off values of tumor size were identified as 8.0 cm and 13.1 cm via the X-tile program (Fig. 1). The identified cutoff values were then rounded of to 8.0 cm and 13.0 cm, dividing the cohort into 3 groups which were < 8.0 cm, 8.0–13.0 cm, and > 13.0 cm. Extent of disease (EOD) was classified into three categories, as has been previously described in the literature [27,28]; localized (defined as tumor confined to the periosteum), regional (defined as tumor extended beyond the periosteum without distant metastasis), and distant (defined

| Year of diagnosis | Univariate analysis | Multivariate analysis |
|-------------------|--------------------|----------------------|
| 1994–2003         |                    |                      |
| 2004–2013         |                    |                      |

| Primary site      | Univariate analysis | Multivariate analysis |
|-------------------|--------------------|----------------------|
| Extremity         |                    |                      |
| Pelvis/spine      |                    |                      |
| Skull             |                    |                      |
| Tumor size (cm)   |                    |                      |
| < 8.0             |                    |                      |
| 8.0–13.0          |                    |                      |
| > 13.0            |                    |                      |
| Median (range)    |                    |                      |

| Surgery           | Univariate analysis | Multivariate analysis |
|-------------------|--------------------|----------------------|
| No                |                    |                      |
| Yes               |                    |                      |

| Extent of disease | Univariate analysis | Multivariate analysis |
|-------------------|--------------------|----------------------|
| Localized         |                    |                      |
| Regional          |                    |                      |
| Distant           |                    |                      |

**Abbreviations:** HR: Hazard Ratio; CI: Confidence Interval; NI: Not Included.

### Table 1
Baseline characteristics of the included patients.

| Characteristic | Total | Training cohort | Validation cohort |
|----------------|-------|-----------------|-------------------|
|                | n = 1990 | n = 1460 | n = 530 |
| Age            |          |          |          |
| < 18           | 1079(54.2) | 796(54.5) | 283(53.4) |
| 18–40          | 617(31.0)  | 455(31.2) | 162(30.6)  |
| > 40           | 294(14.8)  | 209(14.3) | 85(16.0)   |
| Median (range) | 17(3–91)  | 17(3–91) | 17(3–89) |
| Race           |          |          |          |
| Male           | 1152(57.9) | 857(58.7) | 295(55.7) |
| Female         | 838(42.1)  | 603(41.3) | 235(44.3) |
| Sex            |          |          |          |
| Male           | 1481(74.4) | 1078(73.8) | 403(76.0) |
| Female         | 520(25.6)  | 372(26.2) | 127(24.0) |
| Race           |          |          |          |
| White          | 1481(74.4) | 1078(73.8) | 403(76.0) |
| Black          | 222(15.2)  | 161(11.4) | 61(12.0)  |
| Other¹         | 187(9.4)   | 141(9.7)  | 46(8.7)   |
| Age            |          |          |          |
| < 18           | 1152(57.9) | 857(58.7) | 295(55.7) |
| 18–40          | 838(42.1)  | 603(41.3) | 235(44.3) |
| > 40           | 187(9.4)   | 141(9.7)  | 46(8.7)   |

**Abbreviations:** HR: Hazard Ratio; CI: Confidence Interval; NI: Not Included.

### Table 2
Univariate and multivariate analyses of overall survival in the training cohort.

| Characteristic | Univariate analysis | Multivariate analysis |
|----------------|--------------------|----------------------|
| Age            |                   |                      |
| < 18           | Reference          |                      |
| 18–40          | 1.203(0.987–1.467) | 0.67                 |
| > 40           | 2.329(1.858–2.919) | <0.001               |
| Sex            |                   |                      |
| Male           | Reference          |                      |
| Female         | 0.902(0.757–1.073) | 0.24                 |
| Race           |                   |                      |
| White          | NI                 |                      |
| Black          |                   |                      |
| Other²         |                   |                      |
| Year of diagnosis |               |                      |
| 1994–2003       | 0.307              | NI                    |
| 2004–2013       |                    |                      |

**Abbreviations:** HR: Hazard Ratio; CI: Confidence Interval; NI: Not Included.

### Table 3
Univariate and multivariate analyses of cancer-specific survival in the training cohort.

| Characteristic | Univariate analysis | Multivariate analysis |
|----------------|--------------------|----------------------|
| Age            |                   |                      |
| < 18           | Reference          |                      |
| 18–40          | 1.148(0.932–1.415) | 0.195                |
| > 40           | 2.237(1.763–2.839) | <0.001               |
| Sex            |                   |                      |
| Male           | Reference          |                      |
| Female         | 0.919(0.765–1.104) | 0.366                |
| Race           |                   |                      |
| White          | NI                 |                      |
| Black          |                   |                      |
| Other³         |                   |                      |
| Year of diagnosis |               |                      |
| 1994–2003       | 0.292              | NI                    |
| 2004–2013       |                    |                      |

**Abbreviations:** HR: Hazard Ratio; CI: Confidence Interval; NI: Not Included.

Exclusion criteria were as follows: (1) site limited to ribs or sternum; (2) unknown use of surgery; (3) unknown extent of disease.
2.3. Statistical analysis

Data from 12 cancer registries (Los Angeles, California; San Jose and Monterey, California; Iowa; New Mexico; Seattle and Puget Sound, Washington; Utah; metropolitan Atlanta, Georgia; rural Georgia; Kentucky; Louisiana; New Jersey; and Native Alaska) were used as the training cohort ($n = 1460$). Date from 1 cancer registry (California, excluding San Francisco, San Jose and Monterey, and Los Angeles) were

as having metastatic disease at presentation).

![Nomogram](image)

**Fig. 3.**(A)–(B) The graphs show the nomograms which predict 3- and 5-year (A) overall survival and (B) cancer-specific survival of high-grade osteosarcoma patients. Points of each variable was acquired by drawing a vertical line between each variable and the Points scale. By totaling the points of each variable, we then draw a vertical line between the Total Points scale and overall survival or cancer-specific survival scale to calculate the predicted 3- and 5-year survival.
used as the validation cohort \((n = 530)\). Patient baseline characteristics were compared between the training and validation cohort using the fisher exact test.

The primary endpoints were overall survival (OS) and cancer-specific survival (CSS). OS was defined as the time from diagnosis to death from all possible causes. CSS was defined as the time from diagnosis to death attributed to metastatic osteosarcoma. Censored observations referred to patients who were alive at the time of last follow-up.

Variables including patient age, sex, race, year of diagnosis, primary site, tumor size, use of surgery, and extent of disease were enrolled in the univariate log-rank analysis for OS and CSS, respectively. Multivariate Cox proportional hazards models [29] were constructed based on the significant variables in the univariate analysis. Hazard ratios of each variable were calculated with corresponding 95\% confidence intervals.

### 2.4. Nomogram development and validation

Akaike information criterion (AIC) has been widely used to select models and a lower AIC value suggests relative superiority [30,31]. A backward stepwise method was employed to achieve the smallest AIC value for the selection of prognostic factors. Nomograms which estimate 3- and 5-year OS and CSS were developed based on multivariate Cox proportional hazards model and the smallest AIC value.

Internal validation (training cohort from 12 cancer registries) and external validation (validation cohort from 1 cancer registry) were conducted with 500 bootstrap resamples to prevent overfitting and achieve a relatively unbiased estimation. The performance of these predictive models was assessed by Harrell's concordance index (C-index). The value of C-index ranges from 0.5 to 1.0, with 0.5 indicating random chance and 1.0 indicating a perfectly corrected discrimination.

Generally, C-index value over 0.7 implies a relatively accurate prediction [32]. Calibration plots were assessed to compare nomogram predictions with observed outcomes internally and externally.

The SEER database was analyzed via SEER*Stat software (Version 8.3.4; NCI, Bethesda, USA). All statistical analyses were conducted using SPSS 22.0 (IBM Corporation, Armonk, NY, USA). Nomogram development and validation were performed in R version 3.3.1 (Institute for Statistics and Mathematics, Vienna, Austria) with rms [33] library. All \(p\)-values were two-sided and \(p < 0.05\) was considered statistically significant.

### 3. Results

#### 3.1. Patient baseline characteristics

According to the inclusion criteria, 2050 patients with high-grade osteosarcoma were collected from the Surveillance, Epidemiology, and End Results (SEER) database between 1994 and 2013. Among those patients, 60 patients were excluded based on the exclusion criteria. Finally, 1990 patients with high-grade osteosarcoma were included and divided into the training cohort \((n = 1460)\), data from 12 cancer registries) and the validation cohort \((n = 530, data from 1 cancer registry)\) (Fig. 2).

The clinicopathological characteristics of the patients are summarized (Table 1). The median age was 17 years old (range: 3–91 years old). Of the 1990 patients with high-grade osteosarcoma, 1152 patients (57.9\%) were male and 838 patients (42.1\%) were female. Among those patients, 1797 of them (90.3\%) had surgical resection of primary tumor, while 193 patients (9.7\%) were treated with chemotherapy only. The median survival time was 48 months (range: 1–250 months). Until the time of last follow-up, 703 patients (35.3\%) had died attributed to osteosarcoma, and 77 (3.9\%) had died attributed to other causes.

#### 3.2. Screening prognostic factors for OS and CSS

Univariate analyses suggested that age, sex, primary site, tumor size, use of surgery, and extent of disease were associated with OS (all \(p < 0.05\)) (Table 2). Multivariate Cox proportional hazards analyses were used to control for potential confounding variables. Multivariate analyses demonstrated that age (> 40 years old, HR = 2.329, 95\%CI = 1.858–2.919, \(p < 0.001\)), primary site (pelvis/spine, HR = 2.198, 95\%CI = 1.705–2.832, \(p < 0.001\)), tumor size (> 13.0 cm, HR = 1.458, 95\%CI = 1.154–1.843, \(p = 0.002\)), use of surgery (with surgical resection, HR = 0.517, 95\%CI = 0.406–0.660, \(p < 0.001\)), and extent of disease (regional, HR = 1.632, 95\%CI = 1.291–2.063, \(p < 0.001\); distant, HR = 4.106, 95\%CI = 3.180–5.301, \(p < 0.001\)) were independent prognostic factors for OS (Table 2). These variables were also significant (all \(p < 0.05\)) in the multivariate analysis for CSS (Table 3).

#### 3.3. Nomogram development and validation

Nomograms predicting 3- and 5-year OS and CSS were constructed (Fig. 3). Age, primary site, tumor size, use of surgery, and extent of disease were included as prognostic predictors in the nomograms. Detailed points of each predictor were calculated (Table 4). Validation was performed based on the training \((n = 1460)\) and validation \((n = 530)\) cohort. The C-indices were high in both internal validation (OS: 0.726, 95\%CI, 0.704–0.749; CSS: 0.731, 95\%CI, 0.708–0.755) and external validation (OS: 0.716, 95\%CI, 0.681–0.751; CSS: 0.724, 95\%CI, 0.687–0.761). Internal and external calibration plots both demonstrated that the nomograms well predicted 3- and 5-year OS and CSS (Fig. 4).

With the nomograms (Fig. 2), we can predict survival probability of individual patient based on the personalized information. Take this example, a 25-year-old male was diagnosed with localized osteosarcoma with a primary tumor of 10.0 cm in pelvis, he then had chemotherapy followed by a surgical resection of primary tumor. According to the nomograms, the patient got 8.5 points in the OS nomogram and 8.3 points in the CSS nomogram. Therefore, for this patient, his estimated 3- and 5-year OS rate were 69\% and 58\%, respectively. In the same manner, we could also predict 3- and 5-year CSS using the CSS nomogram.

### 4. Discussion

Recently, nomograms have been widely used as tools for...
Fig. 4. (A)–(H) The graphs show the calibration plots for internal validation of (A) actual 3-year and (B) 5-year overall survival; (C) actual 3-year and (D) actual 5-year cancer-specific survival; and external validation of (E) actual 3-year and (F) 5-year overall survival; and (G) actual 3-year and (H) 5-year cancer-specific survival. The dashed line represents an excellent match between nomogram prediction (X-axis) and actual survival outcome (Y-axis). The cohort was divided into ten groups with equal sample size for internal and external validation. Closer distances from the points to the dashed line indicate higher prediction accuracy.
individualized prediction of patient’s survival outcome [11,19–24]. In light of the heterogeneity of high-grade osteosarcoma, a brief nomogram which predicts medium- and long-term survival outcome would be useful and practical for clinicians. However, due to the rarity of high-grade osteosarcoma, nomogram which makes full use of available prognostic factors to predict survival of osteosarcoma patients has not been reported yet. Using the SEER database which represents 28% of US population [25], we were able to collect sufficient cases and therefore developed and validated nomograms which predict 3- and 5-year OS and CSS of high-grade osteosarcoma patients treated with chemotherapy.

Based on multivariate Cox proportional hazards model and the smallest AIC value, several clinicopathological characteristics were identified to be independently associated with survival of patients with high-grade osteosarcoma, including patient age, primary site, tumor size, use of surgery, and extent of disease. In the present study, an increasing age was found to be related to a worse survival outcome. Similar trend has been revealed for patients with osteosarcoma [1,4,5,34,35]. This can be partially explained by the fact that older patients are more likely to have metastatic disease at presentation and receive chemotherapy in lower doses due to lower tolerance [36]. It is noteworthy that there was no significant survival difference between patients < 18 years and 18–40 years of age.

Previous studies have demonstrated that larger tumors and axial tumors both portend a poor prognosis for patients with osteosarcoma [4,5,8,37–40]. Our study revealed that patients with larger tumors or axial tumors had diminished survival compared to those with larger tumors, extremity tumors, or skull tumors. Bielack et al. suggested that patients with larger tumors or axial tumors are more likely to present with metastatic disease [5]. When controlling for metastatic disease at presentation, Duchman et al. reported tumor size and tumor location remained statistically significant and concluded that larger or axial tumors might develop metastases during or after treatment at a higher rate than smaller or extremity tumors [28]. Another possible explanation is that larger or axial tumors pose more difficulties in achieving adequate surgical margins [9].

Currently, neoadjuvant chemotherapy followed by surgical resection of the primary tumor has been the standard treatment for patients with high-grade osteosarcoma [3]. Our study validated the beneficial role of surgery for survival of osteosarcoma patients treated with chemotherapy in the multivariate analysis. With regard to extent of disease, metastatic disease at presentation has been identified as an independent risk factor for higher mortality [4,5,8–10]. Apart from that, we also found patients with regional osteosarcoma had poorer prognosis than those with localized disease when controlling for confounding variables.

Incorporating the independent prognostic factors that we identified, nomograms which predict 3- and 5-year OS and CSS of high-grade osteosarcoma patients were developed, respectively. Using the nomograms, surgeons could conveniently and precisely predict individual patient’s survival probability at certain time intervals. Take this example, for a 14-year-old girl, she was diagnosed with high-grade osteosarcoma with a primary tumor of 8.5 cm in femur. She then had chemotherapy followed by surgical resection of primary tumor. Signs of tumor extending beyond the periosteum was found but without distant metastasis at presentation. Totaling the points of each prognostic predictor, she got 4.9 and 5.7 points in OS and CSS nomograms, respectively. According to the nomograms, her estimated 5-year OS and CSS were 72% and 74%, respectively.

It is important to consider potential limitations in our study. First, we developed and validated the nomograms with retrospective data. Although we collected the largest cohort using the SEER database which represents 28% of US population, the nomograms need to be validated prospectively for more reliability. Second, some serological markers including ALP and LDH, were not included in the present study. It was because such variables were not recorded in the SEER database. Third, we only evaluated 3- and 5-year survival as the primary endpoints. However, local recurrence or distant metastasis could also be considered as one of the endpoints to develop corresponding nomograms, as has been demonstrated in the literature [11,24]. The reason was that the SEER database does not collect information on these endpoints. Finally, since there were only 44 patients with osteosarcoma of short bones, we integrated patients with osteosarcoma of long bones and short bones together into the extremity subgroup.

In summary, we developed and externally validated nomograms which predict 3- and 5-year OS and CSS of high-grade osteosarcoma patients treated with chemotherapy based on a large, population-based cohort. The nomograms only require basic information and demonstrate high degree of predictive accuracy. By these predictive tools, clinicians could not only precisely estimate 3- and 5-year survival of individual patient, but also identify patients with high risk of mortality for clinical trial. 

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Conflict of interest

The authors declare that there are no conflicts of interest.

References

[1] M.U. Jawad, M.C. Cheung, J. Clarke, L.G. Koniatis, S.P. Seiuly, Osteosarcoma: improvement in survival limited to high-grade patients only, J. Cancer Res. Clin. Oncol. 137 (4) (2011) 597–607.
[2] L. Mirabello, R.J. Troisi, S.A. Savage, Osteosarcoma incidence and survival rates from 1973 to 2004: data from the surveillance, epidemiology, and end results program, Cancer 115 (7) (2009) 1531–1543.
[3] M.S. Isakoff, S.S. Bielack, P. Melzter, R. Gorlick, Osteosarcoma: current treatment and a collaborative pathway to success, J. Clin. Oncol. 33 (27) (2015) 3029–3035.
[4] G. Bacci, F. Bertoni, A. Longhi, Neoadjuvant chemotherapy for high-grade central osteosarcoma of the extremity, histologic response to preoperative chemotherapy correlates with histologic subtype of the tumor, Cancer 97 (12) (2003) 3068–3075.
[5] S.S. Bielack, B. Kempf-Bielack, G. Delling, Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols, J. Clin. Oncol. 20 (3) (2002) 776–790.
[6] A.M. Goorin, D.J. Schwartzzenbruter, M. Devidas, Presurgical chemotherapy compared with immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: pediatric oncology group protocol POG-8651, J. Clin. Oncol. 21 (8) (2003) 1574–1580.
[7] P.A. Meyers, C.L. Schwartz, M. Krailo, Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or murremyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate, J. Clin. Oncol. 23 (9) (2005) 2004–2011.
[8] J.C. Clark, C.R. Dass, P.F. Choong, A review of clinical and molecular prognostic factors in osteosarcoma, J. Cancer Res. Clin. Oncol. 134 (3) (2008) 281–297.
[9] L. Kager, A. Zoubek, U. Petchger, Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant cooperative osteosarcoma study group protocols, J. Clin. Oncol. 21 (10) (2003) 2011–2018.
[10] V. Mialou, T. Philip, C. Kalifa, Metastatic osteosarcoma at diagnosis: prognostic factors and long-term outcome – the French pediatric experience, Cancer 104 (5) (2005) 1100–1109.
[11] M.S. Kim, S.Y. Lee, T.R. Lee, Prognostic nomogram for predicting the 5-year probability of developing metastasis after neo-adjuvant chemotherapy and definitive surgery for AJCC stage II extremity osteosarcoma, Ann. Oncol. 20 (3) (2009) 955–960.
[12] R.K. Heck Jr., G.S. Stacy, M.J. Flaherty, A.G. Montag, T.D. Peabody, M.A. Simon, A comparison study of staging systems for bone sarcomas, Clin. Orthop. Relat. Res. 415 (2003) 64–71.
[13] B. Carsi, M.G. Rock, Primary osteosarcoma in adults older than 40 years, Clin. Orthop. Relat. Res. 397 (2002) 53–61.
[14] S. Thampi, K.K. Matthy, R. Goldsby, S.G. DuBois, Adverse impact of regional lymph node involvement in osteosarcoma, Eur. J. Cancer 49 (16) (2013) 3471–3476.
[15] P.A. Meyers, G. Heller, J.H. Healey, Osteogenic sarcoma with clinically detectable metastasis at initial presentation, J. Clin. Oncol. 11 (3) (1993) 449–453.
[16] J.A. Branner, A.A. Abudu, R.J. Grimner, S.R. Carter, R.M. Tillman, Do pathological fractures influence survival and local recurrence rate in bony sarcomas? Eur. J. Cancer 43 (13) (2007) 1944–1951.
[17] T.E. Bertrand, A. Cruz, O. Binetie, D. Cheung, G.D. Letson, Do surgical margins affect local recurrence and survival in extremity, nonmetastatic, high-grade
osteosarcoma? Clin. Orthop. Relat. Res. 474 (3) (2016) 677–683.

[18] A.M. Davis, R.S. Bell, P.J. Goodwin, Prognostic factors in osteosarcoma: a critical review, J. Clin. Oncol. 12 (2) (1994) 423–431.

[19] J.M. Albert, D.D. Liu, Y. Shen, Nomogram to predict the benefit of radiation for older patients with breast cancer treated with conservative surgery, J. Clin. Oncol. 30 (23) (2012) 2837–2843.

[20] F.J. Bianco Jr, Nomograms and medicine, Eur. Urol. 50 (5) (2006) 884–886.

[21] W. Liang, L. Zhang, G. Jiang, Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer, J. Clin. Oncol. 33 (8) (2015) 861–869.

[22] S.F. Shariat, P.J. Karamie, N. Suardi, M.W. Kattan, Comparison of nomograms with other methods for predicting outcomes in prostate cancer: a critical analysis of the literature, Clin. Cancer Res. 14 (14) (2008) 4400–4407.

[23] V. Valentin, R.G. van Stiphout, G. Lammering, Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials, J. Clin. Oncol. 29 (23) (2011) 3163–3172.

[24] K. Ogura, T. Fujiwara, H. Yasunaga, Development and external validation of nomograms predicting distant metastases and overall survival after neoadjuvant chemotherapy and surgery for patients with nonmetastatic osteosarcoma: a multi-institutional study, Cancer 121 (21) (2015) 3844–3852.

[25] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Available at: http://seer.cancer.gov. Accessed November 22, 2017.

[26] R.J. Grimer, S.R. Cannon, A.M. Taminiau, Osteosarcoma over the age of forty, Eur. J. Cancer 39 (2) (2003) 157–163.

[27] M.T. Harting, K.P. Lally, R.J. Andrassy, Age as a prognostic factor for patients with osteosarcoma: an analysis of 438 patients, J. Cancer Res. Clin. Oncol. 136 (4) (2010) 561–570.

[28] K.R. Duchman, Y. Gao, B.J. Miller, Prognostic factors for survival in patients with high-grade osteosarcoma using the surveillance, epidemiology, and end results (SEER) Program database, Cancer Epidemiol. 39 (4) (2015) 593–599.

[29] M.H. Katz, W.W. Hauck, Proportional hazards (Cox) regression, J. Gen. Intern. Med. 8 (12) (1993) 702–711.

[30] E.J. Wagenmakers, S. Farrell, AIC model selection using Akaike weights, Psychon. Bull. Rev. 11 (1) (2004) 192–196.

[31] L. Yang, W. Shen, N. Sakamoto, Population-based study evaluating and predicting the probability of death resulting from thyroid cancer and other causes among patients with thyroid cancer, J. Clin. Oncol. 31 (4) (2013) 468–474.

[32] K. Oyastegui, D.G. Altman, External validation of a Cox prognostic model: principles and methods, BMC Med. Res. Methodol. 13 (2013) 33.

[33] F.J. Harrel, rms: regression modeling strategies. R package version 5.0-0. Available at: http://CRAN.R-project.org/package=rms. Accessed November 22, 2017.

[34] R.J. Grimer, S.R. Cannon, A.M. Taminiau, Osteosarcoma over the age of forty, Eur. J. Cancer 39 (2) (2003) 157–163.

[35] M.T. Harting, K.P. Lally, R.J. Andrassy, Age as a prognostic factor for patients with osteosarcoma: an analysis of 438 patients, J. Cancer Res. Clin. Oncol. 136 (4) (2010) 561–570.

[36] A. Longhi, C. Errani, D. Gonzales-Arabio, C. Ferrari, M. Mercuri, Osteosarcoma in patients older than 65 years, J. Clin. Oncol. 26 (33) (2008) 5366–5373.

[37] P. Bieling, N. Rehan, P. Winkler, Tumor size and prognosis in aggressively treated osteosarcoma, J. Clin. Oncol. 14 (3) (1996) 848–858.

[38] D.G. Jeon, W.S. Song, W.H. Cho, C.B. Kong, S.H. Cho, Proximal tumor location and fluid-fluid levels on MRI predict resistance to chemotherapy in stage IIIb osteosarcoma, Clin. Orthop. Relat. Res. 472 (6) (2014) 1911–1920.

[39] N.J. Lindner, O. Ramm, A. Hillmann, Limb salvage and outcome of osteosarcoma, the University of Munster experience, Clin. Orthop. Relat. Res. 358 (1999) 83–89.

[40] T. Ozaki, S. Flege, M. Keerv, Osteosarcoma of the pelvis: experience of the cooperative osteosarcoma study group, J. Clin. Oncol. 21 (2) (2003) 334–341.