Prognostic Factors for Survival in Patients with Malignant Giant Cell Tumor of Bone: A Risk Nomogram Analysis Based on the Population

**Background:** Malignant giant cell tumor of bone (MGCTB) is a rare histological type of malignant tumor that has a high tendency for local relapse and distant metastasis and ultimately leads to a poor prognosis. The purpose of this study was to describe the epidemiological features, identify the prognostic factors, and construct nomograms for patients with MGCTB.

**Material/Methods:** Patients with MGCTB that was histologically diagnosed between 1973 and 2014 were selected from the Surveillance, Epidemiology, and End Results (SEER) database as a training set. Survival analysis, Lasso regression, and random forests were used to identify the prognostic variables and establish the nomograms for patients with MGCTB, while an external cohort of 37 patients from our own institution and an external cohort of 163 patients from the SEER database in 2016 were used to validate the generalization performance of the nomograms.

**Results:** In total, univariate and multivariable analysis indicated that age, International Classification of Diseases for Oncology, historical stage, primary site, surgery information, radiotherapy, and chemotherapy were independent prognostic variables for overall survival or cause-specific survival. Nomograms based on the multivariable models were built to predict survival, and we achieved a higher C-index in subsequent multidimensional validation.

**Conclusions:** Age, historical stage, and chemotherapy were independent prognostic variables for overall survival and cause-specific survival of MGCTB patients, and radiotherapy and primary site were independent prognostic variables for overall survival. Nomograms based on significant clinicopathological features and clinical experience can be effective in predicting the probability of survival for MGCTB patients.

**Keywords:** Giant Cell Tumor of Bone • Nomograms • Prognosis • Survival Analysis

**Full-text PDF:** [https://www.medscimonit.com/abstract/index/idArt/929154]
Background

A giant cell tumor of bone (GCTB) is an aggressive noncancerous skeletal tumor that consists of osteoclast-like multinucleated giant cells, spindle-like stromal cells, and mononuclear round cells. Malignant GCTB (MGCTB) is the malignant form of GCTB and accounts for 2-9% of all cases [1-4]. Bone destruction is the prevailing clinical feature and results in local pain and pathological fracture. Previous studies have reported that local recurrence and distant metastasis are common, with relatively poor prognosis [5-9].

Due to the relatively infrequent incidence of MGCTB, there is little information available about treatment, and controversies concerning recommendations remain. Treatment protocols typically involve surgery alone or combination therapy of surgery, radiotherapy, and chemotherapy. Although en bloc tumor resection has been regarded as an effective therapeutic method for MGCTB that provides reduced recurrence rates, it is difficult to perform, especially in the axial skeleton. Furthermore, the therapeutic effects of chemotherapy and radiotherapy remain controversial and result in treatment dilemmas [9-11].

In order to improve the prognosis of MGCTB patients, there is a pressing need to identify the significant prognostic factors. Previous studies have reported that factors such as age, primary site, International Classification of Diseases for Oncology, presence and location of metastases, surgical strategy, and histological response to chemotherapy are relevant to the prognosis of patients [1,2,8,12]. However, the small sample sizes and single-center format limited the accuracy of these studies.

To accurately predict the prognosis of MGCTB patients, we selected patients from the Surveillance, Epidemiology, and End Results (SEER) database. Machine learning (random forest) and classic regression methods (Kaplan-Meier curve, Cox proportional hazards regression model, and Lasso regression) were used to identify independent prognostic variables, and nomograms were constructed to estimate overall survival (OS) and cause-specific survival (CSS). Moreover, a high-quality external validation from our own institution and the SEER database in 2016 to construct 2 testing cohorts. Machine learning methods were not overfitting. Finally, a model consisting of optimum variables was established. Based on multivariable analysis, nomograms were constructed to predict the probability of CSS.

Material and Methods

Patient Selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of our institution (No. KEYAN-2018-LW-021), and informed consent was provided by all patients. Patients in the training cohort were selected from the SEER database, which contained cancer data covering around 34.6% of the US population. The SEER database includes information about patient demographics, tumor character information (primary tumor site, tumor morphology, and stage at diagnosis), treatment information, and vital status [13]. Only patients with MGCTB that was histologically diagnosed from 1973 to 2014 were included in our study. Patients were excluded if the MGCTB was not diagnosed by biopsy or if it was not their first tumor. Furthermore, patients whose race, marital status, surgery information, radiotherapy information, historical stage, and primary site were unknown were also excluded. The same criteria were applied in selecting patients from our own institution and the SEER database in 2016 to construct 2 testing cohorts.

Data Extraction

In this study, variables from the training cohort were acquired from the SEER database on July 26, 2018, and included age at diagnosis, sex, race, primary site, radiotherapy, chemotherapy, surgery information, family income, marital status, education background, and employment status. We also extracted OS and CSS as the study endpoints.

Statistical Analysis

Dichotomous variables are expressed as number (percentage), and continuous variables are presented as mean±standard deviation (SD) and median (range). Three statistical methods were applied to evaluate prognostic factors. First, the categorical variables were analyzed using the chi-square test. Second, the Kaplan-Meier method was used as an initial analysis to explore potential variables associated with OS and CSS. In order to select “different” cutoff points, we used X-tile plots to set the interception points (Supplementary Figure 1). Continuous variables were uncoupled to the new classification (age: <39 years, 39-68 years, and >68 years). In this study, random forest (ntree=500) was applied to all variables for further analysis. Mean Decrease Gini (MDG) was used to quantify the classification accuracy of each variable, with a higher MDG indicating that the grade of impurity from a category could be decreased the most by 1 variable, which suggests a significantly associated index [14].

After these programs, the statistically significant variables were selected to build the Cox proportional hazards model. The log-rank test was applied for model diagnosis. Additionally, Lasso regression was performed to ensure that the multifactor models were not overfitting. Finally, a model consisting of optimum variables was established. Based on multivariable analysis, nomograms were constructed to predict the probability of CSS.
and OS. The calibration, discrimination, and generalization of the nomograms were evaluated using calibration curves. The accuracy of the nomograms was then tested and compared with the TNM and AJCC staging systems.

A 2-sided P value < 0.05 was considered statistically significant. All statistical analysis methods were performed using X-tile software version 3.6 and R software version 3.5.1 (Institute for Mathematics and Statistics; www.r-project.org). R packages (survival, random forest, ggplot2, and survminer) were applied to draw survival curves and modeling. The nomograms were drawn using the rms package.

**Results**

**Patient Characteristics**

Among the 454 patients with MGCTB diagnosed from 1973 to 2014, 152 were excluded because they did not meet the inclusion criteria. In total, 302 patients were included in our training cohort. The process of data selection is shown in Figure 1. Based on the same process, the testing cohort consisted of 37 patients for external validation from our own institution, 163 patients for external validation from the SEER database in 2016, 201 patients labeled with TNM staging system, 53 patients labeled with sixth edition AJCC staging system, and 67 patients labeled with seventh edition AJCC staging system.

The patient characteristics are presented in Supplementary Table 1. The study population included 149 males and 153 females, predominantly white (77.2%), with a median age of 38.0 years (range: 1.0-91.0). The MGCTB was primarily localized or regional (83.8%). Among all MGCTB patients, the limbs accounted for the primary site in 72.5% of cases, followed by the trunk (21.9%) and the head-face-neck (5.6%). At the long-term follow-up stage, the median survival time was 75.5 months (range: 0-502.0). At the endpoint, 47 (15.6%) patients succumbed to MGCTB and 77 (25.5%) patients to all causes. The marital status, education levels, and family incomes exhibited relative hypodispersion among all patients.

**Univariate Analysis and Random Forest**

The results of parametric or nonparametric tests, Kaplan-Meier survival analysis, and random forest for OS and CSS are described in Table 1. Six variables (age, primary site, radiotherapy, surgery information, chemotherapy information, and historical stage) showed statistical significance in parametric or nonparametric tests and Kaplan-Meier survival analysis (Figure 2). Moreover, these variables also ranked in the top 30% in MDG of random forest. Potential prognostic factors of these 6 variables were submitted to Cox proportional hazards analysis.

**Cox Proportional Hazards Model and Lasso Regression**

The Cox proportional hazards regression model was constructed to confirm the effects of variables on the OS and CSS of patients (Table 2). The results of Lasso regression suggested that all variables incorporated into the final multivariate models were essential to modeling (Figure 3A-3D). Compared with patients younger than 39 years old, older patients had a poorer prognosis in OS (39-68 years: hazard ratio [HR], 4.933; 95% confidence interval [CI], 2.613 to 9.313; P<0.001; >68 years: HR, 20.043; 9.403 to 42.722; P<0.001), and CSS (39-68 years: HR, 3.772; 1.741 to 8.172; P<0.001; >68 years: HR, 8.733; 3.639 to 20.958; P<0.001).

In the historic stage, localized malignance (OS: HR, 0.281; 0.151 to 0.519; P<0.001; CSS: HR, 0.158; 0.073 to 0.345; P<0.001) and regional malignance (OS: HR, 0.298; 0.158 to 0.562; P<0.001; CSS: HR, 0.290; 0.141 to 0.595; P<0.001) tended to have a better prognosis than the distant stage. Furthermore, patients with a tumor located in a limb were independently associated with a better OS (limbs vs head-face-neck: HR, 0.326; 0.150 to 0.698; P<0.001; limbs vs trunk: HR, 0.231; 0.123 to 0.434; P<0.001).
Table 1. Results of single factor analysis and random forest.

| Variables                     | Overall survival (OS) | Cancer specific survival (CSS) |
|-------------------------------|-----------------------|-------------------------------|
|                               | P value of non-parametric test | P value of Kaplan-Meier analysis | MDG | P value of non-parametric test | P value of Kaplan-Meier analysis | MDG |
| Age                           | <0.001* | <0.001* | 21.381 | <0.001* | <0.001* | 8.839 |
| Race recode                   | 0.387   | 0.190   | 5.088  | 0.077   | 0.037* | 4.569 |
| Gender                        | 0.017*  | 0.023*  | 5.232  | 0.565   | 0.540 | 3.368 |
| Primary site                  | <0.001* | <0.001* | 8.435  | <0.001* | <0.001* | 7.345 |
| ICD-O-3.histology             | 0.001*  | 0.002*  | 6.908  | 0.009*  | 0.037* | 2.926 |
| Surgery information           | 0.144   | 0.012*  | 3.630  | 0.040*  | 0.007* | 2.649 |
| Radiation recode              | 0.017*  | 0.010*  | 3.269  | <0.001* | <0.001* | 3.409 |
| Chemotherapy recode           | <0.001* | <0.001* | 7.740  | <0.001* | <0.001* | 6.832 |
| Historic stage                 | <0.001* | <0.001* | 10.478 | <0.001* | <0.001* | 11.243 |
| Marital status                | 0.064   | 0.120   | 5.054  | 0.005*  | 0.009* | 3.151 |
| 9th grade education           | 0.742   | 0.350   | 4.447  | 0.913   | 0.720 | 2.521 |
| High school education         | 0.355   | 0.730   | 3.772  | 0.634   | 0.750 | 2.395 |
| At least bachelor degree      | 0.692   | 0.920   | 2.420  | 0.874   | 0.750 | 1.790 |
| Median family income          | 0.596   | 0.290   | 3.469  | 0.565   | 0.440 | 2.191 |
| Families below poverty        | 0.647   | 0.260   | 2.836  | 0.335   | 0.250 | 2.040 |
| Unemployed                    | 0.948   | 0.790   | 3.976  | 0.457   | 0.390 | 2.494 |
| White collar                  | 0.400   | 0.550   | 2.958  | 0.554   | 0.570 | 2.155 |

Categorical variables were compared by using the Pearson Chi-square test. Continuous variables in normal distribution and homogeneity of variance were compared by using the two-sample t test. OS – overall survival; CSS – cause-specific survival; MDG – Mean Decrease Gini. * P<0.05.

Surprisingly, surgery information, which showed significant results in the survival curve (Figure 2), was not a significant prognostic indicator for either OS or CSS in the Cox proportional hazards model. Also, chemotherapy was associated with a worse OS (HR, 2.199; 1.293 to 3.739; P=0.004) and CSS (HR, 2.608; 1.373 to 4.954; P=0.003). Radiotherapy was found to be a favorable independent factor for OS (HR, 0.504; 0.276 to 0.920; P=0.026), but not for CSS. The receiver operating characteristic (ROC) curves suggested that the multivariate models had high accuracy (OS: area under the curve [AUC] of 3-year survival: 0.753; AUC of 5-year survival: 0.755; CSS: AUC of 3-year survival: 0.782; AUC of 5-year survival: 0.780) (Figure 3E, 3F).

Nomogram and Validation

Based on the Cox proportional hazards regression model, the nomograms were constructed with the training cohort (Figure 4A, 4B). The calibration plots of the cumulative incidence function are shown in detail in Figure 4C and 4D.

In order to verify the discrimination and practicability of the results in the nomograms, a multidimensional validation was performed. The external validation cohort contained 37 patients from our own institution, comprising 14 males and 23 females, with a median age of 31.0 years (range: 14.0-69.0) and a median survival time of 25.0 months. All patients had a histopathological diagnosis of MGCTB (Figure 5).
Figure 2. Survival curves of age (A, B) and surgery information (C, D) for overall survival (OS) and cause-specific survival (CSS).

The survival time of 120.0 months (range: 4.0-501.0). The 201 patients identified from the SEER database using the TNM staging system included 93 males and 108 females, with a median age of 41.0 years (range: 4.0-91.0) and a median survival time of 102.0 months (range: 4.0-501.0). The 201 patients identified from the SEER database using the TNM staging system included 25 males and 28 females, with a median age of 41.0 years (range: 4.0-91.0) and a median survival time of 17.0 months (range: 0-129.0). The 53 patients identified from SEER using the sixth edition of the AJCC staging system included 25 males and 28 females, with a median age of 48.0 years (range: 16.0-91.0) and a median survival time of 26.0 months (range: 0-126.0). The 67 patients identified from SEER using the seventh edition of the AJCC staging system consisted of 31 males and 36 females, with a median age of 44.0 years (range: 17.0-91.0) and median survival time of 17.0 months (range: 0-59.0).

Compared with the current TNM staging system (0.772 [OS] and 0.837 [CSS]), and the AJCC sixth (0.624 [OS] and 0.641 [CSS]) and seventh (0.747 [OS] and 0.771 [CSS]) editions staging systems (Supplementary Figure 2), the nomograms achieved a higher C-index (internal validation: 0.836 [OS] and 0.827 [CSS]; external validation of our institution: 1.000 (OS) and 0.827 [CSS]).
and 0.810 (CSS); external validation of the SEER in 2016: 0.877 (OS) and 0.894 (CSS).

Discussion

MGCTB is a rare histological type of malignant tumor with a high tendency for local relapse and distant metastasis. Considering the potentially deleterious effects of MGCTB on patients [10,11,15], evaluating the prognostic factors is useful in improving prognosis and assisting clinicians in making accurate survival evaluations and therapeutic decisions. In this study, we constructed a prognostic nomogram for patients with MGCTB based on the SEER database and validated it externally, the first of its kind. Machine learning models (chi-square test and random forest) and classic survival analysis methods (Kaplan-Meier analysis and Cox proportional hazards model) were used to explore the significant prognostic variables in patients with MGCTB. The results suggested that age, historical stage, and chemotherapy were independent prognostic variables for OS and CSS of MGCTB patients and that ICD-O-3 histology, radiotherapy, and primary site were independent prognostic variables for OS.

Similar to previous studies [1,6,16], the mean age in our study cohort was 40.7 years (median 38.0, range: 1.0 to 91.0) with an equal sex distribution. Sex, race, and marital status were not independent prognostic variables for OS and CSS. Similar results were also obtained for high school education, 9th grade education, bachelor’s degree (at least), median family income, families below the poverty line, unemployment, and white-collar employment.

Age was divided into 3 groups, with the cutoff value of young age (<39 years) (50.3%), middle age (39-68 years) (38.1%), and old age (>68 years) (11.6%). The results revealed that age was
Figure 3. The results of the Lasso regression (A–D) and the receiver operating characteristic (ROC) curves (E, F). Lasso regression results suggested including 6 variables when overall survival (OS) was the endpoint (A, B), and 10 variables when cause-specific survival (CSS) (C, D) was the endpoint.
show the analysis results of DATABASE ANALYSIS

This work is licensed under Creative Common Attribution-NoCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)

Figure 4. Nomograms (A, C) and calibration curves (B, D) of overall survival (OS) and cause-specific survival (CSS).

a significant prognostic factor for both CSS and OS, which was similar to previous reports [1,6,16]. Compared with the middle age group, patients in the young age group had a more favorable prognosis, and patients in the old age group had a poorer one. A realistic explanation is that older patients were more easily affected by complex therapeutic complications, which can lead to a poorer prognosis [8].

In this study, the primary site was divided into 3 categories: head-face-neck (5.6%), trunk (21.9%), and limbs (72.5%). Tumors occurring in the limbs were found to be favorable for prognosis, especially considering that a total resection and even amputation can be performed if necessary. In contrast, tumors in the trunk and head-face-neck typically involve essential nerves and vessels, which makes performing a clean resection technically challenging. Additionally, the historical stage was a statistically significant variable for OS and CSS. Compared with regional tumors (31.8%), patients with distant metastatic tumors (16.2%) had a poorer prognosis. Similarly, numerous studies have also found that distant metastasis was also related to poor prognosis [8,17,18]. It not only increased the tumor burden and damaged organ function, but also limited the application of the en bloc tumor resection [1].

Surgery is generally regarded to be the fundamental treatment option for patients with MGCTB [7,19]. In our study, surgery was found to be a significant factor in patients with MGCTB in the Kaplan-Meier survival analysis (OS, P=0.012; CSS, P=0.007) (Figure 2C, 2D), but not in the multivariate analysis. Supplementary Tables 3 and 4 show the analysis results of the cohort without variable surgery information, which presents a noticeable change of C-index in the nomograms. In addition, subgroup analysis was also performed shown in Supplementary Tables 5-11. Therefore, whether surgery affects the prognosis in this study is controversial. On the one hand, this outcome may be attributed to the lack of detailed surgical information in the SEER database and no record of the surgical methods. In the 3 studies of Balke et al [20], Zhao et al [21], and Li et al [22], the selection of surgical methods was proposed to lead to varying degrees of functional impairment and local recurrence, which would cause a different prognosis. Although some studies have shown that 3-dimensional printing technology may solve the problem of limited functions after surgery, the choice of therapeutic methods for some parts with challenging anatomical locations would play a key role in the prognosis [23-25]. Some nonsurgical treatment methods might be beneficial for improving survival and quality of life, such as denosumab and embolization [25,26].
On the other hand, the prognosis was different among various operative methods. Total en bloc resection performed safely would reduce the recurrence rate and be recommended for patients with MGCTB, whereas subtotal resection was reportedly associated with a high recurrence rate and poor prognosis [1,27,28]. This discrepancy might decrease the correlation between surgery information and prognosis. In summary, surgery is still the most direct method of removing lesions and providing a curative effect [2,7,29,30].

Radiotherapy and chemotherapy are controversial treatment regimens for MGCTB [2,7,12,31], and both were demonstrated to be significant prognostic factors for patients with MGCTB in our study. Radiotherapy was found to be a favorable factor, while chemotherapy was a negative predictor. Although MGCTB was initially thought to be radiotherapy resistant and lead to radiotherapy-related malignant transformation [11,32], the efficacy and safety of radiotherapy have significantly improved in recent years [33-36]. Chemotherapy was not commonly used in MGCTB and was reserved only for advanced MGCTB that could not be cured by either surgery or radiotherapy. Thus, the prognosis of chemotherapy-applied patients with MGCTB was worse. Our subgroup analysis also demonstrated that patients who did not undergo surgical therapy preferred to receive chemotherapy (no surgery: OR, 5.944; 4.234 to 8.597; P<0.001) and radiotherapy (no surgery: OR, 7.517; 5.194 to 11.305; P<0.001) (Supplementary Tables 7, 8). Denosumab, an inhibitor of receptor activator of nuclear factor-kappa-B ligand (RANKL), is currently widely used in MGCTB and provides a good therapeutic effect to inhibit bone destruction [37,38]. Moreover, previous studies have suggested that the prognosis of recurrent GCTB could be highly related to early diagnosis and surgery and that early diagnosis was associated with better prognosis and surgical treatment [39,40].

Comprehensive nomograms were found to be useful and convenient tools to evaluate the prognosis of patients, and the nomograms developed in the current study were the first for MGCTB based on the SEER database. The nomograms were verified by internal (C-index: OS, 0.836; CSS, 0.827) and external validation (C-index: OS, 1.000; CSS, 0.810) using the database from our own institution, as well as external validation.
(C-index: OS, 0.877; CSS, 0.894) with additional data of patients with MGCTB from the SEER database in 2016. Moreover, the nomograms were also compared with the TNM staging system (C-index: OS, 0.772; CSS, 0.837), and the sixth (C-index: OS, 0.624; CSS, 0.641) and seventh editions of the AJCC staging system (C-index: OS, 0.747; CSS, 0.771) to verify their reliability. The C-index of our verification cohort was relatively high, although our sample size limited it. Therefore, we obtained additional data from patients with MGCTB from the SEER database in 2016 to further validate our model to reduce bias in external validation. Moreover, compared with the TNM and the AJCC (sixth and seventh editions) staging systems, the nomograms were found to exhibit higher sensitivity and specificity based on the C-index.

There were some additional limitations in our study that need to be addressed. First, although the SEER database contained a large sample size and multiple variables, it still presented some deficiencies. For example, because the SEER database contains information from multiple centers, its intergroup heterogeneity is not processed, even though we have strict inclusion and exclusion criteria to minimize this heterogeneity. Secondly, the median follow-up time of the external validation set from our own institution was not as long as the SEER database. In the future, stricter and more accurate nomograms for prediction need to be combined with genetic factors. Subsequent research should focus on the correlation between deep molecular mechanisms (e.g., the newly discovered long noncoding RNA related to the prognosis of bone tumors) and the independent prognostic variables found in this study, with the assistance of weighted gene co-expression network analysis and deep learning [41].

**Supplementary Data**

**Supplementary Materials A**

Supplementary Table 1 shows the baseline characteristics of patients with malignant giant cell tumor of bone.

Supplementary Table 2 shows the point assignment and prognostic score for each variable in nomograms for overall survival (OS) and cause-specific survival (CSS).

Supplementary Tables 3 and 4 show the analysis results of the cohort without variable “surgery information.”

Supplementary Tables 5-11 show the subgroup univariate analysis results.

**Conclusions**

Age, historical stage, and chemotherapy were independent prognostic variables for OS and CSS of MGCTB patients, and radiotherapy and primary site were independent prognostic variables for OS. Our nomograms were verified internally and externally based on significant clinicopathologic features and clinical experience and may assist clinicians in making more accurate survival evaluations in conjunction with the TNM and AJCC staging systems.

**Acknowledgments**

We thank the Surveillance, Epidemiology, and End Results (SEER) Program team of the National Cancer Institute for their data. We appreciate all the participants for their cooperation. We also thank Penghui Yan, Suna Zhai, Jie Zhang, Junwei Zhuang, and Huabin Yin for their support in collecting data throughout this investigation.

**Statement**

All work was done in the Department of Orthopaedics of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China.

**Conflict of Interests**

None.
### Supplementary Table 1. Baseline characteristics of patients with malignant giant cell tumors of bone.

| Demographic or characteristic | Total patients (N=302) | Alive cohort (N=255) | Dead cohort (N=47) |
|------------------------------|------------------------|----------------------|--------------------|
|                              | No. | %   | No. | %   | No. | %   |
| Age, years                   |     |     |     |     |     |     |
| Mean±SD                      | 40.7±19.1 | 35.5±16.0 | 56.0±19.1 |
| Median (range)               | 38.0 (1.0-91.0) | 32.0 (1.0-88.0) | 55.0 (18.0-91.0) |
| Categorical age              |     |     |     |     |     |     |
| <39                          | 152 | 50.3% | 138 | 61.3% | 14 | 18.2% |
| >68                          | 35  | 11.6% | 9   | 4.0%  | 26 | 33.8% |
| 39-68                        | 115 | 38.1% | 78  | 34.7% | 37 | 48.1% |
| Survival month months        |     |     |     |     |     |     |
| Mean±SD                      | 114.3±123.2 | 138.8±129.1 | 43.0±63.4 |
| Median (range)               | 75.5 (0-502.0) | 102.0 (0-502.0) | 18.00 (0-359.0) |
| Race                         |     |     |     |     |     |     |
| Black                        | 34  | 11.3% | 27  | 12.0% | 7  | 9.1%  |
| Other                        | 35  | 11.6% | 23  | 10.2% | 12 | 15.6% |
| White                        | 233 | 77.2% | 175 | 77.8% | 58 | 75.3% |
| Gender                       |     |     |     |     |     |     |
| Female                       | 153 | 50.7% | 123 | 54.7% | 30 | 39.0% |
| Male                         | 149 | 49.3% | 102 | 45.3% | 47 | 61.0% |
| Primary site                 |     |     |     |     |     |     |
| Head face neck               | 17  | 5.6%  | 8   | 3.6%  | 9  | 11.7% |
| Limbs                        | 219 | 72.5% | 176 | 78.2% | 43 | 55.8% |
| Trunk                        | 66  | 21.9% | 41  | 18.2% | 25 | 32.5% |
| Surgery information          |     |     |     |     |     |     |
| No                           | 47  | 15.6% | 31  | 13.8% | 16 | 20.8% |
| Yes                          | 255 | 84.4% | 194 | 86.2% | 61 | 79.2% |
| Radiation recode             |     |     |     |     |     |     |
| No                           | 247 | 81.8% | 191 | 84.9% | 56 | 72.7% |
| Yes                          | 55  | 18.2% | 34  | 15.1% | 22 | 27.3% |
| Chemotherapy recode          |     |     |     |     |     |     |
| No/unknown                   | 250 | 82.8% | 198 | 88.0% | 52 | 67.5% |
| Yes                          | 52  | 17.2% | 27  | 12.0% | 25 | 32.5% |
| Historic stage               |     |     |     |     |     |     |
| Distant                      | 49  | 16.2% | 24  | 10.7% | 25 | 32.5% |
| Localized                    | 157 | 52.0% | 129 | 57.3% | 28 | 36.4% |
| Regional                     | 96  | 31.8% | 72  | 32.0% | 24 | 31.2% |
Supplementary Table 1 continued. Baseline characteristics of patients with malignant giant cell tumors of bone.

| Demographic or characteristic | Total patients (N=302) | Alive cohort (N=255) | Dead cohort (N=47) |
|-------------------------------|------------------------|----------------------|-------------------|
|                               | No.        | %          | No.       | %          | No.       | %          |
| Marital status                |            |            |            |            |            |            |
| Married                       | 149        | 49.3%      | 104       | 46.2%      | 45        | 58.4%      |
| Single                        | 153        | 50.7%      | 121       | 53.8%      | 32        | 41.6%      |
| 9th grade education           |            |            |            |            |            |            |
| Lower 50%                     | 150        | 49.7%      | 113       | 50.2%      | 37        | 48.1%      |
| Upper 50%                     | 152        | 50.3%      | 112       | 49.8%      | 40        | 51.9%      |
| High school education         |            |            |            |            |            |            |
| Lower 50%                     | 151        | 50.0%      | 109       | 48.4%      | 42        | 54.5%      |
| Upper 50%                     | 151        | 50.0%      | 116       | 51.6%      | 35        | 45.5%      |
| At least bachelor degree      |            |            |            |            |            |            |
| Lower 50%                     | 151        | 50.0%      | 114       | 50.7%      | 37        | 48.1%      |
| Upper 50%                     | 151        | 50.0%      | 111       | 49.3%      | 40        | 51.9%      |
| Median family income          |            |            |            |            |            |            |
| Lower 50%                     | 149        | 49.3%      | 109       | 48.4%      | 40        | 51.9%      |
| Upper 50%                     | 153        | 50.7%      | 116       | 51.6%      | 37        | 48.1%      |
| Families below poverty        |            |            |            |            |            |            |
| Lower 50%                     | 148        | 49.0%      | 112       | 49.8%      | 36        | 46.8%      |
| Upper 50%                     | 154        | 51.0%      | 113       | 50.2%      | 41        | 53.2%      |
| Unemployed                    |            |            |            |            |            |            |
| Lower 50%                     | 150        | 49.7%      | 112       | 49.8%      | 39        | 49.4%      |
| Upper 50%                     | 152        | 50.3%      | 113       | 50.2%      | 39        | 50.6%      |
| White collar                  |            |            |            |            |            |            |
| Lower 50%                     | 134        | 44.4%      | 103       | 45.8%      | 31        | 40.3%      |
| Upper 50%                     | 168        | 55.6%      | 122       | 54.2%      | 46        | 59.7%      |

Supplementary Table 2. Point assignment and prognostic score for each variable.

| Variable              | Overall survival (OS) | Cause-specific survival (CCS) |
|-----------------------|-----------------------|-------------------------------|
| Categorical age       |                       |                               |
| <39                   | 0                     | 0                             |
| >68                   | 100                   | 100                           |
| 39-68                 | 54                    | 62                            |
| Surgery information   |                       |                               |
| No                    | 13                    | 5                             |
| Yes                   | 0                     | 0                             |
Supplementary Table 3. Cox proportional hazards regression model for cancer-specific survival and overall survival in patients with Malignant Giant Cell Tumor of Bone (MGCTB) without surgery information.

| Variable       | Overall survival (OS) | Cause-specific survival (CCS) |
|----------------|-----------------------|-------------------------------|
|                | Hazard ratio (95% CI) | P                             | Hazard ratio (95% CI) | P            |
| **Categorical age** |                       |                               |                        |              |
| < 39           | 1.000 (reference)     |                               | 1.000 (reference)     |              |
| > 68           | 20.043 (9.403-42.722) | <0.001*                       | 8.733 (3.639-20.958)  | <0.001*      |
| 39-68          | 4.933 (2.613-9.313)   | <0.001*                       | 3.772 (1.741-8.172)   | <0.001*      |
| **Primary site** |                       |                               |                        |              |
| Head, face, neck | 1.000 (reference)     |                               | 1.000 (reference)     |              |
| Limbs          | 0.326 (0.150-0.708)   | 0.005*                        | 0.504 (0.276-0.920)   | 0.026*       |
| Trunk          | 0.628 (0.273-1.445)   | 0.274                         |                          |              |
| **Radiation recode** |                   |                               |                        |              |
| No             | 1.000 (reference)     |                               | 1.000 (reference)     |              |
| Yes            | 2.199 (1.293-3.739)   | 0.004*                        | 2.608 (1.373-4.954)   | 0.003*       |
| **Chemotherapy recode** |               |                               |                        |              |
| No/unknown     | 1.000 (reference)     |                               | 1.000 (reference)     |              |
| Yes            | 2.199 (1.293-3.739)   | 0.004*                        | 2.608 (1.373-4.954)   | 0.003*       |
| **Historic stage** |                     |                               |                        |              |
| Distant        | 1.000 (reference)     |                               | 1.000 (reference)     |              |
| Localized      | 0.281 (0.151-0.519)   | <0.001*                       | 0.158 (0.073-0.345)   | <0.001*      |
| Regional       | 0.298 (0.158-0.562)   | <0.001*                       | 0.290 (0.141-0.595)   | <0.001*      |

OS – overall survival; CCS cause-specific survival. * P<0.05.
### Supplementary Table 4. Point assignment and prognostic score for each variable without surgery information.

| Variable       | Overall survival (OS) | Cause-specific survival (CCS) |
|----------------|-----------------------|------------------------------|
| **Categorical age** |                       |                              |
| <39            | 0                     | 0                            |
| >68            | 100                   | 100                          |
| 39-68          | 53                    | 61                           |
| **Primary site** |                       |                              |
| Head, face, neck | 37                    |                              |
| Limb           | 0                     |                              |
| Trunk          | 22                    |                              |
| **Historic stage** |                       |                              |
| Distant        | 42                    |                              |
| Localized      | 0                     |                              |
| Regional       | 2                     |                              |
| **Chemotherapy** |                       |                              |
| Yes            | 26                    | 44                           |
| None/unknown   | 0                     | 0                            |
| **Radiation recode** |               |                              |
| No             | 23                    |                              |
| Yes            | 0                     |                              |

### Supplementary Table 5. Subgroup analysis between age and surgery information.

| Age     | Surgery information | OR       | 95%CI      | P value |
|---------|---------------------|----------|------------|---------|
| 39-68   | No                  | 1.000 (reference) |          |         |
|         | Yes                 | 0.770    | 0.150-0.882 | 0.002*  |
| >68     | No                  | 1.000 (reference) |          |         |
|         | Yes                 | 0.357    | 0.383-1.553 | 0.461   |

Lower 39 years old is the reference group. OR – odds ratio; CI – confidence interval. * P<0.05.

### Supplementary Table 6. Subgroup analysis between primary site and surgery information.

| Primary site | Surgery information | OR       | 95%CI      | P value |
|--------------|---------------------|----------|------------|---------|
| Limb         | No                  | 1.000 (reference) |          |         |
|              | Yes                 | 0.444    | 0.024-2.317 | 0.440   |
| Trunk        | No                  | 1.000 (reference) |          |         |
|              | Yes                 | 0.135    | 0.008-0.843 | 0.080   |

Bone of head, face and neck is the reference group. OR – odds ratio; CI – confidence interval. * P<0.05.
Supplementary Table 7. Subgroup analysis between chemotherapy recode and surgery information.

| Chemotherapy recode | Surgery information | OR       | 95% CI      | P value |
|---------------------|---------------------|----------|-------------|---------|
| Yes                 | No                  | 1.000 (reference) |             |         |
|                     | Yes                 | 0.627 | 0.302-1.382 | 0.225   |
| Unknown/none        | No                  | 1.000 (reference) |             |         |
|                     | Yes                 | 5.944 | 4.234-8.597 | <0.001* |

OR – odds ratio; CI – confidence interval. * P<0.05.

Supplementary Table 8. Subgroup analysis between radiation recode and surgery information.

| Radiation recode | Surgery information | OR       | 95% CI      | P value |
|------------------|---------------------|----------|-------------|---------|
| Yes              | No                  | 1.000 (reference) |             |         |
|                  | Yes                 | 0.273 | 0.138-0.517 | <0.001* |
| No               | No                  | 1.000 (reference) |             |         |
|                  | Yes                 | 7.517 | 5.194-11.305 | <0.001* |

OR – odds ratio; CI – confidence interval. * P<0.05.

Supplementary Table 9. Subgroup analysis between radiation recode and historic stage.

| Historic stage | Radiation recode | OR       | 95% CI      | P value |
|----------------|------------------|----------|-------------|---------|
| Localized      | No               | 1.000 (reference) |             |         |
|                | Yes              | 0.151 | 0.069-0.333 | <0.001* |
| Regional       | No               | 1.000 (reference) |             |         |
|                | Yes              | 0.308 | 0.142-0.657 | <0.001* |

Distant is the reference group. OR – odds ratio; CI – confidence interval. * P<0.05.

Supplementary Table 10. Subgroup analysis between radiation recode and primary site.

| Primary site | Radiation recode | OR       | 95% CI      | P value |
|--------------|------------------|----------|-------------|---------|
| Limb         | No               | 1.000 (reference) |             |         |
|              | Yes              | 0.521 | 0.015-2.385 | 0.335   |
| Trunk        | No               | 1.000 (reference) |             |         |
|              | Yes              | 3.889 | 1.139-18.022 | 0.005*  |

Bone of head, face and neck is the reference group. OR – odds ratio; CI – confidence interval. * P<0.05.

Supplementary Table 11. Subgroup analysis between chemotherapy recode and historic stage.

| Primary site | Radiation recode | OR       | 95% CI      | P value |
|--------------|------------------|----------|-------------|---------|
| Localized    | No               | 1.000 (reference) |             |         |
|              | Yes              | 0.229 | 0.105-0.496 | <0.001* |
| Regional     | No               | 1.000 (reference) |             |         |
|              | Yes              | 0.434 | 0.198-0.950 | 0.004*  |

Distant is the reference group. OR – odds ratio; CI – confidence interval. * P<0.05.
Supplementary Figure 1. The process of screening age cutoff point with X-tile.
Supplementary Figure 2. Survival curves of American Joint Committee on Cancer (AJCC) staging system sixth edition (A, B) (C-index: 0.624 and 0.641) and seventh edition (C, D) (C-index: 0.747 and 0.771) for overall survival (OS) and cause-specific survival (CSS).

Supplementary Materials B

The raw dataset of the training set consisted of 302 patients with malignant giant cell tumor of bone from the Surveillance, Epidemiology, and End Results database.

Supplementary data available from the corresponding author on request.
The raw dataset of the validated set consisted of 37 patients with malignant giant cell tumor of bone.

| Sex  | Age | Radiation | Primary site      | Surgery | Chemotherapy | Historic stage | Survival month | Overall survival | Cause-specific survival |
|------|-----|-----------|-------------------|---------|--------------|---------------|----------------|-------------------|------------------------|
| Male | 44  | Yes       | Head, face, neck  | Yes     | Yes          | Regional      | 82             | 1                 | 1                      |
| Male | 24  | No        | Limb              | Yes     | No/unknown   | Distant       | 16             | 1                 | 1                      |
| Female | 30  | No        | Trunk             | Yes     | No/unknown   | Regional      | 63             | 0                 | 0                      |
| Female | 28  | No        | Limb              | Yes     | No/unknown   | Regional      | 27             | 0                 | 0                      |
| Female | 29  | No        | Limb              | Yes     | No/unknown   | Regional      | 9              | 0                 | 0                      |
| Female | 26  | No        | Trunk             | Yes     | No/unknown   | Regional      | 67             | 0                 | 0                      |
| Female | 30  | No        | Limb              | Yes     | No/unknown   | Localized     | 51             | 0                 | 0                      |
| Female | 39  | No        | Trunk             | Yes     | No/unknown   | Regional      | 51             | 0                 | 0                      |
| Male  | 58  | No        | Trunk             | Yes     | Yes          | Regional      | 50             | 0                 | 0                      |
| Male  | 31  | No        | Limb              | Yes     | No/unknown   | Regional      | 45             | 0                 | 0                      |
| Male  | 29  | No        | Limb              | Yes     | No/unknown   | Localized     | 42             | 0                 | 0                      |
| Female | 51  | No        | Limb              | Yes     | No/unknown   | Regional      | 43             | 1                 | 1                      |
| Male  | 49  | No        | Head, face, neck  | Yes     | No/unknown   | Regional      | 40             | 0                 | 0                      |
| Female | 33  | No        | Trunk             | Yes     | No/unknown   | Distant       | 40             | 0                 | 0                      |
| Female | 68  | No        | Trunk             | Yes     | No/unknown   | Regional      | 33             | 0                 | 0                      |
| Female | 44  | No        | Trunk             | Yes     | No/unknown   | Localized     | 28             | 0                 | 0                      |
| Female | 67  | No        | Trunk             | Yes     | No/unknown   | Localized     | 27             | 0                 | 0                      |
| Female | 66  | No        | Trunk             | Yes     | No/unknown   | Regional      | 26             | 0                 | 0                      |
| Male  | 25  | No        | Limb              | Yes     | No/unknown   | Regional      | 25             | 0                 | 0                      |
| Male  | 54  | No        | Head, face, neck  | Yes     | No/unknown   | Regional      | 22             | 0                 | 0                      |
| Male  | 32  | No        | Head, face, neck  | Yes     | No/unknown   | Regional      | 20             | 0                 | 0                      |
| Female | 35  | No        | Trunk             | No      | No/unknown   | Regional      | 23             | 1                 | 1                      |
| Male  | 14  | No        | Limb              | Yes     | No/unknown   | Regional      | 2              | 0                 | 0                      |
| Female | 28  | No        | Limb              | Yes     | No/unknown   | Regional      | 3              | 0                 | 0                      |
| Male  | 30  | No        | Limb              | Yes     | No/unknown   | Regional      | 3              | 0                 | 0                      |
| Male  | 40  | No        | Limb              | Yes     | No/unknown   | Regional      | 3              | 0                 | 0                      |
| Male  | 34  | No        | Limb              | Yes     | Yes          | Regional      | 20             | 0                 | 0                      |
| Male  | 33  | No        | Head, face, neck  | Yes     | No/unknown   | Regional      | 4              | 0                 | 0                      |
| Female | 24  | No        | Limb              | Yes     | No/unknown   | Regional      | 4              | 0                 | 0                      |
| Female | 18  | No        | Limb              | Yes     | No/unknown   | Regional      | 6              | 0                 | 0                      |
| Female | 59  | No        | Trunk             | No      | No/unknown   | Regional      | 6              | 0                 | 0                      |
| Female | 28  | No        | Trunk             | Yes     | No/unknown   | Regional      | 8              | 0                 | 0                      |
| Male  | 17  | No        | Limb              | Yes     | No/unknown   | Regional      | 10             | 0                 | 0                      |
| Female | 24  | No        | Limb              | Yes     | No/unknown   | Localized     | 10             | 0                 | 0                      |
| Female | 53  | No        | Trunk             | Yes     | No/unknown   | Regional      | 12             | 0                 | 0                      |
The raw dataset of the validated set consisted of 163 patients with malignant giant cell tumor of bone.

| Sex  | Age | Radiation recode | Primary site | Surgery | Chemotherapy recode | Historic stage | Survival month | Overall survival | Cause-specific survival |
|------|-----|------------------|--------------|---------|---------------------|----------------|----------------|-------------------|------------------------|
| Female | 86  | Yes              | Limb         | No      | No                  | Distant        | 12             | 1                 | 1                      |
| Female | 70  | No               | Limb         | Yes     | No                  | Regional       | 22             | 1                 | 0                      |
| Female | 35  | No               | Limb         | Yes     | No                  | Regional       | 299            | 0                 | 0                      |
| Female | 35  | No               | Limb         | Yes     | No                  | Localized      | 252            | 0                 | 0                      |
| Female | 35  | No               | Limb         | Yes     | No                  | Localized      | 189            | 0                 | 0                      |
| Male   | 36  | No               | Limb         | Yes     | No                  | Distant        | 114            | 0                 | 0                      |
| Male   | 62  | No               | Limb         | Yes     | No                  | Localized      | 50             | 1                 | 0                      |
| Female | 40  | No               | Limb         | No      | No                  | Distant        | 72             | 0                 | 0                      |
| Male   | 15  | No               | Limb         | Yes     | No                  | Regional       | 246            | 0                 | 0                      |
| Female | 23  | No               | Limb         | Yes     | No                  | Regional       | 302            | 0                 | 0                      |
| Female | 32  | No               | Limb         | Yes     | No                  | Localized      | 98             | 0                 | 0                      |
| Female | 26  | Yes              | Limb         | Yes     | No                  | Localized      | 190            | 0                 | 0                      |
| Female | 25  | No               | Limb         | No      | No                  | Regional       | 416            | 0                 | 0                      |
| Female | 31  | No               | Limb         | No      | No                  | Localized      | 378            | 0                 | 0                      |
| Male   | 30  | No               | Limb         | Yes     | No                  | Distant        | 242            | 0                 | 0                      |
| Female | 57  | No               | Limb         | No      | No                  | Localized      | 180            | 0                 | 0                      |
| Female | 55  | No               | Limb         | Yes     | No                  | Localized      | 135            | 0                 | 0                      |
| Female | 17  | No               | Limb         | Yes     | No                  | Localized      | 486            | 0                 | 0                      |
| Female | 31  | No               | Limb         | Yes     | Yes                 | Localized      | 464            | 0                 | 0                      |
| Female | 36  | No               | Limb         | Yes     | No                  | Regional       | 501            | 0                 | 0                      |
| Female | 22  | No               | Limb         | Yes     | No                  | Localized      | 338            | 0                 | 0                      |
| Male   | 30  | No               | Limb         | Yes     | No                  | Regional       | 161            | 0                 | 0                      |
| Male   | 25  | No               | Limb         | Yes     | No                  | Localized      | 229            | 1                 | 0                      |
| Male   | 40  | No               | Limb         | Yes     | No                  | Regional       | 158            | 0                 | 0                      |
| Male   | 25  | No               | Limb         | Yes     | No                  | Distant        | 37             | 0                 | 0                      |
| Male   | 30  | No               | Limb         | Yes     | No                  | Localized      | 248            | 0                 | 0                      |
| Female | 40  | No               | Limb         | Yes     | Yes                 | Localized      | 359            | 1                 | 0                      |
| Female | 25  | No               | Limb         | Yes     | No                  | Regional       | 34             | 0                 | 0                      |
| Male   | 26  | No               | Limb         | Yes     | Yes                 | Distant        | 11             | 0                 | 0                      |
| Female | 20  | No               | Limb         | Yes     | No                  | Localized      | 115            | 0                 | 0                      |
| Male   | 52  | No               | Limb         | Yes     | No                  | Regional       | 158            | 1                 | 0                      |
| Female | 30  | No               | Limb         | Yes     | Yes                 | Localized      | 18             | 1                 | 1                      |
| Female | 17  | No               | Limb         | Yes     | No                  | Regional       | 189            | 0                 | 0                      |
| Female | 21  | No               | Limb         | Yes     | Yes                 | Localized      | 130            | 0                 | 0                      |
| Female | 30  | Yes              | Limb         | Yes     | No                  | Localized      | 85             | 0                 | 0                      |
| Female | 24  | No               | Limb         | Yes     | Yes                 | Localized      | 48             | 1                 | 1                      |
| Male   | 26  | No               | Limb         | Yes     | No                  | Regional       | 119            | 0                 | 0                      |
| Female | 41  | No               | Limb         | Yes     | No                  | Localized      | 51             | 0                 | 0                      |
| Sex  | Age | Radiation recode | Primary site | Surgery | Chemotherapy recode | Historic stage | Survival month | Overall survival | Cause-specific survival |
|------|-----|------------------|--------------|---------|---------------------|---------------|----------------|------------------|------------------------|
| Male | 42  | No               | Limb         | Yes     | No                  | Localized     | 54             | 0                | 0                      |
| Male | 59  | No               | Limb         | Yes     | No                  | Regional      | 31             | 0                | 0                      |
| Male | 26  | No               | Limb         | Yes     | No                  | Localized     | 35             | 0                | 0                      |
| Male | 28  | No               | Limb         | Yes     | No                  | Regional      | 128            | 0                | 0                      |
| Male | 32  | No               | Limb         | Yes     | No                  | Localized     | 102            | 0                | 0                      |
| Male | 46  | No               | Limb         | Yes     | Yes                 | Regional      | 175            | 0                | 0                      |
| Female | 87  | Yes              | Limb         | Yes     | No                  | Regional      | 32             | 1                | 0                      |
| Female | 16  | No               | Limb         | Yes     | No                  | Localized     | 42             | 0                | 0                      |
| Male | 45  | No               | Limb         | Yes     | No                  | Localized     | 165            | 0                | 0                      |
| Male | 63  | No               | Limb         | Yes     | No                  | Localized     | 130            | 0                | 0                      |
| Male | 28  | No               | Limb         | Yes     | No                  | Localized     | 103            | 0                | 0                      |
| Male | 37  | No               | Limb         | Yes     | No                  | Localized     | 99             | 0                | 0                      |
| Female | 33  | No               | Limb         | Yes     | No                  | Localized     | 153            | 0                | 0                      |
| Male | 28  | No               | Limb         | Yes     | No                  | Localized     | 495            | 0                | 0                      |
| Male | 28  | No               | Limb         | No      | No                  | Regional      | 44             | 1                | 0                      |
| Male | 16  | Yes              | Limb         | No      | No                  | Distant       | 189            | 0                | 0                      |
| Female | 37  | No               | Limb         | Yes     | No                  | Localized     | 86             | 0                | 0                      |
| Female | 18  | No               | Limb         | Yes     | No                  | Localized     | 87             | 0                | 0                      |
| Female | 16  | Yes              | Limb         | Yes     | No                  | Regional      | 449            | 0                | 0                      |
| Male | 19  | No               | Limb         | Yes     | No                  | Localized     | 131            | 0                | 0                      |
| Female | 15  | No               | Limb         | Yes     | No                  | Localized     | 60             | 0                | 0                      |
| Male | 22  | No               | Limb         | Yes     | No                  | Localized     | 68             | 0                | 0                      |
| Male | 32  | No               | Limb         | Yes     | No                  | Localized     | 419            | 0                | 0                      |
| Male | 42  | No               | Limb         | Yes     | No                  | Distant       | 316            | 0                | 0                      |
| Male | 25  | No               | Limb         | Yes     | No                  | Regional      | 244            | 0                | 0                      |
| Male | 30  | No               | Limb         | Yes     | No                  | Localized     | 97             | 1                | 0                      |
| Female | 23  | No               | Limb         | Yes     | No                  | Localized     | 314            | 0                | 0                      |
| Female | 37  | Yes              | Limb         | Yes     | No                  | Localized     | 215            | 0                | 0                      |
| Male | 46  | No               | Limb         | Yes     | No                  | Distant       | 126            | 1                | 1                      |
| Male | 47  | No               | Limb         | Yes     | Yes                 | Regional      | 6              | 1                | 1                      |
| Female | 34  | No               | Limb         | Yes     | No                  | Localized     | 102            | 0                | 0                      |
| Male | 37  | No               | Limb         | Yes     | No                  | Localized     | 258            | 0                | 0                      |
| Female | 20  | No               | Limb         | Yes     | Yes                 | Regional      | 13             | 1                | 1                      |
| Male | 48  | No               | Limb         | Yes     | Yes                 | Distant       | 63             | 1                | 0                      |
| Female | 21  | No               | Limb         | Yes     | No                  | Localized     | 128            | 0                | 0                      |
| Male | 28  | Yes              | Limb         | Yes     | No                  | Distant       | 170            | 0                | 0                      |
| Male | 43  | No               | Limb         | Yes     | No                  | Localized     | 57             | 0                | 0                      |
| Female | 44  | No               | Limb         | No      | No                  | Localized     | 36             | 1                | 1                      |
| Male | 29  | No               | Limb         | Yes     | No                  | Regional      | 252            | 0                | 0                      |
| Male | 34  | No               | Limb         | Yes     | No                  | Localized     | 30             | 1                | 1                      |
| Male | 18  | No               | Limb         | Yes     | Yes                 | Distant       | 9              | 1                | 1                      |
| Female | 21  | No               | Limb         | Yes     | No                  | Regional      | 204            | 0                | 0                      |
| Sex   | Age | Radiation recode | Primary site | Surgery | Chemotherapy recode | Histologic stage | Survival month | Overall survival | Cause-specific survival |
|-------|-----|------------------|--------------|---------|----------------------|------------------|----------------|-----------------|-------------------------|
| Male  | 44  | No               | Limb         | Yes     | Yes                  | Distant          | 7              | 1               | 1                       |
| Male  | 65  | No               | Limb         | Yes     | No                   | No               | 140            | 1               | 2                       |
| Female| 18  | No               | Limb         | Yes     | No                   | No               | 264            | 0               | 0                       |
| Male  | 34  | No               | Limb         | Yes     | No                   | Regional         | 285            | 0               | 0                       |
| Male  | 12  | No               | Limb         | Yes     | No                   | Distant          | 172            | 0               | 0                       |
| Male  | 35  | No               | Limb         | Yes     | Yes                  | Regional         | 154            | 0               | 0                       |
| Male  | 11  | No               | Limb         | Yes     | No                   | Localized        | 72             | 0               | 0                       |
| Female| 21  | No               | Limb         | Yes     | No                   | Yes             | 75             | 0               | 0                       |
| Male  | 48  | Yes              | Limb         | Yes     | No                   | No               | 196            | 0               | 0                       |
| Male  | 56  | No               | Limb         | Yes     | No                   | No               | 106            | 1               | 0                       |
| Male  | 19  | No               | Limb         | Yes     | No                   | Localized        | 104            | 0               | 0                       |
| Female| 49  | No               | Limb         | Yes     | No                   | No               | 163            | 0               | 0                       |
| Male  | 43  | No               | Limb         | Yes     | No                   | No               | 164            | 0               | 0                       |
| Male  | 21  | No               | Limb         | Yes     | No                   | Localized        | 73             | 0               | 0                       |
| Female| 35  | No               | Limb         | Yes     | Yes                  | Regional         | 16             | 1               | 1                       |
| Female| 29  | No               | Limb         | Yes     | Yes                  | Localized        | 34             | 0               | 0                       |
| Male  | 24  | No               | Limb         | Yes     | No                   | No               | 75             | 0               | 0                       |
| Male  | 37  | No               | Limb         | Yes     | No                   | Localized        | 59             | 0               | 0                       |
| Male  | 41  | No               | Limb         | Yes     | No                   | Localized        | 171            | 0               | 0                       |
| Male  | 68  | No               | Limb         | Yes     | Yes                  | Regional         | 14             | 1               | 1                       |
| Female| 25  | No               | Limb         | Yes     | No                   | Regional         | 182            | 0               | 0                       |
| Female| 55  | No               | Limb         | Yes     | No                   | Localized        | 28             | 1               | 1                       |
| Male  | 38  | No               | Limb         | Yes     | Yes                  | Localized        | 186            | 0               | 0                       |
| Male  | 9   | No               | Limb         | No      | No                   | No               | 186            | 0               | 0                       |
| Male  | 84  | No               | Limb         | Yes     | No                   | Localized        | 24             | 1               | 0                       |
| Male  | 29  | No               | Limb         | Yes     | No                   | Localized        | 147            | 0               | 0                       |
| Male  | 40  | No               | Limb         | Yes     | No                   | Localized        | 117            | 0               | 0                       |
| Male  | 48  | No               | Limb         | Yes     | No                   | Localized        | 129            | 0               | 0                       |
| Female| 29  | No               | Limb         | Yes     | No                   | Localized        | 139            | 0               | 0                       |
| Male  | 22  | No               | Limb         | Yes     | No                   | Regional         | 97             | 0               | 0                       |
| Female| 27  | No               | Limb         | Yes     | No                   | Localized        | 106            | 0               | 0                       |
| Female| 27  | No               | Limb         | Yes     | No                   | Localized        | 88             | 0               | 0                       |
| Male  | 30  | No               | Limb         | Yes     | No                   | Localized        | 59             | 0               | 0                       |
| Female| 21  | No               | Limb         | Yes     | No                   | Localized        | 50             | 0               | 0                       |
| Male  | 69  | No               | Limb         | Yes     | Yes                  | Regional         | 19             | 0               | 0                       |
| Male  | 44  | No               | Limb         | Yes     | No                   | Regional         | 15             | 0               | 0                       |
| Male  | 53  | No               | Limb         | Yes     | No                   | Localized        | 50             | 0               | 0                       |
| Male  | 46  | Yes              | Trunk        | Yes     | No                   | No               | 456            | 0               | 0                       |
| Male  | 28  | Yes              | Trunk        | Yes     | No                   | No               | 11             | 0               | 0                       |
| Male  | 60  | Yes              | Trunk        | Yes     | No                   | Regional         | 20             | 1               | 1                       |
| Female| 67  | Yes              | Trunk        | Yes     | No                   | Regional         | 19             | 1               | 0                       |
| Male  | 55  | Yes              | Trunk        | No      | No                   | Distant          | 184            | 1               | 0                       |
| Sex | Age | Radiation recode | Primary site | Surgery | Chemotherapy recode | Historic stage | Survival month | Overall survival | Cause-specific survival |
|-----|-----|------------------|--------------|---------|---------------------|---------------|----------------|-----------------|------------------------|
| Female | 25 | Yes | Trunk | No | Yes | Regional | 380 | 0 | 0 |
| Female | 55 | No | Trunk | Yes | No | Regional | 189 | 0 | 0 |
| Male | 22 | No | Trunk | Yes | No | Distant | 34 | 1 | 1 |
| Male | 57 | No | Trunk | No | Yes | Distant | 75 | 0 | 0 |
| Female | 58 | Yes | Trunk | Yes | No | Distant | 132 | 0 | 0 |
| Male | 69 | No | Trunk | No | No | Regional | 1 | 1 | 1 |
| Female | 59 | No | Trunk | Yes | No | Distant | 21 | 1 | 1 |
| Female | 26 | Yes | Trunk | No | No | Distant | 395 | 0 | 0 |
| Female | 27 | No | Trunk | Yes | No | Localized | 261 | 0 | 0 |
| Female | 62 | No | Trunk | Yes | No | Regional | 2 | 1 | 1 |
| Female | 45 | No | Trunk | No | No | Regional | 27 | 0 | 0 |
| Female | 58 | No | Trunk | Yes | Yes | Localized | 161 | 0 | 0 |
| Female | 49 | Yes | Trunk | Yes | Yes | Regional | 141 | 0 | 0 |
| Female | 57 | No | Trunk | Yes | No | Regional | 29 | 1 | 1 |
| Female | 29 | No | Trunk | Yes | No | Distant | 73 | 0 | 0 |
| Female | 65 | No | Trunk | Yes | No | Localized | 42 | 0 | 0 |
| Female | 23 | Yes | Trunk | Yes | Yes | Regional | 36 | 0 | 0 |
| Female | 64 | Yes | Trunk | No | Yes | Localized | 35 | 0 | 0 |
| Male | 24 | No | Trunk | Yes | Yes | Regional | 142 | 0 | 0 |
| Female | 66 | No | Trunk | No | No | Regional | 67 | 0 | 0 |
| Male | 55 | No | Trunk | Yes | Yes | Localized | 198 | 0 | 0 |
| Female | 68 | Yes | Trunk | No | Yes | Distant | 13 | 1 | 1 |
| Female | 24 | Yes | Trunk | No | Yes | Regional | 20 | 0 | 0 |
| Female | 22 | No | Trunk | Yes | No | Localized | 24 | 0 | 0 |
| Male | 59 | No | Trunk | No | Yes | Localized | 15 | 0 | 0 |
| Female | 48 | No | Trunk | Yes | No | Regional | 117 | 0 | 0 |
| Female | 17 | No | Trunk | Yes | No | Localized | 137 | 0 | 0 |
| Male | 21 | No | Trunk | Yes | No | Localized | 381 | 0 | 0 |
| Female | 47 | Yes | Trunk | Yes | No | Localized | 49 | 0 | 0 |
| Female | 56 | Yes | Trunk | Yes | No | Distant | 24 | 1 | 1 |
| Female | 13 | Yes | Trunk | Yes | No | Localized | 261 | 0 | 0 |
| Male | 47 | Yes | Trunk | Yes | No | Localized | 18 | 1 | 1 |
| Male | 74 | Yes | Trunk | Yes | No | Regional | 55 | 1 | 1 |
| Male | 42 | No | Trunk | Yes | No | Regional | 62 | 0 | 0 |
| Male | 58 | Yes | Trunk | Yes | No | Localized | 4 | 1 | 1 |
| Male | 24 | No | Trunk | Yes | No | Regional | 62 | 0 | 0 |
| Female | 31 | No | Trunk | Yes | No | Localized | 178 | 0 | 0 |
| Male | 53 | Yes | Trunk | Yes | No | Regional | 93 | 0 | 0 |
| Female | 28 | Yes | Trunk | Yes | No | Localized | 103 | 0 | 0 |
| Female | 32 | Yes | Trunk | No | No | Distant | 32 | 0 | 0 |
| Male | 39 | Yes | Trunk | Yes | No | Regional | 70 | 0 | 0 |
References:

1. Beebe-Dimmer JL, Cetin K, Fryzek JP, et al. The epidemiology of malignant giant cell tumors of bone: An analysis of data from the Surveillance, Epidemiology and End Results Program (1975-2004). Rare Tumors, 2009;1:e52

2. Domovitov SV, Healey JH. Primary malignant giant-cell tumor of bone has high survival rate. Ann Surg Oncol, 2010;17:694-701

3. López-Pousa A, Martín Broto J, Garrido T, Vázquez J. Giant cell tumour of bone: New treatments in development. Clin Transl Oncol, 2015;17:419-30

4. Niu X, Xu H, Inwards CY, et al. Primary bone tumors: Epidemiologic comparison of 9200 patients treated at Beijing J Shui Tan Hospital, Beijing, China, with 10 165 patients at Mayo Clinic, Rochester, Minnesota. Arch Pathol Lab Med, 2015;139:1149-55

5. Raskin KA, Schwab JH, Mankin HJ, et al. Giant cell tumor of bone. J Am Acad Orthop Surg, 2013;21:118-26

6. Amelio JM, Rockberg J, Hernandez RK, et al. Population-based study of giant cell tumor of bone in Sweden (1983-2011). Cancer Epidemiol, 2016;42:82-89

7. Yin H, Cheng M, Li B, et al. Treatment and outcome of malignant giant cell tumor in the spine. J Neurooncol, 2015;124:275-81

8. Gong L, Liu W, Sun X, et al. Histological and clinical characteristics of malignant giant cell tumor of bone. Virchows Arch, 2012,460:327-34

9. Karamanakos PN, Jaaskelainen JE, Alafuzoff I, et al. Malignant giant-cell tumor of bone in the posterior fossa of a neonate. J Neurosurg Pediatr, 2010;5:77-82

10. Sasagawa Y, Tachibana O, Shiraga S, et al. Secondary malignant giant cell tumor of the clivus: Case report. Clin Neurol Neurosurg, 2012;114:786-88

11. Palmieri E, Picci P, Reichardt P, Downey G. Malignancy in giant cell tumor of bone: A review of the literature. Technol Cancer Res Treat, 2019;18:1533033819840000

12. Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumor of bone. Skeletal Radiol, 2003;32:143-46

13. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, 2017. Based on November 2016 SEER data submission, posted to the SEER website, April 2017. https://seer.cancer.gov/csr/1975_2014/

14. Huang Z. Book review. An introduction to statistical learning: With applications in R by Gareth James, Trevor Hastie, Robert Tibshirani, Daniela Witten. J Agric Biol Environ Stat, 2014;19:556-57

15. Leonard J, Gökden M, Kyriakos M, et al. Radiosensitive giant cell tumour of the sphenoid bone. Br J Neurosurg, 2001;15:171-74

16. Ji T, Yang Y, Wang X, et al. Prognostic factors of patients with spinal chordrosarcoma: A retrospective analysis of 98 consecutive patients in a single center. J Neurosurg Oncol, 2014;21:557-78

17. Zhai X, et al. Radiosensitive giant cell tumour of the sphenoid bone. Br J Neurosurg, 2001;15:171-74

18. Feigenberg SJ, Marcus RB JR, Zlotcki RA, et al. Radiation therapy for giant-cell tumors of bone. Clin Orthop Relat Res, 2003;(411):207-16

19. Skubitz KM. Giant cell tumor of bone: Current treatment options. Curr Treat Options Oncol, 2014;15:507-18

20. Lippalaa A, Dijkstra S, Gelderbloom H. Challenges of denosumab in giant cell tumor of bone, and other giant-cell-rich tumors of bone. Clin Opin Oncol, 2019;31:329-35

21. van der Heijden L, Dijkstra PDS, Blay JY, Gelderbloom H. Giant cell tumour of bone in the denosumab era. Eur J Cancer, 2017;77:75-83

22. Lin P, Lin N, Teng W, et al. Recurrence of giant cell tumor of the spine after resection: A report of 10 cases. Orthop Surg, 2018;10:107-14

23. Zhao Y, Tang X, Yan T, et al. Risk factors for the local recurrence of giant cell tumors of the sacrum treated with nerve-sparing surgery. Bone Joint J, 2020;102-B(10):1392-98

24. Li D, Zhang L, Li Y, et al. Surgery methods and soft tissue extension are the potential risk factors of local recurrence in giant cell tumor of bone. World J Surg Oncol, 2016;14:114

25. Luo W, Huang L, Liu H, et al. Customized knee prosthesis in treatment of giant cell tumors of the proximal tibia: Application of 3-dimensional printing technology in surgical design. Med Sci Monit, 2017;23:1691-700

26. Meilcan MC, Zimmerman MC, Dhillon MS, et al. Three-dimensional printing and porous metallic surfaces: A new orthopedic application. J Biomed Mater Res, 2001;55:194-202

27. Ji T, Yang Y, Wang X, et al. Combining of serial embolization and denosumab for large sacropelvic giant cell tumor: Case report of 3 cases. Medicine (Baltimore), 2017;96:e7799

28. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: An open-label, phase 2 study. Lancet Oncol, 2010;11:775-80

29. Freeman JL, Oushy S, Schowinsky J, et al. Invasive giant cell tumor of the lateral skull base: A systematic review, meta-analysis, and case illustration. World Neurosurg, 2016;96:47-57

30. Griffin AM, Ferguson PC, Catton CN, et al. Long-term outcome of the treatment of high-risk tenosynovial giant cell tumor/pigmented villonodular synovitis with radiotherapy and surgery. Cancer, 2012;118:4901-9

31. Yin H, Zhou W, Meng J, et al. Prognostic factors of patients with spinal chordrosarcoma: A retrospective analysis of 98 consecutive patients in a single center. Ann Surg Oncol, 2014;21:3572-78

32. Rao G, Suki D, Chakrabarti I, et al. Surgical management of primary and metastatic sarcoma of the mobile spine. J Neurosurg Spine, 2008;9:120-28

33. Amanatullah DF, Clark TR, Lopez MJ, et al. Giant cell tumor of bone. Orthopedics, 2014;37:112-20

34. Mahadevan A, Miksad R, Goldstein M, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreatic cancer. Int J Radiat Oncol Biol Phys, 2011;81:e615-22

35. Kishima H, Miyao Y, Shimizu K. Radiosensitive giant cell tumour of the sphenoid bone. Br J Neurosurg, 2001;15:171-74

36. Miszczyk L, Wydmański J, Spindel J. Efficacy of radiotherapy for giant cell tumor of bone: Given either postoperatively or as sole treatment. Int J Radiat Oncol Biol Phys, 2001;49:1239-42

37. Skubitz KM. Giant cell tumor of bone: Current treatment options. Curr Treat Options Oncol, 2014;15:507-18

38. Melican MC, Zimmerman MC, Dhillon MS, et al. Three-dimensional printing and porous metallic surfaces: A new orthopedic application. J Biomed Mater Res, 2001;55:194-202

39. Blandino A, Dijkstra S, Gelderbloom H. Challenges of denosumab in giant cell tumor of bone, and other giant-cell-rich tumors of bone. Clin Opin Oncol, 2019;31:329-35

40. van der Heijden L, Ploegstra PDS, Blay JY, Gelderbloom H. Giant cell tumour of bone in the denosumab era. Eur J Cancer, 2017;77:75-83

41. Zhang T, Wan CY, Mei XL, et al. Long non-coding RNA HULC promotes progression of bone neoplasms. Med Sci Monit, 2018;24:5754-60