MEDICAL SCIENCE MONITOR

DATABASE ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2021; 27: e929154
DOI: 10.12659/MSM.929154

Received: 2020.10.12
Accepted: 2020.11.30
Available online: 2020.12.21
Published: 2021.02.17

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

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Source of support: This study was supported in part by the National Natural Science Foundation of China (Grant No. 81702659; 81772856); the National Natural Science Foundation of China, The Joint Fund Cultivation Project (Grant No. U1504822); the Youth Fund of Shanghai Municipal Health Planning Commission (No.2017YQ054); the Henan Medical Science and Technology Research Project (No. 201602031); the Henan Medical Science and Technology Research Plan, the Joint Project of the Ministry and the Province (No. SB201901037); the Henan Provincial Department of Science and Technology, Social Development Project (No. 142102310055)

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

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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 monocytic 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 and commonly used guidelines (Tumor Node Metastasis [TNM] and American Joint Committee on Cancer [AJCC] staging systems) were employed to evaluate the accuracy rate and applicability of the nomograms in clinical work.

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

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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.

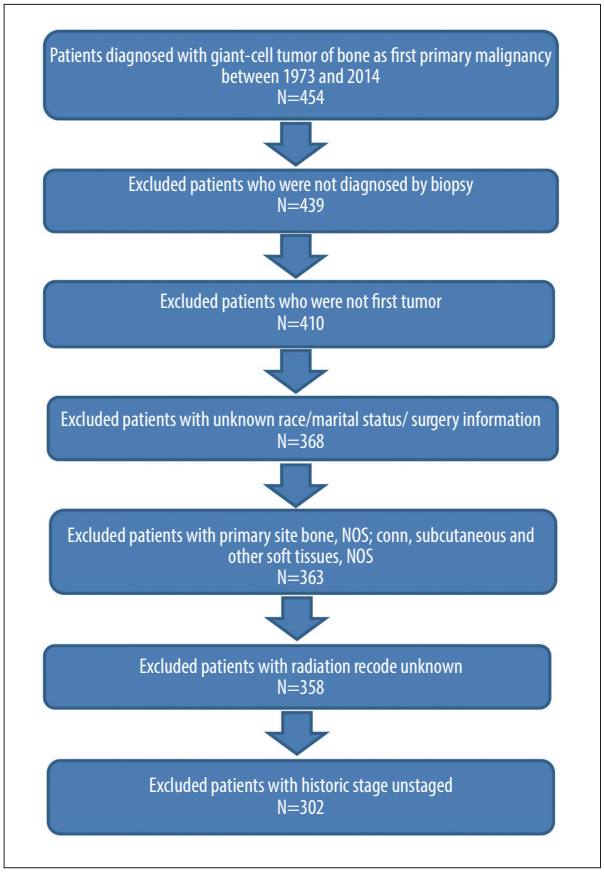

Figure 1. Flow chart showing the patient selection process from the Surveillance, Epidemiology, and End Results database.

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 0.708; *P*=0.005).

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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**. The points further from the 45° line indicated a few inconsistencies between predictions and observations. **Supplementary Table 2** shows the point assignment and prognostic score for each variable in the nomograms.

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**).

Data from the SEER database for patients who received a histological diagnosis of MGCTB in 2016 were used to further validate the model, which included 81 males and 82 females with a median age of 34.0 years (range: 9.0-87.0) and a median

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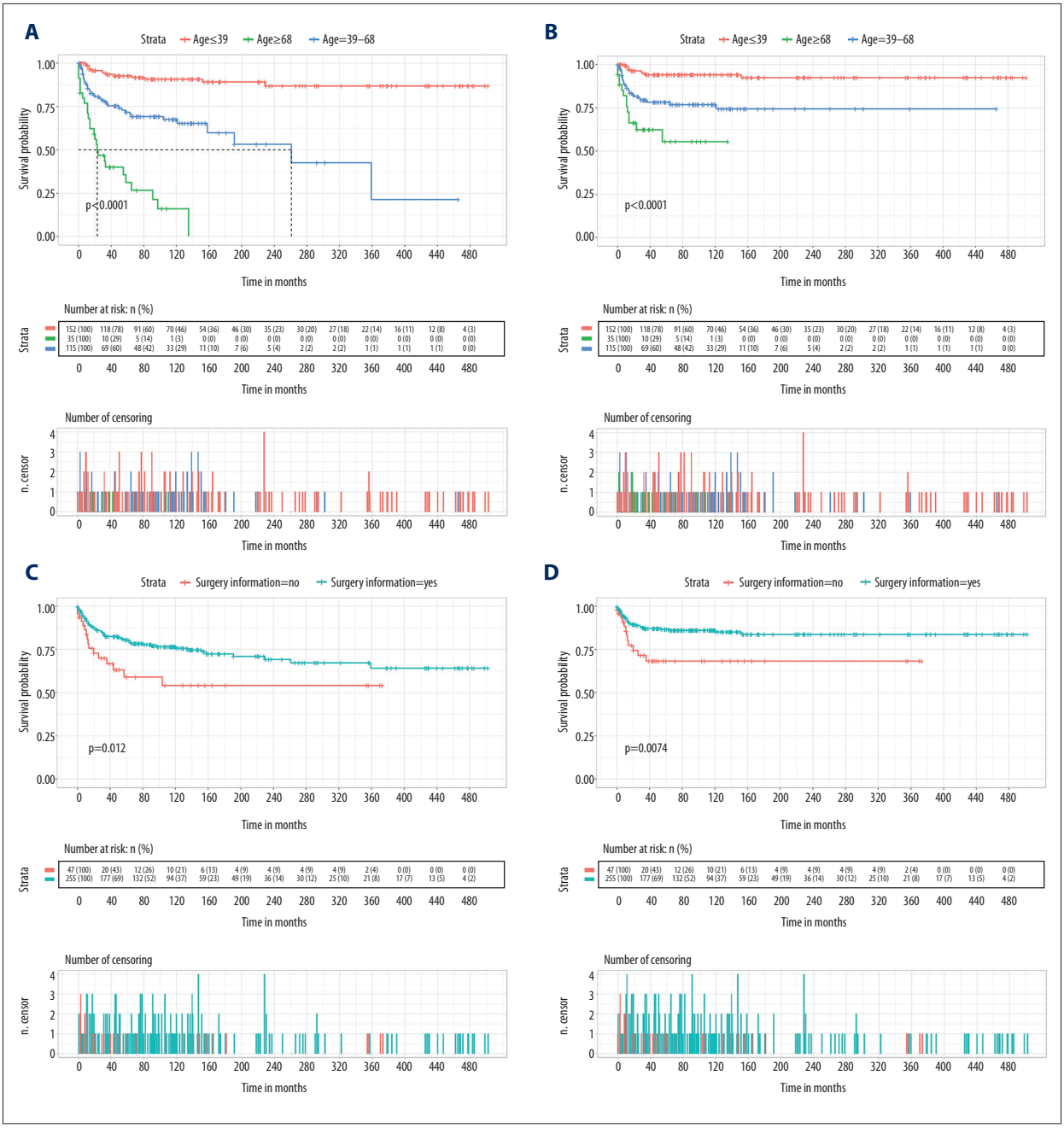

Figure 2. Survival curves of age (**A, B**) and surgery information (**C, D**) for overall survival (OS) and cause-specific survival (CSS).

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 93 males and 108 females, with a median age of 41.0 years (range: 4.0-91.0) and a median survival time of 47.0 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)

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Table 2. Cox proportional hazards regression model for cancer–specific survival and overall survival in patients with malignant giant cell tumor of bone.

Variable	Overall survival (OS)			Cancer Specific Survival (CCS)		
	Hazard Ratio(95% CI)		P	Hazard Ratio(95% CI)		P
Categorical age						
<39	1.000	(reference)		1.000	(reference)	
>68	19.503	(9.131-41.657)	<0.001*	8.592	(3.559-20.475)	<0.001*
39-68	5.022	(2.658-9.490)	<0.001*	3.785	(1.747-8.202)	<0.001*
Surgery information						
No	1.000	(reference)		1.000	(reference)	
Yes	0.681	(0.353-1.314)	0.252	0.890	(0.434-1.824)	0.749
Primary site						
Head face neck	1.000	(reference)				
Limbs	0.313	(0.144-0.682)	0.003*			
Trunk	0.582	(0.249-1.361)	0.212			
Radiation recode						
No	1.000	(reference)				
Yes	0.475	(0.256-0.881)	0.018*			
Chemotherapy recode						
No/unknown	1.000	(reference)		1.000	(reference)	
Yes	2.236	(1.311-3.812)	0.003*	2.619	(1.379-4.974)	<0.001*
Historic stage						
Distant	1.000	(reference)		1.000	(reference)	
Localized	0.308	(0.162-0.586)	<0.001*	0.164	(0.073-0.368)	<0.001*
Regional	0.327	(0.170-0.632)	<0.001*	0.300	(0.142-0.636)	<0.001*

OS – overall survival; CSS cause-specific survival. * P<0.05.

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

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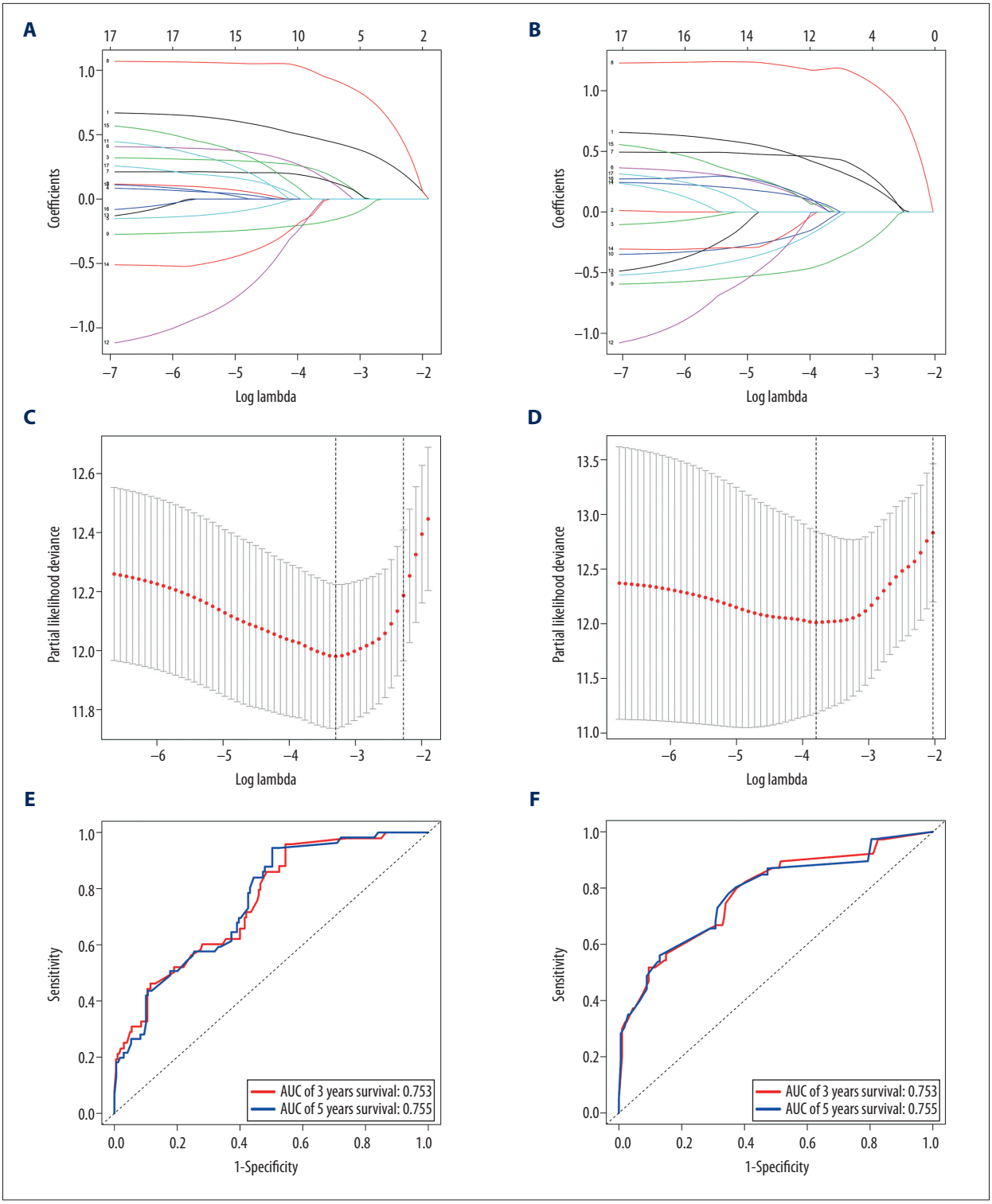

Figure 3. The results of the Lasso regression (**A–D**) and the receiver operating characteristic (ROC) curves (**E, F**). Lasso regression results suggested including 6 variables when overall survival (OS) was the endpoint (**A, B**), and 10 variables when cause-specific survival (CSS) (**C, D**) was the endpoint.

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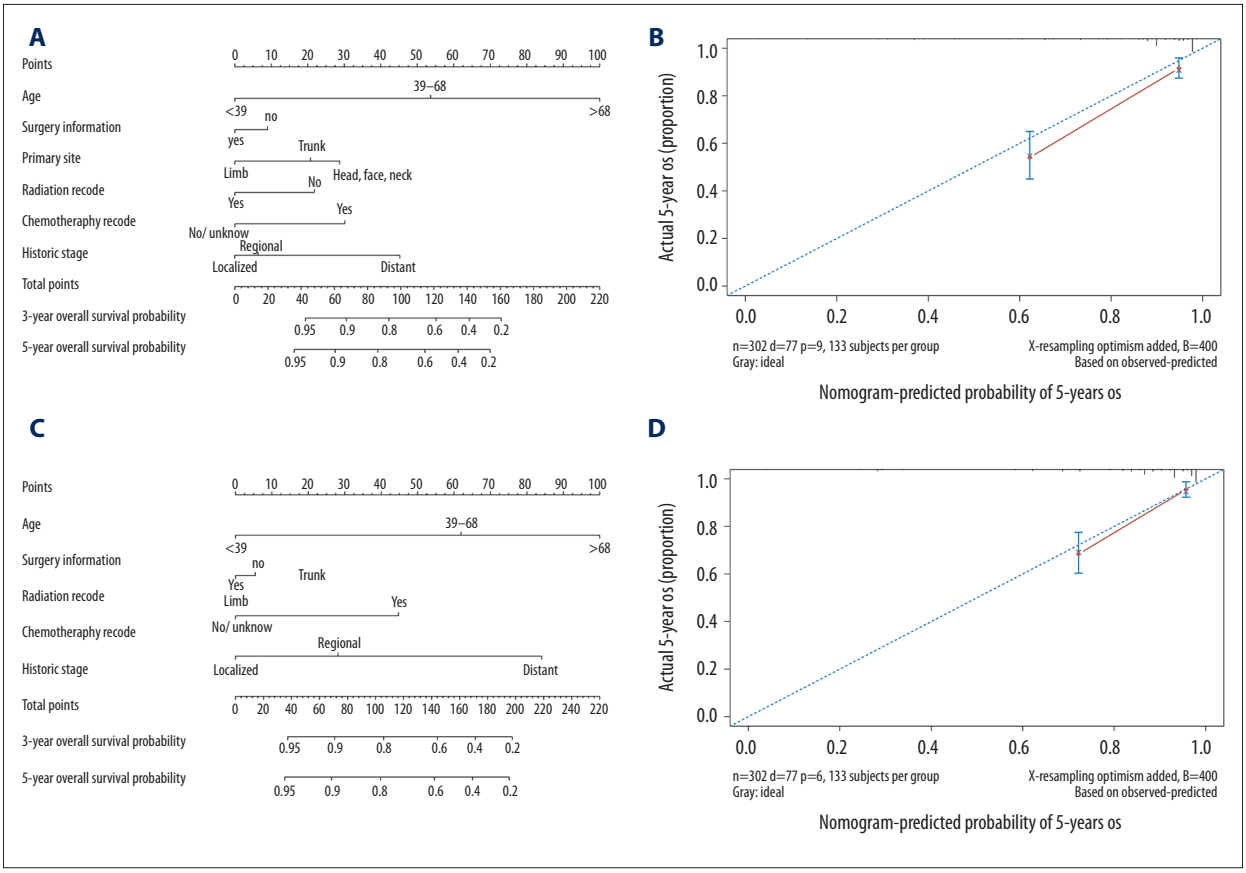

Figure 4. Nomograms (**A, C**) and calibration curves (**B, D**) of overall survival (OS) and cause-specific survival (CSS).

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 shouwn 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].

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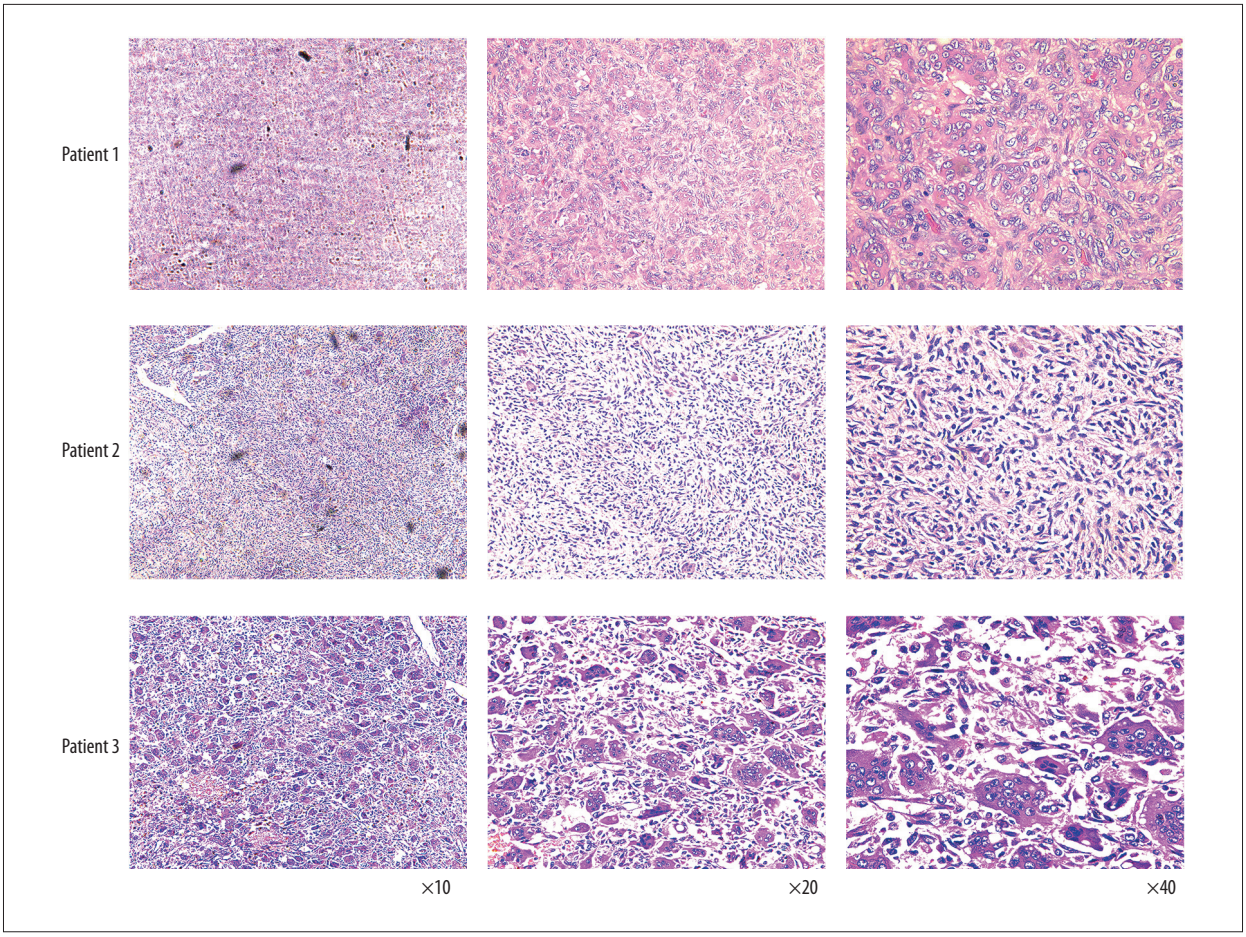

Figure 5. Hematoxylin and eosin (HE) slides and gross specimens of patients in the validation dataset with a histopathological diagnosis of malignant giant cell tumor of bone.

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

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(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 (eg, 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.

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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)		32.00 (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%	21	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%

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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%	38	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

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

Variable	Overall survival (OS)	Cause-specific survival (CCS)
Primary site		
Head, face, neck	39	
Limb	0	
Trunk	21	
Historic stage		
Distant	40	84
Localized	0	0
Regional	2	28
Chemotherapy		
Yes	27	45
None/unknown	0	0
Radiation recode		
No	25	
Yes	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)		Cancer 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)			
Limbs	0.326 (0.150-0.708)	0.005*		
Trunk	0.628 (0.273-1.445)	0.274		
Radiation recode				
No	1.000 (reference)			
Yes	0.504 (0.276-0.920)	0.026*		
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)		1.00 (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; CSS cause-specific survival. * P<0.05.

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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	85
Localized	0	0
Regional	2	28
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	0.155	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.

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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*
Reginal	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.

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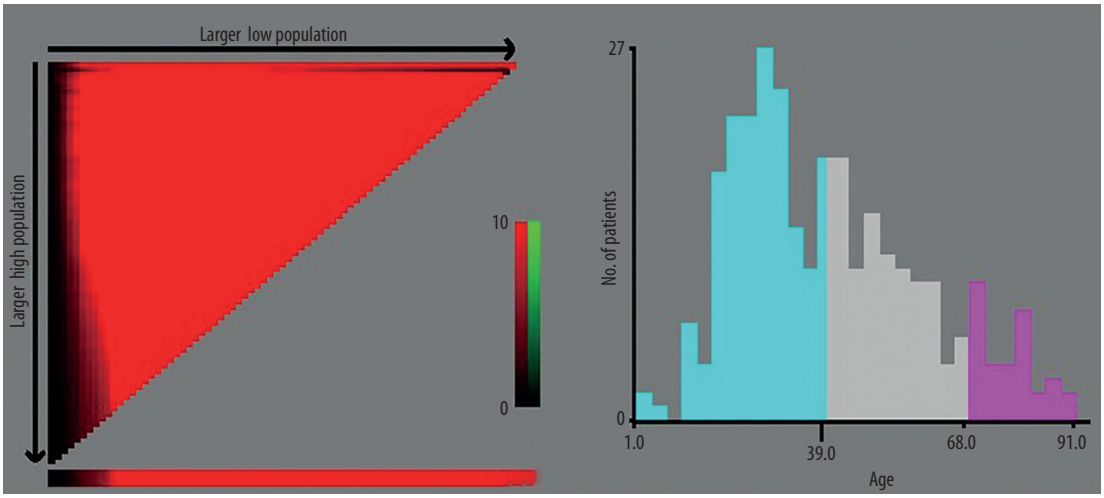
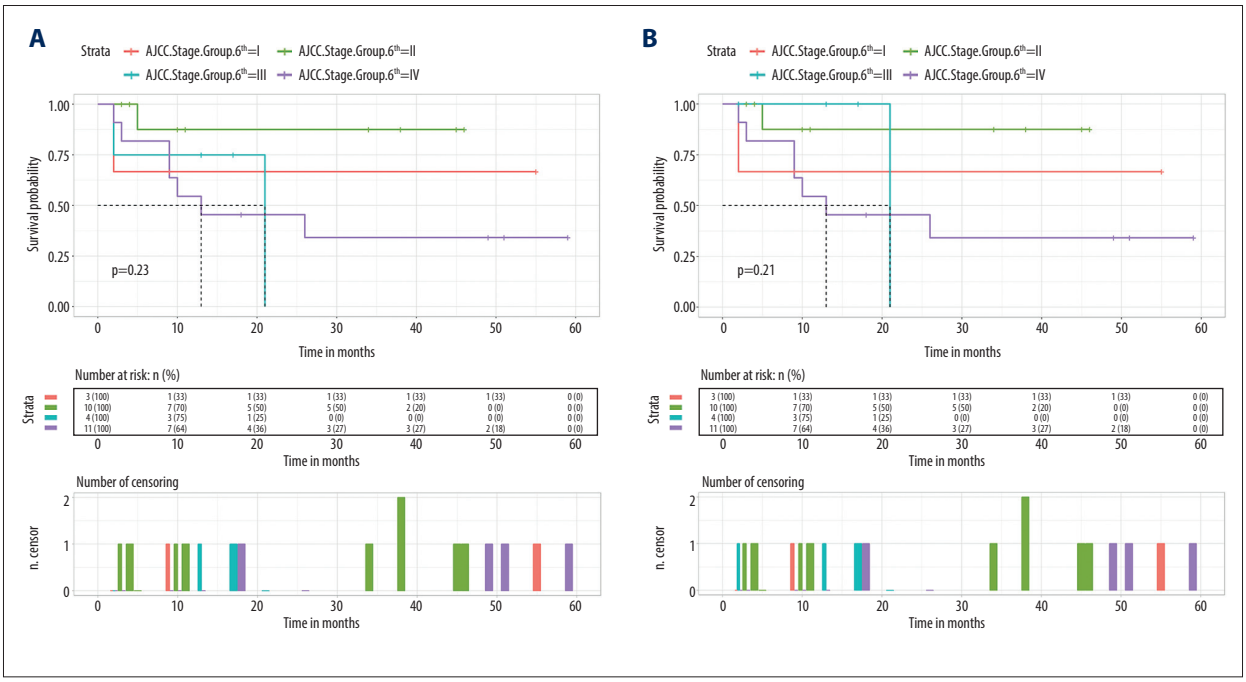
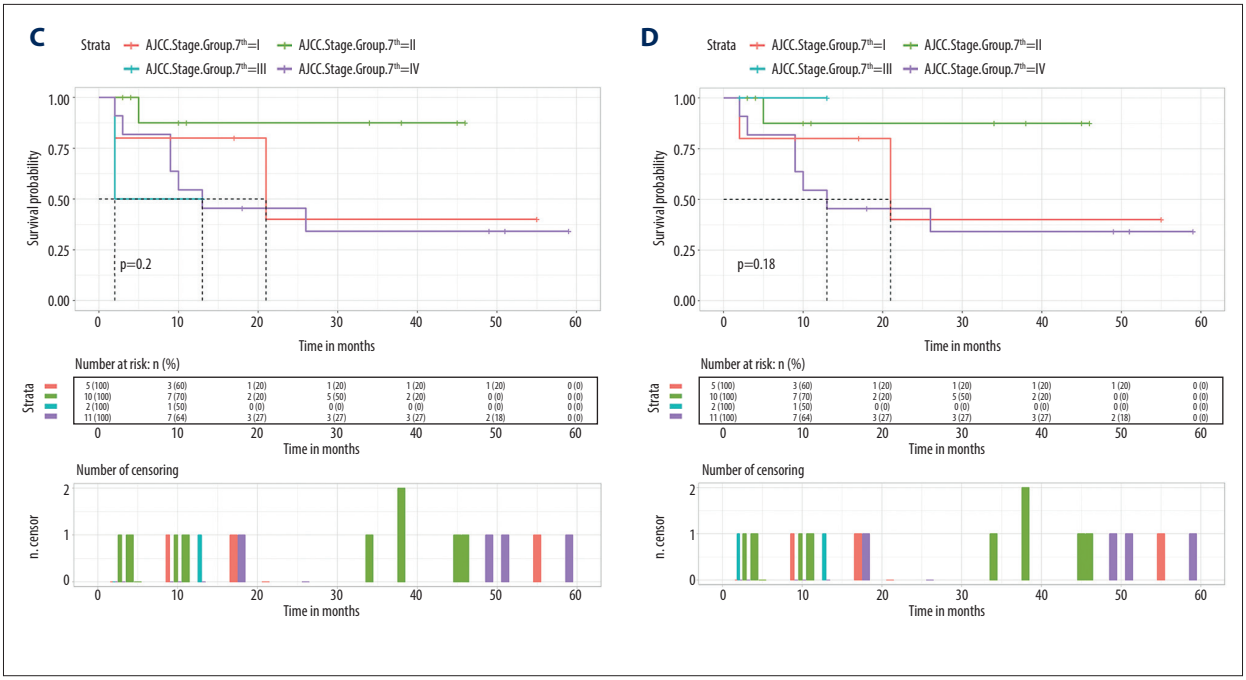


Supplementary Figure 1. The process of screening age cutoff point with X-tile.





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.

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Supplementary Materials C

The raw dataset of the validated set consisted of 37 patients with malignant giant cell tumor of bone.

Sex	Age	Radiation recode	Primary site	Surgery information	Chemotherapy recode	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	Limb	Yes	No/unknown	Regional	37	0	0
Female	43	No	Trunk	Yes	No/unknown	Regional	67	0	0
Female	30	No	Limb	Yes	No/unknown	Localized	51	0	0
Female	29	No	Trunk	Yes	No/unknown	Regional	51	0	0
Female	58	No	Trunk	Yes	Yes	Regional	50	0	0
Male	31	No	Limb	Yes	No/unknown	Regional	45	0	0
Male	28	No	Limb	Yes	No/unknown	Localized	43	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	Limb	Yes	No/unknown	Regional	33	0	0
Female	25	No	Trunk	Yes	No/unknown	Regional	30	0	0
Female	44	No	Limb	Yes	No/unknown	Localized	28	0	0
Female	67	No	Limb	Yes	No/unknown	Localized	27	0	0
Female	65	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	33	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	5	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

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Supplementary Materials D

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	Localized	346	0	0
Female	23	No	Limb	Yes	No	Regional	302	0	0
Female	32	No	Limb	Yes	No	Localized	98	0	0
Female	25	Yes	Limb	Yes	No	Localized	490	0	0
Female	25	No	Limb	No	No	Regional	416	0	0
Female	31	No	Limb	No	No	Localized	378	0	0
Male	36	No	Limb	Yes	No	Regional	242	0	0
Female	57	Yes	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	Yes	Regional	9	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	26	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

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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
Female	32	*No*	Limb	No	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	No	No	Distant	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	Regional	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	Regional	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	Regional	471	0	0
Male	42	*No*	Limb	Yes	No	Distant	316	0	0
Male	25	*No*	Limb	Yes	No	Regional	244	0	0
Male	80	*No*	Limb	Yes	No	Localized	97	1	0
Female	23	*No*	Limb	Yes	No	Localized	314	0	0
Female	37	*Yes*	Limb	Yes	No	Regional	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

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Sex	Age	Radiation recode	Primary site	Surgery	Chemotherapy recode	Historic stage	Survival month	Overall survival	Cause-specific survival
Male	44	*No*	Limb	Yes	Yes	Distant	7	1	1
Male	65	*No*	Limb	No	No	Localized	140	1	1
Female	18	*No*	Limb	Yes	No	Regional	264	0	0
Male	34	*No*	Limb	Yes	No	Regional	285	0	0
Female	12	*No*	Limb	No	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	24	*No*	Limb	Yes	No	Localized	75	0	0
Male	48	*Yes*	Limb	Yes	No	Regional	196	0	0
Male	56	*No*	Limb	Yes	No	Regional	106	1	0
Female	19	*No*	Limb	Yes	No	Localized	164	0	0
Female	49	*No*	Limb	Yes	No	Regional	163	0	0
Male	43	*No*	Limb	Yes	No	Regional	53	1	0
Female	24	*No*	Limb	Yes	No	Localized	71	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	Regional	5	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	Localized	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	30	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	Regional	456	0	0
Male	28	*Yes*	Trunk	No	No	Regional	11	0	0
Male	60	*Yes*	Trunk	No	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

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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	89	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	139	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	60	*No*	Trunk	Yes	No	Regional	6	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	143	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	43	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	No	Localized	198	0	0
Male	68	*Yes*	Trunk	No	Yes	Distant	13	1	1
Male	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
Female	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

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