Survival and prognostic factors analyses in malignant giant cell tumor of bone

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Abstract

Background: The characteristics and survival in patients with malignant giant tumor cancer of bone (GCTB) have not been investigated thoroughly due to the limited population. We evaluated the issues based on a large cohort in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. Methods: Patients who were diagnosed with malignant GCTB from 1975 to 2016 were extracted from the SEER database. The overall survival (OS) was calculated by Kaplan–Meier analysis and the inter-group difference was tested by log-rank test. Univariate and multivariate Cox proportional hazard regression were conducted to identify the independent survival factors. Results: A total of 325 patients with malignant GCTB were included. The overall 1-, 5-, and 10-year survival rates were 94.3% (95% CI: 91.7-96.8), 82.3% (95% CI: 77.9-86.6), and 80.1% (95% CI: 75.4-84.7), respectively. In the univariate analysis, age older than 34 years, grade IV, T2/3 stage, M1, distant and surgery of the primary site were independent factors for worse survival. Multivariate Cox regression showed the poor survival in patients with age older than 34 years (hazard ratio (HR) =3.65, 95% CI: 2.04-6.56, P <0.001), T2 stage (HR=4.85, 95% CI: 1.52-15.47, P =0.008), and distant tumor (HR=2.93, 95% CI: 1.24-6.88, P =0.014), and the extra-skeletal sites (HR=8.84, 95% CI: 2.89-27.07, P <0.001), respectively. Conclusions: This large population-based series described the clinical characteristics of the malignant GCTB. Age >34 years, T2, distant stage and extra-skeletal sites were associated with worse survival in the patients with malignant GCTB.

Background

Giant cell tumors of bone (GCTB) are rare. It was reported that GCTB accounted for approximately 5% to 6% of primary bone tumors [1]. The annual incidence was reported to be 1.7 (1.4-1.9) per million [2]. Metaphysis of long bones were the major affected sites and many studies were conducted to investigate both the clinical characteristics [3,4] and treatments [5].

Most of the GCTB were thought to be pathologically benign cases. Some tumors showed aggressive features such as cortical and subchondral involvement, reactive bony zone infiltration, and soft tissue mass [6,7]. Recently, a study including four large series identified 92 cases with malignant GCTB in 2,315 patients, the incidence was from 1.1% to 11.3% and the cumulative incidence was 4.0% [8]. It's important to perform survival prediction for the arrangement of individual treatment. But the issues were not intensively studied due to the lack of long-term follow-up clinical data [9]. Itkin and his colleagues retrospectively retrieved the data of 242 patients from 26 studies with a median follow-up of 6.9 years [10]. They reported an estimated overall survival rate of 86.9%. Few studies investigated the prognostic factors of patients with malignant GCTB.

The Surveillance, Epidemiology, and End Results (SEER) database is one of the largest cancer databases in USA. Based on this database, a previous study estimated the survival among 117 malignant GCTB from 1975 to 2004. The prognostic factors for poor survival included older patients and the distant metastasis at diagnosis [11].

This database has been extended and some new factors were added including the TNM stages, new version of AJCC grade, insurance status, and records of some specific metastatic organs. Update of the new data should be re-evaluated to provide further understanding on the malignant GCTB. In the present study, based on the updated data from the database, we attempted to evaluate the survival of patients with malignant GCTB and to identify the prognostic factors.

Patients And Methods

Data Source

The SEER database was used to extract information of patients with malignant GCTB by the SEER*Stat Software version 8.3.5 (https://seer.cancer.gov/seerstat/) (Information Management Service, Inc. Calverton, MD, USA). According to the ICD-O-3/WHO2008, patients who were diagnosed as malignant GCTB (Code: 9250/3: giant cell tumor of bone, malignant) between 1975 and 2016 were collected. Patients were excluded if they were diagnosed at autopsy or via death certificate. The malignant GCTB located in extra-skeletal sites such as kidney, lung, pancreas and thyroid were excluded.

Statistical analysis

According to the records and distribution of patients in the SEER database, all the patient-related variables were selected as following: age (<34 or ≥34 years, the cutoff was set according to the distribution of age); gender (male and female); marital status (unmarried or married); race (white, black, Indian/Alaska Native (IA) and Asian or Pacific Islander (API)); primary site (long bones of lower limb with associated joints, long bones of upper limb with scapula and associated joints, pelvis and spine, irregular bone and other site out of bone); tumor grade (I, II, III, or IV); T stage (T1, T2, T3); N stage (N0 and N1); M stage (M0 and M1); SEER historic stage (localized, regional, and distant); years interval of diagnosis (1975-1984, 1985-1994, 1995-2004, and 2005-2016); and the surgical treatments of primary site (none or yes). The patients without clear records were classified as the unknown group for the corresponding parameter.

Continuous data was described as mean ± standard deviation. Differences between groups were analyzed with univariate analysis. Categorical data was presented as the number and percentage, and the difference was evaluated by Pearson chi-square test. The 1-, 5-, and 10-year overall survival (OS) were calculated by the Kaplan–Meier method and the log-rank test was used to evaluate the difference. The variables that have p value <0.05 in the univariable Cox regression and the ones that have significant effect on the prognosis in the biologically-based theoretical were incorporated into the multivariable model. To evaluate the influence of the extra-skeletal sites on survival, a sensitivity analysis was performed by including or excluding these cases. All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY, USA) and MedCalc 15.2.2. Two-sided P-values <0.05 were considered statistically significant.

Results

Patient characteristics

The selection process of the patients is illustrated in Figure 1. According to the inclusion criteria, 334 patients with malignant GCTB were initially selected from 1975 to 2016. After excluding one case which was diagnosed via death certificate and eight patients with extra-skeletal GCTB, 325 patients were finally included. Table 1 showed the detail clinicopathological features of the patients. The median age of the patients was 34 years and a female predomination (52.3%) was observed. More tumors located in the long bones and associated joints (64.6%), especially in the lower limb (48.6%). More than 50% of patients had no clear records in tumor grade, T stage, N stage and M stage. Twenty-two patients showed distant metastasis including lung metastasis (10/22, 45.45%), bone metastasis (5/22, 22.73%) and the other metastasis (7/22, 31.82%). As to SEER historic stage, localized and regional stages were the main types occupying 61.2% of all the patients while 13.5% of patients were at distant stage. Surgery was performed on 53.85% of all the patients.

Eight patients were diagnosed with extra-skeletal GCTB. They were recorded from 1987 to 2016 and five cases were female patients. Two of the patients were diagnosed around 20 years old, while the others were older than 50 years. As to the primary site, three cases were found in pancreas, one in kidney, one in thyroid, one in mediastinum, one in lung and one subcutaneous case. There was not clear record of tumor grade in four patients, one at grade I, two at grade III and one at grade IV. Two patients had long survival (135 and 136 months), one died at 24 months after diagnosis, and five patients died within 7 months.

Survival analysis and prognostic factors identification

The overall survival of the entire cohort is illustrated in Figure 2. The overall 1-, 5-, and 10-year survival rates were 94.3% (95% CI: 91.7-96.8), 82.3% (95% CI: 77.9-86.6), and 80.1% (95% CI: 75.4-84.7), respectively. Detail OS for patients with malignant GCTB originated from bone in each characteristic is summarized in Table 2.

The results of univariate and multivariate Cox hazard regression are summarized in Table 3. Lower OS was noticed in age older than 34 years (P<0.001), grade IV (P=0.041), T2/3 (P<0.001), unknown N stage (P=0.019), M1 stage (P<0.001), the SEER historic distant stage and surgery of the primary (P=0.05) under univariate analysis. Multivariate Cox regression showed the poor survival in patients with age older than 34 years (hazard ratio (HR) =3.65, 95% CI: 2.04-6.56, P<0.001), T2 stage (HR=4.85, 95% CI: 1.52-15.47, P=0.008), and distant tumor (HR=2.93, 95% CI: 1.24-6.88, P=0.014), respectively. The sensitivity analysis suggested that the primary malignant GCTB located in the extra-skeletal sites was associated with poor survival (HR=8.84, 95% CI: 2.89-27.07, P<0.001). Analysis including the extra-skeletal cases did not significantly affect the results (supplementary table).

Discussion

In the present study, with the large cohort of malignant GCTB, the 5- year OS was 82.3% (95% CI: 77.9-86.6). This rate was consistent with the reported rate of 86.9% by Itkin et al[10] and 80% by Domovitov et al[12]. The prognostic factors were revealed, and poor survival was correlated with the following factors including age older than 34 years, higher T stage, distant tumor and the extra-skeletal sites.

Similar with the survival trend from previous SEER cohort analysis [11], in the present study, poor survival can be found in older patients and those with SEER historic distant stage. The records of metastatic sites were added in SEER dataset since 2010. Compared with the 5-year OS of 81.3% for patients without metastasis, it significantly decreased to 53.9 % for those with metastasis. Previous studies reported that the incidence of lung metastasis in benign giant cell tumor was around 3.5% [13,14] while approximately 8% in the malignant cases [15,16]. In our study, 14 out of 89 cases extracted from 2010 to 2016 were recorded as M1 status and lung was the major metastatic site (10 out of 89, 11.2%). The higher incidence of lung metastasis may be caused by regular screening. More lung metastases were reported to develop in the early time after initial diagnosis of GCTB and after recurrence [16,17]. Screening of possible metastasis should be especially performed at these situations.

The classification of TNM was added in the SEER database since 2004 and the results showed a trend of poor survival in higher T stage or higher N stage. The multivariate Cox regression suggested that higher T stage was one of the prognostic factors. Tumor size as the independent risk factor for lung metastasis was previously found [18]. Based on the Campanacci classification, which has been widely accepted in evaluating giant cell tumor, grade III represented the aggressive type. A series of studies reported Campanacci grade III as the risk factor for tumor recurrence [19,20] and lung metastasis [21,22]. The recurrence was also reported to be a risk factor for resulting in metastasis [21,22]. Therefore, T stage and/or Campanacci classification played important role in evaluating the survival of patients with giant cell tumor.

To our knowledge, it was the first time to study the extra-skeletal malignant GCTB. Based on our results, the extra-skeletal site was associated with the poor survival. Only two patients lived longer than 11 years while five patients died less than seven months. Therefore, attention should be paid on the patients with the lesion in the extra-skeletal site. Limited by few available cases, further analysis on revealing potential prognostic factors in such population cannot be conducted. More cases from multiple centers will be needed.

To overcome giant cell tumor, either resection with reconstruction or intralesional curettage has been widely accepted [23-25]. The surgery with/without radiotherapy did not significantly improve the survival in the previous SEER study [11]. Similarly, the surgery was not an independent survival factor of the patients with malignant GCTB in the present study. The effect of surgery on the survival of malignant GCTB was different from other malignant cancers such as colorectal cancer [26] and ovarian cancer[27]. The difference may be caused by significantly higher survival in the giant cell tumor than other malignant cancers.

Undoubtedly, there are some limitations in the present study. More than 50% of patients had no clear records in tumor grade, T stage, N stage and M stage. More clear data was needed to further reveal the effect of AJCC grade and TNM stage on survival. Limited by the absent records of surgery in the SEER database, further analysis of the correlation between surgery and recurrence or metastasis cannot be performed. The results of the present study need further external validation.

Conclusions

In conclusion, based on the large population from the SEER database, the clinical characteristics and prognostic factors among the patients with malignant GCTB were analyzed. Age >34 years, T2, distant stage and extra-skeletal sites were associated with worse survival in the patients with malignant GCTB.

Abbreviations

GCTB: giant cell tumor of bone; SEER: Surveillance, Epidemiology, and End Results database; AJCC: American Joint Committee on Cancer; OS: overall survival; HR: hazard ratio; CI: confidence interval.

Declarations

Acknowledgements

Not Applicable

Authors' contributions

JZ, MM and CZ made contributions to the conception of this study. GX, HW and JD made contributed to acquisition of data and interpretation of results. XW and FL performed statistical analysis. FL, HW and JD prepared the tables and figures. JZ and MM mainly prepared the manuscript. GX and CZ reviewed and reedited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are derived from the Surveillance, Epidemiology, and End Results (SEER) database in USA.

Ethics approval and consent to participate

The patients' consent for the data in the public SEER database was not required due to the data because cancer is a reportable disease in every state of the United States. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Conflict of interest

All the authors report no conflicts of interest in this work.

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Tables

Table 1. Description of the patients with malignant giant cell tumor of bone.

Subject characteristics	Number	Present (%)
Sex		
Male	155	47.69
Female	170	52.31
Age		
<34	159	48.92
≥34	166	51.08
Marital status		
Unmarried	136	41.85
Married	162	49.85
Unknown	27	8.31
Insurance recode		
Uninsured	113	34.77
Insured	8	2.46
Unknown	204	62.77
Race		
White	241	74.15
Black	41	12.62
AI	8	2.46
API	28	8.62
Unknown	7	2.15
Year of diagnosis		
1975-1984	31	9.54
1985-1994	42	12.92

1995-2004	90	27.69
2005-2016	162	49.85
Primary site		
Long bones of lower limb and associated joints	158	48.62
Long bones of upper limb and associated joints	52	16.00
Pelvis and spine	59	18.15
Irregular bone, short bone, and flat bone	47	14.46
Unknown	9	2.77
Grade		
Grade I	9	2.77
Grade II	18	5.54
Grade III	12	3.69
Grade IV	31	9.54
Unknown	255	78.46
T stage 2004+		
T1	61	18.77
T2	41	12.62
T3	4	1.23
Unknown	219	67.38
N stage 2004+		
N0	149	45.85
N1	1	0.31
Unknown	175	53.85

M stage 2004+		
M0	142	43.69
M1	22	6.77
Unknown	161	49.54
SEER historic stage		
Localized	111	34.15
Regional	88	27.08
Distant	44	13.54
Unknown	82	25.23
Surg (prim) 1998+		
None	59	18.15
Yes	175	53.85
Unknown	91	28.00

Note: IA: Indian/Alaska Native; API: Asian or Pacific Islander

Table 2. The overall survival (OS) in patients with malignant giant cell tumor of bone diagnosed between 1975 and 2016.

Factors	1-year OS, % (95% CI)	5-year OS, % (95% CI)	10-year OS, % (95% CI)	*P value*
Sex				0.397
Male	95.4 (92.0-98.7)	83.1 (76.7-89.3)	79.2 (72.1-86.2)	
Female	93.3 (89.5-97.0)	81.6 (75.5-87.5)	80.8 (74.6-86.9)	
Age				< 0.001
<34	98.7 (96.9-100.0)	92.4 (88.1-96.6)	NA	
≥34	89.9 (85.2-94.5)	72.4 (65.1-79.5)	67.9 (60.1-75.6)	
Marital status				0.307
Unmarried	92.2 (87.6-96.8)	79.5 (72.3-86.5)	75.5 (67.7-83.2)	
Married	95.6 (92.4-98.7)	82.9 (76.7-88.9)	NA	
Unknown	96.2 (88.8-100.0)		87.0 (73.1-100.0)	
Insurance recode				0.251
Uninsured	92.5 (87.5-97.4)	76.7 (67.7-85.5)	74.0 (63.9-83.9)	
Insured		NA	NA	
Unknown	95.0 (92.0-97.9)	84.7 (79.7-89.6)	82.6 (77.3-87.8)	
Race				0.560
White	93.5 (90.3-96.6)	82.5 (77.4-87.5)	80.1 (74.6-85.5)	
Black	97.5 (92.7-100.0)	81.9 (69.7-93.8)	NA	
AI		75.0 (45.0-100.0)	NA	
API	89.0 (77.2-100.0)	80.3 (64.7-95.6)	73.0 (53.4-92.2)	

Unknown				
Year of diagnosis				0.124
1975-1984	90.3 (79.9-100.0)	87.1 (75.3-98.7)	NA	
1985-1994	97.4 (92.4-100.0)	92.3 (83.9-100.0)	87.2 (76.7-97.5)	
1995-2004	94.4 (89.6-99.1)	85.1 (77.6-92.4)	82.7 (74.7-90.5)	
2005-2016	93.5 (89.6-97.3)	76.3 (69.0-83.5)	74.9 (67.2-82.4)	
Primary site				0.333
Long bones of lower limb and associated joints	94.7 (91.1-98.2)	84.0 (78.0-89.9)	81.3 (74.7-87.7)	
Long bones of upper limb and associated joints	98.0 (94.0-100.0)	86.9 (77.1-96.5)	84.3 (73.5-94.8)	
Pelvis and spine	94.8 (89.1-100.0)	74.9 (62.9-86.6)	NA	
Irregular, short, and flat bone	91.2 (82.9-99.3)	83.9 (72.9-94.7)	81.0 (69.0-92.7)	
Unknown	77.8 (50.6-100.0)	64.8 (32.5-96.5)	NA	
Grade				< 0.001
Grade I		NA	NA	
Grade II	94.4 (83.8-100.0)	81.9 (63.2-100.0)	NA	
Grade III	91.7 (76.1-100.0)	60.0 (27.3-92.1)	40.0 (1.2-78.0)	
Grade IV	71.8 (55.0-	53.8 (34.0-	47.1 (25.9-	

	88.3)	73.2)	67.8)	
Unknown	96.7 (94.5-98.9)	86.1 (81.6-90.5)	84.4 (79.6-89.1)	
T stage 2004+				< 0.001
T1	96.7 (92.2-100.0)	92.8 (86.0-99.5)	NA	
T2	84.4 (72.9-95.7)	47.0 (26.2-67.4)	NA	
T3		25.0 (-17.5-66.7)	NA	
Unknown	95.3 (92.5-98.1)	85.5 (80.7-90.2)	82.8 (77.6-87.9)	
N stage 2004+				0.050
N0	93.7 (89.7-97.6)	76.2 (68.6-83.6)	74.8 (66.8-82.6)	
N1	NA	NA	NA	
Unknown	94.7 (91.3-98.0)	86.8 (81.6-91.8)	84.2 (78.6-89.7)	
M stage 2004+				< 0.001
M0	97.2 (94.5-99.9)	81.3 (74.1-88.3)	79.8 (72.2-87.3)	
M1	75.4 (56.6-93.8)	53.9 (31.6-75.8)	NA	
Unknown	94.3 (90.7-97.9)	86.5 (81.1-91.8)	83.8 (78.0-89.5)	
SEER historic stage				< 0.001

Localized	97.3 (94.3-100.0)	87.4 (81.0-93.7)	86.1 (79.2-92.8)	
Regional	94.2 (89.3-99.0)	80.0 (71.1-88.7)	78.1 (68.7-87.3)	
Distant	84.0 (73.1-94.6)	65.2 (50.9-79.2)	59.4 (44.3-74.2)	
Unknown	96.0 (91.5-100.0)	87.9 (80.0-95.6)	86.2 (77.8-94.5)	
Surg (prim) 1998+				0.024
None	90.9 (83.3-98.3)	70.3 (56.9-83.4)	67.0 (52.7-81.0)	
Yes	94.7 (91.3-98.0)	82.3 (76.3-88.2)	80.2 (73.7-86.6)	
Unknown	95.5 (91.2-99.7)	88.7 (82.1-95.2)	86.4 (79.2-93.4)	

Abbreviations: OS=overall survival; CI=Confidence Interval; Surg (prim) – surgical treatment of primary site; NA=Not available.

Table 3. Univariate and multivariate Cox regression analyzing the prognostic factors for survival of patients with malignant giant cell tumor of bone (1975 and 2016).

Subject characteristics	Univariate		Multivariate	
	HR (95%CI)	*P-value*	HR (95%CI)	*P-value*
Sex				
Male	1.00(Reference)		1.00(Reference)	
Female	0.82 (0.51-1.31)	0.399	0.90 (0.53--1.52)	0.690
Age				
<34	1.00(Reference)		1.00(Reference)	
≥34	4.28 (2.44-7.51)	<0.001	3.65 (2.04--6.56)	<0.001
Marital status				
Unmarried	1.00(Reference)		NA	NA
Married	0.68 (0.41-1.12)	0.127	NA	NA
Unknown	0.84 (0.37-1.90)	0.669	NA	NA
Insurance recode				
Uninsured	1.00(Reference)			
Insured	0.74 (0.10-5.47)	0.765	NA	NA
Unknown	0.63 (0.37-1.09)	0.100	NA	NA
Race				
White	1.00(Reference)			
Black	0.96 (0.47-1.94)	0.902	NA	NA
AI	1.07 (0.26-4.42)	0.920	NA	NA
API	1.54 (0.73-3.24)	0.258	NA	NA
Unknown				
Year of diagnosis				
1975-1984	1.00(Reference)		1.00(Reference)	
1985-1994	1.09 (0.42-2.79)	0.864	1.12 (0.40--3.14)	0.828
1995-2004	1.56 (0.63-3.89)	0.341	2.36 (0.66--8.47)	0.186
2005-2016	2.37 (0.97-5.81)	0.059	2.81 (0.49--16.09)	0.247
Primary site				
Long bones of lower limb and associated joints	1.00(Reference)		1.00(Reference)	
Long bones of upper limb and associated joints	0.67 (0.31-1.46)	0.317	0.64 (0.28--1.46)	0.288
Pelvis and spine	1.42 (0.77-2.62)	0.263	0.91 (0.45--1.82)	0.787
Irregular bone, short bone, and flat bone	1.25 (0.63-2.47)	0.529	1.16 (0.55--2.42)	0.700
Unknown	2.02 (0.62-6.59)	0.245	1.59 (0.40--6.38)	0.512
Grade				
Grade I	1.00(Reference)		1.00(Reference)	
Grade II	2.14 (0.25-18.45)	0.488	2.42 (0.25--23.58)	0.447
Grade III	5.47 (0.64-47.04)	0.121	5.42 (0.56--52.21)	0.144
Grade IV	8.37 (1.09-64.19)	0.041	5.59 (0.67--46.95)	0.113
Unknown	1.70 (0.23-12.38)	0.599	1.58 (0.20--12.31)	0.660
T stage				
T1	1.00(Reference)		1.00(Reference)	
T2	8.10 (2.68-24.48)	<0.001	4.85 (1.52--15.47)	0.008
T3	16.07 (3.55-72.68)	<0.001	2.64 (0.44--15.67)	0.285
Unknown	2.12 (0.76-5.97)	0.153	2.73 (0.77--9.61)	0.118

N stage				
N0	1.00(Reference)		1.00(Reference)	
N1	NA	NA	NA	NA
Unknown	0.53 (0.32-0.90)	0.019	0.39 (0.05--2.93)	0.360
M stage				
M0	1.00(Reference)		1.00(Reference)	
M1	3.86 (1.83-8.11)	<0.001	1.16 (0.43--3.13)	0.770
Unknown	0.77 (0.44-1.36)	0.374	1.69 (0.20--14.31)	0.632
SEER historic stage				
Localized	1.00(Reference)		1.00(Reference)	
Regional	1.52 (0.79-2.93)	0.209	1.20 (0.58--2.48)	0.614
Distant	3.97 (2.08-7.60)	<0.001	2.93 (1.24--6.88)	0.014
Unknown	1.19 (0.58-2.41)	0.635	1.29 (0.59--2.83)	0.531
Surg (prim)				
None	1.00(Reference)		1.00(Reference)	
Yes	0.55 (0.30-1.00)	0.050	0.62 (0.32--1.23)	0.174
Unknown	0.39 (0.19-0.79)	0.009	1.63 (0.50--5.31)	0.414

Abbreviations: Met=Metastases.

Figures

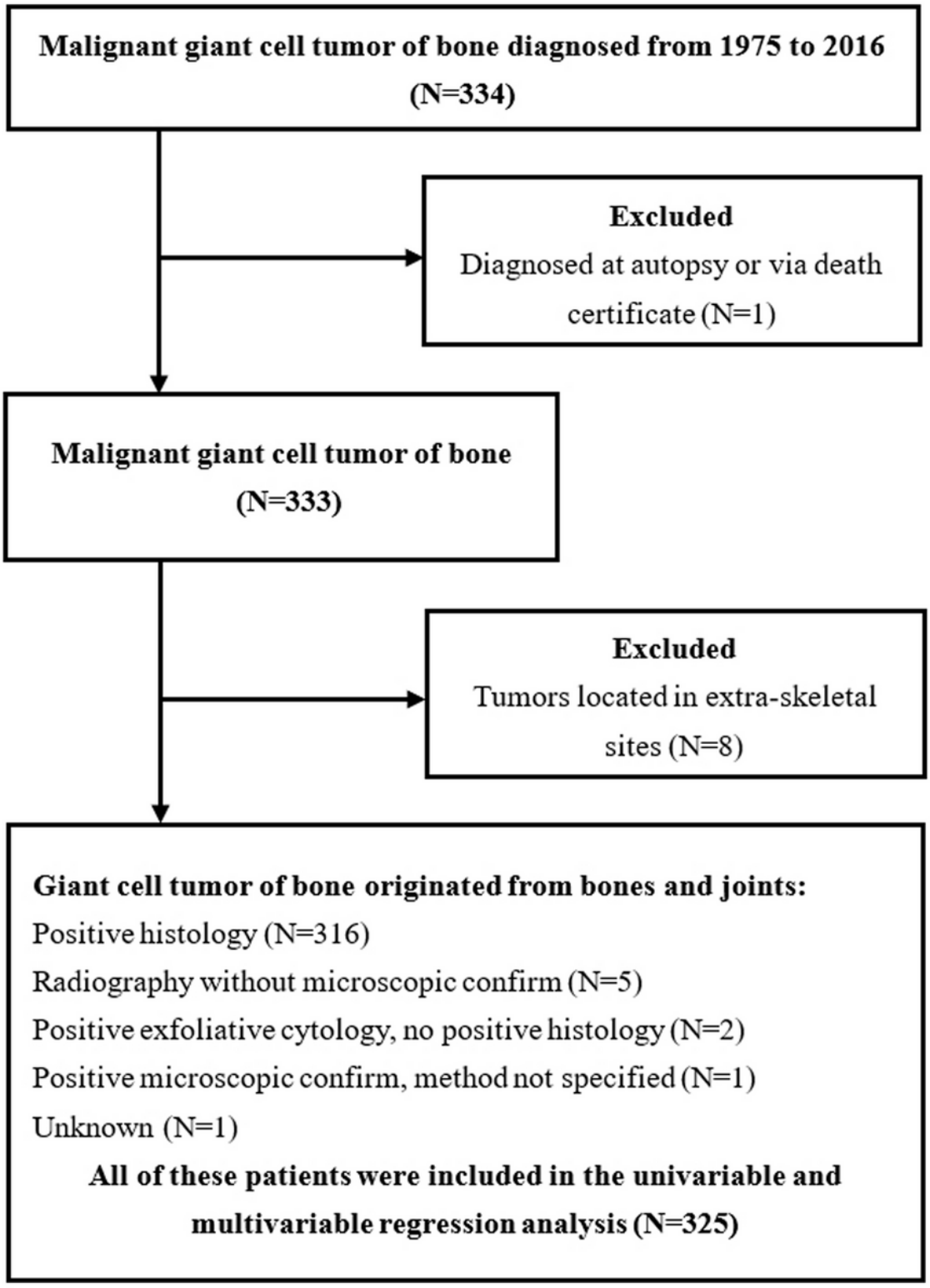

Figure 1

Process of the patient selection for analyzing both the survival and prognostic factors of patients with malignant giant cell tumor of bone.

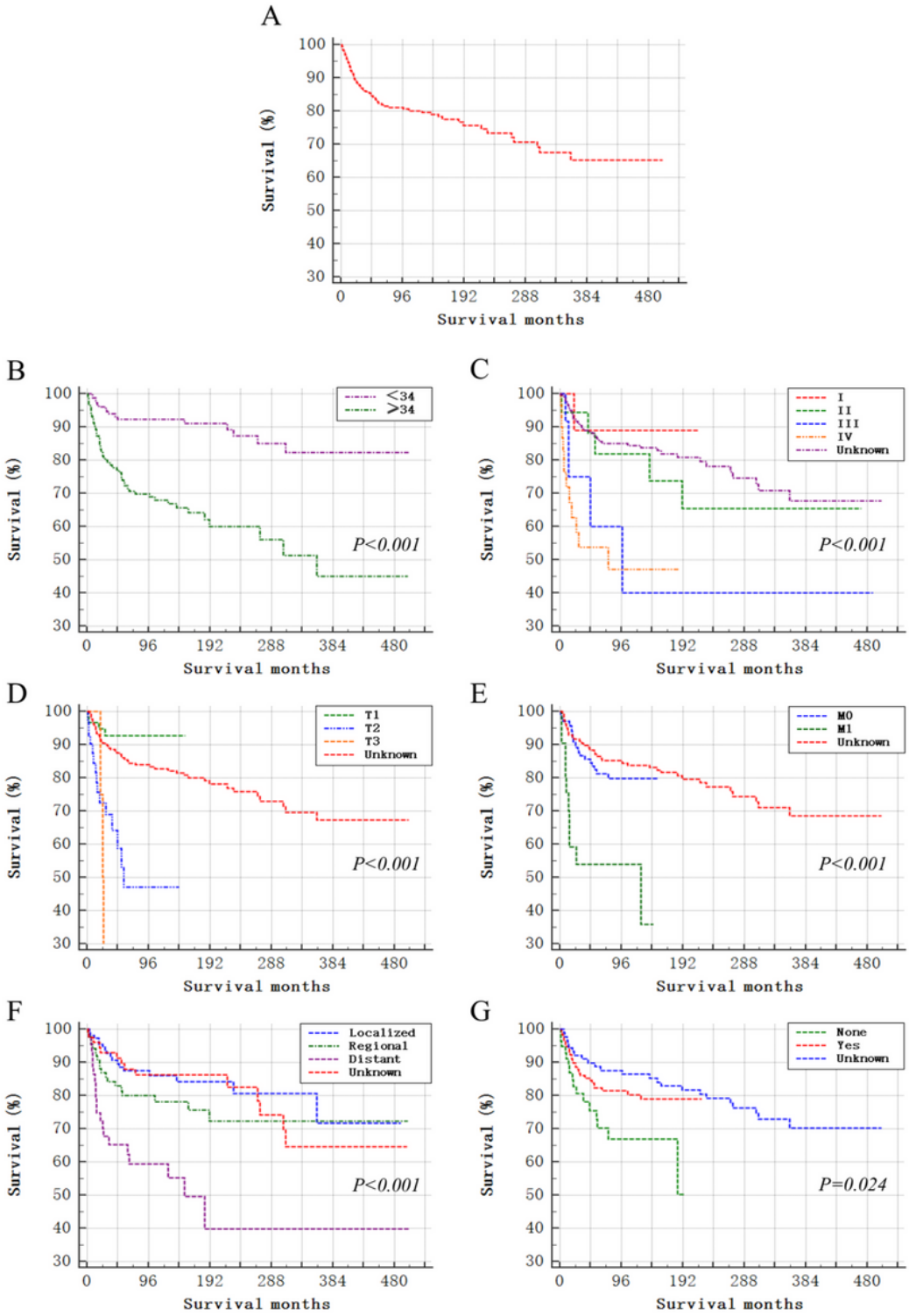

Figure 2

The overall survival of the patients with malignant giant cell tumor of bone from the SEER database.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableCoxRegressionforriskfactors.pdf