

Characteristics and Prognostic Factors of Patients with Chondrosarcoma Older Than 60 Years – An Analysis of 610 Cases from the SEER Database

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Research Article

Keywords: chondrosarcoma, prognosis factor, SEER database, metastasis

Posted Date: September 21st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-689163/v2>

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Abstract

Background: Chondrosarcoma is a rare type of bone tumor which more commonly found in adults range from 40 to 60 years old. Few studies has described the characteristic and prognostic factors of patients older than 60 years. This study aimed to study this feature and identify the prognostic factors based on SEER database.

Methods: Thus, we collected clinicopathological data of chondrosarcoma patients in the Surveillance, Epidemiology, and End Results registry database from 1975 to 2018, and then use the Kaplan-Meier to analyze the patients' survival. We also utilize Cox proportional hazard model to explore the prognostic factors and relevant characteristic including patients' baseline demographics (age, race, and gender), tumor characteristics (tumor extension, histologic subtype, therapy, primary site, stage and grade).

Results: After the implementation of exclusion criteria, there were 610 patients with chondrosarcoma older than 60 years. Our data showed that the incidence of chondrosarcoma is slightly higher in men than in women (52.3% vs 47.7%). In general, 90.8% of tumor had metastasized to distant sites. Meanwhile, 41.8% of tumors occurred in axial location (pelvis, spine, and ribs), 50.8% of tumors occurred in extremity (long or short bones of the upper or lower extremity), and 7.4% in other location (mandible, skull, and other atypical locations). Dedifferentiated chondrosarcoma (hazard ratio [HR] =2.553; 95% confidence interval [CI]= 1.754-3.716), grade (g2:HR:=1.299; 95% CI:=0.888-1.900, g3:HR=1.839;95% CI= 1.174-2.881, g4:HR=3.284,95%CI=2.053-5.253), distant metastasis (HR=3.264; 95% CI= (2.288-4.058), non-surgery perform (HR = 2.854; 95% CI= 2.022-4.028) were independent risk factors for 5-year overall survival.

Conclusion: In conclusion, higher grade, non-surgery perform, dedifferentiated chondrosarcoma and distant metastasis indicated worse prognosis survival. Surgery can significantly improve the survival time of patients.

Introduction

Chondrosarcoma is the third most common primary malignancy of bone after myeloma and osteosarcoma, with an estimated incidence of 1 in 200,000 per year. The majority of these tumors grow slowly and rarely metastasize.¹ Because of highly insensitivity to radiotherapy and chemotherapy, surgical excision is a mainstay of the treatment.^{2; 3} Unlike osteosarcoma and Ewing sarcoma, chondrosarcoma typically manifests in adults 40 to 75 years of age.^{4; 5} Because of the very low incidence, few reports examined the clinical features of chondrosarcoma in patients over 60 years of age. Therefore, we need a large population-based study to identify survival and prognosis in elderly patients with chondrosarcoma.

Materials And Methods

The Surveillance, Epidemiology and End Results (SEER) Program

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) has been a valued source of high-quality information for cancer incidence and survival in the United States since 1973. SEER data are used in a lot of research studies to explore cancer incidence and survival for etiologic and outcomes research related to cancer. These studies include exploring factors that influence trends, analyzing and understanding the cancer burden at a national and local level, and describing health disparities among subpopulations. Data are collected on approximately 450 000 cases of malignant and in situ cancers each year, including information on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and mortality outcomes. The registry community strives to capture clinically relevant information by periodically expanding the scope of data collected, such as incorporating the latest staging definitions, as well as predictive and prognostic factors as they become part of standard care.^{6–8}

Extraction and process of data

Based on SEER database, we selected patients diagnosed with chondrosarcoma according to ICD-0-3 (Histologic International Classification of Disease for Oncology, 3rd Edition) from 1975–2018. Morphology codes for all chondrosarcoma are mesenchymal (9240/3), myxoid (9231/3), clear cell (9242/3), dedifferentiated (9243/3), juxtacortical (9221/3) and chondrosarcoma not otherwise specified (NOS). As is shown in Fig. 1, a total of 610 eligible patients were selected from the seer database. Demographic variables, including age at diagnosis, gender, race/ethnically, and the clinicopathological variables including histological grade, tumor stage, primary tumor site, metastatic status, histologic subtype, surgical resection, survival time, and vital status, were extracted from the database and analyzed in this study. Ethnicity was coded as white, black, and other. Histological grade was stratified into two categories: low grade (including grades 1 and 2), and high grade (including grades 3 and 4). The primary tumor site of chondrosarcoma was classified as axial group (pelvis, sacrum, coccyx, ribs, and mobile spine), extremity group (bones in the upper and lower extremities), and other groups (skull, mandible, and other atypical locations). We classified patients coded with “distant” as metastatic, while patients coded with “localized” or “regional” as nonmetastatic. Surgical resection was classified as “yes” or “no,” Unknown and blank surgery information were excluded from our study. Chondrosarcoma is insensitive to radio-therapy and chemotherapy in clinical practice. Therefore, in the present study, these two variables were not included. All patient identifiers are removed from the database and consequently, studies based on the SEER database, including this one, are exempt from Institutional Review Board (IRB) approval.

Statistical analysis

We performed a basic statistical analysis of 610 patients including age, race, gender, histological grade, tumor stage, primary tumor site, metastatic status, histologic subtype, surgical resection. Kaplan–Meier was used to estimate 3-and 5-year survival and calculate the overall survival rate (OS) and chondrosarcoma cancer-specific survival (CSS). The events for OS were categorized as the deaths

attributed to any cause, and alive cases were considered as censored observations. The events for CSS were defined as the deaths attributed to chondrosarcoma, and the censored observations were defined as alive cases or the deaths by any other causes. Log rank test was utilized to test for differences between groups, Cox regression model including univariate and multivariate regression risk model was used to identify independent prognostic factors related to the prognosis of patients with chondrosarcoma older than 60 years. Hazard ratio (HR) > 1 indicated that prognostic factor was associated with decreasing survival, while HR < 1 indicated that prognostic factor was associated with increasing survival rate compared to the reference. Hazard ratio = 1 revealed that there was no significant relationship between them. All statistical tests were conducted with a level of significance of $p < 0.05$. The statistical analyses were conducted via SPSS statistics software, version 21 (IBM, SPSS, Inc, Chicago, IL) and R version 4.0.5 (R Core Team 2021).

Results

Patient characteristics

We extracted 610 eligible chondrosarcoma patients older than 60 years from the SEER database. (Table 1) Of these patients, 291 (47.7%) patients were females and 319 (52.3%) patients were males. The largest group of ethnic groups is white-race ($n = 563, 92.3\%$), followed by other ethnic groups ($n = 28, 4.6\%$) and black-race ($n = 19, 3.1\%$). As for tumor primary sites, 310 (50.8%) cases occurred in extremity (bones in the upper and lower extremities); 255 (41.8%) cases were located in axial (pelvis, sacrum, coccyx, ribs, and mobile spine), while the rest 45 (7.4%) cases were founded elsewhere (skull, mandible, and other atypical locations). Histologically, 70.5% cases were low-grade tumors (grade I and grade II), 29.5% cases were high-grade tumors (grade III and grade IV). With regard to disease stage, 554 (90.8%) cases were localized/regional, while the remaining cases ($n = 56, 9.2\%$) had metastasized to distant. Historically, arranged in descending order, they were Chondrosarcoma, NOS ($n = 471, 77.2\%$), dedifferentiated chondrosarcoma ($n = 91, 14.9\%$), myxoid chondrosarcoma ($n = 41, 6.7\%$), Juxtacortical chondrosarcoma ($n = 3, 0.5\%$), mesenchymal chondrosarcoma ($n = 1, 0.2\%$) and clear cell chondrosarcoma ($n = 3, 0.5\%$). In addition, in our cohort, 530 (86.9%) cases underwent surgical treatment, the remaining 80 (13.1%) cases, however, did not.

Overall survival and disease-specific survival of each variable

We then performed further survival analysis on this database. We firstly counted the number of surgical resection and metastases at different primary sites (Fig. 2). The statistics shows that chondrosarcoma patients over 60 years of age have a higher resection rate and a lower metastasis rate under different primary sites. Overall survival and disease-specific survival were respectively 69.3% and 74.4% at 3 years, 63.5% and 70.6% at 5 years, and 52.3% and 63.2% at 10 years. As is shown in Fig. 3 and Fig. 4, Kaplan-Meier survival curves with the log-rank test and Univariate analyses suggested that sex ($P = 0.021$), therapy ($P < 0.001$), Histology ($P < 0.001$), Primary site ($P = 0.021$) and Disease stage ($P < 0.001$) were

associated with OS (Table 2). Meanwhile, sex($P = 0.037$), therapy($P < 0.001$), Histology($P < 0.001$), Primary site ($P = 0.002$) and Disease stage($P < 0.001$) were associated with CSS. Multivariate Cox proportional hazards analyses were utilized to control for potential confounding variables. As is shown in Table 3, Multivariate analyses demonstrated that dedifferentiated chondrosarcoma had worse prognosis according to OS (HR = 2.553, 95%CI = 1.754–3.716, $p < 0.001$), Compared with low grade, relative high grade had worse OS (grade III:HR = 1.839, 95%CI = 1.174–2.881, $p = 0.008$; grade IV:HR = 3.284, 95%CI = 2.053–5.253, $p < 0.001$). Compared to cases underwent surgical treatment, those who did not have a surgical resection had a worse prognosis (HR = 2.854, 95%CI = 2.022–4.028, $p < 0.001$) Meanwhile, Patients with distant extension had worse prognosis (HR = 3.264, 95%CI = 2.288–4.658, $p < 0.001$) according to OS.

Discussion

Chondrosarcoma is the second common malignant tumor of bone after osteosarcoma. In general, conventional chondrosarcoma is a disease more commonly found in adults range from 40 to 60 years old. It is also the most common bone sarcoma in the elderly.^{9; 10} Few specific studies had been conducted on chondrosarcoma patients over 60 years of age. Meanwhile, the number of elderly people in the world is increasing, and the number of cases of chondrosarcoma will increase correspondingly. In this study, we performed a survival analysis in patients with chondrosarcoma older than 60 years in order to identify the prognostic factors and guide the clinical treatment based on SEER database.

Overall survival (OS) and cancer-specific survival (CSS) were analyzed in this 610 cases older than 60 years old. Our research shows that overall survival and cancer-specific survival were 69.3% and 74.4% at 3 years, 63.5% and 70.6% at 5 years, and 52.3% and 63.5% at 10 years. Timothy A. Damron had reported that the five-year survival rate for chondrosarcoma is 75.2% based on 9606 cases from the National Cancer Data Base of the American College of Surgeons.¹¹ The reason our results are lower is that age is a strong prognostic factor, as confirmed in Julian Fromm and earlier studies.¹²

Undoubtedly, surgical resection is an important prognostic factor. Surgery is the foundational treatment strategy for chondrosarcoma, on the purpose of preserving or even improving functionality, relieving pain, controlling local recurrence, and promising prolonged survival. One of Douglas J. Pritchard's studies about 280 chondrosarcoma patients who had seen at the Mayo Clinic showed that those who had surgical resection had far fewer relapses than those who had not. Similarly, M. K. Laitinen reported that wide local excision plays an important role in 126 chondrosarcoma patients with local recurrence of the pelvis and limbs.^{13–15} Of course, specific surgical methods is determined based on stage, grade, and location. Unfortunately, specific information on the type of surgery performed and the adequacy of surgical margins is not included in the SEER database.

It is commonly believed that the primary site has a certain influence on the prognosis of chondrosarcoma. It occurs more in the central skeleton, commonly arising from the pelvic girdle, vertebrae, and proximal long bones⁴ The site of origin may affect outcome in chondrosarcoma, with

some anatomic locations such as the pelvis known to predict a worse prognosis than others. This may be due to differences in biological behavior, or may reflect the difficulty achieving an R0 resection in these locations.¹⁶ For example, Those tumors which crossed the sacroiliac joint had a higher incidence of local recurrence compared with those at other sites. As D. Donati analysed, the inaccuracy of estimating the degree of tumor extension across the sacroiliac joint, as well as the difficulty in performing the bony cuts during resection combined with tumor infiltration into the sacral wing, explains the higher incidence of inadequate margins and local failure in these patients.¹⁷ In Axial chondrosarcomas (including pelvic and spine), published 10-year survival rates vary between 52 and 80 %^{12; 17-20} While in extremity, published 10-year survival rates range from 69–81%^{17; 21}. Surprisingly, our study demonstrated that univariate Cox regression analysis of Survival for the anatomical site is significant (P = 0.021) while multivariate Cox regression analysis was not (P = 0.097). One of the possible explanations for this inconsistency is the primary site of the tumor was not subdivided in our study. Confounding factors affected the accuracy of the results.

In this study, we confirmed that metastasis and higher grade suggested poor prognosis, which had been reported in many previous studies. High grade chondrosarcomas have a higher incidence of distant metastasis which made a bad influence on surgical methods and results.¹⁷ Shuting Bai showed that the CXCR4 expression was detected in both the cytoplasm and nucleus of the chondrosarcoma and nonneoplastic cartilage cells. CXCR4 expression levels increased in high-grade chondrosarcoma cells compared with low-grade specimens. high-grade tumor cells show greater CXCR4 expression. This may account for the difference in survival between high-grade and low-grade chondrosarcoma.²² The metastasis of chondrosarcoma is predominantly hematogenous. Distant metastases to the lung are the most common, followed by skin and soft tissue. The rate of metastases has been also found higher in pelvic and chest wall chondrosarcomas, compared to conventional chondrosarcomas of the extremities. Metastatic chondrosarcomas has a better postoperative recurrence rate.^{21; 23}

The present study has several limitations. Firstly, the SEER database does not contain specific treatment information which had been known as potential prognostic factors including pathologic fracture, surgical margin status, resection or amputation, radiotherapy ((doses? adjuvant treatment or neoadjuvant treatment?), and chemotherapy (drugs used as chemotherapy? adjuvant treatment or neoadjuvant treatment?).²⁴ Secondly, this is a retrospective study. Patients were treated through a long period of time, and the fact that treatments may have changed. Thirdly, under strict inclusion and exclusion criteria, our study had eliminated a lot of unknown and blank information, this would lead to the reduction of other eligible cases and thus magnify the statistical difference. Still, the SEER database has a significant advantage in studying rare tumors.

Conclusion

Survival analysis of 610 chondrosarcoma patients over than 60 years were performed by a number of statistical methods to reveal significant clinical pathology features. The overall survival rate and disease-

specific survival rate of the elderly chondrosarcoma patients are worse than those of the young. Tumor in axial site, nonsurgery treatment, dedifferentiated chondrosarcoma and distant metastasis indicated worse prognosis. Meanwhile, surgical resection is still the most effective way to improve the prognosis of patients with chondrosarcoma. Therefore, for elderly patients with chondrosarcoma, surgical resection should be performed early, so as to avoid distant metastasis and miss the opportunity of treatment.

Abbreviations

NOS: not otherwise specified; CS: Chondrosarcoma; CI: confidence interval; HR: hazard ratio; NA: not available.

Declarations

Authors' contributions

Tai-Long Chen conceived of the design of the study. Tai-Long Chen and Zhong-Xin Tang participated in the literature search, study selection, data extraction. Xing Guo performed the statistical analysis. Tai-Long Chen and Nan Zhou wrote this manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank the authors of the included studies for their help.

Funding

No fund support.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This paper does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

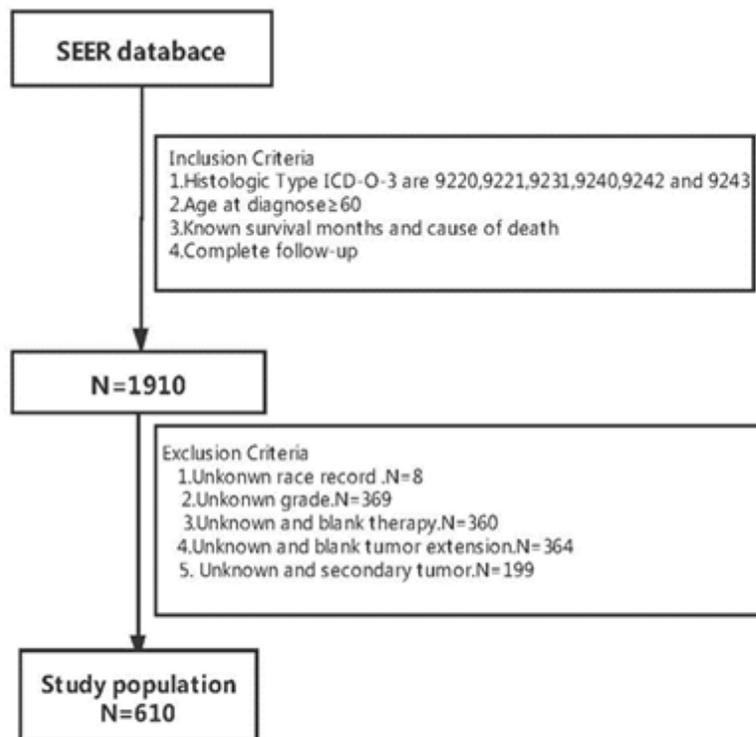


Fig. 1 Flow chart of patient selection from the Surveillance, Epidemiology, and End Results (SEER) database.

Figure 1

Please See image above for figure legend.

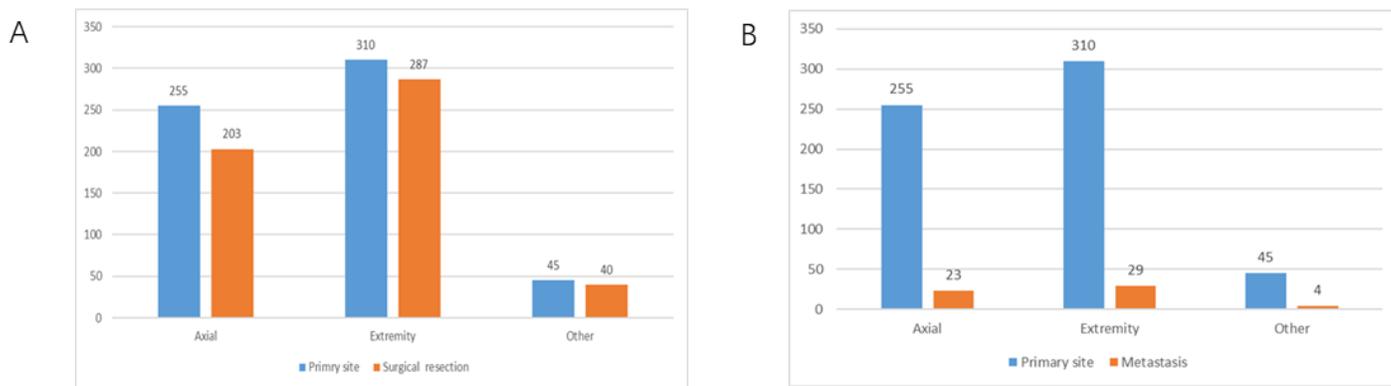


Fig. 2. The proportion of chondrosarcoma patients older than 60 years with surgical resection(A) and metastasis(B) stratified by different tumor primary site.

Figure 2

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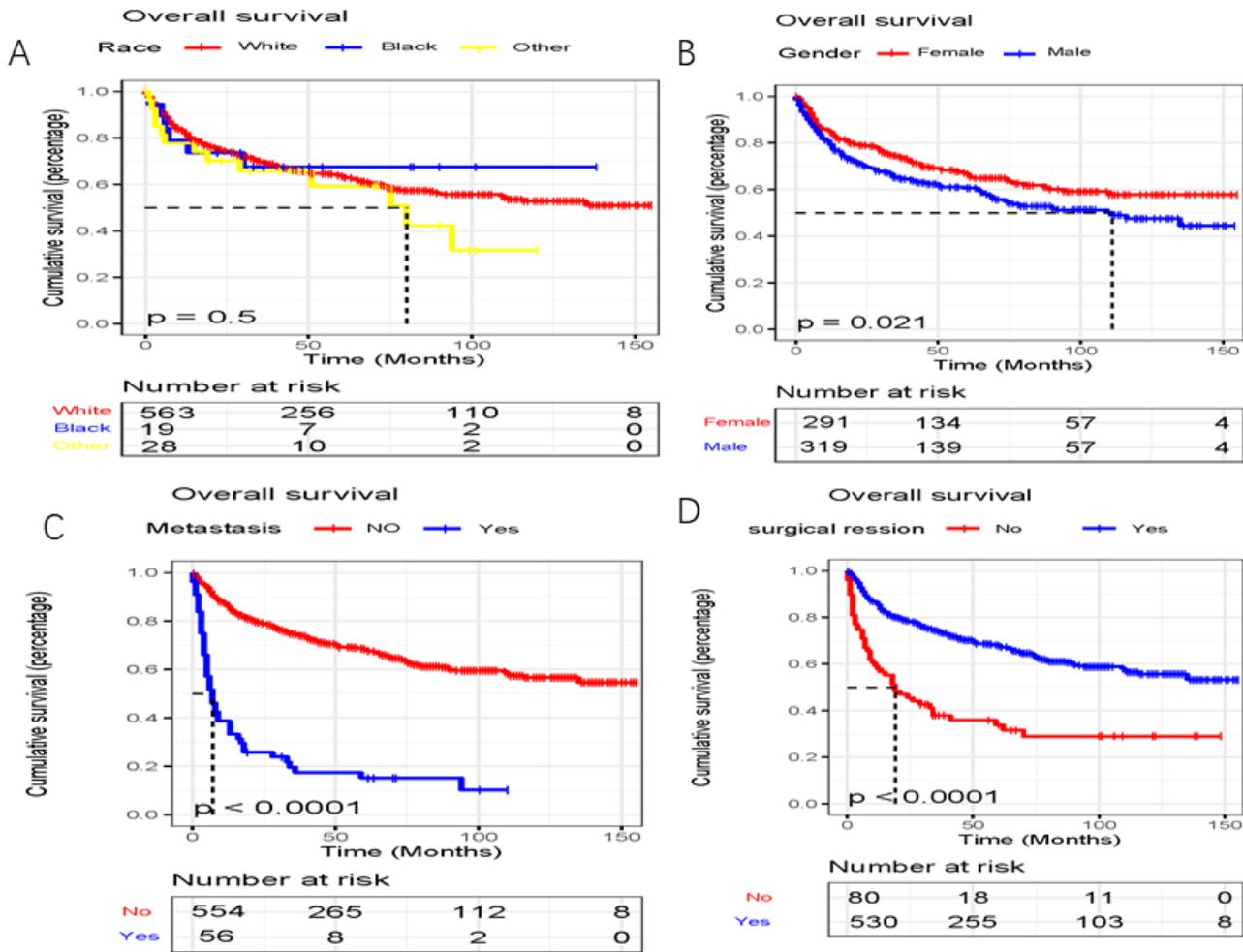


Fig.3.Kaplan-Meier estimated overall survival in patients with chondrosarcoma older than 60 years, stratified by (A) race (white vs black vs other; $P = .5$), (B) gender(female vs male) ($P = .021$), (C) stage (metastasis vs nonmetastasis; $P < .001$), and (D) therapy method (nonsurgery vs surgery perform; $P < .001$).

Figure 3

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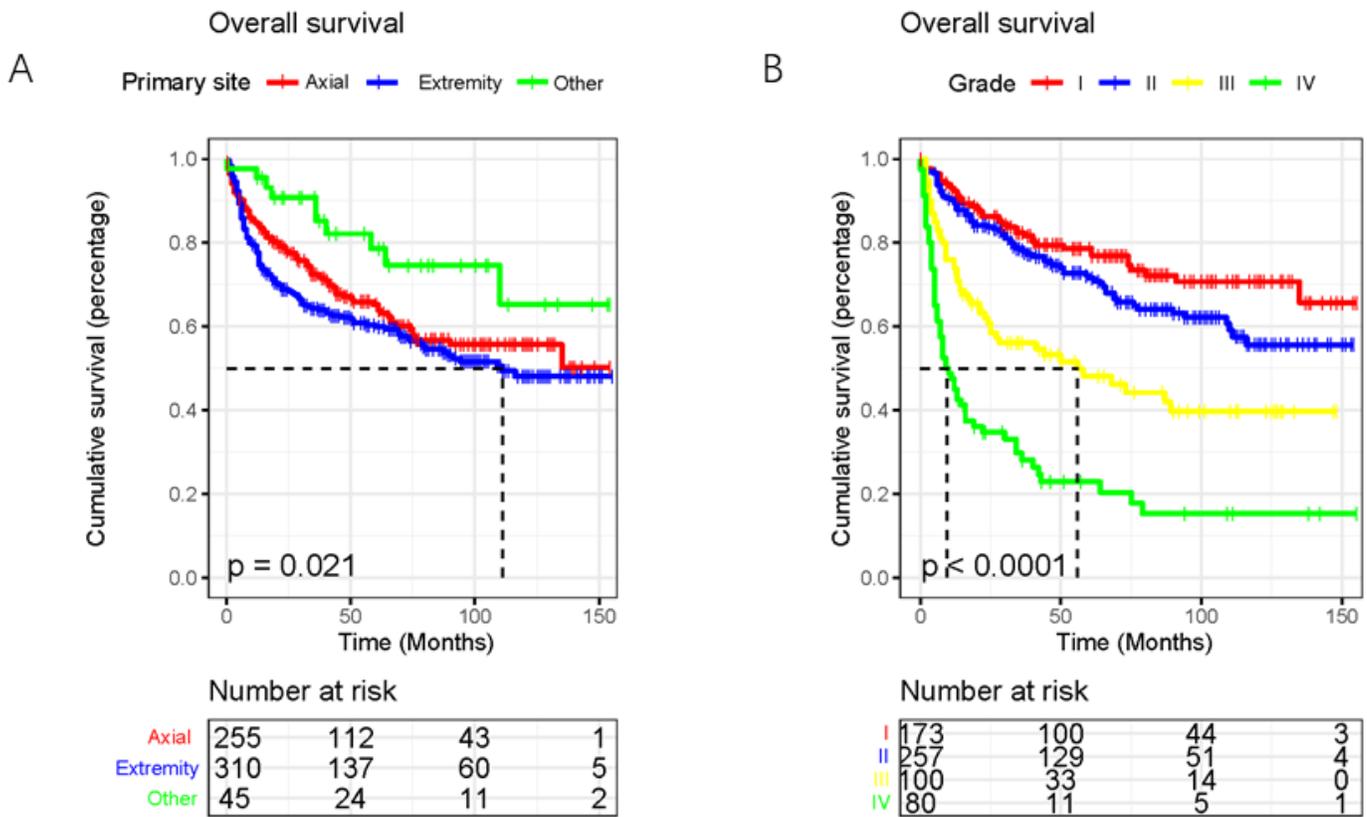


Fig.4. Kaplan-Meier estimated overall survival in patients with osteosarcoma older than 60 years, stratified by (A) primary site (axial bone vs extremity vs other; $P = .021$), (B) grade (G1 vs G2 vs G3 vs G4; $P < .001$),

Figure 4

Please See image above for figure legend.

Supplementary Files

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