Prognostic Factors in Patients with Conventional Chondrosarcoma: A SEER Database Analysis

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Research

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Abstract

Background: Conventional chondrosarcoma, a rare type of bone tumor, is resistant to chemotherapy and radiation therapy. Thus, additional characteristics of this disease are needed to open other treatment modalities. The clinical investigation of chondrosarcoma is limited to small-series and single-institution studies. The Surveillance, Epidemiologic, and End Results (SEER) is the most complete and comprehensive database worldwide. This SEER database study aimed to collect clinicopathological features and determine the prognosis of patients with conventional chondrosarcoma.

Methods: Clinicopathologic and survival data of 782 patients from 2010 to 2016 and 353 patients from 2007 to 2009 were downloaded and analyzed. Overall survival was analyzed using the Kaplan–Meier method and verified by univariable Cox regression. Independent prognostic factors were assessed using the multi-variable Cox regression hazards model. A nomogram was established and used to calculate the one-, three-, and five-year survival rates. Competitive risk models were established to identify the prognostic risk factors related to competitive endpoint events in patients with conventional chondrosarcoma.

Results: In total, 361 extremities, 360 axial bones, and 61 cranial samples were collected from the 2010–2016 cohort. The median survival time of patients with conventional chondrosarcoma was 35 months, and the independent prognostic factors were sex, grade, surgery, AJCC_M age, and tumor size. Thereafter, a nomogram was established basing from those independent prognostic factors. The competitive risk model revealed no competitive risk for the cancer-specific endpoint event. The data from 2007 to 2009 were used to validate the results from 2010 to 2016 with general consistency.

Conclusion: This retrospective study determined the prognostic factors in patients with conventional chondrosarcoma by using the Cox regression hazards model. A nomogram was established to help oncologists assess this rare malignant tumor with low heterogeneity.

Introduction

Chondrosarcoma, which has an estimated incidence of 1:200,000^[1], is a type of malignant bone tumor characterized by the production of a cartilaginous matrix. Chondrosarcoma accounts for approximately 30% of all primary bone malignancies^[2], second only to osteosarcoma. Conventional chondrosarcoma constitutes approximately 85% of all chondrosarcoma cases, and the remaining subtypes include dedifferentiated^[3], mesenchymal^[4], myxoid^[5], and clear cell chondrosarcoma^[6]. The discrepant clinical outcomes of chondrosarcoma depend on histology, grade, and sex. Chondrosarcoma is resistant to chemotherapy and radiotherapy because of its extracellular matrix, low percentage of dividing cells, and poor vascularity^[1, 7]. The identification of IDH1/2^[8], COL2A1^[9], and HIF2α^[10] in chondrosarcoma may be related to targeted agents, although the future role and effectiveness of which are dismal. Surgical excision remains the standard treatment.

The Surveillance, Epidemiology, and End Results (SEER) database comprises approximately 30% cancer survival data of the US population and is used to describe and analyze prognostic factors of malignant tumors worldwide^[11]. The SEER database is important for rare diseases, such as chondrosarcoma. Large multi-agency datasets allow the representation of disease statistics and population levels impossible to replicate outside of national databases. Some studies have collected raw data from the SEER database dating back to the 1970s despite the improvements in diagnosis and treatment with time, which may result in bias. In this study, we collected data on conventional chondrosarcoma from the SEER database from 2010 to 2016 as the test group and data from 2007 to 2009 as the validation group. Thereafter, we identified prognostic factors by using univariable and multivariable regression analyses and established a nomogram to predict the three- and five-year overall survival of patients with chondrosarcoma.

Materials And Methods

This retrospective study utilized the SEER database to acquire cases in accordance with the Declaration of Helsinki (as revised in 2013). All data were collected from 18 local cancer registries, representing the total US population. SEER*Stat^[12] (version 8.3.5; National Cancer Institute, Bethesda, MD, USA) was used to acquire clinical data. The following information was collected in a unified form for each case: patient ID, sex, year of diagnosis, age at diagnosis, race, histology, stage, grade, type of surgery, cause of death, and cause of death to site recode. Samples of chondrosarcoma from 2010 to 2016 were collected as the test group and those from 2007 to 2009 as the validation group.

International Classification of Diseases for Oncology Third Edition^[11, 13] morphology codes were used to differentiate subtypes of conventional chondrosarcoma, excluding rare subtypes of non-conventional chondrosarcoma (mesenchymal [9240/3], myxoid [9231/3], clear cell [9242/3], dedifferentiated [9243/3], and juxtacortical [9221/3]). No information related to chemotherapy was found, whereas a small amount of information related to radiotherapy was collected. However, the radiotherapy plan was not provided; thus, the variable radiotherapy was not added to the information table.

Patient identification was eliminated from the SEER database. Therefore, clinical studies using the SEER database do not require approval from the ethics board. All demographic data and tumor characteristics were identified using the χ^2 test for correlations between categorical variables. Kaplan–Meier and Cox proportional hazard analyses were conducted to evaluate the prognostic value of gender, grade, primary site, AJCC_T, AJCC_N, AJCC_M, tumor size, and surgery group for conventional chondrosarcoma.

Nomograms for one-, three-, and five-year overall survival (not cancer-specific survival) were established in accordance with previously mentioned results of multivariable Cox analysis. Then, the `cmprsk`^[11, 14] package in R was used to detect and visualize competing risk events. More than one endpoint event may occur for chondrosarcoma, and all other causes of death unrelated to the tumor are referred to as competing risk events. Patients died due to the tumor, the side effects of treatment, or cardiovascular disease. All statistical tests were performed at a significance level of $p < 0.05$.

Results

In this study, data were collected from the SEER database, from which 782 patients with conventional chondrosarcoma from 2010 to 2016 were categorized as the test group and 353 patients from 2007 to 2009 were classified as the validation group. All demographic data from the test and validation groups are listed in Table 1. No significant difference in the distribution of data was found between the two groups. The mean age of the test group was 53.05 ± 17.88 , and the mean age of the validation group was 50.31 ± 17.94 . Sex was a significant factor, with male patients having worse prognosis than female patients ($p < 0.05$) (Table 1). Regarding histological grade, patients with undifferentiated grades had the shortest survival ($HR = 21.88$, $p < 0.001$). In addition, an increase in tumor stage (based on the American Joint Committee on Cancer staging system, AJCC system), age, and tumor size resulted in shortened survival for patients. Patients undergoing surgery had prolonged survival. Statistical tests were consistent between the test and validation groups, except for sex and surgery.

Table 1
characteristics of conventional chondrosarcoma patients.

2010–2016				2007–2009		
Variables	Total number	HR(95%CI)	P	Total number	HR(95%CI)	P
Gender			0.01			0.22
Female	345	Ref		152	Ref	
Male	437	1.67(1.13–2.47)		201	1.37(0.82–2.27)	
Primary site			0.10			0.46
Bones of Limbs	361	Ref		176	Ref	
Axial bones	360	1.04(0.72–1.50)		159	0.79(0.48–1.31)	
Bones of skull	61	0.23(0.05–0.92)		18	0.52(0.13–2.16)	
Grade			< 0.001			< 0.001
Well-differentiated	309	Ref		143	Ref	
Moderately differentiated	365	2.32(1.23–4.40)		157	2.66(1.12–6.28)	
Poorly-differentiated	88	6.70(3.45–13.00)		37	9.26(3.86–22.19)	
undifferentiated	20	21.88(11.67–41.05)		16	16.95(7.15–40.15)	
AJCC_T			< 0.001			< 0.001
T1	515	Ref		235	Ref	
T2	261	3.89(2.67–5.72)		115	6.57(3.72–11.59)	
T3	6	3.93(0.95–16.29)		3	13.81(3.17–60.219)	
AJCC_N			0.01			< 0.01
N0	776	Ref		351	Ref	
N1	6	4.43(1.41–13.97)		2	6.55(1.60–26.86)	

2010–2016			2007–2009	
AJCC_M		< 0.001		< 0.001
M0	757	Ref	341	Ref
M1	25	20.02(13.50–29.69)	12	11.37(6.14–21.07)
Tumor size(cm)		< 0.001		< 0.001
<=8	517	Ref	238	Ref
> 8, <=13	159	3.11(1.98–4.88)	74	4.63(2.53–8.50)
> 13	106	5.31(3.41–8.27)	41	8.51(4.56–15.90)
Age		< 0.001		< 0.001
< 45	272	Ref	129	Ref
>=45, < 65	369	2.45(1.40–4.29)	150	2.19(1.12–4.30)
>=65	265	3.56(2.02–6.28)	74	4.10(2.05–8.22)
Surgery		< 0.001		0.23
No sugery	71	Ref	25	Ref
Excision	711	0.20(0.13–0.30)	328	0.57(0.23–2.27)

Kaplan–Meier analysis and Cox regression model establishment

Kaplan–Meier and log-rank tests were used to compare the differences between variables (Table 1). Factors that had a better outcome included tumors with a lower histological grade, smaller tumor size, female sex, and a history of surgery (Fig. 1, Figure S1). Patients with an undifferentiated pathologic grade had the worst survival rate. In this study, a history of radiotherapy was included in the “type of resource” term, but we failed to segregate the variable because of the small sample size of patients undergoing radiotherapy. No differences were observed with respect to primary site.

On the basis of the aforementioned results of the univariable analysis, a multivariable Cox regression model was established to find the independent factors associated with long-term survival. A forest map

was then established (Fig. 2). Sex, tumor size, surgery history, distant metastasis, grade, and age were independent prognostic factors for patients with conventional chondrosarcoma. All the above results were consistent in the validation group. In the validation test, age and sex were heterogeneous factors (Figure S2). Therefore, we searched the “PubMed” database for confirmation, and we found a study reporting that females under 50 years old have a better outcome than those older than 50.

Nomogram prediction establishment

The significant prognostic factors generated from the multivariable Cox regression model were matched to establish a nomogram for one-, three-, and five-year overall survival (Fig. 3). In the nomogram, every variable had a scale value, and the sum of the scores predicted the survival rate. Thereafter, internal validation was performed using the bootstrapping method (parameter: $m = 40$, $b = 1000$), and the c-index was 0.85 (Fig. 4).

Competing risk model analysis

In this retrospective study, causes of death other than conventional chondrosarcoma were found. All the above analyses were related to overall survival rather than cancer-specific survival. Therefore, we conducted a competing risk analysis to differentiate the endpoint events (cancer-specific and non-cancer-related death, and death from other causes). In total, 52 patients died from other causes of death, including infection, heart disease, and chronic obstructive pulmonary disease. The model (Fig. 5, Table S1) indicated that the other causes of death had minor effects on the survival of patients with conventional chondrosarcoma.

Discussion

The incidence of chondrosarcoma is increasing. van Praag et al. reported that the incidence of chondrosarcoma is 8.78 per million people between 2005 and 2013 in the Netherlands^[15], which is three times higher than that in the 1990s, and similar data have been recorded for Norway^[16]. The most common primary sites of chondrosarcoma are the bones of the limbs and associated joints, pelvic bones, ribs, clavicles, and the vertebral column^[15, 17]. To date, histological grade may still be the most important factor related to the prognosis of chondrosarcoma. Patients with grade II/III/IV disease have a significantly worse prognosis than those with grade I. Chondrosarcoma has four main pathological forms: conventional, myxoid, juxtacortical, and dedifferentiated^[18–20]. In our study, 20 patients (2.6%) were diagnosed with a dedifferentiated morphology, which was reported to have a high distant metastasis rate. Nie et al.^[21] demonstrated that the prognosis of chondrosarcoma is improved when comparing outcomes by decade on the basis of the SEER database. However, chemotherapy and radiotherapy are not the standard therapies for chondrosarcoma. The primary goal is to better understand the characteristics of conventional chondrosarcomas since Amer et al.^[13, 22] reviewed and described non-conventional chondrosarcomas. In the present study, we identified prognostic factors of chondrosarcoma

by using the data from the SEER database from 2010 to 2016, and the findings were verified using the data from 2007 to 2009. Then, we established a nomogram to predict the overall survival of patients with chondrosarcoma.

We found that females had a better prognosis in the univariable and multivariable analyses than males. The effect of sex on the prognosis of conventional chondrosarcomas is controversial. Several studies^[9, 20, 23, 24] based on the SEER database have reported sex as an independent risk factor; however, sex did not influence survival in other studies^[25–27]. Notably, Laitinen et al.^[19] found that females of hormone active age with chondrosarcoma have an improved overall survival and that survival is not carried forward in elderly patients. This result is consistent with previous studies demonstrating that estrogen receptor β can be found in bone and endometrial sarcoma. Patients expressing hormone receptors have favorable outcomes^[11, 28, 29]. Further studies are necessary to elucidate the mechanism of sex hormones and chondrosarcoma.

Multivariable analysis showed that age, grade, AJCC_M, tumor size, sex, and surgery are independent risk factors for the overall survival of patients with conventional chondrosarcoma, which is in line with previous studies. Surgery remains the optimal treatment for conventional chondrosarcoma and is associated with better outcomes than other treatments. However, the type of surgery for low-grade chondrosarcomas remains controversial. Donati^[30] suggested intralesional curettage in grade 1 pelvic chondrosarcoma to reduce operative morbidity, and Verdegaaal^[31] reported that the use of phenol as an adjuvant after intralesional curettage of low-grade chondrosarcoma of a long bone has a good prognosis. However, Bus^[25] found that wide resection margins are associated with better outcomes compared with intralesional curettage in conventional chondrosarcoma of the pelvis. Hodel found that a wide resection is associated with a better prognosis than an unplanned intralesional resection, and the presence of an anatomical barrier is more important than the metric distance of the surgical margin. Stevenson^[19] reported that local recurrence in patients treated with intralesional curettage is high, which significantly affects survival, and suggested a 4 mm margin in all grades of chondrosarcoma because inadequate margins are associated with a high local recurrence rate. Therefore, we recommend that wide resection be performed for all grades of chondrosarcoma.

We then established a nomogram based on the multivariable regression model from the 2010–2016 cohort. From the dispersion of the nomogram, distant metastasis other than in the lung, histological grade, and surgery were the most significant prognostic factors related to overall survival. The C-index calculated by bootstrap was 0.85, confirming the reliability of our nomogram. Thus, we expect it to be useful for clinicians and patients in the prognosis of conventional chondrosarcoma. Finally, we established a competing risk model to compare the competing risks of other death events reported in previous studies. The model showed no competing risks regarding the endpoint events. However, we would like to clarify the discrepancy between the 2007–2009 and 2010–2016 cohorts. In the univariable analysis of the 2007–2009 cohort, sex and surgery were not significant prognostic factors for survival. Some possible reasons could explain this result. First, the surgical procedure was not as advanced as

later years; second, the average age and the proportion of males and females in the 2007–2009 and 2010–2016 cohorts were different, which may have caused a bias in the results of the 2007–2009 cohort.

Several limitations should be considered in the present study. First, we did not include variables, such as specific tumor location, radiotherapy, and chemotherapy, which were associated with prognosis. Second, the SEER database does not provide information on local recurrence or marginal status. Third, the category of histological grade from the SEER database was different from the World Health Organization classification, which may be inaccurate. Finally, given its retrospective design, this study may have introduced bias.

In conclusion, we identified risk factors for the overall survival of patients with conventional chondrosarcoma on the basis of the SEER database in the modern era and established a nomogram to predict three- and five-year overall survival rates. New advances in the treatment of chondrosarcoma are expected, especially for patients with unresectable and metastatic diseases.

Abbreviations

SEER, Surveillance, Epidemiology, and End Results;

ICD-O-3, International Classification of Diseases for Oncology Third Edition; American Joint Committee on Cancer, AJCC_T.

Declarations

Ethics approval and consent to participate

All data were downloaded from online database, thus no ethical approval and patient consent are required.

Availability of data and materials

All the data used in this study can be acquired from the online SEER database.

Consent for publication

None.

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

Z. Gao was responsible for the design. G. Chen and Y. Bao provided the administrative support. P. Fu and T. Sun were for the collection and assembly of data. P. Fu and Z. Gao were responsible for manuscript writing. All the authors approved the final manuscript.

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Figures

Figure 1

Kaplan–Meier analysis of patients with conventional chondrosarcoma, including (A) grade, (B) AJCC_T, (C) tumor size, and (D) surgery.

Figure 2

Multivariable Cox regression analysis of patients with conventional chondrosarcoma visualized with a forest map.

Figure 3

Nomogram composed of tumor size, AJCC_M, grade, surgery, age, and sex. Age: ≤ 45 , (0); $>45, \leq 65$, (1); >65 , (2). Grade: well, (0); moderate, (1); poor, (2); undifferentiated, (3). Tumor size: ≤ 8 , 0; $>8, \leq 13$, 1; >13 , 2. Surgery, 0; no surgery, 1.

Figure 4

Internal validation of (A) three-year and (B) five-year overall survival with calibration curves.

Figure 5

Competitive factors that may affect chondrosarcoma-specific death with the x-axis representing the survival of months and the y-axis representing cumulative incidence.

Supplementary Files

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