

## RESEARCH COMMUNICATION

# Multivariate Analysis of the Prognosis of 37 Chondrosarcoma Patients

Zheng-Ming Yang, Hui-Min Tao\*, Zhao-Ming Ye, Wei-Xu Li, Nong Lin, Di-Sheng Yang

### Abstract

**Objective:** The current study aimed to screen for possible factors which affect prognosis of chondrosarcoma. **Methods:** Thirty seven cases were selected and analyzed statistically. The patients received surgical treatment at our hospital between December 2005 and March 2008. All of them had complete follow-up data. The survival rates were calculated by univariate analysis using the Kaplan-Meier method and tested by Log-rank,  $\chi^2$  or Fisher exact tests were carried out for the numeration data. The significant indexes after univariate analysis were then analyzed by multivariate analysis using COX regression model. Based on the literature, factors of gender, age, disease course, tumor location, Enneking grades, surgical approaches, distant metastasis and local recurrence were examined. **Results:** Univariate analysis showed that there were significant differences in Enneking grades, surgical approaches and distant metastasis related to the patients' 3-year survival rate after surgery ( $P < 0.001$ ). No significant difference was not found in gender, age, disease course, tumor location or local recurrence ( $P > 0.05$ ). Multivariate analysis showed that Enneking grade ( $P = 0.007$ ) and surgical approaches ( $P = 0.010$ ) were independent factors affecting the prognosis of chondrosarcoma, but distant metastasis was not ( $P = 0.942$ ). **Conclusion:** Enneking grades, surgical approaches and distant metastasis are risk factors for prognosis of chondrosarcoma, among which the former two are independent factors.

**Keywords:** Chondrosarcoma - prognostic factors - univariate analysis - multivariate analysis

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### Introduction

Originating from cartilage tissues, chondrosarcoma is the second most common malignant bone tumor (Lee et al., 1999; Rizzo et al., 2001; Reith et al., 2003; Riedel et al., 2009). Each year, about 200,000 patients suffer from it (Giuffrida et al., 2009). In America, it accounts for 20% among all bone malignancies (Bjornsson et al., 1998; Murphey et al., 2003; de Camargo et al., 2010; Guo et al., 2010). Among different groups of people, chondrosarcoma is most commonly found in adults (more males than females), showing an increasing tendency in incidence among those over 40. It may arise at any site of the whole body bones, especially at the pelvis, femurs, humeruses and scapulas.

Chondrosarcoma can occur at any site of endochondral ossification in the body, taking the production of cartilage matrix as its characteristic (Chow, 2007; Rozeman et al., 2002). According to differences in clinical characteristics and microstructure, chondrosarcoma is classified into typical (85%), periosteal (2%), dedifferentiated (10%), mesenchymal (2%) and clear cell (1-2%) chondrosarcoma (Rozeman et al., 2002). 90% of typical chondrosarcoma belong to low-grade malignances and grow slowly with a low distant metastasis rate, leaving 10% high-malignant

with a strong distant invasiveness (Chow, 2007). Most of periosteal and clear cell chondrosarcoma belong to low-grade malignancies. Dedifferentiated and mesenchymal chondrosarcoma were high-grade malignancies.

Typical chondrosarcoma can be sub-typed into primary and secondary chondrosarcoma according to its origin. Primary chondrosarcoma shows tumor characteristics at the onset and accounts for 85% among chondrosarcoma (Riedel et al., 2009). It often occurs among adults aged 40 to 60. The long bones of limbs, especially the metaphyses of the inferior extremities of the femurs and superior extremities of the tibias and humeruses, are the places where primary chondrosarcoma often arises. Primary chondrosarcoma grows slowly. Its cardinal symptoms include dull pain, which can transform from periodicity into continuity, affect the adjacent joint and restrict its movement, a local bump sometimes but without noticeable tenderness, and congestion, redness and heat on the surrounding skin. Secondary chondrosarcoma evolves from benign chondrogenic tumors, such as osteochondroma, enchondroma, simple bone cyst, etc. It is often found among adults aged 25 to 45 at the pelvis, scapulas, femurs and humeruses with a slow pathological course. Its cardinal signs include unnoticeable pain, no signs of redness and heat on the surrounding skin, joint

Department of Orthopedics, Second Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, China \*For correspondence: [huiमितo@126.com](mailto:huiमितo@126.com)

swelling and limited movement if it occurs near the joint, radiating pain and numbness when it constricts the nerves, etc. Among all the patients involved in the present study, two of them suffered from secondary chondrosarcoma which was located at the pelvis. After curettage in the focus, both of them survived without relapse. Typical chondrosarcoma can also be sub-typed into central and peripheral chondrosarcoma according to occurrence locations. Most of central chondrosarcoma are primary. They arise from the marrow cavity, representing osteolytic changes. X-ray examination demonstrates a big or multiple small lucent lesions with irregular rims and star-like calcified spots in them. Neoplastic bones are often formed under the activation of the tumor, due to which the cortical bone is thickened or the tumor breaks through the neoplastic bones to show a cuff appearance. This is also an important characteristic to differentiate central chondrosarcoma from enchondroma. Most of peripheral chondrosarcoma are secondary. They occur at the periosteum and cortical bone. Examination often demonstrates augmented and thickened cartilaginous caps on the basis of primary cartilaginous diseases to form fuzzy cartilaginous tissue lumps with sporadic mottling or flocculent irregular calcified spots.

Chondrosarcoma has a poor blood supply and lymph circulation. It is insensitive to traditional chemotherapeutic drugs or radiotherapy. To date, wide surgical resection is still an important treatment method for chondrosarcoma, which can bring about a 10-year survival rate of 30-80% (Gelderblom et al., 2008). In this study, we made a retrospective analysis of data from 37 patients with chondrosarcoma who received treatment in our hospital. Based on literatures, we discussed eight possible factors in order to screen those which are associated with the prognosis of chondrosarcoma.

## Materials and Methods

### Subjects

A total of 45 patients with chondrosarcoma received treatment in our hospital between December 2005 and March 2008, among which 9 cases failed to follow up. The rest 37 patients with complete follow-up data were involved in the present study.

### General data

Among the 37 patients, 16 were males and 21 were females. Their age ranged from 11 to 84 with the median age of 43. According to age, they were divided into two groups, 16 cases who were less than 40 years old and 21 were more than 40. Their pathological course was 1-96 mon with the average of 19.3 mon, among which 8 cases were less than 6 mon and 29 were more than 6 mon. According to occurrence locations, limb bone chondrosarcoma was found in 18 patients and non-limb chondrosarcoma in 19 cases, among which 10 cases were at the acetabulum, 3 cases at the pubis, 3 at the vertebrae, 1 at the mandible, 1 at the clavicle, 1 at the sacrum, 4 at the proximal femur, 4 at the distal femur, 4 at the proximal humerus, 2 at the proximal tibia, 2 at the distal tibia, 1 at the calaneus and 1 at the patella.

According to pathological classification, typical, clear cell, mesenchymal and dedifferentiated chondrosarcoma were found in 32, 2, 2 and 1 case, respectively. According to Enneking staging criteria (Enneking, 1988), Grade I chondrosarcoma was found in 26 cases, Grade II in 7 cases and Grade III in 4. According to different surgical methods, total and partial resections were divided. Total resection included amputation of limbs and wide resection. Partial resection included curettage in the focus and palliative resection. In the present study, total resection was performed for 29 patients, among which 20 received salvage limb operation and 9 received amputation of the limb. Pulmonary metastasis was found in 4 patients during visiting or follow-up and local relapse was found in 8 after operation.

### Follow-up

Follow-up took the forms of out-patient clinic visits and telephones. It lasted till March 2011 or death of the patient. The 37 patients were followed up 3-63 mon with the average time of 39.2 mon. Among them, 11 died, who were followed up 3-35 mon with the average of 18.3 mon, and 26 survived, who were followed up 36-63 mon with the average time of 48 mon. Patients who didn't receive doctor's visits or telephones three times were treated as loss to follow-up.

### Statistical analysis

Survival rates were analyzed by univariate analysis using Kaplan-Meier method and tested by Log-rank.  $\chi^2$  or Fisher exact test was performed for enumeration data. The significant indexes after univariate analysis were further analyzed by multivariate analysis using COX regression model to screen the independent factors affecting prognosis. All data were analyzed by SPSS16.0 software.  $P < 0.05$  was considered significant.

## Results

### Survival analysis

The survival time of these patients was 3-63 mon with the average and median time of 39.2 mon and 40 mon. 11 patients died and 26 survived. The 1-, 2- and 3-year survival rates were 89.2%, 75.5% and 70.3%, respectively. The survival curve is shown in Figure 1.

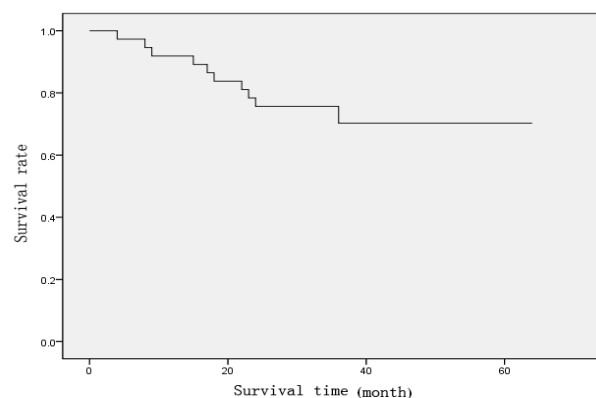
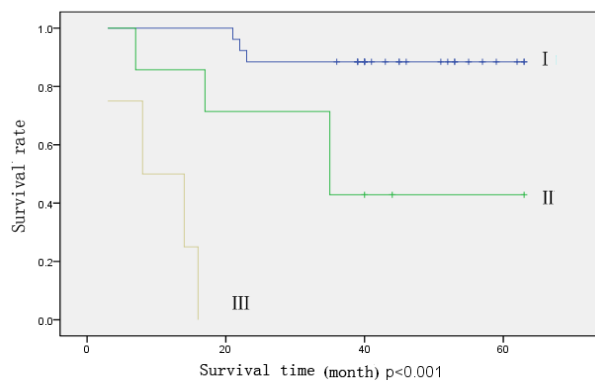


Figure 1. The Survival Curve of 37 Patients with Chondrosarcoma

**Table 1. Univariate Analysis of the Possible Prognosis-Related Factors**

Variables	Number of cases	3-year survival rate (%)	3-year death rate (%)	Log-ranks statistic	P values
Sex				0.057	0.811
male	16	11 (71.4%)	5 (28.6%)		
female	21	15 (68.8%)	6 (31.2%)		
Age				0.011	0.915
<40	21	15 (68.8%)	6 (31.2%)		
>40	16	11 (71.4%)	5 (28.6%)		
Pathological course				0.244	0.621
<6 mon	8	5 (62.5%)	3 (37.5%)		
>6 mon	29	21 (72.4%)	8 (27.6%)		
Tumor location				0.874	0.35
limb bone	18	14 (77.8%)	4 (22.2%)		
non-limb bone	19	12 (63.2%)	7 (36.8%)		
Enneking grades				44.145	<0.001*
Grade I	26	23 (88.5%)	3 (11.5%)		
Grade II	7	3 (42.9%)	4 (57.1%)		
Grade III	4	0 (0)	4 (100%)		
Surgical approaches				14.386	<0.001*
total	29	24 (82.8%)	5 (17.2%)		
partial	8	2 (25.0%)	6 (75.0%)		
Local recurrence				0.78	0.377
yes	30	20 (66.7%)	10 (33.3%)		
no	7	6 (85.7%)	1 (14.3%)		
Distant metastasis				39.306	<0.001*
yes	33	24 (78.8%)	9 (21.2%)		
no	4	0 (0)	4 (100%)		
Total	37	26 (70.3%)	11 (29.7%)		

\*represents a significant difference



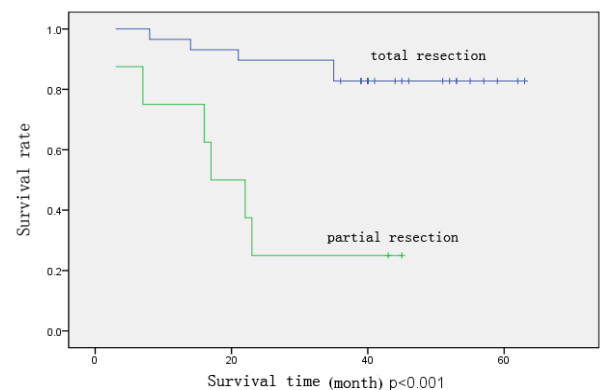
**Figure 2. The Survival Curves of the Three Groups According to Enneking Staging Criteria**

#### Univariate analysis

Factors of sex, age, pathological course, tumor locations, Enneking grades, surgical approaches, local recurrence and distant metastasis were analyzed and then tested by Log-rank. The results showed that there were significant differences in Enneking grades ( $P<0.001$ ), surgical approaches ( $P<0.001$ ) and distant metastasis ( $P<0.001$ ), which indicated that they were associated with the 3-year survival rate. But such significant differences were not found in sex, age, pathological course, tumor locations or local recurrence ( $P>0.05$ ) (Table 1).

#### Enneking grades

According to Enneking staging criteria, Grade I chondrosarcoma was found in 26 patients. Their survival rate was 88.5% and their survival time was 21-63 mon with the average and median time of 44.9 and 44 mon, respectively. Grade II was found in 7 patients, among



**Figure 3. The Survival Curves of the Two Groups Receiving Different Surgical Approaches**

which 4 died. Their survival rate was 42.9% and survival time was 7-63 mon with the average and median time of 34.4 and 35 mon. Grade III was found in 4 patients. They all died. Their survival time was 3-16 mon with the average and median time of 10.3 and 11 mon. The comparisons among the three groups showed that there were significant differences ( $P<0.001$ ), indicating that Enneking grades were associated with the prognosis of chondrosarcoma. The survival curves of the three groups are shown in Figure 2.

#### Surgical approaches

Twenty-nine patients received total resection, among which 20 received salvage limb operation and 9 received limb resection. Five died. The 3-year survival rate was 82.8%, and the survival time was 8-63 mon with the average and median time of 43.9 and 41 mon. Eight patients received partial resection, among which 6 died.

**Table 3. Multivariate Analyses of Enneking Grades, Surgical Approaches and Distant Metastasis**

Factors	Regression coefficient	Standard error	P value	Relative risk (RR)	95% confident intervals (CI)	
					Lower limit	Upper limit
Enneking grades	2.238	0.832	0.007*	9.377	1.835	47.925
Surgical approaches	2.054	0.793	0.010*	7.801	1.65	36.878
Distant metastasis	-0.115	1.594	0.942	0.891	0.039	20.287

\*represents a significant difference

**Table 2. The Influences of Salvage Limb Operation and Limb Resection on Prognosis**

Surgical approach	Number of cases	3-year survival rate (%)	Death cases (%)	Fisher exact test
Limb salvage	20	17 (85.0%)	3 (15.0%)	P=0.633
Limb resection	9	7 (77.8%)	2 (22.2%)	
Total	29	24	5	

\*represents a significant difference

The 3-year survival rate was 25% and the survival time was 3-45 mon with the average and median survival time of 22.0 and 19.5 mon. The comparison between these two groups showed that there was a significant difference (P<0.001). The survival curves of these two groups are shown in Figure 3.

In addition, among 29 patients who received total resection, 20 received salvage limb operation and 9 received limb resection. Three out of the patients receiving salvage limb operation died. The 3-year survival rate was 85.0%. Two out of the patients receiving limb resection died. The 3-year survival rate was 77.9%. There was no significant difference between these two groups (P=0.633) (Table 2).

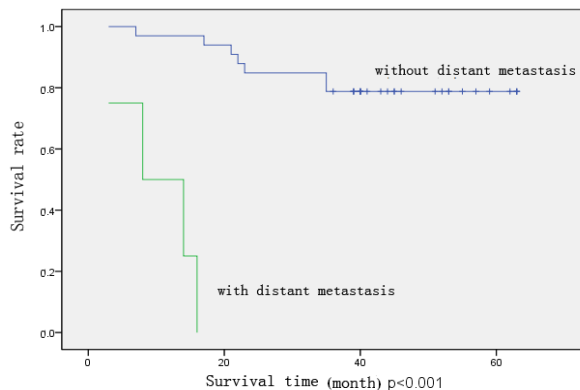
*Distant metastasis*

Among 37 patients, 4 were found with pulmonary metastasis. They all died with the death rate of 100%. Their survival time was 3-16 mon with the average and median survival time of 10.3 and 11 mon. Among 33 patients without distant metastasis, 7 died. The 3-year survival rate was 78.8%, and the survival time was 7-63 mon with the average and median time of 42.7 and 41 mon. The comparison showed that there was a significant difference between these two groups (P<0.001). The survival curves are shown in Figure 4.

*Multivariate analysis*

The significant factors after univariate analysis were further analyzed by multivariate analysis. The results showed that Enneking grades (P=0.007) and surgical approaches (P=0.010) were prognosis-related independent factors (Table 3).

Enneking grades and surgical approaches were prognosis-related independent factors. The RR of Enneking grades was 9.377 and the 95% CI of the RR was 1.835-47.925, which meant that the risk of death would be increased 9.377 times when one stage increased. Similarly, the RR of surgical approaches was 7.801 and the 95% CI of the RR was 1.605-36.878, which meant that the death risk for patients receiving total resection was 7.801 times high of that for patients receiving partial resection. The P value of distant metastasis was 0.942, which meant that distant metastasis was not an independent factor for prognosis.



**Figure 4. The Survival Curves of Patients with and Without Distant Metastasis**

But distant metastasis could influence prognosis indirectly via its influence on Enneking grades, i.e. chondrosarcoma with distant metastasis was also Grade III chondrosarcoma which had a poor prognosis.

**Discussion**

It is rather definite that the pathological stage of chondrosarcoma is closely associated with its prognosis. According to Lichtenstein and Jaffe’s histological staging criteria, chondrosarcoma can be divided into Grade I, II and III (Lichtenstein and Jaffe, 1943). Among which Grade I is believed to be low-malignant and Grades II and III high malignant (de Camargo et al., 2010). The 5-year survival rate of Grade I chondrosarcoma can reach 90%, whereas those of Grade II and III can only range from 40% to 60% (Etchebehere et al., 2005; Streitburger et al., 2009; de Camargo et al., 2010). For other factors which affect the prognosis of chondrosarcoma, controversies arise. Therefore, we conducted this study to screen prognosis-related factors. As chemotherapy and radiotherapy only have small effects on chondrosarcoma, they were not involved in the present study.

The univariate analyses in the present study showed that sex or age has no obvious association with prognosis. Up to now, no study has reported that there is association between sex and the prognosis of chondrosarcoma. Though female chondrosarcoma patients are better at prognosis than male patients according to the analysis of 2,890 cases of chondrosarcoma from the SEER databank (there was a significant difference in the 30-year survival rate between females (78.6%) and males (68.7%) and such a difference was maintained from the first ten years), the multivariate analysis showed that sex is not a prognosis-related independent factor, which suggests that the difference in prognosis between females and males may be caused by tumor locations (Giuffrida et al., 2009). 60.9% of female chondrosarcoma patients and 46.7% of



male patients suffer chondrosarcoma at limb bones. The overall survival rates of patients with chondrosarcoma at limb bones and at non-limb bones are 82.7% and 61.6%, respectively (Giuffrida et al., 2009). Chondrosarcoma at limb bones has a better prognosis with a higher survival rate and a lower relapse rate compared to that at non-limb bones (4). The 5- and 10-year survival rates of limb chondrosarcoma are 81% and 71% whereas those of pelvis chondrosarcoma are 69% and 59% (Fiorenza et al., 2002). Meanwhile, patients more than 50 years old have a poorer prognosis compared to those less than 50, in which the respective 30-year survival rates are 20% and 60% (Giuffrida et al., 2009). Most of chondrosarcoma develop slowly, and most scholars believe that there is no correlation between the survival rate and the course of chondrosarcoma. No report has claimed a correlation between the course of chondrosarcoma and its prognosis till now.

There are disagreements. The prognosis of chondrosarcoma is associated with Enneking grades, histological grades and local recurrence rather than distant metastasis, surgical approaches or the size of the tumor (Fiorenza et al., 2002). The 10-year survival rates of Grade I, II and III patients according to histological staging criteria are 89%, 53% and 38%. The 10-year survival rate of patients with Grade II B-phase chondrosarcoma without local recurrence is 64% whereas that with local recurrence is only 5%. The prognosis-related factors are histological stages, the resection scope, tumor size and pelvis tumors, but Enneking grades are not (Lee et al., 1999). Both the death and distant metastasis rates of patients with histological Grade III chondrosarcoma are higher than those of Grade II patients. Wide resection has a better prognosis in the 5- and 10-year survival rates and local recurrence compared to curettage in the focus and palliative resection. Tumor size is correlated with prognosis, in which a larger high-malignant tumor predicts a higher probability of distant metastasis. Pelvis tumors also suggest higher metastasis and death rates, and they have a poorer prognosis compared to limb bone tumors (Weber et al., 2002). The prognosis of chondrosarcoma is not associated with malignant grades, surgical grades, locations, size of the tumor or local recurrence, but associated with surgical approaches and the augmentation index (AI) (Giuffrida et al., 2009). Though data showed that high malignancies have higher metastasis and death rates compared to low ones, there is no significant difference between them. Patients receiving wide resection show significantly lower local recurrence, metastasis and death rates than those receiving in partial resection. The more the augmentation index (evaluated by detection of the MIB-1 expression (monoclonal antibodies of Ki-67 nuclear antigen) is, the poorer the prognosis is. Only histological and surgical grades are the prognosis-related independent factors of chondrosarcoma (Giuffrida et al., 2009). The results in the present study showed that Enneking grades, surgical approaches and metastasis can influence the prognosis of chondrosarcoma, among which the former two are independent factors. There is no significant difference between salvage limb operation and limb resection.

As chondrosarcoma is insensitive to radiotherapy and chemotherapy, surgical treatment is still the main method for its treatment (Bjornsson et al., 1998; Lee et al., 1999; de Camargo et al., 2010; David et al., 2011). Generally, wide resection is considered to be suitable for high-malignant chondrosarcoma (histological Grade II and III). Whether the damaged function of the resected part needs to be reconstructed depends on the primary location of the tumor and resection scope. When chondrosarcoma occurs at the proximal extremity of the fibula or at the scapular, there is not severe functional loss normally, for which function reconstruction is not needed. However, when it occurs at weight-bearing bones such as the femur and tibia, adoption of the prosthesis, autogenous bone or xenogenous bone is often needed, after which nearly half of the patients can get a good prognosis and functional restoration. The greatest difficulty comes from high-malignant chondrosarcoma at the pelvis and vertebral column. Normally, tumors at these places are larger in size than those at the limbs, and even worse, they are close to important organs such as the bladders and notochord. They often lead to high relapse and death rates. For low-malignant chondrosarcoma, the adoption of curettage in the focus combined with adjuvant treatment is more and more inclined (specifically, the areas surrounding the focus are grinded by a high-speed grinder after curettage of the lesions through a sufficiently large bone window and then treated with an adjuvant such as carbolic acid and liquid nitrogen). Compared to wide resection, curettage in the focus can keep the normal function basically. For non-pelvis low-malignant chondrosarcoma, it can get similar prognosis in overall survival, metastasis and relapse rates, and its postoperative 10-year survival rate can reach 80% or so (Leerapun et al., 2007). For histological Grade I chondrosarcoma, it only increases the local relapse rate but has no influence on the distant metastasis or survival rate (Streitburger et al., 2009). But for Grade I chondrosarcoma at the pelvis, its relapse rate is 100% (Schwab et al., 2007; Donati et al., 2010).

To draw a conclusion, there are many factors which can affect prognosis of chondrosarcoma. Due to differences in geography, methodology, follow-up time and sample size as well as the development in surgical, diagnostic and therapeutic technologies, different scholars hold different views towards chondrosarcoma treatment, as a result of which their outcomes are also different. The present study shows that Enneking grades, surgical approaches and distant metastasis are risk factors for the prognosis of chondrosarcoma, and the former two are prognosis-related independent factors.

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