

Prognostic factors and survival in conventional chondrosarcoma: A single institution review

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Abstract

Background: Chondrosarcoma is the second most common primary sarcoma of the bone. Surgery remains the gold standard for treatment due to chemotherapy and radiotherapy resistance in chondrosarcoma. The main aim of our study was to analyze patients with primary chondrosarcoma of the bone who were treated in a single tumor center. Our study team identified the prognostic factors for overall survival, metastasis-free survival, and recurrence-free survival.

Methods: From 1998 to 2012, 55 consecutive patients were treated surgically. All patients were followed for local recurrence or distant metastasis. Uni- and multivariate analyses were performed for overall, metastasis-free, and recurrence-free survival.

Results: Local recurrence developed in 29 of the 55 patients (52.7%). Recurrence-free survival in the multivariate analysis showed a significant association with the surgical margin, and high-grade lesions were an independent factor for local recurrence. In total, 11 patients died of the disease in the study, and the 5- and 10-year survival rates were 84.4% and 78.1%, respectively. The tumor grade and local recurrence were significant factors in the univariate analysis but were insignificant in the Cox regression with time-dependent covariates ($p = 0.327$ and $p = 0.82$, respectively). The development of distant metastasis was a significant poor prognostic factor in both the uni- and multivariate analyses.

Conclusion: Chondrosarcoma of the bone is a disease with surgery-dependent outcomes; but, however, patients often develop subsequent recurrence of the disease. The surgical margins were statistically associated with the risk of subsequent local recurrence but did not predict survival. The development of distant metastases was an independent prognostic factor for poor survival.

Keywords: Chondrosarcoma; Multivariate analysis; Survival rate

1. INTRODUCTION

Chondrosarcoma is the second most common primary sarcoma of the bone and accounts for approximately 20% of all malignant bone cancers.^{1,2} Chondrosarcoma typically occurs in adults aged between 20 and 60 years. Conventional chondrosarcoma is the most common type of pathophysiology, of which, several types have been classified. The current WHO classification, established in 2013, redefined grade I chondrosarcoma as an intermittent tumor, which is regarded as local aggressive behavior. Surgery remains the gold standard for treatment due to chemotherapy and radiotherapy resistance in chondrosarcoma.³

It has been established that the incidence of metastasis and overall survival rate are dependent on the histologic grade. In

addition, an inadequate surgical margin is associated with local recurrence. However, the effect of local recurrence on overall survival remains controversial. Currently, a wide surgical margin to minimize local recurrence is the only modifiable prognostic feature for chondrosarcoma.^{4,5}

The main aim of this retrospective study was to analyze patients with primary chondrosarcoma of the bone who were in a single tumor center. Our study team identified the prognostic factors for overall survival, metastasis-free survival, and recurrence-free survival. The secondary aim was to evaluate our results, which were contrary to the published data.

2. METHODS

This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (TPEVGH IRB No.: 2016-11-002AC; Taipei, Taiwan). A retrospective search of our departmental database from 1998 to 2012 identified 105 patients with chondrosarcoma. The data for this study were retrieved from hospital records, maintained oncologic files, surgical files, and clinical examinations at the most recent outpatient clinic visit. Among these patients, 29 patients were excluded due to incomplete medical and clinical records or unrecorded follow-up data. To construct a homogenous group to analyze prognostic factors, we focused the study on conventional chondrosarcoma, for which secondary (n = 5), mesenchymal (n = 6), clear-cell (n = 4),

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and soft tissue chondrosarcoma (n = 6) were excluded, leaving 55 patients in the study.

There were 36 men and 19 women with a mean age of 49.4 ± 16.1 years (range, 18–84 years). The average follow-up time of the patients was 89.44 ± 59.7 months (range, 8–239 months). There were 25 lesions in the appendicular skeleton and 30 in the axial skeleton, which included the shoulder girdle, spine, and pelvis (Table 1). The tumor size was defined as the maximum length measured on the computed tomography or magnetic resonance imaging scans in either the coronal or sagittal view. The analysis of the histological grade, based on nuclear and mitotic activity and cellularity,⁶ revealed that 27 patients (49.1%) had grade 1 disease, 25 (45.5%) had grade 2 disease, and 3 (5.5%) had grade 3 disease. However, for analysis, the disease grades were grouped as low grade (grade 1, n = 27) and high grade (grades 2 and 3, n = 28).

All patients underwent surgical resection. Our strategies included wide excision, intralesional curettage, and marginal resection. The preoperative imaging studies, including magnetic resonance imaging, computed tomography, or plain film X-ray, were the principal methods for deciding the surgical strategy. Our aim for treating chondrosarcoma was tumor eradication and functional preservation; however, curettage with extensive local adjuvant treatment was provided for patients with intracompartmental lesions. When patients had tumor lesions jeopardizing the neurovascular bundle or other vital structures, marginal resection may be performed to preserve function. We preoperatively explained the advantages and disadvantages, and the choice of surgical treatment was decided with the patient

or his/her family. The tumor lesions were excised with a rim of healthy tissue, defined as wide resection. In contrast, marginal resection involved an intact tumor capsule but suspicious contamination. The surgical margin was defined as Gitelis et al,⁶ ie, an adequate surgical margin was uncontaminated, such as those obtained with wide excision; intralesional, marginal, or contaminated margins were considered inadequate.

2.1. Statistical analysis

The oncological outcomes in the study were local recurrences, metastasis, and overall survival. Various factors were analyzed for their prognostic effect on these oncological outcomes. To perform univariate analysis, we used log-rank test. Besides, time-dependent covariates in the Cox proportional-hazards regression model was constructed to perform multivariate analysis. A *p* value less than 0.05 was considered significant. Statistical analyses were performed using STATA 12 (StataCorp, TX).

3. RESULTS

The tumors of 20 patients (36.4%) were treated with wide excision, 16 (29.1%) with intralesional curettage, and 19 (34.5%) with marginal resection. One patient in our series had neurovascular invasion and wide soft tissue extension of the chondrosarcoma at the right proximal femur and underwent a right lower leg amputation through the hip joint. In total, 20 patients had adequate surgical margins, and 35 patients had inadequate margins (intralesional curettage and marginal resection). For some patients with high-grade lesions, suspicious contamination from inadequate surgery and primary metastasis, adjuvant treatment, chemotherapy, or radiotherapy was given, although no defined protocol was followed. Seven patients received chemotherapy, and 2 patients underwent concomitant chemotherapy and radiotherapy.

Sixteen patients had arthroplasty reconstruction after tumor resection. Nineteen patients had biological reconstruction, including eight patients who underwent reconstruction with structural allografts and 11 with recycled bone (five with the liquid nitrogen technique and six with extracorporeal radiation). During the follow-up of all the patients, there were six complications (10.9%), including two cases of nonunion, two periprosthetic fractures, one implant failure, and one deep wound infection. Thirty-two patients underwent at least two surgeries due to resection of recurrent tumors, excision of metastatic lesions, or complications.

Local recurrence developed in 29 of the 55 patients (52.7%), and the median time of local recurrence was 39.0 (2–165) months. There were 19 recurrent lesions (65.5%) in the axial skeleton and 10 in the appendicular skeleton. According to the grading system, 10, 17, and two patients had grade 1, 2, and 3 lesions, respectively. In the univariate analysis, recurrence-free survival showed a significant association with the tumor distribution, treatment method, and tumor grade. Furthermore, the Cox regression showed that marginal resection (hazard ratio = 4.57; *p* = 0.02) and high-grade resection (hazard ratio = 3.62; *p* = 0.002) were the independent factors for local recurrence (Table 2).

Three primary metastases (5.5%) were found in our study, and 12 (23.1%) other patients developed metastatic disease during the follow-up period. The median time of metastasis development was 14.0 (1–170) months. Lung metastasis was the most common type of metastasis with eight cases, and there are two cases of bone-to-bone metastasis and one metastatic lymphadenopathy. Only three of these patients were alive with the disease at the final follow-up. Tumor grade was the only independent factor for metastasis-free survival (hazard ratio = 3.95, *p* = 0.042; Table 3).

Table 1

Demographic characteristics of study patients^a

Demographic factors	Number (%) ^a
Gender	
Male	36 (65.5)
Female	19 (34.5)
Distribution	
Axial	30 (54.5)
Extremity	25 (45.5)
Treatment	
Wide excision	20 (36.4)
Intralesional curettage	16 (29.1)
Marginal resection	19 (34.5)
Soft tissue break	
Yes	24 (43.6)
No	31 (56.4)
Grading	
Low	27 (49.1)
High	28 (50.9)
Complication	
Yes	11 (20)
No	44 (80)
Metastasis	
Yes	15 (27.2)
No	40 (72.8)
Local recurrence	
Yes	29 (52.7)
No	26 (47.3)
Die-of-death	
Yes	11 (20)
No	44 (81.8)
Age (y)	49.4 (18–84, 16.0)
Size (cm)	10.2 (3.0–29.8, 5.0)
Follow-up period	89.4 (8–239, 59.7)

^aAll data, except age, size, and follow-up period (min–max, standard deviation), present as percentage.

Table 2
Analysis of recurrence-free survival (n = 55)

Variable	Recurrence-free survival (%)			Multivariate analysis	
	Patients	5 y	10 y	<i>p</i> ^a	Hazard ratio (95% CI) <i>p</i> ^b
Gender				0.168	
Female	19	70.7	52.8		
Male	36	45.7	32.7		
Age (y)				0.633	
≤50	26	57.1	27.9		
>50	29	53.7	53.7		
Distribution				0.087	
Upper ext.	10	80	60		
Lower ext.	13	53.9	53.9		
Trunk	10	45	-		
Pelvic	22	44.3	19.6		
Metastasis (primary)				0.393	
No	52	56.1	41.2		
Yes	3	66.7	66.7		
Treatment				0.038	
Wide excision	20	74.1	55.6		-
Curettage	16	47.7	47.7		1.97 (0.72–5.42) 0.187
Marginal	19	39.4	16.5		4.57 (1.76–11.87) 0.02
Size (cm)				0.205	
<10	28	70.1	48.3		
≥10	27	40.7	33.9		
Soft tissue break				0.640	
No	24	61.5	43.2		
Yes	31	50.4	40.3		
Tumor grade				0.015	
Low grade	27	69.2	58.2		-
Non-low grade	28	41.5	24.2		3.62 (1.60–8.20) 0.002
Overall	55	55.4	40.7		

p value in bold indicates significant.

CI = confidence interval.

^aLog-rank test.

^bCox regression.

Ten patients died of the disease in the study. The 5- and 10-year survival rates were 84.4% and 77.9%, respectively. The median duration of disease-specific death was 48.7 months (8–182 months). The tumor grade was significant factors in the univariate analysis but were insignificant in the Cox regression (Table 4). The development of distant metastasis was a significant prognostic factor in both the uni- and multivariate analyses (Fig. 1).

4. DISCUSSION

Low-grade chondrosarcoma showed a good prognosis in many studies. The 5-year survival ranged from 82% to 99% and 10-year survival from 89% to 95%.⁷ The local recurrence rate varied from 0% to 18%.^{8–11} In our study, the 10-year survival was 88.6%. Ten of our 22 patients (45.5%) developed local recurrence, and two patients (9%) had metastatic disease. Reviewing the 10 patients with local recurrence, we found that seven patients underwent marginal resection, which was a significant prognostic factor for local recurrence in our study. In addition, the two patients with metastatic low-grade chondrosarcoma were also treated with marginal resection. We believe that marginal resection is inadequate for the management of chondrosarcoma, even if the tumor was a low-grade lesion.

Although intralesional curettage was regarded as a method that led to inadequate surgical margins, in our recent study,¹² patients with intracompartmental low-grade chondrosarcoma was a distinct subgroup that could be treated with extended

Table 3
Metastasis-free survival (n = 52)

Variable	Metastasis-free survival (%)			Multivariate analysis	
	Patients	5 y	10 y	<i>p</i> ^a	Hazard ratio (95% CI) <i>p</i> ^b
Gender				0.1662	
Female	19	94.7	86.8		
Male	33	77.6	67.9		
Age (y)				0.4814	
≤50	24	83.1	69.5		
>50	28	81	81		
Distribution				0.878	
Upper ext.	9	77.8	77.8		
Lower ext.	13	91.7	78.6		
Trunk	8	87.5	87.5		
Pelvic	22	76.7	67.1		
Treatment				0.5312	
Wide excision	19	89.5	78.3		
Curettage	16	80.8	80.8		
Marginal	17	70.2	64		
Size (cm)					
<10	14	78.6	65.5		
≥10	38	83.3	78.7		
Soft tissue break				0.7141	
No	24	82.1	82.1		
Yes	28	85.5	71.7		
Grading				0.0287	
Low grade	27	92.3	92.3		
Non-low grade	25	75.3	59.9		3.97 (1.05–14.97) 0.042
Overall	52	79.8	68.1		

p value in bold indicates significant.

CI = confidence interval.

^aLog-rank test.

^bCox regression.

intralesional curettage. This treatment was a safe procedure for low-grade intraosseous chondrosarcoma without increasing the risk for local recurrence. A recent meta-analysis¹³ also reached a similar conclusion. In this study, intralesional curettage was not a significant factor for either local recurrence or overall survival. Previous studies concluded that a high recurrence rate was associated with inadequate surgical margins. However, in a meta-analysis from 2015 with 1114 patients,⁷ the surgical margin was not identified as a prognostic factor for the overall survival rate. For chondrosarcoma, an adequate surgical margin is essential to cure this disease, and we believe that extensive intralesional curettage for intracompartmental low-grade chondrosarcoma is appropriate.

According to previous studies, the recurrence rate of chondrosarcoma was approximately 20% to 58%.^{5,11,14–16} In our study, the local recurrence rate was 52.7% for all patients, of whom, 49.1% had low-grade chondrosarcoma. The local recurrence-free survival was significantly associated with marginal resection and histologic grade in both the univariate and multivariate analyses, whereas tumor distribution was only significant in the univariate analysis. Local recurrence influenced overall survival in some of the published studies.⁵ However, in our data as well as in some previous studies,¹¹ local recurrence showed no effect on overall survival.

In our study, the incidence of metastatic disease was 27.2%, and previous studies showed a rate of 9.7% to 26.1%.^{11,14,17} The variability depends on which histology types were included, whether peripheral chondrosarcomas were included and how

Table 4
Univariate analysis of survival (n = 55)

Variable	Survival (%)			Multivariate analysis	
	Patients	5 y	10 y	Hazard ratio (95% CI)	p ^b
Gender					0.440
Female	19	88.8	81.4		
Male	36	82.2	76.7		
Age (y)					0.763
≤50	26	80	74.3		
>50	29	88.3	81.5		
Distribution					0.912
Upper ext.	10	80	80		
Lower ext.	13	90	77.1		
Trunk	10	80	80		
Pelvic	22	83.1	74.8		
Treatment					0.278
Wide excision	20	84.6	84.6		
Curettage	16	85.9	85.9		
Marginal	19	81.2	64.6		
Size (cm)					0.4236
<10	14	92.3	80.8		
≥10	41	81.6	77.3		
Soft tissue break					0.265
No	20	89	89		
Yes	35	86.9	73.5		
Grading					0.018
Low grade	27	95.5	88.6		
Non-low grade	28	73.9	67.7	2.24 (0.45–11.36)	0.327
Local recurrence					0.049
No	26	92.3	92.3		
Yes	29	76.9	65.9	1.27 (0.16–9.93)	0.82
Metastasis					<0.0001
No	40	97.1	97.1		
Yes	15	46.8	24.5	62.11 (5.33–722.97)	0.001
Multiple surgery					0.381
No	23	86.5	86.5		
Yes	32	82.8	72.4		
Overall	55	84.4	78.1		

p value in bold indicates significant.
CI = confidence interval.
^aLog-rank test.
^bCox regression with time-dependant covariates.

many patients in the study had recurrent disease. Metastatic disease is a significant negative prognostic factor for the overall survival rate, and the 5-year overall survival rate is less than 50%. Some of the patients with metastatic disease underwent local treatment, metaectomy, or systemic therapy; however, the 10-year survival rate is only 14%. Similar to the results of previous studies,^{4,11,17,18} metastatic disease was common in patients with high-grade lesions. However, the tumor location did not affect metastasis, as described.¹⁴ In our study, we also found that high-grade lesion is an independent prognostic factor for metastasis-free survival (Fig. 2).

Age was an influential factor for overall survival, as shown in the data from the SEER database (United States),¹⁹ but this factor was insignificant in our study. In some studies, local recurrence did influence overall survival,^{4,6,20} but we observed the opposite, which has also been described.^{11,14,17} In terms of margins, marginal resection was associated with local recurrence

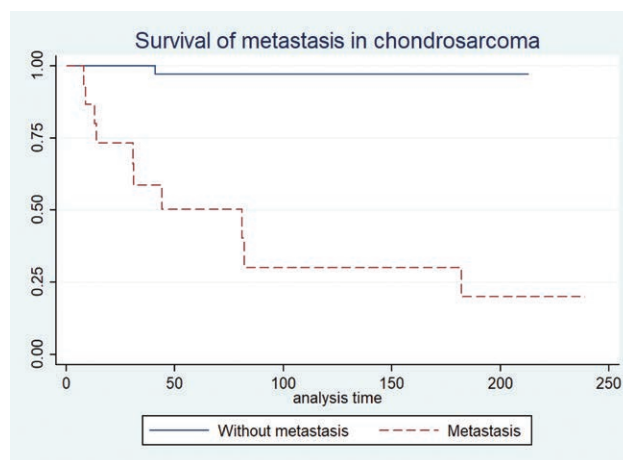


Fig. 1. Survival of metastatic patients in chondrosarcoma.

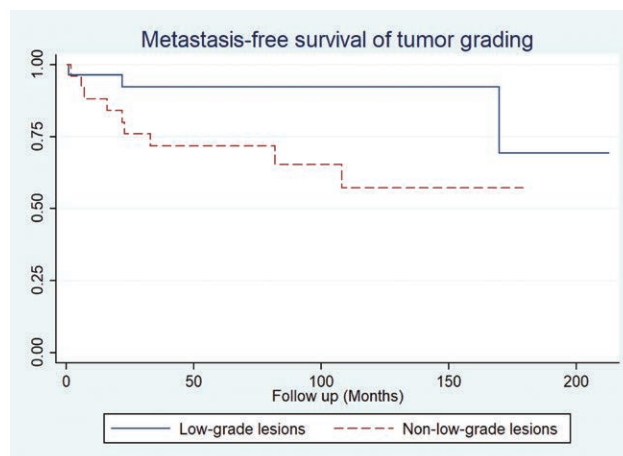


Fig. 2. Metastasis-free survival of tumor grading.

but not overall survival. To the best of our knowledge, only two studies^{21,22} concluded that margin status was associated with overall survival in multivariate analyses.

Tumor size was also reported to adversely influence prognosis in primary chondrosarcoma. In the study from Fiorenza et al,⁴ lesions with diameters over 10cm reduced the overall 10-year survival rate from 83% to 55%. In our series, the average tumor size was 10.2cm, and tumor size did not influence the overall survival rate. Similarly, chondrosarcoma lesions in the pelvis were reported to lead to a poor prognosis^{7,11}; however, this factor was not related to overall survival in our study. The 5- and 10-year survival rates for our patients with pelvic chondrosarcoma were 83.1% and 74.8%, respectively; the 10-year survival rate was reported to be between 54% and 88%.^{23–28}

Thirty-two patients underwent more than two surgeries due to complications or repeated surgery for local recurrence. Lin et al²⁹ found that 60% of chondrosarcoma patients who survived for 10 years had a local recurrence. Their team thought that these patients did not necessarily continuously live disease-free. Most patients had at least two recurrences. We observed similar findings that local recurrence and multiple surgeries did not affect the overall survival rate.

There were several limitations to our study. First, this is a retrospective study, and many variables could not be controlled, including the surgical techniques for treatment. Second, the

study group was small, and further studies with a large population should be designed to validate the conclusions. Third, the effects of chemotherapy or radiotherapy could not be evaluated. These modalities were applied to a few patients as palliative treatment, and its efficacy for treating local recurrence and metastasis could not be concluded.

In conclusion, chondrosarcoma of the bone is a disease with surgery-dependent outcomes; however, patients often develop subsequent recurrence of the disease. The surgical margins were statistically associated with the risk of subsequent local recurrence but did not predict survival. The development of distant metastases is an independent prognostic factor of poor survival.

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