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Prognostic Factors for Survival in Patients With High-grade Chondrosarcoma

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Abstract. *Background/Aim: Chondrosarcoma (CS) is a rare primary malignant bone tumor, which is the second most common tumor after osteosarcoma. Since chemotherapy and radiotherapy have poor efficacy for CS, amputation or surgical wide resection is the main strategy for localized high-grade CS, making CS therapy difficult. As studies on high-grade CS are limited owing to its rare nature, there are many unknown prognostic factors for survival. Patients and Methods: This retrospective cohort study included 44 patients with high-grade CS who underwent surgery at a single institution. Overall survival (OS), distant failure-free survival (DFFS), and local failure-free survival (LFFS) were evaluated using the Kaplan–Meier method. Furthermore, we evaluated prognostic factors for survival in patients with high-grade CS using univariate and multivariate analyses. Results: The 5-year OS, LFFS, and DFFS rates of high-grade CS were 75.9%, 90.8%, and 66.5%, respectively. Univariate analysis revealed that tumor size, tumor grade, and surgical margin were significant prognostic factors for OS and DFFS, and distant metastasis was significantly associated with OS. Furthermore, the multivariate analysis indicated that the presence of local recurrence and distant metastasis was significantly associated with OS. Conclusion: Local recurrence and distant metastasis were significant prognostic factors for high-grade CS.*

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Key Words: Chondrosarcoma, prognostic factor, overall survival, local recurrence, distant metastasis.

Chondrosarcoma (CS) is a rare primary malignant bone tumor with an estimated incidence of 2-3 per 1,000,000 patients per year (1, 2) and the second most common tumor after osteosarcoma. CS is common among patients aged between the 30s and 50s and rare in younger patients. However, secondary CS may also occur in a slightly younger population. Histologically, CS is characterized by the formation of a non-osteoid cartilage matrix by tumor cells (3). Since chemotherapy and radiotherapy have poor efficacy for CS, amputation or surgical wide resection is the main strategy for localized CS (4, 5). Although curettage has become common for low-grade CS (grade 1), high-grade CS (grades 2 and 3) is prone to distant metastasis and has a poor prognosis, requiring extensive resection (6). A previous study reported that 8-38% of patients with CS developed distant metastasis (7). Distant metastasis is considered an independent prognostic factor associated with poor prognosis in patients with CS (8). A major site of distant metastasis is the lungs; patients with CS having lung metastases depict increased mortality rate (5). Prognostic factors for patients with CS have been studied in single-center trials (9), systematic reviews (10), and meta-analyses (11). Although Fromm *et al.* reported that risk factors such as age, tumor location, tumor grade, and distant metastasis significantly correlated with the overall survival of patients with CS, no consensus has been reached yet (12). Since studies on high-grade CS are limited owing to its rare nature, there are many unknown prognostic factors for survival. In the current study, we investigated the prognostic factors for survival in patients with high-grade CS at a single institution.

Patients and Methods

Study design and patients. Approval from the review board of Chiba Cancer Center and informed consent from each patient prior to

Table I. *Patient demographics and disease characteristics*.

Characteristics	N or Median (range)
Sex	
Male	27
Female	17
Age at operation (years)	67 (24-90)
Follow-up period after operation (months)	48 (1-126)
Tumour size (cm)	10 (2.5-26)
Tumour site	
Upper extremity	5
Lower extremity	17
Trunk	22
Grade	
2	38
3	6
Surgical margin	
R0	37
R1	7
R2	0
Chemotherapy	
Yes	4
No	40
Radiotherapy	
Yes	5
No	39

inclusion were obtained before starting the study. We retrospectively reviewed our institution's database for 62 patients with CS who underwent surgery between 2006 and 2020. Among them, patients diagnosed with grade 1 disease by postoperative histological evaluation, those who underwent curettage, and those with distant metastasis at initial diagnosis were excluded. Finally, 44 patients were included in this study.

Clinical characteristics and parameters for investigation. Sex, age at operation, follow-up period after surgery, tumor size and site, grade, surgical margin, and whether chemotherapy and radiotherapy were used were investigated (Table I). Histological grading was performed using the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system. The surgical margin was microscopically categorized; a positive margin (R1 resection) was defined as the presence of tumor cells at the closest margin, and a negative margin (R0 resection) was defined as the absence of tumor cells at the margin. R2 resection was defined as a macroscopic residual tumor after surgery.

Statistical analysis. Overall survival (OS) was defined as the time from the date of surgery to the last follow-up or death. Local failure-free survival (LFFS) and distant failure-free survival (DFFS) were defined as the time from the date of surgery to local or distant failure, respectively, or the last follow-up for patients without events. OS, LFFS, and DFFS were evaluated using the Kaplan–Meier method. Differences in survival were assessed using Cox proportional hazard regression and log-rank tests. Differences were defined statistically significant when p-values were less than 0.05. All analyses were performed with SAS software, version 14.2 (SAS Institute, Inc.; Cary, NC, USA).

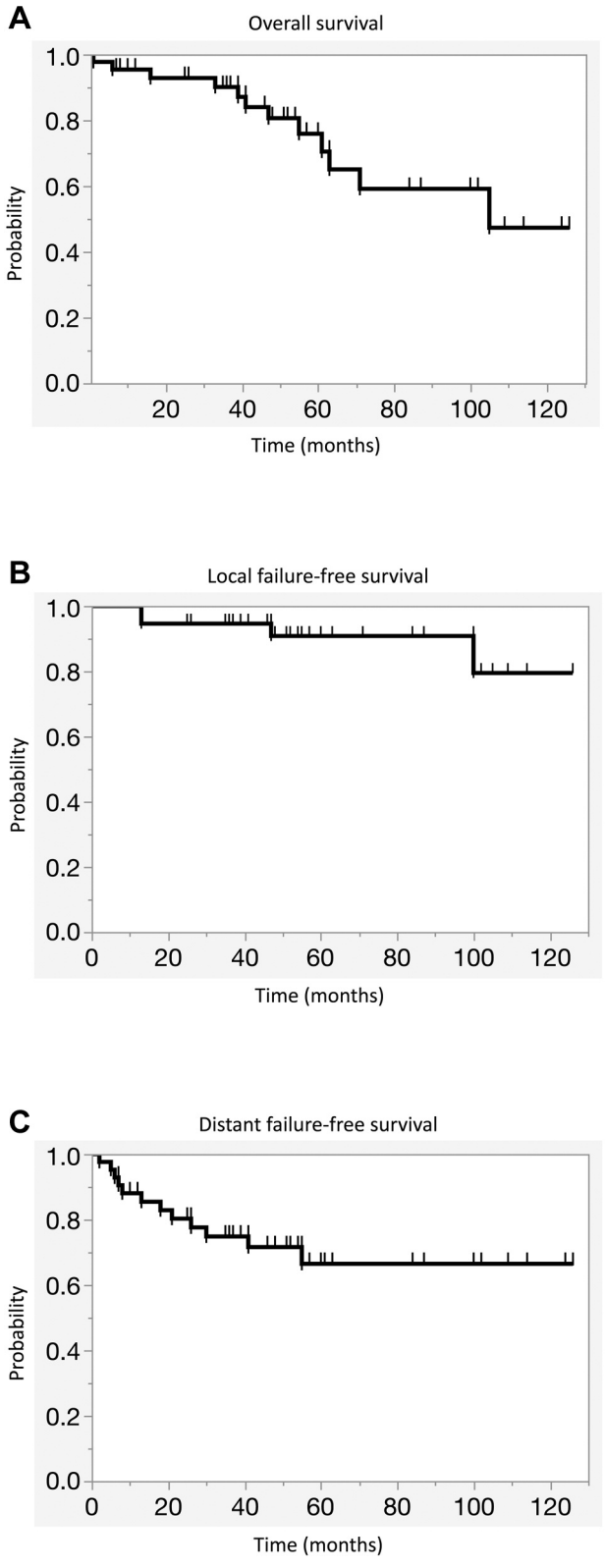

Figure 1. *Kaplan–Meier survival curves demonstrating (A) overall survival, (B) local failure-free survival, and (C) distant failure-free survival of 44 patients*.

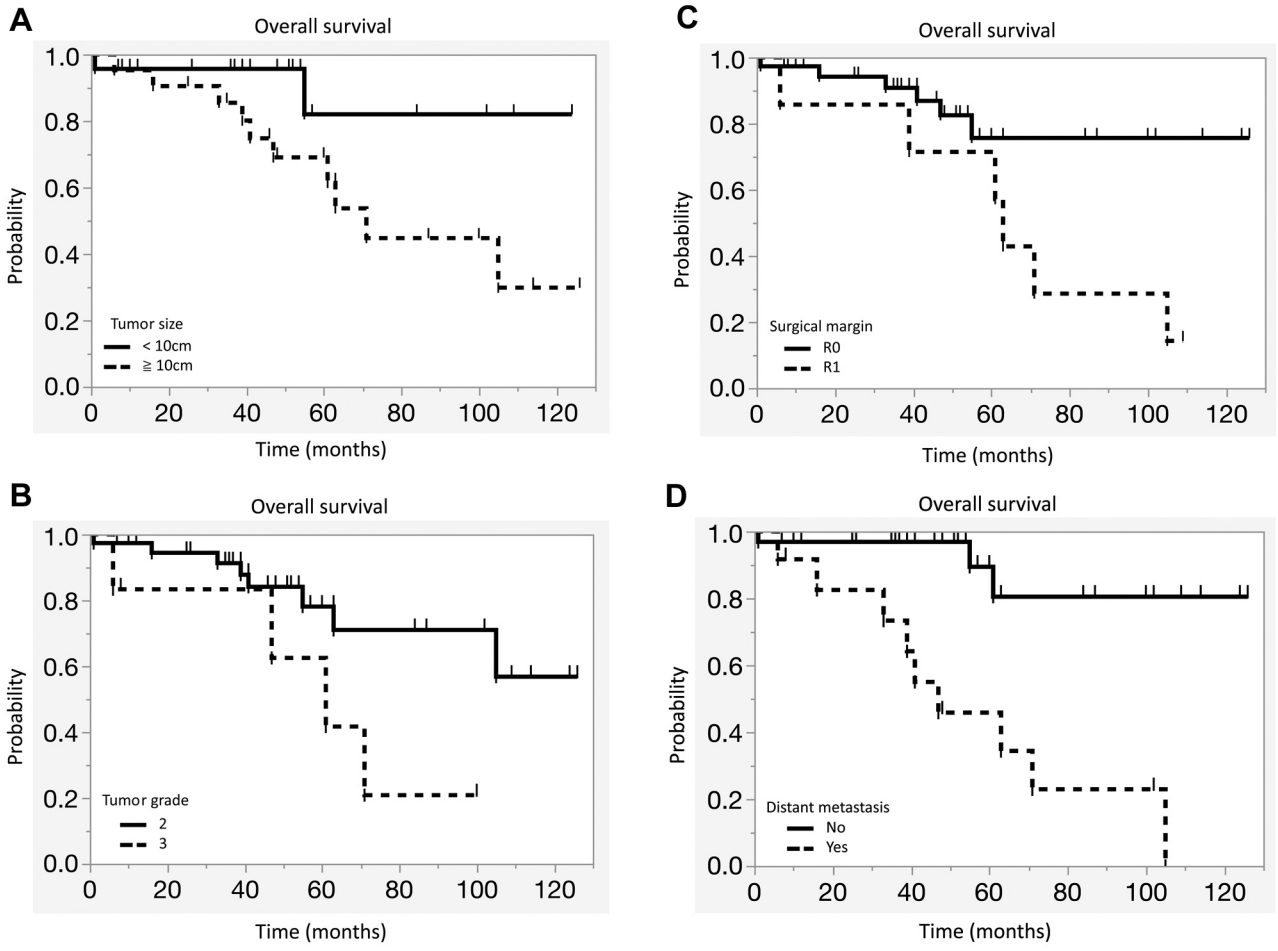

Figure 2. *Kaplan–Meier survival curves demonstrating the impact of (A) tumor size, (B) tumor grade, (C) surgical margin, and (D) distant metastasis on the overall survival of 44 patients.*

Results

Data regarding the patient and tumor characteristics are presented in Table I. Twenty-seven patients were male, and 17 patients were female. The median age at surgery and follow-up period after surgery was 67 years (range=24-90 years) and 48 months (range=1-126 months), respectively. The median tumor size was 10 cm (range=2.5-26 cm). Tumors were located in the upper extremities (n=5), lower extremities (n=17), and trunk (n=22). According to the FNCLCC grading, 38 and 6 cases accounted for grade 2 and grade 3 tumors, respectively. The surgical margins were R0 and R1 in 37 and 7 patients, respectively. Chemotherapy and radiotherapy after surgery were performed in 4 and 5 cases, respectively.

The 5-year OS, LFFS, and DFFS of the 44 patients were 75.9%, 90.8%, and 66.5%, respectively (Figure 1). In this study, local control was good, with only 4 cases (9%) of local recurrence. However, distant metastases occurred in 12 patients, including 10 with pulmonary metastases and 2 with spinal metastases. All 10 patients with pulmonary metastases died of the tumor, regardless of which 4 patients had pulmonary metastasis resections. The median time from lung metastasis to death was 9 months (range=5-88 months).

Univariate analysis of potential prognostic factors for OS and DFFS was performed in all 44 patients (Table II). Tumor size, grade, and surgical margins were significant prognostic factors for OS and DFFS, and distant metastasis was significantly associated with OS. Although chemotherapy and radiotherapy were not significant prognostic factors for OS, they were significant prognostic factors for DFFS. This may be because chemotherapy was given to patients with poor disease conditions, such as distant metastasis. The 5-year OS was significantly different between the <10 cm (82.0%) and ≥10 cm (69.0%) groups (p=0.049) (Figure 2A). Regarding FNCLCC grading, the 5-year OS rate of grade 2 (78.1%) was better than that of grade 3 (62.5%) (p=0.049) (Figure 2B). Similarly, the 5-year OS was significantly different between the R0 (75.6%)

Table II. *Univariate analysis investigating prognostic factors for overall survival and distant failure-free survival.*

Factors		N	5-year OS (%)	*p*-Value	5-year DFFS (%)	*p*-Value
Sex	Male	27	72.4	0.571	58.9	0.232
	Female	17	79.6		79.1	
Age at operation	≥65 years old	23	67.9	0.314	71.5	0.859
	<65 years old	21	83.5		61.3	
Tumour size	≥10 cm	21	69	0.0493*	50.7	0.013*
	<10 cm	23	82		81.6	
Tumour site	Extremity	22	62.4	0.225	57.1	0.297
	Trunk	22	88.8		74.8	
Grade	2	38	78.1	0.0491*	71.5	0.0055*
	3	6	62.5		33.3	
Surgical margin	R0	37	75.6	0.031*	73.7	0.0009*
	R1	7	71.4		28.6	
Chemotherapy	Yes	4	50	0.0853	0	0.0006*
	No	40	79.3		76.8	
Radiotherapy	Yes	5	60	0.0515	0	<0.0001*
	No	39	78.5		76.8	
Local recurrence	Yes	4	50	0.0895	50	0.424
	No	40	78.6		67.8	
Distant metastasis	Yes	12	45.8	0.0001*		
	No	32	89.4			

OS: Overall survival; DFFS: distant failure-free survival. *Statistically significant.

and R1 (71.4%) groups (p=0.031) (Figure 2C). Furthermore, the 5-year OS of the distant metastasis group (45.8%) was significantly worse than the non-metastasis group (89.4%) (p=0.0001) (Figure 2D). Multivariate analysis performed on all 44 patients confirmed that the presence of local recurrence and distant metastasis was significantly associated with OS (Table III). In contrast, tumor size, grade, and surgical margins did not influence the OS in the multivariate analysis.

Table III. *Multivariate analysis investigating prognostic factors for overall survival.*

Factors	Risk ratio	95%CI	*p*-Value
Tumour size, ≥10 cm	1.62	0.25-10.26	0.6075
Grade, 3	1.75	0.45-6.85	0.4198
Surgical margin, R1	1.02	0.2403-4.3364	0.9776
Local recurrence, Yes	5,498	1.2027-25.136	0.0279*
Distant metastasis, Yes	9,177	1.9320-43.5892	0.0053*

CI: Confidence interval. *Statistically significant.

Discussion

In the current study, the 5-year OS, LFFS, and DFFS rates of high-grade CS were 75.9%, 90.8%, and 66.5%, respectively. Univariate analysis revealed that tumor size, tumor grade, and surgical margin were significant prognostic factors for OS and DFFS, and distant metastasis was significantly associated with OS. Furthermore, the multivariate analysis indicated that the presence of local recurrence and distant metastasis was significantly associated with OS.

Julian *et al*. reported that the 5-year OS and LFFS were 79% and 75%, respectively, including grade 1 CS (6). The reason for the better LFFS in the current study may be the exclusion of grade 1. Grade 1 CS is usually treated with curettage because of its good prognosis; however, recurrence is more frequent. Twelve patients in the current study had distant metastases, including lung and spinal metastases. Sarcomas usually cause pulmonary metastasis, and in the current cases of CS, most patients had pulmonary metastases. However, in two cases, spinal metastasis without pulmonary metastasis, and in one of them, paralysis of the lower limbs appeared due to spinal metastasis, requiring emergency surgery. This indicates that we need to pay attention not only to lung metastasis but also to bone metastasis, such as urgent spinal metastasis preceding pulmonary metastasis. In the current study, all 10 patients with pulmonary metastasis died of tumors, among which 4 had pulmonary metastasis resections. Pulmonary metastasis of high-grade CS showed an extremely poor prognosis, which is consistent with previous reports (12). Although this study did not include cases of metastasis at initial diagnosis, the need for local resection has been reported, even in cases of distant metastasis at initial diagnosis (13). Kehan *et al*. indicated a favorable association between primary tumor resection and survival in patients with CS with metastasis at the initial diagnosis, especially in patients with conventional subtypes and grade 2 malignancies. High-grade CS with or without distant metastases requires extensive resection.

Wang *et al*. evaluated the effects of surgery and radiotherapy on the survival of patients with CS and concluded that radiotherapy confers no significant advantage in improving patient survival time (14). In the present study, postoperative radiotherapy was administered to a patient with R1 disease, but no improvement in survival was observed. Italiano *et al*. analyzed the effects of chemotherapy on 180 patients with advanced CS who received chemotherapy in multiple institutions. Among them, 73% of patients received an anthracycline-containing regimen. Conventional chemotherapy has very limited efficacy in patients with advanced CS (5). In the current study, we administered chemotherapy containing an anthracycline-containing regimen to younger patients with distant metastases. However, chemotherapy was not a significant prognostic factor for OS. Although some reports have shown that CS of the pelvis was a negative prognostic factor for OS and LFFS (12), in the present study, even if the trunk was subdivided into the pelvis and others, it had no correlation with prognosis.

The current study has certain limitations. First, it was a retrospective cohort study. Second, the number of cases was extremely small. Third, the study was conducted at a single institution.

In the current study, we evaluated the prognostic factors for survival in high-grade CS. Multivariate analysis indicated that local recurrence and distant metastasis were significantly associated with OS.

Conflicts of Interest

The Authors have no conflicts of interest directly relevant to the content of this article.

Authors' Contributions

H.K designed and performed study, analyzed data, and wrote the article; H.K, Y.H, S.K, S.O and T.Y provided technical support and conceptual advice.

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