Pathology International

Pathology International 2015; **65**: 468–475 doi:10.1111/pin.12324

Original Article

Primary central chondrosarcoma of long bone, limb girdle and trunk: Analysis of 174 cases by numerical scoring on histology

Eiichi Konishi,[1*] Yasuaki Nakashima,[2*] Masayuki Mano,[3*] Yasuhiko Tomita,[4*] Ikumitsu Nagasaki,[5] Toshikazu Kubo,[6*] Nobuhito Araki,[7*] Hironori Haga,[2*] Junya Toguchida,[8*] Takafumi Ueda,[9*] Toshiko Sakuma,[10*] Masaya Imahori,[11*] Eiichi Morii,[12*] Hideki Yoshikawa,[13*] Yoshitane Tsukamoto,[14*] Hiroyuki Futani,[15*] Kenichi Wakasa,[16*] Manabu Hoshi,[17*] Shinshichi Hamada,[18*] Hideyuki Takeshita,[19*] Takeshi Inoue,[20*] Masanari Aono,[21*] Kenji Kawabata,[22*] Hiroaki Murata,[23*] Kanade Katsura,[24*] Yoji Urata,[25*] Hideki Ueda[26*] and Akio Yanagisawa[1*]

Departments of [1]Pathology, [5]Mathematics and [6]Orthopedics, Graduate School of Medicine, Kyoto Prefectural University of Medicine, Departments of [2]Diagnostic Pathology and [8]Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, [24]Department of Pathology, Japanese Red Cross Kyoto Daini Hospital, Departments of [25]Pathology and [26]Orthopedic Surgery, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Departments of [3]Pathology and [9]Orthopaedic Surgery, Osaka National Hospital, Departments of [4]Pathology and [7]Orthopedic Surgery, Osaka Medical Center of Cancer and Cardiovascular Diseases, Departments of [16]Diagnostic Pathology and [17]Orthopedic Surgery, Osaka City University Graduate School of Medicine, Departments of [20]Pathology and [21]Orthopedic Surgery, Osaka City General Hospital, Osaka, Departments of [10]Pathology and [11]Orthopedic Surgery, Hyogo Cancer Center, Akashi, Departments of [12]Pathology and [13]Orthopaedic Surgery, Osaka University Graduate School of Medicine, Suita, Departments of [14]Pathology and [15]Orthopaedic Surgery, Hyogo College of Medicine, Nishinomiya, Departments of [18]Pathology and [19]Orthopedic Surgery, Otsu Municipal Hospital, Otsu, Departments of [22]Pathology and [23]Orthopedic Surgery, Matsushita Memorial Hospital, Moriguchi, Japan

The aims of this study were: (i) to elucidate clinicopathological characteristics of pcCHS of long bones (L), limb girdles (LG) and trunk (T) in Japan; (ii) to investigate predictive pathological findings for outcome of pcCHS of L, LG and T, objectively; and (iii) to elucidate a discrepancy of grade between biopsy and resected specimens. Clinicopathological profiles of 174 pcCHS (79 male, 95 female), of L, LG, and T were retrieved. For each case, a numerical score was given to 18 pathological findings. The average age was 50.5 years (15–80 years). Frequently involved sites were femur, humerus, pelvis and rib. The 5-year and 10-year disease-specific survival (DSS) rates [follow-up: 1–258 months (average 65.5)] were 87.0% and 80.4%, respectively. By Cox hazards analysis on pathological findings, age, sex and location, histologically higher grade and older age were unfavorable predictors, and calcification was a favorable predictor in DSS. The histological grade of resected specimen was higher than that of biopsy in 37.7% (26/69 cases). In conclusion, higher histological grade and older age were predictors for poor, but calcification was for good prognosis. Because there was a discrepancy in grade between biopsy and resected specimens, comprehensive evaluation is necessary before definitive operation for pcCHS.

Key words: grade, pathology, prognosis, primary central chondrosarcoma, statistical analysis

Correspondence: Eiichi Konishi, MD, PhD, Department of Pathology, Graduate School of Medicine, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto, Kyoto, 602-8566 Japan. Email: konie@koto.kpu-m.ac.jp

*The Kansai Musculoskeletal Oncology Group, Japan

Received 15 March 2015. Accepted for publication 1 June 2015.

Chondrosarcoma is the second most common primary sarcoma of the bone, the majority of which are primary central chondrosarcoma (pcCHS).[1] Pathological diagnosis of pcCHS is still challenging. One of the reasons for this is because it is not easy to differentiate grade 1 chondrosarcoma from enchondroma,[2,3] especially by a tiny biopsy specimen, and another is that it is still unclear which pathological

findings are objectively significant for patient's prognosis, although histological grade has been thought to be important.[4–10]

In this study, we performed histopathological and prognostic study on 174 pcCHS cases in long bones, limb girdles and trunk. The aims of this study are to demonstrate the clinicopathological features of pcCHS, and to investigate the objective pathological findings affecting the outcome of pcCHS. In addition, we elucidated the difference in grade between biopsy and resected specimens. This study was conducted with the approval of the institutional review board of each institution.

MATERIALS AND METHODS

A total of 174 cases of pcCHS were retrospectively collected from 14 institutions (members of the Kansai Musculoskeletal Oncology Group, Japan). Patients' first presentation was during November 1984–August 2012. For each case, the medical charts, including radiographs were reviewed. The clinical data (gender, age, localization, method of treatment and follow-up data) and all pathological glass slides were retrieved.

Histological review

All histological slides of each case, obtained at the definitive surgery, were reviewed. For the most representative slide, a numerical score was given to each histopathological finding by three investigators (E.K., M.M and Y.N.) with information of age, sex and location. The scoring system of Eefting *et al.*[2] was modified for this study (Table 1, Fig. 1a–i). All pcCHSs were graded, using the histological criteria for grading based on the World Health Organization (WHO) blue book.[12]

Statistical analysis

Statistical analysis was performed with the SPSS Statistics 22 (IBM, Armonk, NY) with the significance level at 0.05 (two-sided, * $P < 0.05$, ** $P < 0.01$).

Table 1 Scores of pathological parameters on primary central chondrosarcoma of long bones, limb girdles and trunk (174 cases)

Maximum number of nucleus in a tumor cell	≤2: 158 (90.80%)	>2: 16 (9.2%)	
Nuclear pleomorphism	absent: 7 (4.02%)	mild: 71 (40.80%) moderate: 74 (42.53%) severe: 22 (12.64%)	
Pyknotic change of nuclei	absent: 5 (2.87%)	present: 167 (95.98%)	NA:2 (1.15%)
Pale chromatin of nuclei	absent: 115 (66.09%)	present: 59 (33.91%)	
Mitosis	absent: 152 (87.36%)	present: 22 (12.64%)	
Peripheral condensation of the tumor cells at the chondroid nodule	absent: 152 (87.36%)	present: 22 (12.64%)	
Cellularity	sparse: 34 (19.54%)	low: 64 (36.78%) moderate: 59 (33.91%) high: 17 (9.77%)	
Secondary ossification around the chondroid nodule	absent: 73 (41.95%)	present: 101 (58.05%)	
Calcification	absent: 88 (50.57%)	present: 86 (49.43%)	
Encasement†	absent: 119 (68.39%)	present: 43 (24.71%)	NA:12 (6.90%)
Entrapment‡	absent: 60 (34.48%)	present: 93 (53.45%)	NA:21 (12.07%)
Cortical invasion	absent: 9 (5.17%)	present: 68 (39.08%)	NA: 97 (55.75%)
Hyperchromasia	absent: 3 (1.72%)	mild: 82 (47.13%) moderate: 80 (45.98%) severe: 9 (5.17%))	
Number of mitosis	absent: 152 (87.36%)	1–2/10HPF: 22 (12.64%) ≥3/10HPF: 0 (0%)	
Multinucleated cell	absent: 10 (5.74%)	occasional: 138 (79.31%) moderate: 26 (14.94%) numerous: 0 (0%)	
Proportion of chondroid matrix	absent: 15 (8.62%)	≤1/3: 64 (36.78%) ≤2/3: 60 (34.48%) ≤1: 35 (20.11%)	
Proportion of myxoid matrix	absent: 1 (0.57%)	≤1/3: 42 (24.14%) ≤2/3: 55 (31.61%) ≤1: 76 (43.68%)	
Necrosis	absent: 0 (0%)	rare: 46 (26.44%) common: 111 (63.79%) prominent: 17 (9.77%)	

†Having shell of host-lamellar or woven-lamellar bone at the periphery of the cartilage nodules (ref. [11]).
‡Trapping normal host bone trabeculae within the neoplastic cartilage (ref.[11]).
HPF, high power field (objective lens: x40); NA, Data could not be obtained.

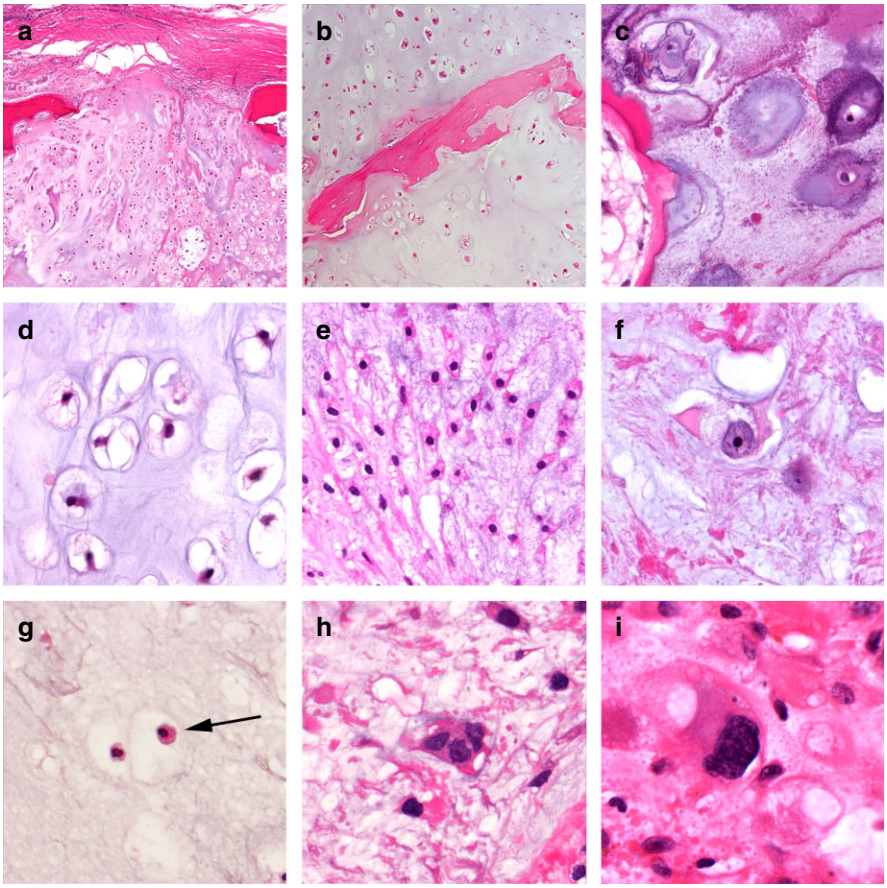

Figure 1 Histopathological features. (**a**) Cortical invasion, (**b**) entrapment of host bone, (**c**) calcification, (**d**) hyaline chondroid matrix, (**e**) myxoid matrix, (**f**) pale chromatin of nucleus, (**g**) pyknotic change of nucleus (arrow), (**h**) multinucleated tumor cell, and (**i**) pleomorphic tumor cell.

Predictive factors for outcome of primary central chondrosarcoma

To elucidate the predictive factors for patient's death, we compared the survival curve, estimated by the Kaplan–Meier method, of the patients in each histological grade, and of the patients with different clinicopathological characters, by the log-rank test. Cox proportional hazards analysis was also conducted as multivariate analysis on both histopathological findings and clinical findings including age, sex, and bone location.

Difference in tumor grade between biopsy and operation

We compared the tumor grade between the biopsy and surgically resected specimens on 69 pcCHS of long bones, limb girdles and trunk in which the glass slides of both biopsy and surgery were available for review.

RESULTS

Age, sex, localization and follow-up

All 174 pcCHS cases were Japanese (male: female = 79: 95). The age at the presentation ranged 15–80 years (average: 50.5, median: 52.5) (Fig. 2). One hundred and six cases (60.9%) were of long bones (humerus, radius, ulna, femur, tibia, and fibula), 38 (21.8%) of the bones of limb girdles (scapula, pelvis), and 30 cases (17.2%) were of the bones of trunk (rib, spine and sternum) (Fig. 2). Frequently involved sites were proximal humerus (22.4%), proximal (10.9%) and distal femur (14.9%), pelvic bones (16.7%) and rib (14.4%). The follow-up period ranged 1–258 months (average: 65.5, median: 50.0). Twenty one patients died of the disease (ranged 2–106 months, average: 36.0, median: 23.0).

Histological review

The results of the score given to histopathological findings are shown (Table 1). Of 174 pcCHS cases, 90 (51.7%) were grade 1 (G1), 67 (38.5%) were grade 2 (G2), and 17 (9.8%) were grade 3 (G3).

Treatment

Among the 174 pcCHS cases, curettage was performed on 61 cases, en bloc resection on 104, and irradiation without

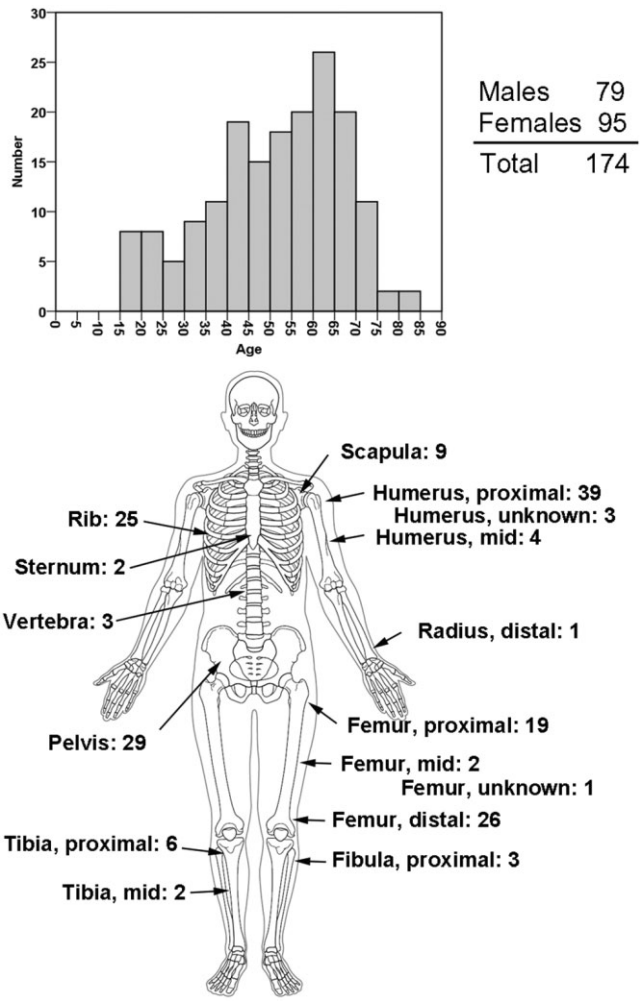

Figure 2 Age, gender and anatomic distribution of primary central chondrosarcoma.

surgery on 9 (Table 2). Radiotherapy was used only for pcCHS of limb girdles or trunk, and heavy particle beam was used on eight cases. PcCHS of the long bones was treated mainly with curettage (58/106 cases, 54.7%), especially G1 tumors (48/71 cases, 67.6%). However, pcCHS of other locations were usually treated with en bloc resection (56/68 cases, 82.4%) and radiotherapy was another choice (9/68 cases, 13.2%). Gade 1 pcCHS was often treated with curettage (49/90 cases, 54.4%), whereas G2 and G3 pcCHS were usually treated with en bloc resection (67/84 cases, 79.8%) (Table 2).

Table 2 Summary of treatment

Location				
	L	LG	T	
C	58	3	0	61
R	48	27	29	104
I	0	8	1	9
	106 (60.9%)	38 (21.8%)	30 (17.2%)	174
Histological grade				
	Grade 1	Grade 2	Grade 3	
C	49	12	0	61
R	37	50	17	104
I	4	5	0	9
	90 (51.7%)	67 (38.5%)	17 (9.8%)	174

C, curettage; I, Irradiation; L, long bones; LG, limb girdles; R, en bloc resection; T, trunk.

Survival analysis

The 5-year and 10-year disease-specific survival (DSS) rates of 174 pcCHS were 87.0% and 80.4%, respectively (Fig. 3a). The 5-year and 10-year DSS rates of each grade were 98.7:95.1% (G1); 84.5:71.7% (G2); and 33.1:33.1% (G3), respectively (Fig. 3b). Log-rank test revealed statistical significance within entire three grades (P = 3.72E-09**). The results after Bonferroni correction[13] between G1 and G2 (P = 0.003**), G2 and G3 (P = 0.003**), and G1 and G3 (P = 6.29E-11**) were also significant.

The 5-year and 10-year DSS rates of each location were 95.7:93.0% (long bones); 74.0:54.4% (limb girdles), respectively (Fig. 3c). The 5-year DSS rate of trunk was 75.1% but data was not available for the 10-year rate (Fig. 3c). Log-rank test showed statistical significance within entire three locations (P = 4.79E-06**). The results after Bonferroni correction[14] between long bones and limb girdles (P = 7.82E-05**), long bones and trunk (P = 2.62E-04**) were significant, but there was no statistical difference between limb girdles and trunk (P = 0.867). Comparison between long bone and bones of limb girdles and trunk showed the 5-year and 10-year DSS rates to be 95.7:93.0% (long bones) and 73.1:57.7% (limb girdles and trunk), respectively (Fig. 3d) and statistically different (P = 2.75E-05**).

Predictive factors for outcome of primary central chondrosarcoma

We compared the DSS curve of the patients in each grade, and of the patients with different clinicopathological characteristics, using the log-rank test. The maximum number of nuclei in a cell, nuclear pleomorphism, pale chromatin, mitosis, cellularity, calcification, encasement, entrapment, hyperchromasia, proportion of chondroid and myxoid matrix, treatment, location (including long bones vs limb girdles and trunk), grade, peripheral condensation of tumor cells and sex were significant predictors (P < 0.05*) (Table 3a).

We performed Cox proportional hazards analysis on the above mentioned clinicopathological features. We excluded treatment from the analysis, because in this study, not only

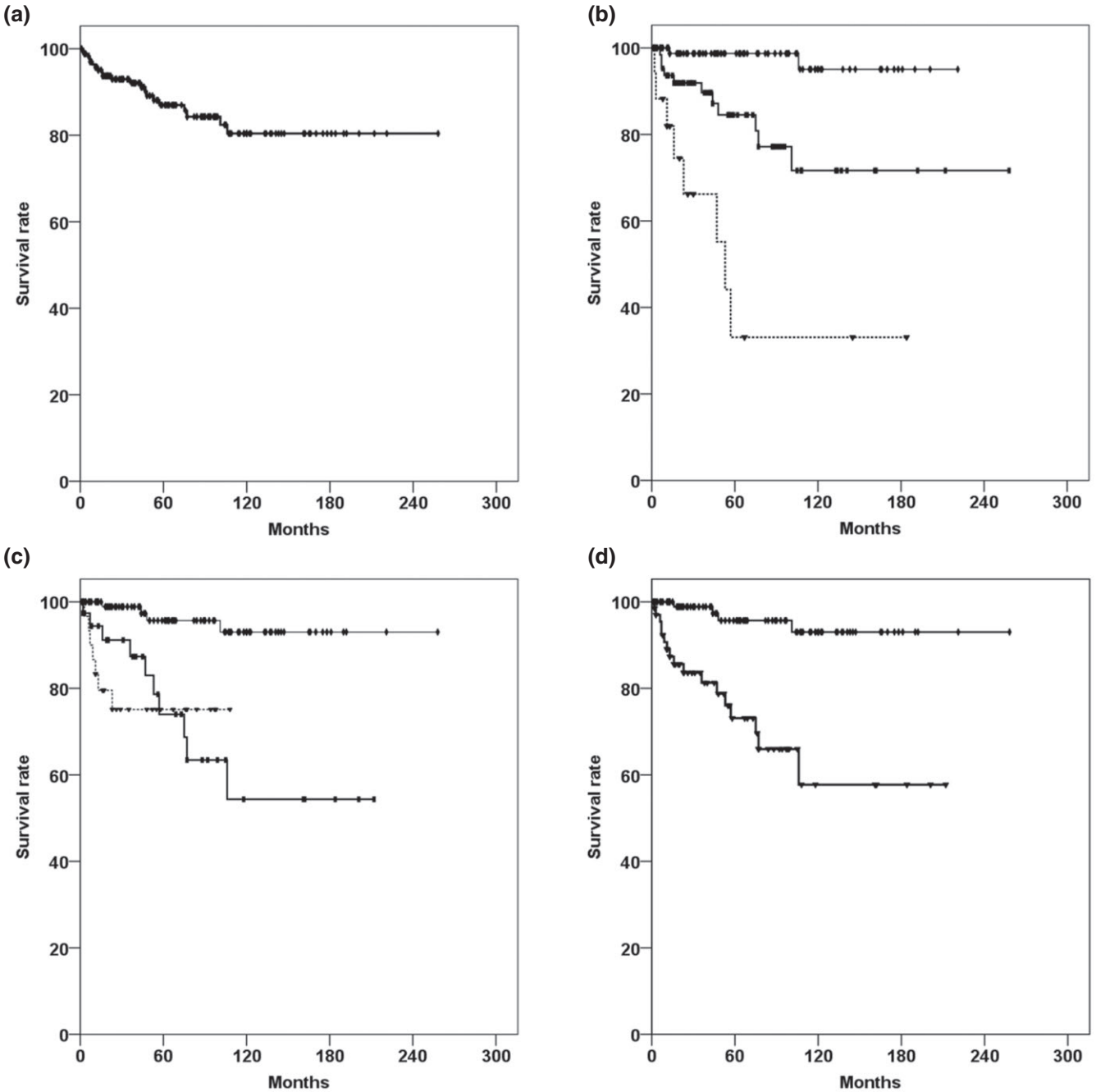

Figure 3 Disease-specific survival curves of primary central chondrosarcoma of long bones (L), limb girdles (LG) and trunk (T). (**a**) All cases. (**b**) Each grade (1 to 3). (**c**) Each location (L, LG, T). (**d**) Location (L vs LG+T). (**a**) ⌐¬, DSS; ⧫, DSS, censored; (**b**) ⌐¬, Grade 1; ⌐¬, Grade 2; ⌐¬, Grade 3; ⧫, Grade 1 censored; ▮, Grade 2 censored; ▼, Grade 3 censored; (**c**) ⌐¬, L; ⌐¬, LG; ⌐¬, T; ⧫, L, censored; ▮, LG, censored; ▼, T, censored; (**d**) ⌐¬, L; ⌐¬, LG and T; ⧫, L, censored; ▼, LG, and T, censored.

we did not stratify the cases according to the tumor stage (e.g., size, growth pattern, metastasis)[12] that must strongly affect choice of therapy, but there were considerable variations in the surgical procedures among the 14 institutions. In order to improve the quality of statistical model, we excluded nuclear pyknotic change, entrapment, encasement and cortical invasion, because they had missing values (Table 1).

As the criteria of histological grade[12] include some pathological features which are used here, we performed a hazard analysis excluding histological grade, at first. However, the analysis could not be completed by SPSS Statistics 22 (data not shown). When analyzed with histological grade, age, grade and calcification were selected for the equation for DSS of pcCHS of long bones, limb girdles and trunk. It was

Table 3 a. Comparison of disease-specific survival curves in different clinicopathological findings of primary central chondrosarcoma of long bones, limb girdles and trunk. b. Correlation coefficient between histological grade and each parameter

	a. *P*-value	b. Correlation coefficient between histological grade and each parameter
Maximum number of nucleus in a tumor cell: ≦ 2 or >2	<0.001**	0.406**
Nuclear pleomorphism: absent, mild, moderate, severe	<0.001**	0.637**
Pyknotic change of nuclei: absent or present	0.75	–0.052
Pale chromatin of nuclei: absent or present	<0.001**	0.581**
Mitosis: absent or present	<0.001**	0.502**
Peripheral condensation of the tumor cells at the chondroid nodule: absent or present	0.014*	0.349**
Cellularity: sparse, low, moderate, high	<0.001**	0.853**
Secondary ossification around the chondroid nodule: absent or present	0.086	–0.189*
Calcification: absent or present	<0.001**	–0.389**
Encasement: absent or present	0.021*	–0.413**
Entrapment: absent or present	0.031*	0.214**
Cortical invasion: absent or present	0.147	0.297**
Hyperchromasia: absent, mild, moderate, severe	<0.001**	0.658**
Mitosis: absent, 1–2/10HPF, 3/10HPF≤	<0.001**	0.502**
Multinucleated cell: absent, occasional, moderate, numerous.	0.175	0.388**
Proportion of chondroid matrix: absent, ≤ 1/3, ≤ 2/3, ≤ 1	<0.001**	–0.531**
Proportion of myxoid matrix: absent, ≤ 1/3, ≤ 2/3, ≤ 1	<0.001**	0.511**
Necrosis: absent, rare, common, prominent.	0.085	0.431**
Treatment: C vs R vs I	0.002**	
Location: L vs LG vs T	<0.001**	
Location: L vs LG and T	<0.001**	
Grade: 1 vs 2 vs 3	<0.001**	1
Gender: male or female	0.025*	

Log-rank test and Spearman's rank correlation coefficient, *$P < 0.05$; **$P < 0.01$

C, curettage; I, Irradiation; L, long bone; LG, limb girdle; R, en bloc resection; T, trunk.

Table 4 Result of hazard analysis on clinicopathological features of primary central chondrosarcoma of long bones, limb girdles and trunk

Omnibus tests of model coefficients

	Overall (score)			
-2 Log Likelihood	Chi-square	df	*P*-value	AIC
152.960	52.885	4	9.01E-11**	160.960

Variables in the equation

			95% Confidence Interval for hazard ratio	
	P-value	Hazard ratio	Lower	Upper
Age	0.017*	1.041	1.007	1.075
Grade	0.0010**			
Grade(1)	0.038*	5.241	1.098	25.023
Grade(2)	<0.001**	18.564	3.514	98.070
Calcification	0.029*	0.182	0.040	0.839

*$P < 0.05$; **$P < 0.01$.

Cox proportional hazard analysis, forward stepwise (likelihood ratio).

Grade (1), grade 1 vs grade 2; Grade (2), grade 1 vs grade 3.

AIC, Akaike's Information Criterion.

statistically significant (P = 9.01E-11**) and each selected feature was also significant ($P < 0.05$*) (Table 4). The hazard ratios of age, G1 vs G2, and G1 vs G3 were 1.041, 5.241 and 18.564, respectively, but that of calcification was 0.182. Older age and higher grade were significant predictors for a poor prognosis but the presence of calcification was a significant predictor for favorable prognosis. The result was unchanged even when using two groups (long bones vs limb girdles and trunk) instead of three (long bone, limb girdles, trunk) as the location.

Because the grade was a strong predictor and its criteria include some pathological parameters used here, we elucidated Spearman's rank correlation coefficient between histological grade and each parameter (Table 3b). Only cellularity had a strong correlation (correlation coefficient > 0.7). Other features, such as the maximum number of nuclei

per cell, nuclear pleomorphism, pale chromatin, mitosis, encasement, hyperchromasia, proportion of chondroid or myxoid matrix, and necrosis had only a moderate correlation (0.4 < correlation coefficient ≤ 0.7) (Table 3b).

Difference in tumor grade between biopsy and operation

Of the 69 cases of pcCHS, the histological grade of operated specimens was higher than that of biopsy specimens in 26 cases (37.7%). The grade did not change in 43 cases (62.3%). Of the 69 cases, entrapment was observed in only 18 cases (26.1%) in biopsy.

DISCUSSION

Chondrosarcoma is the second most common primary sarcoma of the bone[1] and is about 14% of all malignant bone tumors in Japan.[14] It has been difficult to accumulate a high enough number of chondrosarcoma cases to elucidate clinicopathological aspects in Japan because the sarcoma centers are relatively small. We performed a multi-institutional study and collected 174 cases of pcCHS of long bones, limb girdles and trunk. For this study, we excluded secondary chondrosarcoma because the histological criteria are different.[1,15]

In this study, the age distribution of pcCHS of long bones, limb girdles and trunk showed a peak at after the fifth decade of life as seen in previous reports.[1,4,5,8,10,16–18] Regarding the sex ratio, females showed a mild preponderance (male: female = 79:95), while the previous reports argued conversely.[1,4,5,8,10,16–19] It might be caused by the ethnic variation including hormonal condition,[20] and/or the bias for sample selection, but the true reason is unclear. In this study, the most affected bone was the long bone (60.9%), followed by limb girdles (21.8%) and trunk (17.2%). In systemic distribution, the frequency of long bones, especially the proximal humerus, was higher in the current series than in other series.[1,4,5,9,10,21]

Recently, curettage has been selected as treatment of G1 chondrosarcoma of long bones.[22–24] In this study, pcCHS of long bones, especially G1 tumor, was often treated with curettage [all grade: 58/106 case (54.7%), G1: 48/71 case (67.6%)]. Local adjuvant procedures (e.g. liquid nitrogen, ethanol, bone cement)[22–24] were frequently used together. Although some G2 pcCHS of long bones were treated with curettage, a log-rank analysis of DSS curve between the cases with curettage and with resection failed to reveal a statistical difference ($P = 0.164$, data not shown). The reason for this might be that the G2 area was very small within the tumor, and/or that the tumor itself was small-sized. For pcCHS of limb girdles and of trunk, or for high-grade (G2 or G3) pcCHS, resection or radiation was usually chosen as in the previous reports.[9,10,22–24]

We used the WHO criteria for histological grading,[12] but historically, there have been several systems used.[5,7,18,25,26] The proportion of grades in this study (G1: G2: G3 = 51.7%: 38.5%: 9.8%) was similar to the previous results (G1: G2: G3 = 27–61%: 30–62%: 3–17%).[4–6,8,9,16,18] The DSS rates (G1, G2, G3) were statistically different from each other, as in previous reports.[4,5,7,10,17] The 5-year and 10-year DSS rates in this study were as follows: 98.7: 95.1% (G1), 84.5: 71.7% (G2), and 33.1: 33.1% (G3). In the previous reports, the 5-year and 10-year survival rates were as follows: 89–96% (G1), 63–90% (G2), and 39–80% (G3);[4–6,9,16] and 77–95% (G1), 58–85% (G2), and 29–50% (G3), respectively.[5,6,9,10,16] The outcome of chondrosarcoma had remained basically unchanged for the latest three decades.[8] It might be difficult to improve the outcome strikingly, as long as surgery is the first choice of therapy.

By the hazards analysis, we extracted significant predictive factors for pcCHS of long bones, limb girdles and trunk: age, grade, and calcification. Grade has been regarded as an important predictive factor in many studies,[4–10] as in this study, but not in others.[27] As is well known, the criteria of the grade contains some histological features, such as cellularity, nuclear atypia, mitoses, etc.[5,7,12,18,25,26] In this study, grade has a correlation with some histological parameters, as shown above, but the hazard analysis except grade was not completed by SPSS Statistics 22. The selected histological parameter in the hazard analysis with grade was only calcification that showed only a weak correlation (correlation coefficient ≤ 0.4) with grade. It might mean that histological grade is comprehensive and overriding histological parameter for prognosis.

Presence of calcification was a salient predictive factor for favorable prognosis but older age was a predictive factor for worse prognosis. Dense map-like calcification is regarded as a feature of enchondroma.[28] Even in pcCHS, the presence of microscopic calcification will have a strong value for favorable outcome. The above three features were significant predictors for outcome, although the clinical stage which must affect the outcome was not analyzed here. Further study with more clinical factors is necessary to find out more accurate prognostic indicators.

There was a discrepancy in histological grade between biopsy specimens and operated materials (resections). In 37.7% of the cases, the grade of the operated material was higher than that of the biopsy. Dahlin *et al*. explained that this was caused by the heterogeneity of chondrosarcoma.[18] Mirra *et al*. suspected that it was due to the coexistence of enchondroma and chondrosarcoma in the same lesion and that enchondroma progressed to chondrosarcoma.[11] Entrapment was reported as the most important pathological feature for

invasiveness,[2,11] but only 26.1% of the biopsy specimen of pcCHS contained this feature. The result supports the requirement of the modalities other than the biopsy which can evaluate the lesion correctly before the operation. It is more critical when we need to differentiate G1 pcCHS from solitary enchondroma of the long bone, which is one of the most challenging diagnoses in the field of surgical pathology. Objective pathological criteria should be investigated in this differentiation.

In conclusion, we analyzed clinicopathological features of 174 pcCHS of long bones, limb girdles and trunk. Female and long bone preponderance for pcCHS were present in Japan, but the clinicopathological features, treatment and outcome were not substantially different from the previous results. The predictors for the DDS of pcCHS of long bones, limb girdles and trunk were age, grade, and calcification. In contrast to older age and higher grade, the presence of calcification was a predictor for favorable prognosis. Because the grade is often higher in the resected specimen than in biopsy and the biopsy specimen has limitations in diagnostic histological findings, comprehensive clinicopathological evaluation of pCHS is mandatory before the operation.

ACKNOWLEDGMENTS

The study was partly funded by Ministry of Education, Culture, Sports, Science and Technology, Japan (EK, MM, HT and AY, Grant no. 25462349).

DISCLOSURE STATEMENT

None declared.

REFERENCES

1 Unni KK, Inwards CY. *Dahlin's Bone Tumors: General Aspects and Data on 10,165 Cases*, 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2010.
2 Eefting D, Schrage YM, Geirnaerdt MJ *et al*. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. *Am J Surg Pathol* 2009; **33**: 50–57.
3 Jones KB, Buckwalter JA, McCarthy EF *et al*. Reliability of histopathologic and radiologic grading of cartilaginous neoplasms in long bones. *J Bone Joint Surg Am* 2007; **89**: 2113–23.
4 Björnsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. *Cancer* 1998; **83**: 2105–19.
5 Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone. A clinicopathologic analysis with emphasis on histologic grading. *Cancer* 1977; **40**: 818–31.
6 Fiorenza F, Abudu A, Grimer RJ *et al*. Risk factors for survival and local control in chondrosarcoma of bone. *J Bone Joint Surg Br* 2002; **84**: 93–9.
7 Gitelis S, Bertoni F, Picci P, Campanacci M. Chondrosarcoma of bone. The experience at the Istituto Ortopedico Rizzoli. *J Bone Joint Surg Am* 1981; **63**: 1248–57.
8 Giuffrida AY, Burgueno JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): An analysis of 2890 cases from the SEER database. *J Bone Joint Surg Am* 2009; **91**: 1063–72.
9 Lee FY, Mankin HJ, Fondren G *et al*. Chondrosarcoma of bone: An assessment of outcome. *J Bone Joint Surg Am* 1999; **81**: 326–38.
10 Pritchard DJ, Lunke RJ, Taylor WF, Dahlin DC, Medley BE. Chondrosarcoma: A clinicopathologic and statistical analysis. *Cancer* 1980; **45**: 149–57.
11 Mirra JM, Gold R, Downs J, Eckhardt JJ. A new histologic approach to the differentiation of enchondroma and chondrosarcoma of the bones. A clinicopathologic analysis of 51 cases. *Clin Orthop Relat Res* 1985; **201**: 214–37.
12 Fletcher C, Bridge J, Hogendoorn P, Mertens F, eds. *WHO Classification of Tumours of Soft Tissue and Bone*, 4th edn. Lyon: IARC, 2013.
13 Dunn OJ. Multiple comparisons among means. *J Am Stat Assoc* 1961; **56**: 52–65.
14 The Japanese Orthopaedic Association, Committee of Tumors, ed. *General Rules for Clinical and Pathological Studies on Malignant Bone Tumors (in Japanese)*, 3rd edn. Tokyo: Kanehara&CO, LTD, 2000.
15 Liu J, Hudkins PG, Swee RG, Unni KK. Bone sarcomas associated with Ollier's disease. *Cancer* 1987; **59**: 1376–85.
16 Andreou D, Ruppin S, Fehlberg S, Pink D, Werner M, Tunn PU. Survival and prognostic factors in chondrosarcoma: Results in 115 patients with long-term follow-up. *Acta Orthop* 2011; **82**: 749–55.
17 Angelini A, Guerra G, Mavrogenis AF, Pala E, Picci P, Ruggieri P. Clinical outcome of central conventional chondrosarcoma. *J Surg Oncol* 2012; **106**: 929–37. doi: 10.1002/jso.23173.
18 Dahlin DC, Henderson ED. Chondrosarcoma, a surgical and pathological problem; review of 212 cases. *J Bone Joint Surg Am* 1956; **38A**: 1025–38. passim.
19 O'Neal LW, Ackerman LV. Chondrosarcoma of bone. *Cancer* 1952; **5**: 551–77.
20 Chagin AS, Sävendahl L. Estrogens and growth: Review. *Ped Endocrinol Rev* 2007; **4**: 329–34.
21 Henderson ED, Dahlin DC. Chondrosarcoma of bone–a study of two hundred and eighty-eight cases. *J Bone Joint Surg Am* 1963; **45**: 1450–58.
22 Gelderblom H, Hogendoorn PCW, Dijkstra SD *et al*. The clinical approach towards chondrosarcoma. *Oncologist* 2008; **13**: 320–29.
23 Mavrogenis AF, Gambarotti M, Angelini A *et al*. Chondrosarcomas revisited. *Orthopedics* 2012; **35**: e379–90. doi: 10.3928/01477447-20120222-30.
24 Riedel RF, Larrier N, Dodd L, Kirsch D, Martinez S, Brigman BE. The clinical management of chondrosarcoma. *Curr Treat Options Oncol* 2009; **10**: 94–106.
25 Mankin HJ, Cantley KP, Lippiello L. The biology of human chondrosarcoma. I. Description of the cases, grading, and biochemical analyses. *J Bone Joint Surg Am* 1980; **62**: 160–76.
26 Sanerkin NG. The diagnosis and grading of chondrosarcoma of bones. A combined cytologic and histologic approach. *Cancer* 1980; **45**: 582–94.
27 Rizzo M, Ghert MA, Harrelson JM, Scully SP. Chondrosarcoma of bone: Analysis of 108 cases and evaluation for predictors of outcome. *Clin Orthop Relat Res* 2001; **391**: 224–33.
28 Schiller AL. Diagnosis of borderline cartilage lesions of bone. *Semin Diagn Pathol* 1985; **2**: 42–62.