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A new scoring system for the grading of conventional chondrosarcoma: Its clinicopathological significance

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ABSTRACT

Background: Chondrosarcoma is the second most common primary malignant bone tumor, which produces cartilaginous matrix without neoplastic osteoid or bone formation. The histological grade in the WHO Classification of Soft Tissue and Bone (2020 edition) is the most important factor in predicting the clinical outcome of conventional chondrosarcoma, but the lack of clarity in its detailed definition is occasionally problematic. Here, we reviewed conventional chondrosarcoma cases and validated the significance of histological findings. Moreover, we proposed a new scoring system of conventional chondrosarcoma.

Material and methods: Clinicopathological features of 60 cases of conventional chondrosarcoma and 21 cases of dedifferentiated chondrosarcoma were reviewed.

Results: Moderate to severe nuclear atypia was correlated with distant metastasis. Moderate and severe nuclear atypia, high cellularity, and >1 % myxoid change were correlated with adverse overall survival. On the other hand, cases with mild nuclear atypia showed no tumor-related death and no metastases. Based on the above results, we proposed a new scoring system based on nuclear atypia (mild: 0, moderate: +1, severe: +2), cellularity (no and mildly increased cellularity: 0, moderately and diffusely increased cellularity: +1), necrosis [(-): 0, (+): +1], and chondromyxoid area [(-): 0, (+): +1]. Each grade was defined as follows: cases with only mild nuclear atypia as grade 1, cases with total score 1–3 excluding mild nuclear atypia as grade 2, and cases with total score 4 or 5 as grade 3. There were 18 cases (30 %) of grade 1 including 5 cases (28 %) of local recurrence, but no metastasis or tumor-related death; 26 cases (43 %) of grade 2 including 2 cases (8 %) of local recurrence, 3 cases (12 %) of metastasis, and 1 case (4 %) of tumor-related death; and 16 cases (27 %) of grade 3 including 4 cases (25 %) of local recurrence, 6 cases (38 %) of metastasis, and 5 cases (31 %) of tumor-related death. There was no statistically significant association between the histological findings and dedifferentiation.

Conclusion: From this study, we propose a new histological scoring system for the grading of conventional chondrosarcoma, based on nuclear atypia, cellularity, necrosis, and myxoid change. Using this system, conventional chondrosarcoma may be clearly classified into three grades: grade 1, non-metastasizing; grade 2, metastasizing but rarely life-threatening; and grade 3, frequently metastasizing and life-threatening.

1. Introduction

Chondrosarcoma is the second most common primary malignant bone tumor, with cartilaginous matrix but a lack of neoplastic osteoid or bone formation. Conventional chondrosarcoma, known as conventional central chondrosarcoma, is the most common type. Local recurrence and distant metastasis often occur. Special subtypes include secondary,

periosteal, clear cell, mesenchymal, and dedifferentiated chondrosarcoma [1]. The standard treatment is surgery with wide surgical margins. There is no effective therapy for unresectable chondrosarcoma, recurrence, or distant metastatic lesion, which are associated with a poorer clinical outcome.

The diagnosis of chondrosarcoma has been historically based on the histological criteria described in the WHO Classification of Soft Tissue

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Tumors [2,3]. However, the WHO system only defines the grades of chondrosarcoma descriptively. Histopathologically, chondrosarcoma usually reveals atypical chondrocytes with nuclear atypia, nuclear pleomorphism and/or binucleation, chondroid stroma, and a permeating pattern. Although histological grading is known to be useful for prognostic prediction, the definitive histological criteria of the grading system are still unclear.

In addition, about 15 % of chondrosarcoma cases are accompanied by dedifferentiation. Dedifferentiated chondrosarcoma is defined as a high-grade transformation from the conventional type of chondrosarcoma [4]. Although dedifferentiated chondrosarcoma is also well known to have a poorer prognosis than conventional chondrosarcoma [5], to the best of our knowledge no reports on the histological risk factors for the dedifferentiation of conventional chondrosarcoma have been reported.

In this study, we reviewed the clinical and histological features of chondrosarcoma to reveal the prognostic factors and risk factors for dedifferentiation. We also attempted to establish a new and more objective histological scoring system for the grading of conventional chondrosarcoma.

2. Material and methods

2.1. Case selection

We reviewed a total of 87 chondrosarcoma cases [60 cases of conventional chondrosarcoma, 6 cases of atypical cartilaginous tumor (ACT), and 21 cases of dedifferentiated chondrosarcoma] that had been diagnosed at the Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, between 1978 and 2020. The ACT cases were excluded from the current study. All cases were surgically resected and histologically diagnosed and classified into three grades, based on the current WHO Classification of Tumors of Soft Tissue and Bone published in 2020; conventional chondrosarcoma was diagnosed when either apparent nuclear atypia or bone destruction (permeating pattern) was observed [2]. We excluded the cases with only a biopsy specimen and those involving non-conventional chondrosarcoma, including secondary chondrosarcoma (Ollier disease and multiple osteochondroma), periosteal chondrosarcoma, clear cell chondrosarcoma, and mesenchymal chondrosarcoma, as well as the cases with preoperative chemotherapy or radiotherapy.

2.2. Clinicopathological data

Survival data of chondrosarcoma were available for 87 cases [60 cases of conventional chondrosarcoma, 6 cases of ACT (minimum cytological atypia with permeating pattern), and 21 cases of dedifferentiated chondrosarcoma], with follow-up ranging from 0 to 395 months (mean 72, median 37). Clinical outcome was evaluated according to age, sex, tumor location, tumor size, extraosseous extension, and the history of local recurrence, distant metastasis, and tumor-related death. The tumor sites were divided into two categories, namely, appendicular skeleton (humerus, femur, tibia, fibula, and phalanges) and non-appendicular skeleton (vertebrae, ribs, sternum, clavicle, pelvis, and scapula).

The Enneking classification and the American Joint Committee on Cancer (AJCC) staging system 8th edition were used to evaluate extension of the tumors. As chondrosarcoma of neither the pelvis ($N = 12$) nor the vertebrae ($N = 6$) is staged in the AJCC staging system 8th edition, these sites were excluded. In the Enneking classification and AJCC 8th edition, grade 2 and 3 tumors are classified as high grade [6].

2.3. Histopathological data

For conventional light microscopy, tumor tissue was fixed in 10 % formalin, embedded in paraffin, sliced at a thickness of 3 μm , and

Table 1

A scoring system for the grading of conventional chondrosarcoma.

Scoring	0	1 +	2 +
Nuclear atypia	Mild	Moderate	Severe
Cellularity	No and mildly increased cellularity	Moderately and diffusely increased cellularity	
Necrosis	(-)	(+)	
Myxoid change	(-)	(+)	

stained with hematoxylin and eosin. All specimens were reviewed by two pathologists (YS and YY). The average number of slide glasses reviewed in each case for this study was 14 (1 at minimum and 109 at maximum, depending on the tumor size). Dedifferentiated chondrosarcoma was defined as a high-grade subtype of chondrosarcoma with the histological appearance of a conventional chondrosarcoma component with abrupt transition to a high-grade, non-cartilaginous sarcoma.

Histopathologically, the cartilage matrix-producing component of conventional chondrosarcoma and that of dedifferentiated chondrosarcoma were compared to each other. Nuclear atypia, cellularity, presence of mitotic figures, binucleation or necrosis, and the cut-off percentage of myxoid area in the maximum cut surface (1 %, 10 %, 30 %) were evaluated. Histologically, nuclear atypia was classified as mild, moderate, or severe. Cellularity was defined in terms of the tumor cells per unit area, and areas with > 50 % cellularity were defined as having high cellularity, in accordance with previous research [7]. The rate of high cellularity relative to a representative specimen was calculated as a percentage. The proportion occupied by high cellularity was calculated as follows: mildly increased cellularity indicates that the high-cellularity area occupies 1–10 % in the representative specimen, moderately increased cellularity indicates 10–49 %, diffusely increased cellularity indicates ≥ 50 %, and no increased cellularity indicates 0 %. The percentage of myxoid area in the maximum cut surface was classified into three categories: > 1 %, 10 %, and 30 %. Mitotic activity was also evaluated; a mitotic count of ≥ 2 per 10 high-power fields was judged as “high mitotic activity.” The presence of both coagulative and liquefactive necrosis within chondrosarcoma was judged to represent tumor necrosis.

The histological grading of chondrosarcoma was performed in accordance with the current WHO classification, reflecting the levels of nuclear atypia, cellularity, and mitotic activity. Grade 1 shows minimal nuclear atypia and increased cellularity; grade 2 shows moderate nuclear atypia and cellularity; and grade 3 shows high cellularity, marked atypical cells, pleomorphic appearance, and easily identifiable mitotic figures.

A new scoring system (modified WHO grade classification) was also proposed in this study, which is based on nuclear atypia (mild: 0, moderate: +1, severe: +2), cellularity (no and mildly increased cellularity: 0, moderately and diffusely increased cellularity: +1), necrosis [(-): 0, (+): +1], and chondromyxoid area [(-): 0, (+): +1] (Table 1). Each grade was defined as follows: cases with only mild nuclear atypia as grade 1, cases with total score 1–3 excluding mild nuclear atypia as grade 2, and cases with total score 4 or 5 as grade 3.

2.4. Statistical analysis

Fisher's exact test was used to evaluate differences between pairs of populations. Thus, all of the clinicopathological and histopathological factors (age, sex, tumor size, tumor location, local recurrence, distant metastasis, extraosseous extension, and tumor-related death) were analyzed using Fisher's test. The survival information is illustrated with Kaplan-Meier curves, and survival analyses were performed with the clinicopathological data using the log-rank test. A two-sided P value of < 0.05 was considered to indicate statistical significance. Kappa

Table 2

Clinicopathological and histopathological findings of conventional chondrosarcoma.

		N (%)	Local recurrence*	Distant metastasis*	Tumor- related death*
Age	≥ 50	27 (45 %)	0.0356	0.5752	0.9807
	< 50	33 (55 %)			
Sex	M	36 (60 %)	0.9184	0.2638	0.6072
	F	24 (40 %)			
Tumor location	Non- appendicular skeleton	34 (57 %)	0.0102	0.9142	0.6356
	Appendicular skeleton	26 (43 %)			
Tumor size	≥ 8 cm	14 (23 %)	0.6115	0.4895	0.0862
	< 8 cm	23 (38 %)			
	Uncertain	23 (38 %)			
Extrasosseous extension	+	27 (45 %)	0.5225	0.1232	0.8309
	–	12 (20 %)			
	Uncertain	21 (35 %)			
Local recurrence	+	11 (18 %)	–	–	0.7965
	–	49 (82 %)			
Distant metastasis	+	9 (15 %)	–	–	0.0001
	–	51 (85 %)			
Nuclear atypia	Mild vs. moderate to severe	18 (30 %) vs. 42 (70 %)	0.4721	0.0123	0.0387
Increased cellularity	No vs. mildly, moderately, and diffusely	21 (35 %) vs. 39 (65 %)	0.9531	0.2261	0.2241
	No and mildly vs. moderately and diffusely	36 (60 %) vs. 24 (40 %)	0.6899	0.0370	0.0167
		53 (88 %)	0.4857	0.3921	0.1540

Table 2 (continued)

		N (%)	Local recurrence*	Distant metastasis*	Tumor- related death*
Mitosis	No, mildly, and moderately vs. diffusely	% vs. 7 (12 %)			
	+	2 (3 %)	0.3395	0.5068	0.5634
Necrosis	–	58 (97 %)			
	+	29 (48 %)	0.6003	0.1162	0.0428
Myxoid change (%)	–	31 (52 %)			
	> 1 vs. ≤ 1	31 (52 %) vs. 29 (48 %)	0.8638	0.4113	0.0387
	≥ 10 vs. < 10	26 (43 %) vs. 34 (57 %)	0.8002	0.9499	0.8186
Binucleation	≥ 30 vs. < 30	17 (28 %) vs. 43 (72 %)	0.4015	0.5319	0.3903
	+	47 (78 %)	0.5899	0.9640	0.6533
	–	13 (22 %)			

* Log-rank test.

coefficient was also calculated to evaluate the concordance between two observers. Data analysis was conducted with the JMP statistical software package (version 14.0.0; SAS Institute Inc.).

3. Results

3.1. Clinicopathological findings

The clinicopathological results are summarized in Table 2. The 60 patients with conventional chondrosarcoma were aged from 16 to 89 years (mean 49.9, median 48). Age ≥ 50 and < 50 years were noted in 27 cases (45 %) and 33 cases (55 %). There was a slight male predominance. Male and female were noted in 36 cases (60 %) and 24 cases (40 %). The tumors were located in appendicular skeleton (humerus in 8 cases, ulna in 1 case, phalanx in 1 case, femur in 10 cases, tibia in 5 cases, and fibula in 1 case) and non-appendicular skeleton (rib bone in 6 cases, sternum in 3 cases, thoracic vertebrae in 6 cases, sacrum in 1 case, scapula in 7 cases, and pelvic bone in 11 cases). Tumor size ranged from 1.5 to 32 cm (mean 8.4 cm, median 14.3 cm). Size ≥ 8 and < 8 cm were noted in 14 cases (23 %) and 23 cases (38 %). Local recurrence and distant metastasis were noted in 11 cases (18 %) and 9 cases (15 %), respectively. There were no cases of lymph node metastasis.

The 21 patients with dedifferentiated chondrosarcoma were aged from 38 to 79 (mean 58, median 59). Age ≥ 50 and < 50 years were

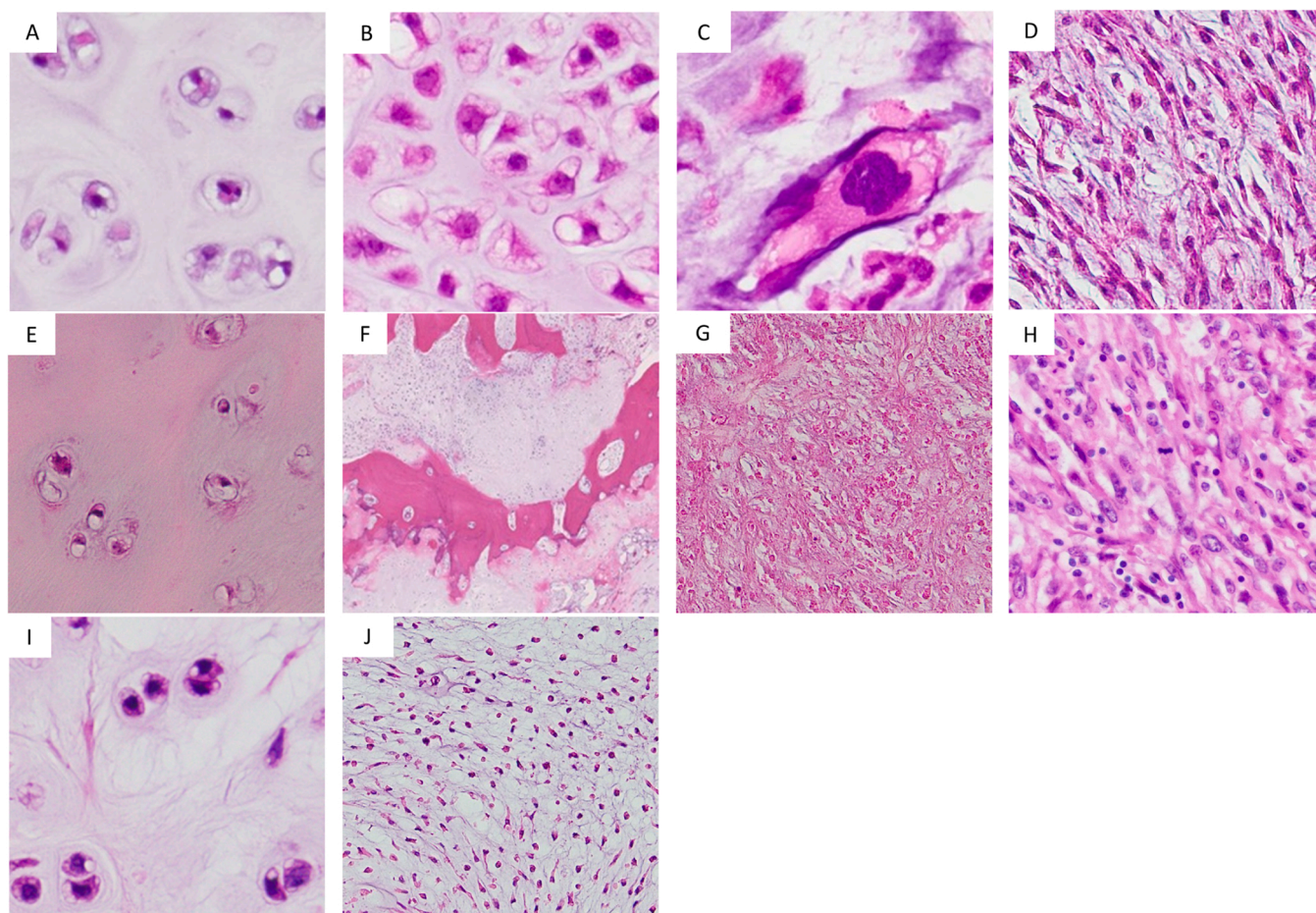


Fig. 1. The pathological findings of conventional chondrosarcoma cases. The histological features of nuclear atypia were divided into mild nuclear atypia (A), moderate nuclear atypia (B), and severe nuclear atypia (C). In addition, cellularity was described as high cellularity (D) and no increased cellularity (E). Permeating pattern (F), necrosis (G), mitotic figure (H), binucleation (I), and chondromyxoid stroma (J) are shown.

noted in 16 cases (76 %) and 5 cases (24 %). There was no clear difference between the sexes. Male and female were noted in 10 cases (48 %) and 11 cases (52 %). The tumors were located in non-appendicular skeleton (rib in 2 cases and pelvis in 5 cases) and appendicular skeleton (humerus in 2 cases, femur in 10 cases, and tibia in 2 cases). Tumor size ranged from 4.5 cm to 25 cm (mean 12.5 cm, median 10 cm). Size ≥ 8 and < 8 cm were noted in 8 cases (38 %) and 4 cases (19 %). Information on the surgical margin was not available. Local recurrence and distant metastasis were noted in 7 cases (33 %) and 13 cases (62 %), respectively. In this study, it was difficult to measure the tumor size of all patients.

3.2. Histopathological findings

Nuclear atypia of conventional chondrosarcoma was as follows: mild: 18 cases (30 %), moderate: 39 cases (65 %), and severe: 3 cases (5 %) [Fig. 1]. The cellularity of conventional chondrosarcoma was as follows: no increased cellularity in 21 cases (35 %), mildly increased cellularity in 15 cases (25 %), moderately increased cellularity in 17 cases (28 %), and diffusely increased cellularity in 7 cases (12 %). Mitotic figures were seen in two conventional chondrosarcoma cases (3 %). Necrosis was present in 29 cases (48 %). Binuclear tumor cells were present in 47 cases (78 %). The range of the percentage of chondromyxoid matrix was 0–90 % (mean 21 %, median 24 %). 0–1 %, 2–9 %, 10–29 %, and ≥ 30 % were noted in 32 cases (53 %), 5 cases (8 %), 3 cases (5 %), and 20 cases (33 %).

Nuclear atypia of the conventional chondrosarcoma component of

dedifferentiated chondrosarcoma was as follows: mild: 3 cases (14 %), moderate: 18 cases (86 %), and severe: 0 cases (0 %). The cellularity of the conventional component of dedifferentiated chondrosarcoma was as follows: no increased cellularity in 7 cases (33 %), mildly increased cellularity in 11 cases (52 %), moderately increased cellularity in 2 cases (10 %), and diffusely increased cellularity in 1 case (5 %). Mitotic figures were not seen. Necrosis was present in 20 cases (95 %). Binuclear cells were present in 16 cases (76 %). The range of the percentage of chondromyxoid matrix was 0–60 % (mean 17 %, median 22 %). 0–1 %, 2–9 %, 10–29 %, and ≥ 30 % were noted in 5 cases (24 %), 6 cases (29 %), 5 cases (24 %), and 5 cases (24 %).

Kappa coefficients of the two observers were calculated for the histological findings of nuclear atypia and cellularity, which were 0.85 and 0.68, respectively.

3.3. Statistical analysis

Statistical results are summarized in Table 2. Kaplan-Meier analysis is shown in Fig. 2. In conventional chondrosarcoma, age (≥ 50) and tumor location (non-appendicular skeleton) correlated with local recurrence ($p = 0.0356$ and $p = 0.0102$, respectively). Moderate and severe nuclear atypia correlated with distant metastasis ($p = 0.0123$). There was no tumor-related death or metastasis in cases with mild nuclear atypia. Moderate and severe nuclear atypia, cellularity (no and mildly increased cellularity vs. moderately and diffusely increased cellularity), and presence of necrosis correlated with overall survival ($p = 0.0387$, $p = 0.0167$, and $p = 0.0428$, respectively). In addition, the

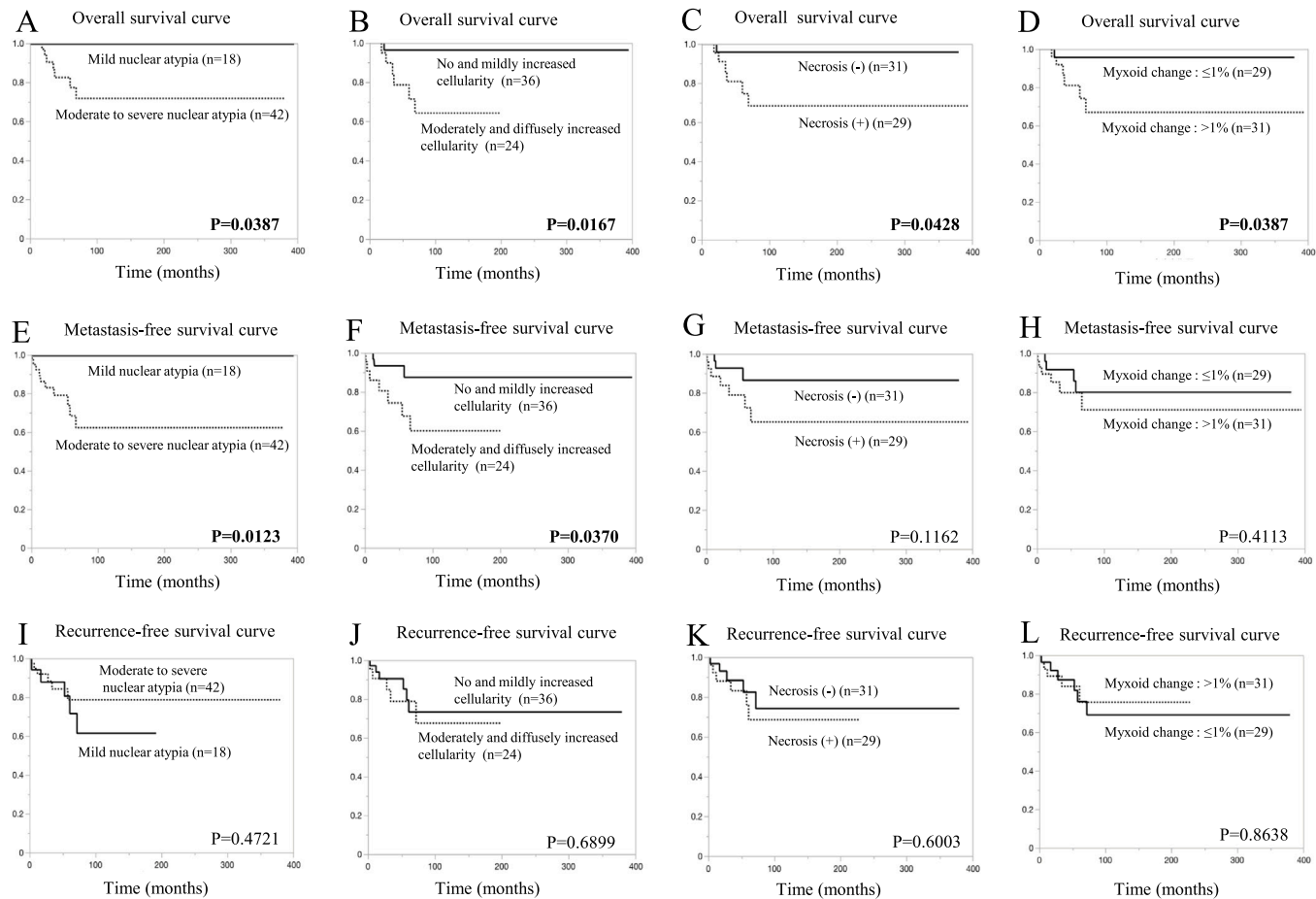


Fig. 2. Representative survival curves for chondrosarcoma. Overall survival curve of mild nuclear atypia versus moderate to severe nuclear atypia (A), no and mildly increased cellularity versus moderately and diffusely increased cellularity (B), presence of necrosis (C), and myxoid change (D). Distant-metastasis-free survival curves of mild nuclear atypia versus moderate to severe nuclear atypia (E), no and mildly increased cellularity versus moderately and diffusely increased cellularity (F), presence of necrosis (G), and myxoid change (H). Recurrence-free survival of mild nuclear atypia versus moderate to severe nuclear atypia (I), no and mildly increased cellularity versus moderately and diffusely increased cellularity (J), presence of necrosis (K), and myxoid change (L).

Table 3
Clinical outcome of each grade of conventional chondrosarcoma based on the current WHO classification.

Grade	N	Local recurrence	Distant metastasis	Tumor-related death
G1	18	5	0	0
G2	40	5	9	6
G3	2	1	0	0

presence of > 1 % myxoid area in the largest cross section correlated with tumor-related death ($p = 0.0387$). Distant metastasis was also associated with tumor-related death ($p = 0.0001$). Age, sex, tumor site, extraosseous extension, the presence of binuclear cells, and local recurrence did not correlate with overall survival.

Multivariable analysis of the overall survival curve using the Cox proportional hazard model demonstrated no independently significant prognostic factor. In dedifferentiated chondrosarcoma, statistical significance was not evident in any of the clinicopathological and

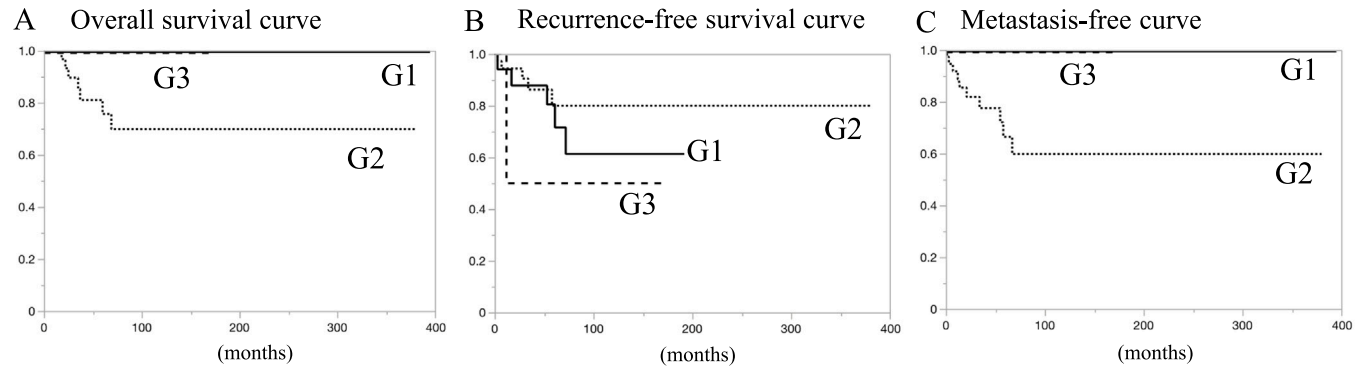


Fig. 3. Survival curve analysis. Overall survival curve (A), distant-metastasis-free survival curves (B), and recurrence-free survival curves (C) of grades 1–3 based on the current WHO classification (2020 edition).

Table 4

Clinical outcome of each grade of conventional chondrosarcoma based on the new scoring system.

Grade	Total Score	N	Local recurrence	Distant metastasis	Tumor-related death
G1	*	18	5	0	0
G2	1 – 3 (excluding mild nuclear atypia)	26	2	3	1
G3	4 or 5	16	4	6	5

* cases with only mild nuclear atypia.

histopathological findings, potentially due to the small number of cases.

3.4. Risk stratification - a new histological scoring system of conventional chondrosarcoma (modified WHO grade classification)

Based on the current WHO classification (2020 edition), there were 18 cases (30 %) of grade 1 including 5 cases (28 %) of local recurrence but no metastasis or tumor-related death; 40 cases (67 %) of grade 2 including 5 cases (13 %) of local recurrence, 9 cases (23 %) of metastasis, and 6 cases (15 %) of tumor-related death; and 2 cases (3 %) of grade 3 including 1 case (50 %) of local recurrence but no metastasis or tumor-related death (Table 3, Fig. 3).

Based on the above results, we proposed a new scoring system (modified WHO grade classification), based on nuclear atypia (mild: 0, moderate: +1, severe: +2), cellularity (no and mildly increased cellularity: 0, moderately and diffusely increased cellularity: +1), necrosis [(-): 0, (+): +1], and chondromyxoid area [(-): 0, (+): +1]. Each grade was defined as follows: cases with only mild nuclear atypia as grade 1, cases with total score 1–3 excluding mild nuclear atypia as grade 2, and cases with total score 4 or 5 as grade 3. There were 18 cases (30 %) of grade 1 including 5 cases (28 %) of local recurrence but no metastasis or tumor-related death; 26 cases (43 %) of grade 2 including 2 cases (8 %) of local recurrence, 3 cases (12 %) of metastasis, and 1 case (4 %) of tumor-related death; and 16 cases (27 %) of grade 3 including 4 cases (25 %) of local recurrence, 6 cases (38 %) of metastasis, and 5 cases (31 %) of tumor-related death (Table 4, Fig. 4).

Kappa coefficient was calculated for the histological grades based on the current WHO grade classification and based on the new scoring system, which was 0.62.

3.5. Enneking classification and AJCC by modified WHO grade classification

In accordance with AJCC stage IV 8th edition and Enneking

classification, 28 cases were staged under the AJCC 8th edition (IA 5 cases, IB 1 case, IIA 7 cases, IIB 9 cases, III 0 cases, IVA 5 cases, and IVB 1 case) and 43 cases were staged under the Enneking classification [IA (low grade, intra-compartmental) 4 cases, IB (low grade, extra-compartmental) 10 cases, IIA (high grade, intra-compartmental) 7 cases, IIB (high grade, extra-compartmental) 12 cases, and III (presence of metastasis) 10 cases]. There were no cases of AJCC stage III. The results of statistical analysis were as follows: There were statistically significant differences in the comparisons of Enneking classification stage I vs. II+III ($p = 0.0377$), Enneking classification stage I+II vs. III ($p = 0.0001$), and AJCC stage I+II vs. IV ($p = 0.0011$) in terms of distant metastasis, and of Enneking classification stage I+II vs. III ($p = 0.0001$) and AJCC stage I+II vs. IV ($p = 0.0186$) in terms of tumor-related death.

3.6. Risk analysis for dedifferentiation

Fisher's exact test was performed for each clinical and histological finding between conventional chondrosarcoma and dedifferentiated chondrosarcoma. The presence of dedifferentiated chondrosarcoma was correlated with age ($p = 0.0212$), distant metastasis ($p = 0.0001$), and tumor-related death ($p = 0.0057$). There were no statistically significant correlations between dedifferentiation and the other clinical and histological findings.

4. Discussion

The prognostic factors of chondrosarcoma have previously been investigated in various studies from both clinical and histological perspectives. The current grading system of the WHO classification is based on a large histological study by Evans [3]. Moreover, grading systems by O'Neal & Ackerman [8] and Campanacci [9] are also utilized in daily practice to evaluate the malignant potential of conventional chondrosarcoma. Meanwhile, the optimal classification system of conventional chondrosarcoma has remained unclear because histological criteria of each grade have been not definitively defined. We reviewed conventional chondrosarcoma cases for which long-term follow-up information was available and proposed precise criteria for a grading system. By using these new criteria, conventional chondrosarcoma could be classified into groups according to prognostic difference. In the current criteria of the grading system, conventional chondrosarcoma of grade 1 was almost always a tumor of low-grade malignancy with only a low recurrence rate. Meanwhile, conventional chondrosarcoma of grade 2 was a tumor of intermediate malignancy rarely showing metastatic potential and having a low risk of tumor-related death. Finally, conventional chondrosarcoma of grade 3 was a very malignant tumor exhibiting high recurrence and metastatic potential and causing

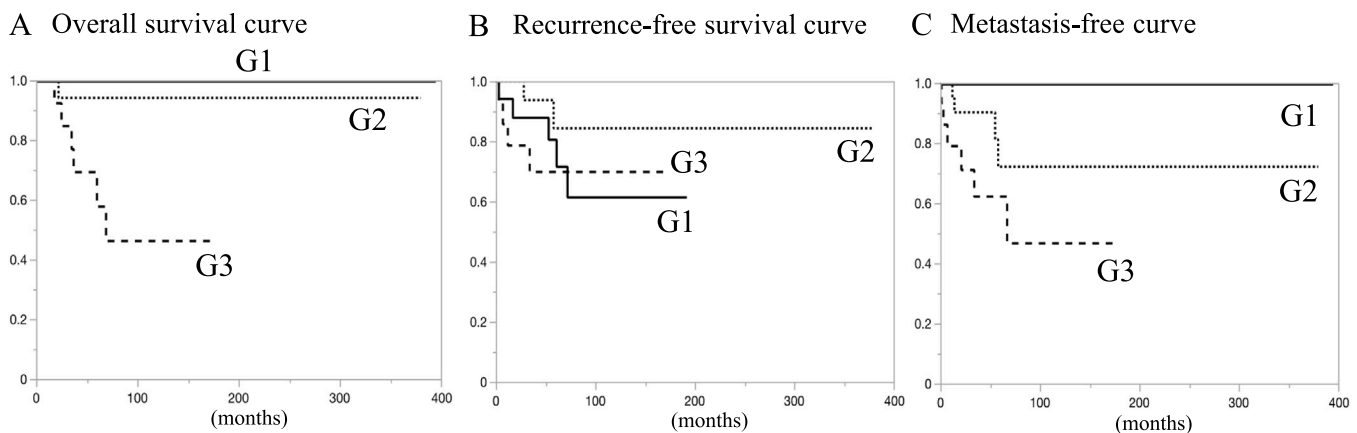


Fig. 4. Survival curve analysis. Overall survival curve (A), distant-metastasis-free survival curves (B), and recurrence-free survival curves (C) of grades 1–3 based on the new scoring system.

occasional tumor-related death. It was suggested that the new criteria of the grading system of conventional chondrosarcoma may be a simple and useful way to predict prognosis.

In the current investigation, we confirmed that nuclear atypia, high cellularity, the presence of necrosis, and myxoid change were statistically significant prognostic factors of conventional chondrosarcoma. To the best of our knowledge, the current investigation is the first to demonstrate the clinicopathological significance of myxoid change as a histological prognostic factor of conventional chondrosarcoma by using statistical analysis, although myxoid change is described as a histopathological feature of conventional chondrosarcoma in the current WHO classification. The detailed mechanism of the myxoid change in conventional chondrosarcoma remains unclear. We considered that myxoid change may be a malignant progression-associated histological feature and that it should be evaluated in addition to nuclear atypia, cellularity, and necrosis.

Both the Enneking classification and AJCC include histological grading, so there is a need for precise criteria for the histological grading of conventional chondrosarcoma. We evaluated conventional chondrosarcoma cases using the new histological scoring system and demonstrated a statistically significant difference between the results of the Enneking classification and AJCC in terms of clinical outcome. It was also proposed that the new histological scoring system of conventional chondrosarcoma that we established may be useful for a clinical staging system such as the Enneking classification and AJCC.

According to the new histological criteria of the new grading system, no cases of conventional chondrosarcoma at our institution were reclassified as ACT (data not shown). Meanwhile, one case of ACT was reclassified as conventional chondrosarcoma by the presence of myxoid change, but no ACT cases presented malignant biological behavior in the current investigation. Although ACT is considered as a tumor of low-grade malignancy [10], the accumulation of further ACT cases and an associated prognostic review are desired.

The histological background of dedifferentiated chondrosarcoma has yet to be explored. In the current investigation, it had no statistically significant association with the pathological features of the conventional chondrosarcoma component. We considered that necrosis is not useful to predict dedifferentiation in chondrosarcoma because the origin of necrotic tissue may be the dedifferentiated component, not the conventional chondrosarcoma component. Although the molecular mechanism behind the dedifferentiation in chondrosarcoma remains incompletely understood, dedifferentiation may involve a poorly differentiated form of conventional chondrosarcoma because conventional chondrosarcoma of a higher histological grade also loses the features of hyaline cartilage. Further molecular analysis is desired. The conventional chondrosarcoma component of dedifferentiated chondrosarcoma is thought to range from enchondroma-like appearance to grade 1 or grade 2 chondrosarcoma. In the current investigation, two dedifferentiated chondrosarcoma cases affecting the appendicular skeleton presented grade 1 histology. The conventional chondrosarcoma component of these two cases was histologically consistent with atypical cartilaginous tumor (ACT). Atypical cartilaginous tumor is basically thought to be a tumor of low-grade malignancy, but the risk of differentiation of ACT has remained unclear. Here, we considered that ACT has a potential risk of dedifferentiation.

Recently, some reports have been published about *IDH1/IDH2* gene and *TERT* promoter mutations, and loss of *H3K27me3* expression. It was reported that *IDH1* and *IDH2* mutations are present in ~50 % of conventional chondrosarcomas [11]. In addition, loss of *H3K27me3* was described in 32 % of dedifferentiated chondrosarcomas and the genetic aberration was restricted to the dedifferentiated component [12]. Meanwhile, the usefulness of *IDH1* antibody for demonstrating *IDH* mutations in chondrosarcoma is limited, because there are no antibodies available against the mutation type predominantly found in chondrosarcoma. Most antibodies are adapted to the mutation found in glioblastoma. There have been published many papers on the usability

of paraffin embedded tissue for molecular analysis also for bone tumors [13]. However, surgical specimens of bone tumor often require decalcification to cut and process the specimen for practical reasons, resulting in a poorer condition of the sample for molecular analysis. We considered that the biological behavior of chondrosarcoma remains unclear because of the poor utility of molecular analysis. Although decalcification by EDTA is usually recommended, another method of decalcification or specimen processing may be needed to promote the pathological analysis of chondrosarcoma.

5. Conclusion

In this study, we proposed a new histological scoring system for the grading of conventional chondrosarcoma. By using this system, conventional chondrosarcoma may be clearly classified into three grades: grade 1: non-metastasizing, grade 2: metastasizing but rarely life-threatening, and grade 3: frequently metastasizing and life-threatening.

Compliance with ethical standard

This study was conducted in accordance with the principles embodied in the Declaration of Helsinki. This study was also approved by the Ethics Committee of Kyushu University (No. 29-625) and conducted in accordance with the Ethical Guidelines for Epidemiological Research enacted by the Japanese Government. Informed consent was obtained from the subjects or their guardians.

CRedit authorship contribution statement

Yosuke Susuki performed the research and wrote the paper. Yuichi Yamada contributed to the research design and slide review. Kenichi Kohashi, Kenichi Taguchi, Izumi Kinoshita, Yoshihiro Ito, Kengo Kawaguchi and Hiroshi Furukawa contributed to the sample collection and research design. Clinical data were provided by Yasuharu Nakashima. Yoshinao Oda designed the research and gave final approval of the manuscript. All authors critically reviewed and approved the manuscript.

Declaration of Competing Interest

The authors declare that there are no potential conflicts of interest.

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