Clin Orthop Relat Res (2020) 00:1-11
DOI 10.1097/CORR.0000000000001266

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Selected Proceedings of the 2019 International Society of Limb Salvage Meeting

What Factors Are Associated with Treatment Outcomes of Japanese Patients with Clear Cell Chondrosarcoma?

Robert Nakayama MD, PhD, Keiko Hayakawa MD, Eisuke Kobayashi MD, PhD, Makoto Endo MD, PhD, Naofumi Asano MD, PhD, Tsukasa Yonemoto MD, PhD, Hiroyuki Kawashima MD, PhD, Kenichiro Hamada MD, PhD, Itsuo Watanabe MD, PhD, Hiroyuki Futani MD, PhD, Takahiro Goto MD, PhD, Yoshihiro Nishida MD, PhD, Toshifumi Ozaki MD, PhD

Received: 21 November 2019 / Accepted: 27 March 2020 / Published online: 14 April 2020

Abstract

Background Clear cell chondrosarcoma is an extremely rare chondrosarcoma subtype; thus, its treatment outcomes and associated factors have not been widely studied. Knowing more about it is potentially important because clear cell chondrosarcomas are often misdiagnosed as other benign lesions and subsequently treated and followed inappropriately.

Questions/purposes (1) What are the patient- and tumor-related characteristics of clear cell chondrosarcoma? (2) What proportion of patients with clear cell chondrosarcoma

Each author certifies that neither he or she, nor any member of his or her immediate family, has funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article. Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.
This work was performed at the Department of Orthopedic Surgery, Keio University School of Medicine, Tokyo, Japan.

R. Nakayama, N. Asano, Department of Orthopaedic Surgery, School of Medicine, Keio University, Tokyo, Japan

K. Hayakawa, Department of Orthopaedic Surgery, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

E. Kobayashi, Division of Musculoskeletal Oncology and Rehabilitation, National Cancer Center Hospital, Tokyo, Japan

M. Endo, Department of Orthopaedic Surgery, Kyushu University, Fukuoka, Japan

T. Yonemoto, Department of Orthopaedic Surgery, Chiba Cancer Center, Chiba, Japan

H. Kawashima, Department of Orthopaedic Surgery, Niigata University, Niigata, Japan

K. Hamada, Department of Orthopaedic Surgery, Osaka University, Osaka, Japan

I. Watanabe, Department of Orthopaedic Surgery, Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan

H. Futani, Department of Orthopaedic Surgery, Hyogo College of Medicine

T. Goto, Department of Musculoskeletal Oncology, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital

Y. Nishida, Department of Rehabilitation Medicine, Nagoya University, Aichi, Japan

T. Ozaki, Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Okayama, Japan

R. Nakayama (✉), Department of Orthopedic Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku, Tokyo 1608582 Japan, Email: robert.a2@keio.jp

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research®* editors and board members are on file with the publication and can be viewed on request.

Wolters Kluwer

initially had a misdiagnosis or a misleading initial biopsy result? (3) What is the survivorship of patients with clear cell chondrosarcoma free from death, local recurrence, and distant metastasis, and what factors are associated with greater survivorship or a reduced risk of local recurrence?

Methods Between 1985 and 2018, 12 Japanese Musculoskeletal Oncology Group (JMOG) hospitals treated 42 patients with a diagnosis of clear cell chondrosarcoma. All 42 patients had complete medical records at a minimum of 1 year or death, and were included in this multicenter, retrospective, observational study. No patients were lost to follow-up within 5 years of treatment but four were lost to follow-up greater than 5 years after treatment because their physicians thought their follow-up was sufficient. Clinical data were collected by chart review. The median (range) follow-up period was 69 months (2 to 392). In general, when a possibly malignant bone tumor was found on imaging studies, the histological diagnosis was made by biopsy before initiating treatment. Once the diagnosis had been made, the patients were treated by surgery only, complete resection if technically possible, because chondrosarcomas are known to be resistant to chemotherapy and radiotherapy. Unresectable tumors were treated with particle-beam radiation therapy. When patients with chondrosarcoma were referred after unplanned surgical procedures with inadequate surgical margins, immediate additional wide resection was considered before local recurrence developed. This diagnostic and treatment strategy is common to all JMOG hospitals and did not change during the study period. Primary wide resection was performed in 79% (33 of 42) patients, additional wide resection after initial inadequate surgery in 12% (five of 42), curettage and bone grafting in 5% (two of 42) patients, and radiotherapy was administered to 5% (two of 42). Surgical margins among the 40 patients who underwent surgery at JMOG hospitals were no residual tumor in 93% (37 of 42) of patients, microscopic residual tumor in 2% (one of 42), and macroscopic residual tumor or state after curettage or intralesional excision in 5% (two of 42). The oncological endpoints of interest were 5- and 10- year overall survival, disease-free survival, survival free of local recurrence, and survival free of distant metastases; these were calculated using the Kaplan-Meier method and compared using the log-rank test. Risk ratios with their respective 95% confidence intervals (CIs) were estimated in a Cox regression model. The Bonferroni adjustment was used for multiple testing correction.

Results The sex distribution was 74% men and 26% women (31 and 11 of 42, respectively), with a mean age of 47 ± 17 years. Eighty one percent (34 of 42) of tumors occurred at the ends of long bones, and the proximal femur was the most common site accounting for 60% (25 of 42). The mean size of the primary tumors was 6.3 ± 2.7 cm. Definite pathologic fractures were present in 26% (10 of 42) and another 26% (10 of 42) had extraskeletal involvement. None had metastases at presentation. Twenty four percent (six of 25) tumors in the proximal femur were misdiagnosed as benign lesions and treated inadequately without biopsy. Twenty nine percent (10 of 35) patients had initial misdiagnoses by biopsy and core needle biopsies had a greater risk of resulting in inaccurate histological diagnoses. The study patients' 5- and 10-year overall survival rates were 89% (95% CI 74 to 96) and 89% (95% CI 74 to 96), respectively; 5- and 10- year disease-free survival rates 77% (95% CI 58 to 89) and 57% (95% CI 36 to 75), respectively; 5- and 10-year local recurrence-free survival rates 86% (95% CI 68 to 95) and 71% (95% CI 49 to 86), respectively; and 5- and 10-year distant metastasis-free survival rates 84% (95% CI 67 to 93) and 74% (95% CI 53 to 88), respectively. Notably, bone metastases (17%, seven of 42) were as common as pulmonary metastases (14%, six of 42); four patients developed both bone and pulmonary metastases. The difference between 10-year overall survival rates and 10-year disease-free survival indicated very late recurrence more than 5 years after the initial treatment. After controlling for multiple comparisons, the only factor we found that was associated with local recurrence-free survival was initial treatment (positive margin versus primary wide resection) (risk ratio 8.83 [95% CI 1.47 to 53.1]; p = 0.022 after the Bonferroni adjustment). Additional wide resection reduced the risk of local recurrence.

Conclusions The femoral head was the most common location of clear cell chondrosarcoma and had a high risk of misdiagnosis as common benign lesions that resulted in initial inadequate surgery and a consequent high risk of local recurrence. Immediate additional wide resection should be considered in patients who had initial inadequate surgery to reduce the risk of local recurrence. Because clear cell chondrosarcoma can recur locally or distantly in the bones and lungs in the long term, patients should be informed of the risk of very late recurrence and the necessity of decades-long with surveillance for local recurrence and lung and bone metastases.

Level of Evidence Level IV, therapeutic study.

Introduction

Chondrosarcomas, a variety of malignant cartilaginous tumors, account for 15% to 20% of primary malignant bone tumors [21]. Conventional chondrosarcoma accounts for approximately 85% of all chondrosarcomas. Patients with conventional chondrosarcoma are characteristically older than 50 years of age. The most common sites are the pelvic bones followed by the femur, humerus, and ribs. In the long bones, these tumors are usually located in the metaphysis.

Chondrosarcomas are graded on a scale of I to III, the grade being important in prediction of oncological outcomes [3, 8, 9]. Secondary chondrosarcomas arise in pre-existing enchondromas or osteochondromas and are treated similarly to primary conventional chondrosarcoma. Other rare chondrosarcoma subtypes include dedifferentiated chondrosarcoma [10], mesenchymal chondrosarcoma [18] and clear cell chondrosarcoma. Clear cell chondrosarcoma, an extremely rare chondrosarcoma subtype, is characterized by a proliferation of tumor cells with clear cytoplasm [8]. This entity was first reported by Unni et al. [20] in 1976 and comprises only 1% to 2% of all chondrosarcomas [4, 17]. Its causes have not yet been identified.

Clear cell chondrosarcoma is extremely rare, therefore, fully assessing its clinical presentation and treatment outcomes has been challenging; most previous papers have been case reports. Only several small (mostly $n < 20$) case series have been published [4, 6, 7, 11-13, 17, 20] and these mainly focus on histological and/or radiological findings, but they did not provide much detail regarding treatment, survivorship and local recurrence. These studies demonstrate that clear cell chondrosarcoma is histologically similar to other chondrogenic tumors. Many contain zones of conventional low-grade chondrosarcoma with hyaline cartilage and/or a few osteoclast-like giant cells characteristic of benign chondroblastoma; these similarities can lead to misdiagnoses [4]. Clear cell chondrosarcoma is characterized by a proliferation of tumor cells with clear cytoplasm [8, 20], but no tumor-specific histological markers have been established. The previous reports also indicate that clear cell chondrosarcomas characteristically arise in the epiphyses of long bones and have indolent clinical courses. However, to the best of our knowledge, only two small case series studies have documented survival rates, one with 16 patients [11] and the other seven patients; there is also a systematic review of published reports [14]. We still do not know why or how often clear cell chondrosarcoma is misdiagnosed, precisely how indolent clear cell chondrosarcoma is, or and how to best treat and follow-up on patients with clear cell chondrosarcoma. We conducted a nationwide multicenter study to investigate the clinical presentations, diagnosis, and treatment outcomes of patients with clear cell chondrosarcoma in Japan and determine their associated factors.

Therefore, we asked: (1) What are the patient- and tumor-related characteristics of clear cell chondrosarcoma? (2) What proportion of patients with clear cell chondrosarcoma initially had a misdiagnosis or a misleading initial biopsy result? (3) What is the survivorship of patients with clear cell chondrosarcoma free from death, local recurrence and distant metastasis, and what factors are associated with greater survivorship or a reduced risk of local recurrence?

Patients and Methods

We conducted a multicenter, retrospective, observational study by chart review through the Japanese Musculoskeletal Oncology Group (JMOG), and analyzed data of 42 patients with clear cell chondrosarcoma who were treated between 1985 and 2018 at 12 JMOG institutions. JMOG, a group for multicenter clinical studies organized by orthopaedic oncologists in Japan, was established in 1981. One of the JMOG's missions has been to investigate the clinical outcomes of extremely rare musculoskeletal tumors [16, 18], including clear cell chondrosarcoma.

In total, 42 clear cell chondrosarcoma patients were treated at 12 JMOG hospitals. All patients had complete medical records at a minimum of 1 year or death and were included in this multicenter, retrospective, observational study; the median (range) follow-up period was 68 months (2 to 392) (Table 1). No patients were lost to follow-up within 5 years of treatment, but four were lost to follow-up greater than 5 years after treatment. The percentages of patients with complete follow-up at 1, 5, and 10 year were 98% (41 of 42), 55% (23 of 42) and 33% (14 of 42), respectively. There were a median (range) of 3.5 clear cell chondrosarcoma patients (1 to 8) treated at each JMOG hospital during the study period. The number of clear cell chondrosarcoma patients at 12 JMOG hospitals increased over time (1985-1994, n = 7; 1995-2004, n = 11; 2005-2014, n = 15; 2015-, n = 9).

Biopsy and Histological Diagnosis

In general, when a possibly malignant bone tumor was found on imaging studies, the histological diagnosis was made by biopsy before treatment initiation. This diagnostic strategy is common to JMOG hospitals and did not change over the study period. However, 17% (seven of 42) of patients with clear cell chondrosarcoma were radiologically misdiagnosed as having various benign lesions, leading to these patients undergoing inappropriate treatment without biopsy (Table 1). Additionally, 29% (10 of 35) of patients with clear cell chondrosarcoma were diagnosed inaccurately by biopsy (Table 2); in these patients the final diagnosis of clear cell chondrosarcoma was made by pathological examination of specimens obtained by subsequent definitive surgical procedures.

The final histologic diagnoses of all patients were reviewed and confirmed by pathologists at the relevant institution before the patient was registered in the present study.

Initial Local Treatment

Once the diagnosis of chondrosarcoma was made, the patients were managed surgically, by complete resection if

Table 1. Characteristics of 42 patients with clear cell chondrosarcoma and their tumors

Factors	% (n)
Sex	
Male	74% (31)
Female	26% (11)
Age (mean ± SD in years)	47 ± 17
0-20	24% (1)
21-40	40% (17)
41-60	31% (13)
61-80	26% (11)
> 81	0% (0)
Tumor location	
Proximal femur	60% (25)
Proximal humerus	12% (5)
Ilium	10% (4)
Distal femur	5% (2)
Other (one each)[a]	14% (6)
Tumor size	
Mean: 6.3 cm (range 2.5 to 14)	
< 8 cm	76% (32)
≥ 8 cm	24% (10)
Extraskeletal involvement	
Yes	24% (10)
No	76% (32)
Pathologic fracture	
Yes	24% (10)
No	76% (32)
Metastasis at presentation	
Yes	0% (0)
No	100% (42)
AJCC TNM Stage	
IA	76% (32)
IB	24% (10)
Biopsy	
No	17% (7)
Yes	83% (35)
Needle	21% (9)
Incisional	62% (26)
Initial treatment before referral	
Yes	17% (7)
No	83% (35)

[a]Others included the proximal tibia, distal tibia, sacrum, sternum, sphenoid, and cuboid; AJCC = American Joint Committee on Cancer; TNM = tumor, node, metastasis.

technically possible, because it is generally accepted that these tumors are highly resistant to chemotherapy and radiotherapy [9]. Unresectable tumors were treated with particle-beam radiation therapy. When patients with chondrosarcomas were referred after unplanned surgical procedures with inadequate surgical margins, immediate additional wide resection was considered before a local recurrence developed. This treatment strategy was common to the participating JMOG hospitals and did not change over the study period.

The surgical margins were histologically evaluated in accordance with the residual tumor (R) classification of the Union for International Cancer Control (RX, the presence of residual tumor cannot be assessed; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor or state after curettage or intralesional excision) [22].

Initial treatments were administered to 17% (seven of 42) patients before referral to a JMOG hospital, including four who underwent simple excisions by intralesional procedure, one who underwent curettage, one who received neoadjuvant chemotherapy and underwent hemipelvectomy (no residual tumor; diagnosed as a chondroblastic osteosarcoma), and one who underwent radiotherapy for a sphenoid bone tumor. Four of five patients who had initial inadequate surgery before referral underwent additional wide resections at JMOG hospitals; the fifth had been referred after local recurrence had developed.

Initial local treatment was administered at a JMOG hospital in 83% (35 of 42) patients. Two patients with suspected benign tumors in the femoral head underwent curettage and bone grafting without biopsies; one underwent hip disarticulation immediately after establishment of a definitive diagnosis of clear cell chondrosarcoma, whereas the other had no additional treatment until after development of local recurrence 6 years later.

Collectively, 79% (33 of 42) patients underwent primary wide resection, 12% (five of 42) underwent additional wide resection after initial inadequate surgery, 5% (two of 42) underwent curettage and bone grafting, and 5% (two of 42) received radiotherapy (one underwent carbon ion radiotherapy for a sacral tumor and one had cyber-knife radiotherapy for a sphenoid tumor). Resection with no residual tumor was achieved in 93% (37 of 40) of the patients who underwent surgery, microscopic residual tumor in one, and macroscopic residual tumor or state after curettage or intralesional excision in two.

Amputations were used to achieve initial or additional wide resections in 10% (four of 40) patients, comprising two hemipelvectomies for iliac tumors, one unplanned hip disarticulation for a proximal femur tumor after curettage, and one below-the-knee amputation for a foot tumor. For limb salvage reconstruction after wide resections in the 34 patients with tumors at the ends of the long bones, 85% (29 of 34) patients underwent endoprosthetic reconstruction, 12% (four of 34) biologic reconstruction, and one hip disarticulation, as mentioned above.

Table 2. Biopsy and accuracy of diagnosis (n = 35)

Biopsy type	Accurate (CCCS)	Inaccurate diagnosis[a]	Number	%
Needle[b]	3	6	9	26%
Incisional	22	4	26	74%
Number (%)	71% (25)	29% (10)	35	100%

[a]Inaccurate diagnoses: conventional chondrosarcoma (n = 5), chondroblastic osteosarcoma (n = 4), and chondroblastoma (n = 1).
[b]p = 0.0074, chi-square test; CCCS = clear cell chondrosarcoma.

The only patients who received adjuvant chemotherapy were four patients whose tumors were initially incorrectly diagnosed as chondroblastic osteosarcomas. These four patients underwent neoadjuvant chemotherapy with doxorubicin and cisplatin, with or without high-dose methotrexate and high-dose ifosfamide. None of them showed a radiologic or histologic response to neoadjuvant chemotherapy. Adjuvant radiotherapy was administered to only one patient, whose humeral tumor was removed with a positive margin.

Variables, Outcome Measures, Data Sources, and Bias

Information on the patients' clinical features, including sex, age at first visit, location of primary tumor, tumor size (maximum extent determined by imaging), presence of extraskeletal extension and pathologic fractures, American Joint Committee on Cancer stage, presence or absence of metastasis at the time of diagnosis, details of biopsies and initial diagnoses, and details of initial local treatments was obtained by reviewing their charts. There were no missing data for any of our study's variables. Initial treatment was defined as the first treatment regardless of whether the treating hospital was within the JMOG or not. Overall survival was defined as the time from treatment commencement to the date of the last visit to the clinic or death. Disease-free survival was defined as the time from treatment commencement to the date of the last visit to the clinic, death, local recurrence, or distant metastasis.

Statistical Analysis, Study Size

Survival rates were estimated using the Kaplan-Meier method. The effect of each associated factor was assessed using the log-rank test. The Bonferroni adjustment was used for multiple testing correction. p values < 0.05 were considered to denote significant differences. Risk ratios with their respective 95% confidence intervals (CIs) were estimated in a Cox regression model. All statistical analyses were performed using the JMP 14 software program (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics, Tumor Location, Size, and Stage

Patient and tumor characteristics revealed some distinctive features. The sex distribution was 74% men, 26% women (31 and 11 of 42, respectively), with a mean ± SD age of 47 ± 17 years, without any sharp peak in age distribution (Table 1).

The primary tumors were located in the lower extremities in 71% (30 of 42) patients, the trunk, head, and neck in 17% (seven of 42), and the upper extremities in 12% (five of 42) (Table 1). The proximal femur was the most common location, accounting for 60% (25 of 42), followed by the proximal humerus in 12% (five of 42) and the ilium in 10% (four of 42). The primary tumors were in the femur, tibia, or humerus in 81% (34 of 42) patients, and they all arose at the end of a long bone, which is consistent with the epiphyseal origin of these tumors. Unusual locations included the sacrum, sternum, sphenoid, and cuboid (one of each).

The mean size of the primary tumors was 6.3 ± 2.7 cm. Clear pathologic fractures were present in 24% (10 of 42), seven in the proximal femur and three in the proximal humerus. Extraskeletal extension was seen in 24% (10 of 42) patients; 76% (32 of 42) had Stage IA disease and 24% (10 of 42) had Stage IB disease; none had lymph node or distant metastases at the initial presentation.

Biopsy and Diagnosis

Evaluation of the diagnostic process revealed a number of difficulties in the diagnosis of clear cell chondrosarcoma, both from the radiological and histological perspective. Biopsies were obtained before initiation of treatment in 83% (35 of 42) patients, whereas the remaining 17% (seven of 42), including three who were treated at nearby hospitals before referral to an JMOG hospital, did not undergo biopsy before commencing treatment (Table 1). Six of seven patients who did not have biopsies had primary tumors in their proximal femurs, the provisional diagnoses before their initial surgery included femoral-head necrosis (two of

seven) and benign bone lesions such as chondroblastoma in the femoral head (four of seven). The remaining patient underwent curettage for a suspected benign tumor of the cuboid.

Twenty-six percent (nine of 35) of biopsies were core needle biopsies and 74% (26 of 35) were incisional biopsies. Biopsies yielded accurate diagnoses of clear cell chondrosarcoma in only 71% (25 of 35) of patients; the initial diagnoses in the other 29% (10 of 35) of patients were conventional chondrosarcoma (five patients), chondroblastic osteosarcoma (four), and benign chondroblastoma (one) (Table 2). Six of 10 patients with incorrect biopsy diagnoses had undergone needle biopsy rather than incisional biopsy; the accuracy rate was lower for needle biopsies (33%, three of nine) than for incisional biopsies (85%, 22 of 26) (p = 0.007) (Table 2). Those 10 patients were finally diagnosed with clear cell chondrosarcoma by pathological examination of the specimens obtained by their definitive surgical procedures.

Survivorship and Factors Associated with Survivorship

The 5- and 10-year overall survival rates were 89% (95% CI 74 to 96) and 89% (95% CI 74 to 96), respectively, the 5- and 10-year disease-free survival rates being 77% (95% CI 58 to 89) and 57% (95% CI 36 to 75), respectively (Fig. 1 A-B). At the most-recent follow-up examination of 42 patients, four had died of their disease, two had died of unrelated causes, three were alive with disease, 29 were alive without evidence of disease, and the remaining four had been lost to follow-up after the first 5 years because their physicians were not aware of the possibility of late recurrence. Thirteen patients had local recurrences and/or distant metastases.

The local recurrence-free survival rates were similar to the distant metastasis-free survival rates. The 5- and 10-year local recurrence-free survival rates were 86% (95% CI 68 to 95) and 71% (95% CI 49 to 86), respectively; the 5- and 10-year distant metastasis-free survival rates being 84% (95% CI 67 to 93) and 74% (95% CI 53 to 88), respectively (Fig. 1C-D). As of the last follow-up examination, seven of 42 patients had local recurrences (median [range] interval, 58 months [7 to 108]). All seven underwent surgical treatment for their recurrent tumors; none died of uncontrollable local recurrence (Table 3). Nine patients had distant metastases (median [range] interval 56 months [8 to 195); three also had local recurrences (Table 4). Notably, bone metastases (seven patients) were as common as pulmonary metastases (six patients); four patients had both bone and pulmonary metastases (Table 4). Only three patients underwent surgery for metastatic tumors. Four patients with bone metastases received palliative radiotherapy and two received chemotherapy (regular denosumab), which resulted in stable disease.

Univariate analyses of factors potentially associated with overall survival, local recurrence-free survival and distant metastasis-free survival (Table 5), revealed that

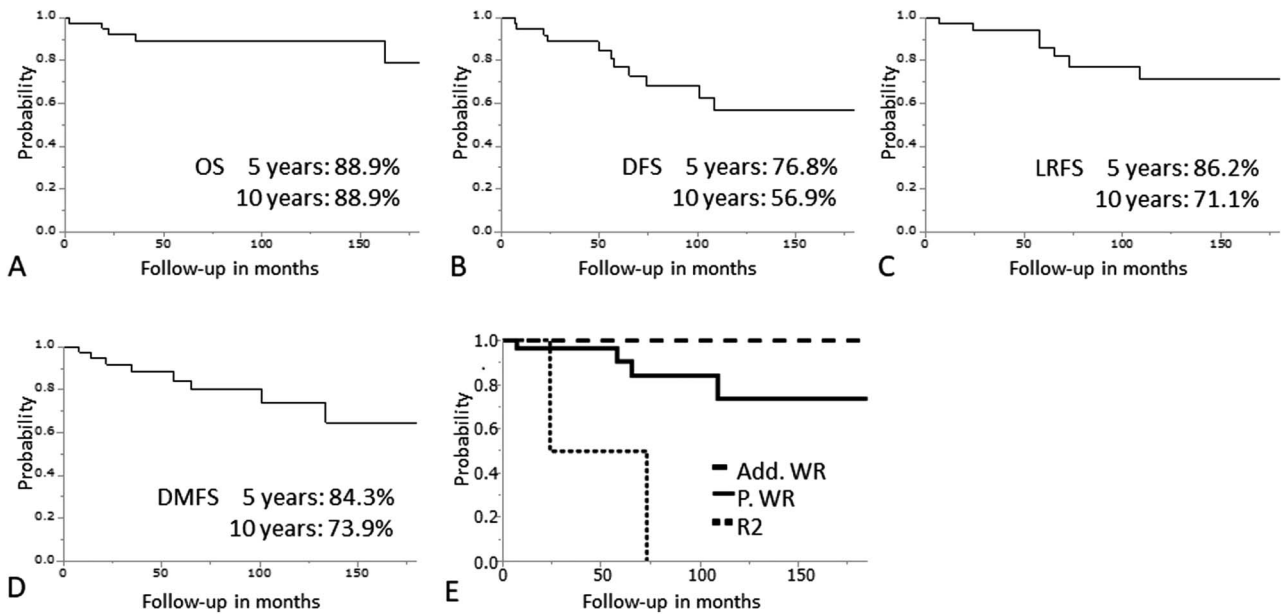

Fig. 1 A-E The graphs show Kaplan-Meier curves for (**A**) overall survival (OS), (**B**) disease-free survival (DFS), (**C**) local recurrence-free survival (LRFS), (**D**) distant metastasis-free survival (DMFS), and (**E**) local recurrence-free survival according to the local treatment; Add.WR = additional wide resection after initial inadequate surgery; P. WR = primary wide resection; R2 = macroscopic residual tumor or state after curettage or intralesional excision..

Table 3. Seven patients with clear cell chondrosarcoma who had local recurrence

Patient number	Age at diagnosis (years)	Sex	Primary site	Initial treatment	Interval to local recurrence (months)	Treatment for local recurrence	Further local recurrence	Distant metastasis	Oncologic outcome
1	46	Male	Proximal femur	Curettage alone (R2)	73	Wide resection with endoprosthetic reconstruction	No	No	NED
2	26	Male	Proximal humerus	Wide resection (R0)	65	Wide resection	No	Yes	AWD
24	39	Male	Ilium	Hemipelvectomy (R0)	108	Wide resection	No	Yes	DOD
27	38	Female	Proximal femur	Unplanned resection (R2)	24	Wide resection with endoprosthetic reconstruction	Twice, ultimate hemipelvectomy required	Yes	NED
28	27	Male	Sphenoid	Radiation	58	Intralesional resection	NA	No	AWD
37	41	Male	Proximal femur	Wide resection (R0)	7	Hemipelvectomy	No	Yes	DOD
40	68	Male	Ilium	Hemipelvectomy (R0)	58	Wide resection	No	No	NED

NED = no evidence of disease; AWD = alive with disease; DOD = dead of disease; R0 = no residual disease; R2 = macroscopic residual tumor or state after curettage or intralesional excision.

initial treatment was the only factor associated with local recurrence-free survival (risk ratio [positive margin to primary wide resection] 8.83 [95% CI 1.47 to 53.1]; p = 0.022 after the Bonferroni adjustment). In the present study, most (five of seven) patients who had initial inadequate surgery with positive margins underwent immediate additional wide resection in conformity with the treatment strategy of JMOG hospitals and none of them developed local recurrence (Fig. 1E).

Discussion

Clear cell chondrosarcoma is an extremely rare and distinct subtype of chondrosarcoma. Previous case reports and several small case series have suggested that these are indolent tumors; however, most of these studies did not report survival estimates or factors associated with outcomes [4, 6, 7, 12, 13, 17]. To widen our knowledge on the clinical presentations of clear cell chondrosarcoma and to identify factors that are possibly associated with outcomes, we conducted a multicenter retrospective study in Japan. The present findings highlight the difficulties in achieving accurate pretreatment diagnoses both radiologically and histologically, with such errors sometimes leading to inadequate initial surgery. Initial inadequate surgery was highly associated with local recurrence; however, immediate additional wide resection reduced this risk. In addition, the present study found that very late recurrences involve bone and lung in approximately equal proportions.

This study had several limitations. The first was caused by the known rarity of clear cell chondrosarcoma, which resulted in an accumulation of only 42 patients in this nationwide, multicenter study over many years (1985-2018). Because the median (range) number of patients from each JMOG hospital was only 3.5 (1 to 8), we were not able to assess differences in treatment outcomes across the 12 JMOG hospitals. Additionally, because some patients with clear cell chondrosarcoma would have been treated in hospitals other than the 12 JMOG hospitals, we were not able to analyze all clear cell chondrosarcoma patients in Japan during the study period. The increase in the number of patients over time may have been attributable to increasing recognition of this rare chondrosarcoma subtype, rather than an actual increase in the incidence of clear cell chondrosarcoma. In addition, the sample size (n = 42) was too small for many log-rank analyses to be performed (Table 5); thus, the factors that we identified as associated with treatment outcomes may have been false positives.

Next, follow-up protocols and intervals varied between the participating hospitals. Although most patients (55%, 23 of 42) were followed for more than 5 years (median 68 months), the durations of follow-up varied greatly among patients, which could have resulted in a wide margin of error for long-term outcomes. Given the fact that

Table 4. Nine patients with clear cell chrondrosarcoma who had distant metastasis

Patient number	Age at diagnosis (years)	Sex	Primary site	Initial treatment	Metastatic sites	Interval to distant metastasis (months)	Treatment for distant metastasis	Local recurrence	Oncologic outcome
2	26	Male	Proximal humerus	Wide resection with endoprosthetic reconstruction	Sacrum	65	Curettage, radiation, and denosumab	Yes	AWD
3	39	Male	Distal tibia	Wide resection with biologic reconstruction	Lung (solitary), skull (solitary)	101	Resection (both lung and skull)	No	NED
22	58	Male	Foot	Below-the-knee amputation after unplanned excision	Lung (multiple) and bone (multiple)	22	Palliative radiation to bones	No	DOD
23	39	Female	Ilium	Wide resection with endoprosthetic reconstruction	Lung (multiple) and thoracic spine (solitary)	8	Palliative radiation to bone	No	DOD
24	39	Male	Ilium	Hemipelvectomy	Lung (multiple)	128		Yes	DOD
25	68	Female	Proximal femur	Additional wide resection with endoprosthetic reconstruction after unplanned excision	Sacrum (solitary)	195	Palliative radiation	No	NED
27	38	Female	Proximal femur	Unplanned resection with endoprosthetic reconstruction	Lung (multiple)	11	Six metastasectomies	Yes	NED
32	47	Male	Proximal femur	Wide resection with endoprosthetic reconstruction	Bone (multiple)	56	Denosumab	No	AWD
37	41	Male	Proximal femur	Wide resection with endoprosthetic reconstruction	Lung (multiple) and lumbar spine (solitary)	14	Palliative radiation to bone	No	DOD

NED = no evidence of disease; AWD = alive with disease; DOD = dead of disease.

some patients developed recurrences after very long intervals and the possibility that some patients who were lost to follow-up after 5 years may have died of clear cell chondrosarcoma or other causes, the actual survival rates could be worse than is shown by our data.

This was a chart review-based, retrospective, observational study and there was no central radiological or pathological review process, consequently, we were unable to access several key data, in particular the duration of symptoms, radiological findings, details of prior diagnoses and treatment before referral to a JMOG hospital, and surgical margin status beyond the R0–2 grading system.

Patient Characteristics, Tumor Location, Size, and Stage

In this study, we analyzed the records of 42 patients with clear cell chondrosarcoma who were treated at 12 JMOG institutions. We found that the patients were predominately male (ratio of 2.8:1 in this study), with a wide age distribution (19 to 79 years); these characteristics have been reported for other ethnic groups [14]. Male predominance is common to other chondrogenic tumors but it is particularly marked for clear cell chondrosarcoma. The age distribution of clear cell chondrosarcoma has no particular

Table 5. Associated factors of oncological outcomes using the Kaplan-Meier method (n = 42)

			OS			LRFS			DMFS			
Factors	Number	Percent	10-year	(95% CI)	p value	10-year	(95% CI)	p value	10-year	(95% CI)	p value	
Total		42	100	89%	(74 to 96)		71%	(49 to 86)		74%	(53 to 88)	
Sex	Male	31	74	93%	(76 to 98)	0.613	67%	(43 to 85)	0.565	73%	(48 to 89)	0.640
	Female	11	26	80%	(46 to 95)		89%	(50 to 98)		81%	(47 to 95)	
Age (years)	< 46	22	52	89%	(66 to 97)	0.797	68%	(42 to 87)	0.541	69%	(43 to 87)	0.583
	≥ 46	20	48	88%	(63 to 97)		76%	(39 to 94)		82%	(47 to 96)	
Tumor size (cm)	< 8	32	76	93%	(76 to 98)	0.595	71%	(45 to 88)	0.745	72%	(47 to 89)	0.728
	≥ 8	10	24	80%	(46 to 95)		71%	(31 to 93)		80%	(46 to 95)	
Extraskeletal involvement	Yes	10	24	89%	(71 to 96)	0.358	40%	(11 to 78)	0.04	79%	(44 to 95)	0.304
	No	32	76	89%	(50 to 98)		84%	(59 to 95)		74%	(50 to 89)	
Pathologic fracture	Yes	10	24	100%	NA	0.087	71%	(31 to 93)	0.899	58%	(24 to 86)	0.500
	No	32	76	85%	(66 to 94)		70%	(43 to 88)		79%	(51 to 93)	
Biopsy	Yes	35	83	87%	(69 to 95)	0.457	71%	(45 to 88)	0.755	73%	(47 to 90)	0.661
	No	7	17	100%	NA		67%	(27 to 92)		67%	(27 to 92)	
Initial treatment	P. WR	32	76	89%	(71 to 97)	0.489	74%	(44 to 91)	0.003[a]	71%	(43 to 89)	0.955
	Add. WR	5	12	100%	NA		100%	/A		75%	(24 to 97)	
	positive margin	2	5	100%	NA		0%	NA		50%	(6 to 04)	
Local recurrence	Yes	7	17	86%	(42 to 98)	0.835	NA	NA	NA	54%	(19 to 85)	0.084
	No	35	83	90%	(72 to 97)		NA	NA	NA	80%	(54 to 93)	

[a]p < 0.05 after the Bonferroni adjustment (p = 0.022); NA = not available; OS = overall survival; LRFS = local recurrence-free survival; DMFS = distant metastasis-free survival; P. WR = primary wide resection; Add. WR = additional wide resection after inadequate surgery.

characteristics, whereas most patients with conventional chondrosarcomas are older than 50 years, and chondroblastomas typically affect adolescent and very young adults [8, 9, 19]. Eighty-one percent (34 of 42) of these tumors arose at the ends of the long bones, the proximal femur was the most common location accounting for 60% of all clear cell chondrosarcoma. No tumors in our study were located in the diaphyses of long bones, ribs, or vertebrae of the mobile spine; however, these locations have been reported by others [7, 11].

Biopsy and Diagnosis

The diagnosis of clear cell chondrosarcoma is challenging, both because of the radiological and histological resemblance of clear cell chondrosarcoma to low-grade conventional chondrosarcoma and chondroblastoma [1, 4, 6], and the rarity of clear cell chondrosarcoma. In fact, 17% (seven of 42) of tumors in our series were misdiagnosed as benign lesions on the basis of the radiological findings and inappropriately treated with intralesional surgeries. Of note, six of these tumors were in the femoral head; they thus accounted for 24% of all proximal femoral clear cell chondrosarcoma. These misdiagnoses may, at least in part, be attributable to the fact that the femoral head is also the location of predilection for the relatively common benign counterpart, chondroblastoma, and other common causes of bone destruction, such as avascular necrosis of the femoral head. Extra care must be taken to avoid inappropriate curettage or intralesional excision of femoral head lesions; two of our patients eventually underwent amputations.

Additionally, the distinctive epiphyseal location of these tumors can cause technical difficulties in biopsy, especially when the lesions are relatively small and located in the femoral head [15]. These difficulties may have prompted adoption of the less-invasive biopsy technique of core needle biopsy; however, this technique was associated with a higher risk of inaccurate diagnosis in our study (Table 2). The higher risk of inaccurate diagnosis by core needle biopsy could be attributable to the technical limitations of core needle biopsies (the hard bone sample is crushed); the extreme rarity of clear cell chondrosarcoma, which could result in pathologists hesitating to make this diagnosis on a very small samples; the lack of specific

histologic markers for clear cell chondrosarcoma; and the histologic resemblance of clear cell chondrosarcoma to other chondrogenic tumors (clear cell chondrosarcomas often contain zones of low-grade conventional chondrosarcoma or a few osteoclast-like giant cells, which are characteristic of chondroblastoma) [4]. The histologic diagnosis of clear cell chondrosarcoma depends largely on morphologic features (as shown by hematoxylin and eosin staining), therefore, it is difficult to distinguish clear cell chondrosarcoma from other chondrogenic tumors with only a small tumor specimen. One small study of six patients with clear cell chondrosarcoma diagnosed by fine needle aspiration and/or touch preparations of needle biopsy samples [12] reported that relevant cytologic features include large, plasmacytoid cells with foamy cytoplasm and extracellular chondroid-type matrix material. Definitive diagnoses were made by identifying clear cells in cell block material, which highlights the difficulty of diagnosing clear cell chondrosarcoma from tiny samples. Novel tumor-specific histologic markers, such as H3.3K36M for chondroblastoma [5], which would enable diagnosis of clear cell chondrosarcoma from small samples obtained by needle biopsy, are necessary.

Taken together, although clear cell chondrosarcomas are very rare, orthopaedic surgeons should always be aware of the possibility of this diagnosis, take care with their diagnostic process, and consider an incisional biopsy when a potentially neoplastic lesion is detected in the epiphysis of long bones, especially in the femoral head.

Oncologic Outcomes

To the best of our knowledge, only one small case series (n = 16) has reported the outcomes and estimated survival of patients with clear cell chondrosarcoma [11]. A systematic review was also published recently [14]. According to published studies, the 10-year overall survival rate is 80% to 89% and 10-year disease-free survival rate 60% to 68%. In our series, the 10-year overall survival was 89% and disease-free survival was 57%. The prognosis of clear cell chondrosarcoma is clearly better than that of Grade II/III (high-grade) conventional chondrosarcoma, the 5-year survival of which is 53% [9]. The large discrepancy between overall and disease-free survival strongly indicates the indolent but malignant nature of clear cell chondrosarcoma.

Two reports have documented that patients with clear cell chondrosarcoma can develop very late local recurrences (288 months) [7] and distant metastasis (276 months) [2]. The present study provides further evidence that clear cell chondrosarcoma can recur locally very late (median interval 58 months; range 7 to 108) and metastasize very late (median interval 56 months; range 8 to 195). Notably bone metastases were as common as pulmonary metastases; additionally, four of nine patients developed both bone and pulmonary metastases. Thus, decades-long follow-up with surveillance for local recurrence and lung and bone metastases seems mandatory. However, given the slow-growing nature of clear cell chondrosarcoma and the lack of treatment other than surgery, carefully informing patients with clear cell chondrosarcoma that their tumors could recur after a very long period may be more realistic than following them with regular CT scans for decades for selected patients with low recurrence risk (no extraskeletal involvement, initial wide resection with no residual tumor and no recurrence by then).

Lastly, we found that that initial inadequate surgery with positive margins would result in a high risk of local recurrence (Table 5) and that there is a definite role for immediate additional wide resection to prevent such recurrence (Fig. 1E). Some previous studies have concluded that inadequate surgical resection with positive margins increases the risk of local recurrence and overall survival [4, 11, 14, 17]; however, these studies did not report the details of treatment after initial inadequate surgical procedures with positive margins, whether they simply subjected the patients to ongoing active surveillance or performed additional wide resection. Although clear cell chondrosarcoma is an indolent chondrosarcoma subtype, it is totally different from Grade I conventional chondrosarcoma in the extremities in that the latter can be treated by extensive curettage, whereas wide en-bloc resection is indicated for clear cell chondrosarcoma [9]. In contrast with previous studies [11, 14], initial inadequate treatment did not affect overall survival and distant metastasis in the present study, this discrepancy is likely attributable to our adoption of the policy of immediate additional wide resection when positive margins are identified.

Conclusions

We found that patients with clear cell chondrosarcoma in Japan were predominately male and had a wide age range. Most tumors arose in the ends of the long bones and the proximal femur was the most common site. Immediate additional wide resection should be considered to prevent local recurrence when patients with clear cell chondrosarcoma are found to have had initial inadequate surgery. Extra care must be taken to avoid inappropriate excision, especially of femoral head lesions. In our series, one quarter of patients with clear cell chondrosarcoma in the femoral head were misdiagnosed and treated inappropriately, and two patients eventually underwent amputations. Ten-year overall and disease-free survival

rates were 89% and 57%, respectively, indicating that these tumors are generally indolent. However, clear cell chondrosarcoma can recur locally or distantly in the bones and lungs after a long period. Thus, patients need to be informed of the risk of very late recurrence and the necessity of decades-long surveillance for local recurrence and lung and bone metastases. Novel clear cell chondrosarcoma-specific markers in histology and serological screening would improve the diagnosis and follow-up.

Acknowledgments We thank the patients with clear cell chondrosarcoma in the study and all members of the JMOG for providing the information about their patients. We also thank Marla Brunker and Dr. Trish Reynolds, MBBS, FRACP, from Edanz Group (www.edanzediting.com/ac), for editing a draft of this manuscript, and Makana Suzuki for administrative support.

References

1. Ayoub KS, Grimer RJ, Carter SR, Mangham DC, Davies AM, Tillman RM. Clear cell chondrosarcoma of bone. *Sarcoma*. 1999;3:115-119.
2. Bagley L, Kneeland JB, Dalinka MK, Bullough P, Brooks J. Unusual behavior of clear cell chondrosarcoma. *Skeletal Radiol*. 1993;22:279-282.
3. Bjornsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. *Cancer*. 1998;83:2105-2119.
4. Bjornsson J, Unni KK, Dahlin DC, Beabout JW, Sim FH. Clear cell chondrosarcoma of bone. Observations in 47 cases. *Am J Surg Pathol*. 1984;8:223-230.
5. Cleven AH, Hocker S, Briaire-de Bruijn I, Szuhai K, Cleton-Jansen AM, Bovee JV. Mutation Analysis of H3F3A and H3F3B as a Diagnostic Tool for Giant Cell Tumor of Bone and Chondroblastoma. *Am J Surg Pathol*. 2015;39:1576-1583.
6. Collins MS, Koyama T, Swee RG, Inwards CY. Clear cell chondrosarcoma: radiographic, computed tomographic, and magnetic resonance findings in 34 patients with pathologic correlation. *Skeletal Radiol*. 2003;32:687-694.
7. Donati D, Yin JQ, Colangeli M, Colangeli S, Bella CD, Bacchini P, Bertoni F. Clear cell chondrosarcoma of bone: long time follow-up of 18 cases. *Arch Orthop Trauma Surg*. 2008;128:137-142.
8. Fletcher CDM, World Health Organization., International Agency for Research on Cancer. *WHO classification of tumours of soft tissue and bone.* Lyon: IARC Press; 2013.
9. Gelderblom H, Hogendoorn PC, Dijkstra SD, van Rijswijk CS, Krol AD, Taminiau AH, Bovee JV. The clinical approach towards chondrosarcoma. *Oncologist*. 2008;13:320-329.
10. Grimer RJ, Gosheger G, Taminiau A, Biau D, Matejovsky Z, Kollender Y, San-Julian M, Gherlinzoni F, Ferrari C. Dedifferentiated chondrosarcoma: prognostic factors and outcome from a European group. *Eur J Cancer*. 2007;43:2060-2065.
11. Itala A, Leerapun T, Inwards C, Collins M, Scully SP. An institutional review of clear cell chondrosarcoma. *Clin Orthop Relat Res*. 2005;440:209-212.
12. Jiang XS, Pantanowitz L, Bui MM, Esther R, Budwit D, Dodd LG. Clear cell chondrosarcoma: Cytologic findings in six cases. *Diagn Cytopathol*. 2014;42:784-791.
13. Kaim AH, Hugli R, Bonel HM, Jundt G. Chondroblastoma and clear cell chondrosarcoma: radiological and MRI characteristics with histopathological correlation. *Skeletal Radiol*. 2002;31:88-95.
14. Klein A, Tauscher F, Birkenmaier C, Baur-Melnyk A, Knosel T, Jansson V, Durr HR. Clear cell chondrosarcoma is an underestimated tumor: Report of 7 cases and meta-analysis of the literature. *J Bone Oncol*. 2019;19:100267.
15. Liu PT, Valadez SD, Chivers FS, Roberts CC, Beauchamp CP. Anatomically based guidelines for core needle biopsy of bone tumors: implications for limb-sparing surgery. *Radiographics*. 2007;27:189-205; discussion 206.
16. Mori T, Nakayama R, Endo M, Hiraga H, Tomita M, Fukase N, Kobayashi E, Kawai A, Ueda T, Morioka H. Forty-eight cases of leiomyosarcoma of bone in Japan: A multicenter study from the Japanese musculoskeletal oncology group. *J Surg Oncol*. 2016;114:495-500.
17. Present D, Bacchini P, Pignatti G, Picci P, Bertoni F, Campanacci M. Clear cell chondrosarcoma of bone. A report of 8 cases. *Skeletal Radiol*. 1991;20:187-191.
18. Tsuda Y, Ogura K, Hakozaki M, Kikuta K, Ae K, Tsuchiya H, Iwata S, Ueda T, Kawano H, Kawai A. Mesenchymal chondrosarcoma: A Japanese Musculoskeletal Oncology Group (JMOG) study on 57 patients. *J Surg Oncol*. 2017;115:760-767.
19. Turcotte RE, Kurt AM, Sim FH, Unni KK, McLeod RA. Chondroblastoma. *Hum Pathol.* 1993;24:944-949.
20. Unni KK, Dahlin DC, Beabout JW, Sim FH. Chondrosarcoma: clear-cell variant. A report of sixteen cases. *J Bone Joint Surg Am*. 1976;58:676-683.
21. Unni KK, Inwards CY, Mayo Foundation for Medical Education and Research. *Dahlin's bone tumors general aspects and data on 10,165 cases*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010: 402.
22. Wittekind C, Compton C, Quirke P, Nagtegaal I, Merkel S, Hermanek P, Sobin LH. A uniform residual tumor (R) classification: integration of the R classification and the circumferential margin status. *Cancer*. 2009;115:3483-3488.