Research Paper

Clear cell chondrosarcoma is an underestimated tumor: Report of 7 cases and meta-analysis of the literature

Alexander Klein[a,*], Felix Tauscher[a], Christof Birkenmaier[d], Andrea Baur-Melnyk[b], Thomas Knösel[c], Volkmar Jansson[d], Hans Roland Dürr[a]

[a] *Musculoskeletal Oncology, Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Marchioninistraße 15, 81377 Munich, Germany*
[b] *Department of Radiology, University Hospital, LMU Munich, Germany*
[c] *Institute of Pathology, University Hospital, LMU Munich, Germany*
[d] *Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Germany*

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ABSTRACT

Introduction: Clear cell chondrosarcoma (CCC) is a rare subtype of chondrosarcoma and it is commonly considered a low-grade tumor and less aggressive than atypical cartilaginous tumor (grade 1 central chondrosarcoma). However, the experience even of musculoskeletal tumor centres with this rare entity is limited. The aim of this study is to analyse our own treatment results and those of the literature regarding the therapy and outcome of this lesion.
Material and Methods: 7 cases of CCC have been treated in our department between 2003 and 2015. Their follow-up data were collected retrospectively. 187 literature cases with histopathological and clinical characteristics were retrieved by means of a PubMed search with the key word "clear cell chondrosarcoma". The data pertaining to treatment and follow up were extracted. We analysed the survival of patient and the risk factors for local recurrence (LR) as well as metastatic disease (MD).
Results: The mean age at the time of diagnosis was 40 years. Two thirds of the patients were male. The mean follow-up time was 109 months. To our surprise, there was a high rate of LR (30%) and of MD (20%) when compared to low-grade conventional chondrosarcomas. 15% of LR and 20% of metastatic disease were observed after more than 10 years follow-up. Uncommon locations of MD such as in the spine is a unique observation in chondrosarcomas and underlines the high aggressiveness of this tumor. 10-year overall survival was almost 80%, 10-years disease free survival 60%. Positive margins ($p = 0.038$) and metastases ($p = 0.006$) impaired the overall survival significantly. The rate of local recurrence was significantly dependent on resection margin ($p < 0.001$); however there was no correlation with the grade of differentiation of the tumor. The development of MD was affected by local recurrence ($p = 0.006$), but we could not detect a significant association with margin status ($p = 0.184$).
Conclusions: A wide resection is the advocated treatment option. Long term follow-up for at least 10 years is necessary in order to not overlook late LR or MD. This work demonstrates for the first time the apparent aggressiveness of the CCC.

1. Introduction

Clear cell chondrosarcoma (CCC) is a rare subtype of chondrosarcoma (CS) with the proportion of CCC being 2,7% of all CS. In 1976, the first cases of CCC were described by Unni et al. [1] Males are predominantly affected and mostly in their fifth decade of life. The

typical radiographic manifestation of this tumor is a slow growing epiphyseal osteolytic lesion. The most common localisation of CCC is the proximal femur [2]. The slow growth of these sarcomas often leads to delayed diagnosis or misinterpretation of the imaging findings. There are a several radiological and histological similarities with chondroblastoma or conventional CS. The typical characteristics of CCC in the radiological findings are well-delineated osteolytic lesions; often with typical chondroid matrix mineralisation surrounded by a sclerotic rim (Fig. 1). It is not uncommon for these tumors to show cystic changes with a fluid level. Hence, a cystic bone lesion is one of the most common misdiagnoses. Histopathology shows the typical cartilaginous structure of a chondrosarcoma with lobular pattern. Multiple cells with clear cytoplasm and round, large, centrally located nuclei characterize the CCC (Fig. 2). Prominent areas of haemorrhage have been observed

and may be misdiagnosed as aneurysmal bone cysts [3]. The lesion is usually characterized by well differentiated tumor cells (low-grade). However, there are some reported cases of dedifferentiated CCC (high-grade) [4]. The small number of CCC-patients even in musculoskeletal tumor centres result in inconsistent therapy recommendations. Frequently, intralesional curettage in analogy to central low-grade chondrosarcomas is recommended as the treatment of choice. We were unable to find any comparisons of different therapy strategies in the limited literature. The risk of local recurrence or metastatic disease from CCC is generally considered to be low [6,11,12]. The aim of our study is to confirm or disprove those assumptions, to evaluate the outcome of treatment in CCC, to define prognostic factors and to generate treatment recommendations based on a profound literature review and own experiences.

Fig. 1. a,b: X-rays of a 29 year-old male patient (patient #2) with a osteolytic lesion of the epiphysis and metaphysis of the proximal humerus. The lesion has sharp rims and shows a slight sclerosis of the borders, an unspecific finding, but typical of CCC; c-e: the MRI clearly shows the exact location and extent of the tumor but is unspecific. Coronal STIR (e) shows hyperintensity of the lesion. T1 –w TSE sequence pre- and post-contrast (c, d) show a homogeneous enhancement within the tumor. There are no rings or arcs patterns of enhancement which would be typical for chondroid tumors.
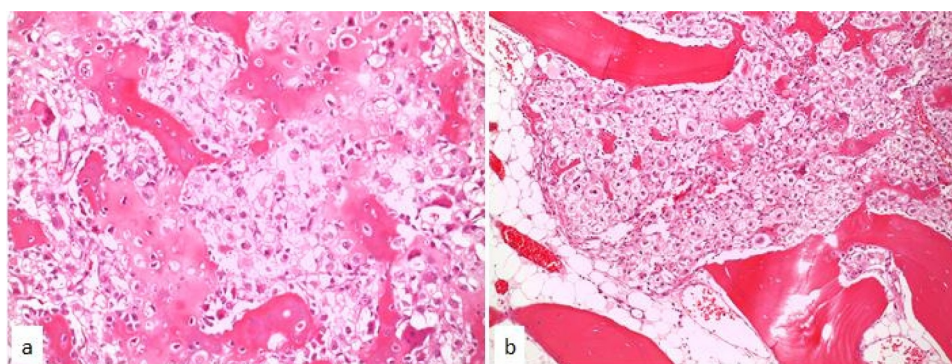
Fig. 2. Clear cell chondrosarcoma (patient #2): a: Sheets of clear cells with areas of mature hyaline cartilage (40x magnification); b: atypical clear cells with permeative growth (10x magnification).

2. Material and methods

We included all 7 patients with CCC, they had been treated between in our university hospital. The diagnosis of a CCC was established based on a biopsy and confirmed by an experienced pathologist after resection of the tumor. All tumor characteristics were described based on TNM classification. All patients underwent a wide surgical resection and were followed for evidence of local recurrence or metastatic disease by means of local magnetic resonance imaging (MRI) and computed tomography (CT) scans of the chest for 10 years on an out-patient basis. The survival data were collected retrospectively.

A literature search was performed using the PubMed database with "clear cell chondrosarcoma" as key word. In total, 233 reported cases were found. Cases with skull involvement and those published in languages other than English or German were excluded. 48 publications with a total of 187 cases, published between 1976 and 2015 were analysed. In all patients, the clinical data were available; follow-up had been reported in 136 cases. The largest series included 47 cases.

For statistical analysis, the data of our own patient cohort were merged with the literature data. All cases with missing treatment results and/or follow-up data were excluded from analysis. The overall and the disease-free survival were calculated according to the Kaplan-Meier method based on the available individual patient follow-up results. Significance analysis was performed using the Log-Rank test or the Chi-Square test using 95% confidence interval. The multivariate analysis (Cox proportional-hazards regression) was used for the evaluation of influence of grading, age, margin status, metastatic disease and local recurrence on overall survival. The level of significance was set at less than 0.05. The data analysis software used was IBM® SPSS® Statistics 25.

This study was approved by the local ethics committee. Written consent was obtained from all surviving patients included in this study. For non-surviving patients data were irreversibly anonymized as recommended by the ethics committee.

3. Results

3.1. Own patients

Our cohort of seven patients consisted of six males and one female. The mean age was 39.1 years (range 25–52). Five of the 7 tumors were located in the proximal femur, plus one each in the proximal tibia and the proximal humerus. All patients underwent a wide R0 resection with clear margins. No adjuvant radiotherapy or systemic treatment was applied. 6 of 7 tumors were well differentiated, in case the tumor included dedifferentiaded areas. Preoperative staging by means of a CT scan of thorax and abdomen showed no metastatic disease. The mean follow-up was 84 months (range 22–160).

Patient 1: 50-years old male patient who had experienced pain in the left hip joint during the proceeding twelve months. Because of radiological signs of initial osteoarthritis of the hip, he underwent a hip arthroplasty at another hospital. The large osteolysis of the femoral neck was not detected. The pathological examination of the femoral head showed a CCC. Metastases were excluded in a PET-CT scan. Seven weeks after the first operation, the patient was operated by wide resection of the proximal femur and reconstruction using a megaprosthesis. 55 months after the tumor resection, the patient is still without signs of recurrence or metastatic disease.

Patient 2: 29-years old male patient who had shoulder pain for 21 months. The radiological examination showed a large osteolysis of the humeral head (Fig. 1). An incisional biopsy was performed that resulted in the histopathological diagnosis of a CCC. After a negative staging, we resected the tumor and implanted an inverse shoulder prosthesis. Fifty months after the operation, the patient is currently free of disease.

Patient 3: A 51-years old male patient who underwent an MRI of the pelvis because of low back pain. Incidentally, an osteolysis of the right femoral head was detected which had no clinical correlation with the low back pain. The radiological control six months later showed progression of the lesion. Seven months after the diagnosis of an osteolysis, an intralesional curettage was performed. The histological examination showed CCC. The first follow-up consultation took place four months after the operation. An MRI could not detect residual tumor and no metastases were seen on chest CT. The suggested tumor resection and prosthesis implantation was refused by patient. 155 months later, there are no signs of metastases or local recurrence.

Patient 4: A 59-year old female patient complained of pain in the left hip joint for the preceding 2 years. The radiological examination showed an osteolytic tumor and the incisional biopsy showed the typical characteristics of CCC embedded in areas of classical central low-grade CS. Staging was negative and a wide tumor resection and megaprosthesis reconstruction of the hip joint were performed. Histopathological evaluation of the resected tumor showed low differentiation and the tumor was consequently classified as a G2-tumor. Nine months later, lung metastases were detected during restaging. 10 and 15 months after the hip reconstruction, lung metastases were removed. However, several months later, lung metastases appeared again. Chemotherapy was started (initially doxotaxel), which had to be modified several times because of disease progression. Eventually, the patient died from pulmonary metastases 83 months after initial diagnosis.

Patient 5: 41-years old male patient that was initially treated with screw osteosynthesis for a femoral neck at another institution. The pathologic nature of the fracture was not understood at that point and the duration of symptoms before the fracture is unknown. Twenty months after the initial operation, pathological refracture of the proximal femur reoccurred. The implantation of a hip arthroplasty was performed at yet another institution, but at that point, the diagnosis of CCC was established. Twenty one months after the first fracture the patient presented to our department with no metastatic disease. We performed a wide resection and joint reconstruction by means of a megaprosthesis. Seventy one months after resection, local recurrence was detected. A second wide resection was performed and 14 years after the wide resection there are no signs of recurrent disease.

Patient 6: A 31-years old male patient had pain in the left knee for 9 months. The diagnosis of CCC in an osteolysis of the proximal tibia was made by core needle biopsy. A wide resection was performed, the tumor was radiosterilized and the bone segment was reimplanted, supported by plate stabilisation. 34 months after resection, the patient is free of tumor.

Patient 7: A 28-years old male patient presented to our department because of a very large soft tissue tumor of the left thigh. Three years earlier, he had undergone screw osteosynthesis for a medial fracture of the femoral neck. The pathological character of that fracture remained undiagnosed at the time. Three months later, the change to total hip arthroplasty was necessary because of progredient osteolysis of the proximal femur. The histopathologic examination showed an aneurysmal bone cyst. Two years after the initial treatment, the soft tissue swelling of the left thigh was increasing. We secured the diagnosis of CCC and metastases could be excluded. 35 months after the initial treatment, we resected the tumor *in toto* and implanted a megaprosthesis. 46 months after that last operation, the patient is alive and free of disease.

3.2. Meta-analysis of data

123 male and 64 female patients were identified. Including our own 7 cases, 194 patients could be analysed (Table 1). The gender-ratio was 2:1 (132 male und 62 female; $p = 0.037$). The mean age at the time of diagnosis was 40 years (range 12–68, median 38). The most common site of the tumor was the proximal femur in 101 cases (52%), followed by the proximal humerus and the spine (Fig. 3).

Treatment modalities could be evaluated in 153 cases (78.9%). 150

Table 1

data of evaluated cases (Abbreviations: N/A – not available; Grading: Low - low-grade; High - high-grade; FU: NED - No Evidence of Disease; AWD – alive with disease; DOD – dead of disease).

| Author	Year	Patients (n)	Grading	Follow-up (FU)	Follow-up (months)	Margins	Local recurrence		Metastatic disease (MD)		
							LR (n;%)	Time to local recurrence (months)	Mets (n;%)	Time to MD	Location
Unni et al. [1]	1976	16	2 × × N/A	1 × N/A	4–252	1 × N/A	4; 25%	3–60 (median 24)	6; 38%	71–228 (median 81)	5 × lung
			8 × Low	10 × NED		8 × R0					2 × bone
			6 × High	1 × AWD.	(median 63)	7 × R1/2					
				4 × DOD							
Le Charpentier et al. [29]	1979	5	4 × Low	4 × NED	24–156 (median 30)	4 × R0	1; 20%	36	0	–	–
			1 × High	1 × DOD		1 × R1					
Salzer-Kuntschik et al. [30]	1981	1	1 × Low	NED	69	R1	1	46	0	–	–
Bjornsson et al. [5]	1985	47	N/A	9 × N/A	2–323 (median 72)	5 × N/A	16; 34%	56	7; 15%	42–84 (median 48)	5 × lung
				22 × NED		23 × R0					3 × bone
				8 × AWD		19 × R1					
				8 × DOD							
Komiya et al. [31]	1986	1	1 × Low	DOD	54	R2	0	–	1	48	Bones / lung
Ohno et al. [32]	1986	1	1 × Low	NED	39	R0	0	–	0	–	–
Present et al. [33]	1988	1	1 × Low	NED	18	R0	0	–	0	–	–
Chan et al. [34]	1989	1	N/A	N/A	N/A	N/A	–	–	–	–	–
Lee at al. [35]	1989	1	1 × Low	NED	70	R1	1	64	0	–	–
Welkerling et al. [36]	1990	1	1 × Low	NED	22	R0	0	–	0	–	–
Sreekantaiah et al. [37]	1991	1	1 × Low	NED	11	R0	0	–	0	–	–
Bosse et al. [38]	1991	3	3 × Low	N/A	N/A	N/A	–	–	–	–	–
Singh et al. [39]	1991	2	N/A	NED	5; 7	–	0	–	o	–	–
Bagley et al. [40]	1993	2	2 × LG	1 × NED	6; 280	2 × R0	0	–	1; 50%	276	Bones
				1 × AWD.							
Ron et al. [41]	1995	1	1 × LG	AWD	13	R0	1	5	1	12	Lung
Aigner et al. [42]	1995	2	2 × LG	N/A	N/A	N/A	0	–	0	–	–
Brien et al. [43]	1996	1	1 × LG	NED	24	N/A	0	–	0	–	–
Pinieux et al. [44]	1998	1	N/A	N/A	N/A	N/A	–	–	–	–	–
Masui et al. [7]	1999	4	4 × LG	N/A	N/A	N/A	–	–	–	–	–
Ishida et al. [45]	1999	1	1 × LG	NED	11	R0	0	–	0	–	–
Nathan et al. [46]	1999	1	N/A	N/A	N/A	N/A	–	–	–	–	–
Ayoub at al. [47]	1999	6	N/A	4 × NED	12–240 (median 51)	3 × R0	3; 50%	34–228 (mean 60)	1; 17%	66	Lung
				1 × AWD		3 × R1/2					
				1 × DOD							
Hartwright et al. [48]	2000	1	1 × LG	NED	252	R0	1	228	0	–	–
Kalil et al. [4]	2000	3	3 × HG	3 × DOD	36–98 (median 72)	2 × R0	2; 67%	8; 72	3; 100%	15–72 (median 66)	3 × lung
						1 × R1					2 × bone
Engels et al. [6]	2000	16	N/A	N/A	N/A	N/A	–	–	–	–	–
Cannon et al. [49]	2002	1	N/A	NED	24	R0	0	–	0	–	–
Memis et al. [50]	2002	2	N/A	N/A	N/A	2 × R0	0	–	0	–	–
Itälä et al. [51]	2005	16	N/A	11 × NED	88–233 (median 161)	10 × R0	3; 19%	2–22 (median 20)	3; 16%	48–196 (median 84)	1 × lung
				4 × AWD		6 × R1					2 × bone
				1 × DOD							
Kawano et al. [52]	2005	1	1 × HG	NED	50	R0	0	–	1	48	Bone
Srikanth et al. [53]	2006	1	1 × HG	DOD	N/A	R0	0	–	1	x	Lung
Simsek et al. [54]	2005	1	1 × LG	NED	72	R2	1	36	0	–	–
Nishio et al. [55]	2005	4	N/A	N/A	N/A	N/A	–	–	–	–	–
Tessitore et al. [56]	2006	1	N/A	NED	12	R1	0	–	0	–	–
Donati et al. [57]	2008	18	N/A	15 × NED	60–445 (median 240)	17 × R0	5; 28%	6–288 (median 56)	2; 11%	12; 64 (mean 38)	Bone
				3 × AWD		1 × R1					
Kuroda et al. [58]	2009	1	N/A	NED	6	R0	0	–	0	–	–
Hsu et al. [59]	2011	1	N/A	NED	24	R0	0	–	0	–	–
Sisu et al. [60]	2011	1	1 × HG	N/A	N/A	N/A	–	–	–	–	–
Paidakakos et al. [61]	2012	1	1 × LG	NED	12	R0	0	–	0	–	–
Ryu et al. [62]	2012	1	1 × LG	NED	42	R0	0	–	0	–	–
Elojeimi et al. [63]	2013	1	1 × HG	1 × AWD	36	R0	0	–	1	12	Bone
Matsuura et al. [8]	2013	5	N/A	N/A	N/A	N/A	–	–	–	–	–

Table 1 (*continued*)

| Author	Year	Patients (n)	Grading	Follow-up (FU)	Follow-up (months)	Margins	Local recurrence		Metastatic disease (MD)		
							LR (n;%)	Time to local recurrence (months)	Mets (n;%)	Time to MD	Location
Manfrini et al. [64]	2014	1	N/A	NED	240	R0	0	–	0	–	–
Jiang et al. [65]	2014	5	N/A	1 × NED	14–242 (median 120)	3 × R0	3; 60%	12–96 (median 30)	3; 60%	110–240 (median 120)	Bone
				3 × AWD 1 × DOD		2 × R1					
Laitinen et al. [66]	2014	1	1 × LG	AWD	378	R1	1	348	1	348	Lung
Tay et al. [67].	2014	1	N/A	NED	N/A	R0	0	–	0	–	–
Nagmani et al. [68]	2015	1	N/A	AWD	18	R0	0	–	1	18	Lung
Liska et al. [69]	2015	1	1 × LG	NED	106	R1	1	84	0	–	–
Moura et al. [70]	2016	1	N/A	NED	204	R1	1	192	0	–	–
Own cases		7	7 × LG	6 × NED	22–160 (mean 55)	7 × R0	1; 14%	71	1; 14%	9	Lung
				1 × DOD							
Total		194	55 × Low	96 × NED	2–445 (Median 83)	99 × R0	46; 32,2%	2–348 (mean 64, median 34)	34; 23,8%	9–348 (mean 92, median 71)	15 × Lung
			6 × High	23 × AWD 24 × DOD		48 × R1/2					13 × bone 6 × multiple

Patients (98%) underwent surgery, three patients radiotherapy only. A R0-resection with clear margins was performed in 99 (66.9%) cases, R1-resection with contaminated margins in 45 (30.6%) and an incomplete resection (R2) in 3 cases (2%). The margins remained unknown in 3 cases. In 3 cases with wide and in 2 with R1 resections, adjuvant radiotherapy (n = 4) and chemotherapy (n = 1) were administered.

Grading was available in only 61 cases. In 6 of those (9.8%) a high-grade component or dedifferentiated area was evident. For those 61 patients, follow-up was available in 51 cases (including all 6 with a high-grade component).

Follow-up could be obtained in 143 cases (73.7%). The mean follow-up was 105 months (range 2–445, median 72). 96 Patients
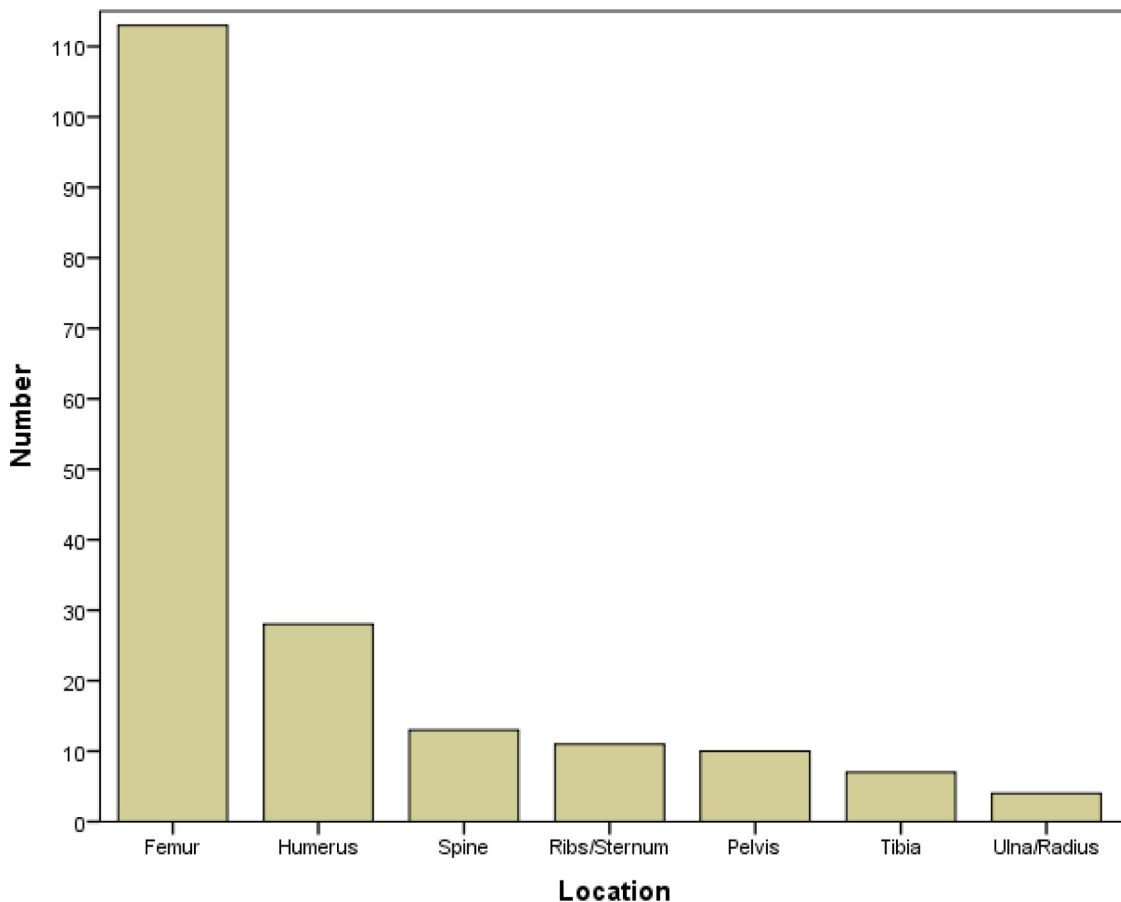
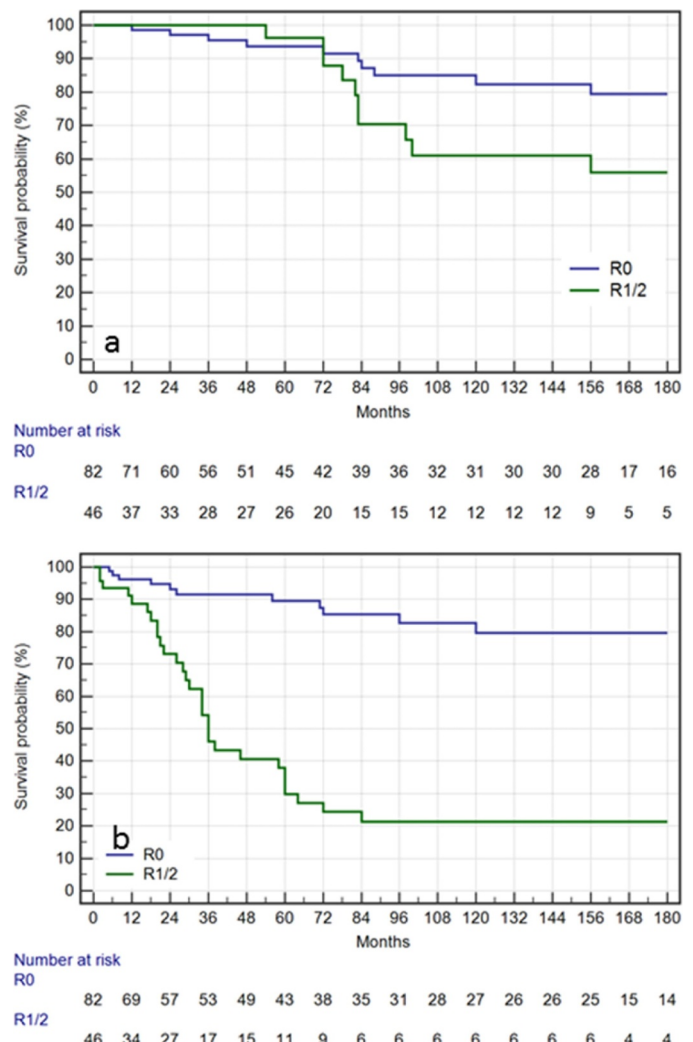**Fig 3.** Location of tumor in all patients.
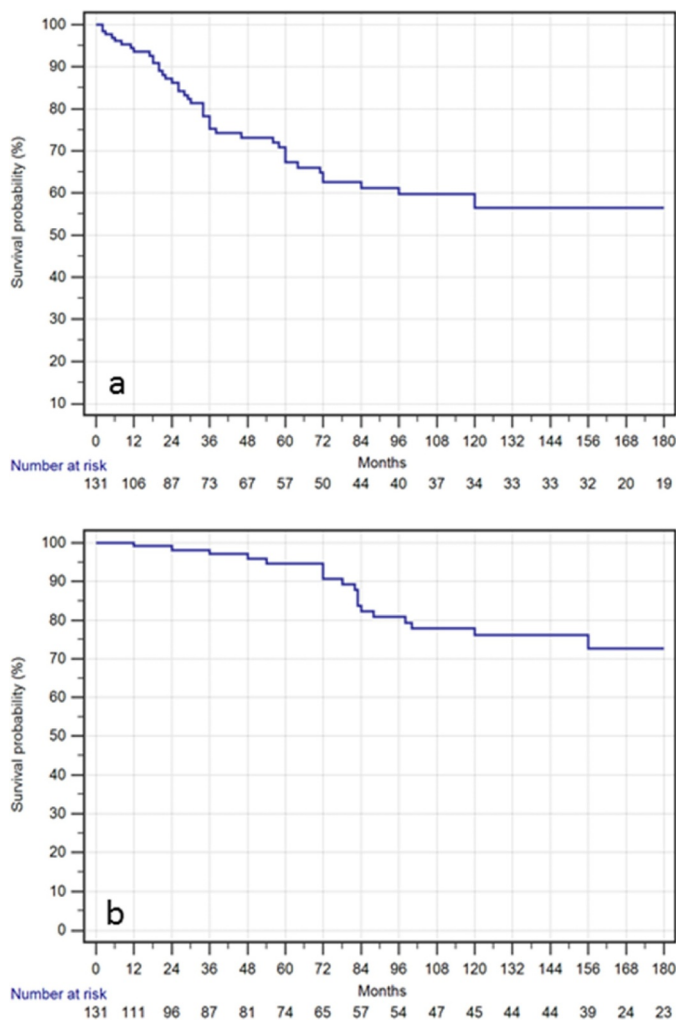
Fig 4. Overall survival (a) and disease free survival (b) in 143 patients with CCC.

Fig. 5. a: overall (*p* = 0.047) and b: local recurrence free survival (LRFS) (*p* = <0,001) of patients depending on resection margin.

Fig 6. Overall survival depending on local recurrence (LR) (*p* = 0,006).

(67.1%) were alive and free of tumor, 23 patients (16.1%) were alive with local recurrence or metastatic disease at last FU. 24 patients (16.8%) died due to the tumor, in the mean after 111.6 months (range 36–336). 23 of them had metastatic disease (Fig. 4).
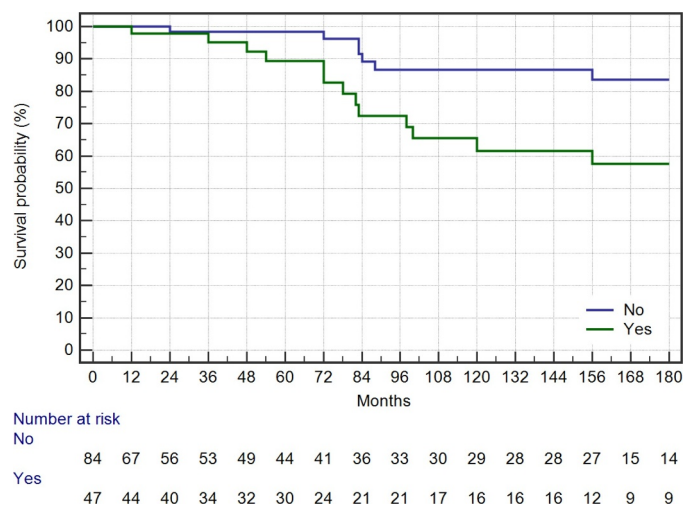
LR was observed in 46 of 143 patients (32.1%), in the mean 64 months after resection of the tumor (median 34, range 2–348 months). 15% of them were seen later than 10 years. 33 local recurrences occurred in 48 patients (68.8%) with incomplete and 13 in 99 patients with clear margins (13.1%) (*p* <0.001). Overall survival (351 ± 26 vs 231 ± 31 months, *p* = 0.047) and local recurrence free survival (339 ± 26 vs. 95 ± 20 months, *p* <0.001) was significantly correlated with R0- and R1/2-margin status. (Fig. 5a and +b).

LR negatively influenced the overall survival (OS) of the patients and this effect reached statistical significance (367 ± 26 vs 230 ± 26 months, *p* = 0.006) (Fig. 6). We could not detect any correlation between the grading of the tumor and the rate of LR (*p* = 0.635). In all 2 cases with R2 resection and in 2 of 3 cases with radiation therapy, only progression of local disease was evident. Two of those patients developed metastases after 48 and 228 months, respectively.

MD at the time of diagnosis was described in only one patient with the primary tumor being located in the proximal humerus. During follow-up, 34 patients (23.8%) developed MD. In 17 of them, additional LR was evident. One third of patients had a multilocular MD. In 21 patients the lung was affected. There were also 19 cases with bone metastases with the spine being the most common site with 10 cases, followed by the sternum and the ribs in 4 cases. Mean time to MD was
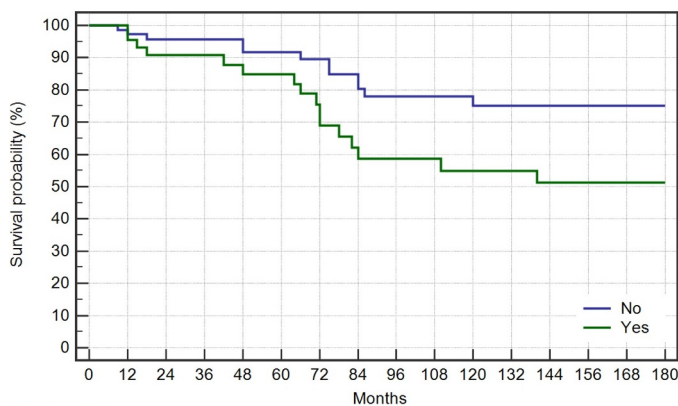
92 months (median 71; range 12–348) after surgery. Seventeen patients with MD had an initial R0 resection of the primary. In 44 patients with G1 lesions, 10 (22.7%) patients developed MD and in all 6 cases with G2/3 lesions (100%) MD was seen. A significant correlation was found

Fig. 7. Metastasis-free survival depends on occurring of local recurrence (LR) (*p* = 0,034).

between MD and LR (*p* = 0.006) and also between MD and the grading of the tumor (*p* = 0.001). However, no significant correlation was detected between MD and margin status (*p* = 0.184). The metastasis-free survival was clearly influenced by LR (312 ± 28 vs. 203 ± 25 months, *p* = 0.034) (Fig. 7).

With regards to overall survival, LR, margins, grading and occurrence of MD all proved to be significant in univariate analysis. However, in multivariate analysis only margins and MD maintained statistical significance (Table 2).

4. Discussion

CCC's are generally considered to be well differentiated and low-aggressive tumors. The largest published series including 47 patients collected over several decades highlights this [5]. In the first published pathologic analysis of CCC, a low malignancy with low proliferative activity (Ki 67 index < 5%) is described [6]. Therefore, a close relationship to low-grade central chondrosarcomas was suspected. Further findings show expression patterns of proteins such as PTH-LP, PDGF and PDGF-R as is also the case in central chondrosarcoma. Consequently, CCC may have a heterogenous histological aspect associated with different cytokines [7]. Contrary to those observations, *Kalil* et al. described 4 cases of dedifferentiated CCC with much more aggressive behaviour [4]. Most important in the more aggressive behaviour of CCC's appears to be the clear cell component. In immunohistochemical analysis, an epithelial lineage has been demonstrated in addition to the cartilaginous cell differentiation [8]. In view of those findings, CCC's seems to be more aggressive than central low-grade CS.

Based on these aspects, treatment strategies based on the historically assumed less aggressive behaviour of CCC may lead to an untertreatment approach in these patients. In many of the included cases, intralesional surgery in the sense of curettage had been chosen. A

recurrence rate of less than 20% in low-grade central CS (in most of the studies lower than 10% [9–12], also with long-term follow-up) led to the assumption of a similar behaviour in CCC. Most LR in central G1 CS occurred within the first 5 years [13,14]. This meta-analysis in CCC demonstrates a much higher rate of LR (30%) with 15% of them occurring later than 10 years after the initial resection.

The demonstrated correlation of LR and resection margins discourages intralesional (R1) resections. This is a striking difference to intralesional surgery in low-grade central CS [10,15]. In CS, the influence of LR on OS is controversially discussed [11,16–18] as also seen in our own data in this group of patients [19]. In this study on CCC, a significant correlation was evident in univariate analysis. MD was also significantly associated with LR. Thus, more aggressive surgery, such as wide (R0) resection is advised. Striking is also the frequency of late LR, indicating that a long period of surveillance is necessary. Interestingly, this observation has also been made in high-grade CS [11,20].

Radiotherapy only or additional irradiation after R2 resections does not result in long-term local tumor control. Almost all patients developed local or systemic progression of disease. This corresponds well to central CS [21,22].

A significant correlation between MD and tumor grading in central CS is well described [11,18,23–25]. The high rate of MD (24%) in a lesion that has traditionally been considered to be low-malignant was an unsuspected finding. Despite the fact, that all 6 patients with high-grade CCC had developed MD, also in those 44 patients with available follow-up data and low-grade differentiation, 23% showed MD. The MD rate of 24% is comparable to the published data of high-grade central chondrosarcoma. The median time of 71 months until the diagnosis of MD was comparatively long. Almost 25% of MD was detected more than 10 years after surgery. *Angelini* et al. did not observe metastatic events after 8 years in central CS [20]. The earlier works from *Lee* et al. and *Ozaki* et al. showed the same results [18,26]. This therefore seems to be a remarkable feature of CCC in contrast to central CS. The high rate (59%) of metastatic bone lesions and especially in the spine is astonishing and reminiscent of the biology of myxoid liposarcoma [27] whereas it is untypical for central CS [26,28]. We could not evaluate any patterns or dependences of metastases in respect to the location of the primary, grading or resection margins.

The risk factors for shorter survival with CCC appear to be the same as in conventional central CS: positive margins and the occurrence of metastatic disease negatively influence the prognosis [19].

There are certain limitations to our study. As is the case with most of the literature on this subject, only a small number of own cases were available over a period of 15 years. The heterogeneous quality of the published data and missing follow-up data in a quarter of researched cases does not permit for a precise statistical approach. Sparse histological characteristics do not allow a more profound evaluation of the influence of differentiation on recurrence and survival. However, in contrast to the previously published literature and to the opinion of many sarcoma specialists, the behaviour of CCC is much more aggressive than and very different from low-grade central CS.

5. Conclusions

Clear cell chondrosarcoma should be treated as an aggressive malignant tumor with a high rate of local recurrences and metastatic disease in more than 20% of cases. A wide resection is the most appropriate surgical approach and improves prognosis. Metastatic disease is seen in the bone as often as in the lung, hence in addition to thoracic CT scans, MRI of the spine, the most common bone location, is advised. Due to local recurrence in 15% and MD in 20% after more than 10 years in all recurrent cases, a longer time of surveillance is advocated. Surveillance hence should be at least 10 years.

Table 2
Cox proportional-hazards regression for overall survival in relation to grading, metastatic disease, margin status and local recurrence.

Varriables	Univariate analysis Hazard ratio (95% CI)	*p*-value	Multivariate analysis Hazard ratio (95% CI)	*p*-value
Grading	1,44–142,56	**< 0,001**	0,136 - 2572	0,484
Metastatic disease	65–110	**< 0,001**	0,002 - 0,343	**0,006**
Margin status	69–410	**0,047**	1138 - 112,152	**0,038**
Local recurrence	112–357	**0,006**	0,020 - 1309	0,088

Declarations

Ethics approval and consent to participate: this study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from all surviving patients included in this study. For non-surviving patients data were irreversibly anonymized as recommended by the ethics committee.

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CRediT authorship contribution statement

Alexander Klein: Conceptualization, Data curation, Writing - original draft, Formal analysis, Project administration. **Felix Tauscher:** Investigation, Formal analysis. **Christof Birkenmaier:** Writing - review & editing. **Andrea Baur-Melnyk:** Investigation, Methodology. **Thomas Knösel:** Investigation, Methodology. **Volkmar Jansson:** Writing - review & editing. **Hans Roland Dürr:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2019.100267.

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