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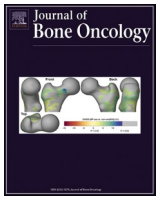

Intraosseous conventional central chondrosarcoma does not metastasise irrespective of grade in pelvis, scapula and in long bone locations

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HIGHLIGHTS

- The metastatic potential of intraosseous conventional central chondrosarcoma is negligible.
- The presence of an extraosseous tumour component may be used for prognostication and possible change in treatment pathways for patients with central cartilage tumours.

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ABSTRACT

Background: Histological grade has been regarded as the most important prognostic factor in conventional central chondrosarcoma. To evaluate whether the presence of an extraosseous tumour component is associated with a decreased metastasis-free survival or disease-specific survival and alternatively to develop a simple prognostic and clinical decision-making tool.

Material and methods: We searched two prospectively maintained international sarcoma centre databases for primary non metastatic central conventional chondrosarcomas of all grades in pelvis, scapula or long bone location, undergoing curative treatment, diagnosed between 2000 and 2020. Pre-treatment MRI scans were reviewed for the presence of an extraosseous mass. The metastasis-free survival (MFS) and disease-specific survival (DSS) were estimated by the Kaplan-Meier method from surgery to event, death or last follow-up.

Results: 336 patients were identified between 2000 and 2020, undergoing surgical treatment for conventional central chondrosarcoma. 111 patients (33 %) had grade 1 tumours, 149 patients (44 %) had grade 2, and 76 patient (23 %) had grade 3 chondrosarcomas determined as the highest grade in the final resected specimen. An extraosseous soft tissue component was more frequent in higher grade tumours ($p < 0.001$) and present in 200 cases (60 %). None of the patients with an intraosseous tumour developed metastases or died of the disease. For patients with extraosseous tumour component, MFS was 92 % (95 % CI, 96–100) at 2-years and 74 % (95 % CI, 67–81) at 10-years and DSS was 91 % (95 % CI, 87–95) at 2-years and 75 % (95 % CI, 68–82) at 10-years. The MFS and DSS was significantly different ($p < 0.001$) for those patients with or without an extraosseous tumour component, irrespective of grade or anatomical location.

Discussion: The results of this study has shown that the metastatic potential of intraosseous conventional central chondrosarcoma is negligible. The presence of an extraosseous soft tissue component may be used for prognostication and to guide treatment pathways for patients with central cartilage tumours.

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1. Background

Central cartilage tumours (CCT) of bone include a spectrum of benign to malignant conditions. Enchondromas (benign) may, in a small proportion of cases, transition into malignant chondrosarcomas with an incidence of conversion in one study of 4 % [1]. Chondrosarcoma is the second most common surgically treated primary sarcoma of bone but remains rare with an age-standardized incidence of approximately 3.4–4.1/million inhabitants/year [2]. CCTs are found as incidental findings on MRI of the knee, hip or shoulder in up to 3 % of scans [3,4] Most CCTs do not require intervention but still represent a significant diagnostic and surveillance quandry for sarcoma units. In the new WHO classification, extremity grade 1 chondrosarcoma has been renamed as atypical cartilage tumours (ACT) to better reflect their low metastatic potential [5]. However, since the change in definition, the incidence of cases falling into the definition of ACT/grade 1 chondrosarcoma has rison dramatically increased and the degree of intervention for ACT has not been clearly determined [6,7].

Traditionally, the risk of metastatic disease has been predicted by the histological grade of the tumour, with an incremental increase in risk depicted by increasing grade. Biopsy of CCTs has been shown to be highly inaccurate at predicting the final grade of chondrosarcoma on the resection specimen, leading to possible over or undertreatment [8]. There are also controversies relating to the surgical management of chondrosarcoma based on tumour grade. Some units advocate intralesional curettage of ACT/grade 1 chondrosarcoma lesions but wide excision of high-grade lesions, whilst other units prefer *en bloc* excision for all grades due to the high risk of locally recurrent disease and subsequent metastatic disease if an intralesional treatment is mistakenly undertaken on a high grade chondrosarcoma.

A simple classification system to predict outcome and guide treatment based on imaging alone is needed with several classifications reported recently [9,10].

2. Methods

Following institutional ethical approval, we identified patients who were diagnosed and surgically treated for conventional central grade 1, 2 or 3 chondrosarcoma of axial (pelvic and scapula) or long bones without metastases at diagnosis (or within 3 months of diagnosis), between January 2000 and December 2020 at two large tertiary referral sarcoma centres from their prospectively maintained tumour databases (Royal Orthopaedic Hospital, Birmingham, UK; Helsinki University Hospital, Helsinki, Finland). Spine, skull, thoracic wall and acral locations were excluded due to evidence that these locations have different clinical behaviour to the long bones or axial skeleton. Since tumours both in pelvis, scapula and long bones were included, the term grade 1 chondrosarcoma was used instead of ACT. All patients were diagnosed and treated at the referral hospital with those previously treated elsewhere excluded. A minimum of two years follow-up for survivors was required for inclusion. All patients had continuous follow-up data from the surgery until the first event (metastasis or death) or until last clinical assessment. Kaplan-Meier (K-M) method was used as median observation times to estimate metastasis-free survival (MFS) and disease-specific survival (DSS). The presence of a soft tissue component was verified in each centre on standard diagnostic MRI. Details of the clinical and radiological data were collected from the registry and clinical files. Primary surgery was defined by the method that concluded the first-line treatment. The resection specimens were examined by specialist bone sarcoma pathologists, for grade in each centre [11]. The grade was defined by internationally agreed-upon standards and described according to the WHO classification [5].

3. Results

The study population comprised 336 patients, of which 111 (33 %)

Table 1
Characteristics of 336 conventional central grade 1, 2 and 3 chondrosarcoma cases.

Variable freq.	Specification	Total n = 336	No extraosseous component n = 136 (40 %)	Extraosseous component n = 200 (60 %)
Sex	Male	183(55 %)	56(41 %)	127(64 %)
freq.(%)	Female	153(45 %)	80(59 %)	73(36 %)
Age at diagnosis	Mean	53	49	56
(years)	Range	8–95	8–85	10–95
Anatomical location	Axial (pelvic/ scapula)	108(32 %)	27(20 %)	81(41 %)
freq.(%)	Extremity (long bones)	228(68 %)	109(80 %)	119(59 %)
Pathological fracture	Present	29(9 %)	9(7 %)	20(10 %)
freq.(%)	Not	307(91 %)	127(93 %)	180(90 %)
Tumor size cm	Mean	9.2 cm	7.5 cm	10.4 cm
	V	1–60 cm	1–40 cm	1.5–60 cm
Malignancy grade	Grade 1	111(33 %)	81(60 %)	30(15 %)
freq.(%)	Grade 2	149(44 %)	43(32 %)	106(53 %)
	Grade 3	76(23 %)	12(8.8 %)	64(32 %)
Surgical Treatment	Curettage	40(12 %)	37(27 %)	3(1.5 %)
freq.(%)	Resection	269(80 %)	99(73 %)	170(85 %)
	Amputation	27(8 %)	0	27(13 %)
Metastasis	Yes	50(25 %)	0	50(25 %)
freq.(%)	No	286(75 %)	136(100 %)	150(75 %)
Metastasis Free Survival -MFS% (95 % CI)	2 year	89 % (85–92)	100 %	92 %(96–100)
	5 year	84 % (79–88)	100 %	81 %(75–87)
	10 year	83 % (79–88)	100 %	74 %(67–81)
Disease Specific Survival -DSS % (95 %CI)	2 year	98 % (96–100)	100 %	91 %(87–95)
	5 year	94 % (91–96)	100 %	78 %(71–84)
	10 year	91 % (88–94)	100 %	75 %(68–82)
Status last follow-up freq.(%)	Alive without disease	261(78 %)	128(94 %)	133(67 %)
	Alive with disease	14(4 %)	1(1 %)	13(7 %)
	Death of Sarcoma	35(10 %)	0	36(18 %)
	Death of treatment	3(1 %)	0	3(2 %)
	Death other reason	23(7 %)	7(5 %)	16(8 %)
Location	Pelvis	84(25 %)	20(15 %)	64(32 %)
	Femur	127(38 %)	54(40 %)	73(37 %)
	Tibia and fibula	35(20 %)	19(14 %)	16(8 %)
	Humerus and forearm	66(20 %)	36(26 %)	30(15 %)
	Scapula	24(7 %)	7(5 %)	17(8 %)

freq. = frequency.

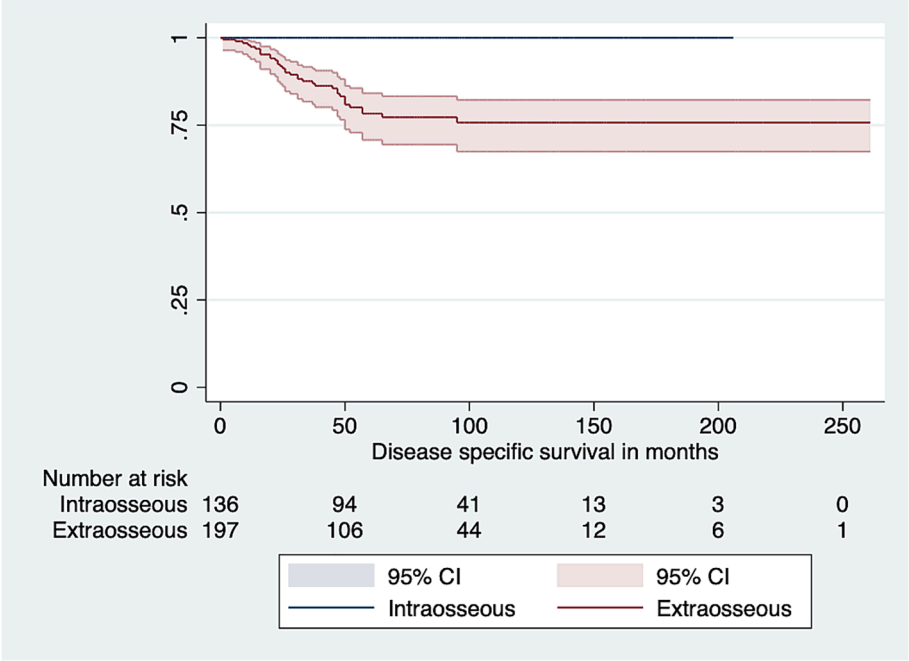

Fig. 1. Disease specific survival by presence of soft tissue component.

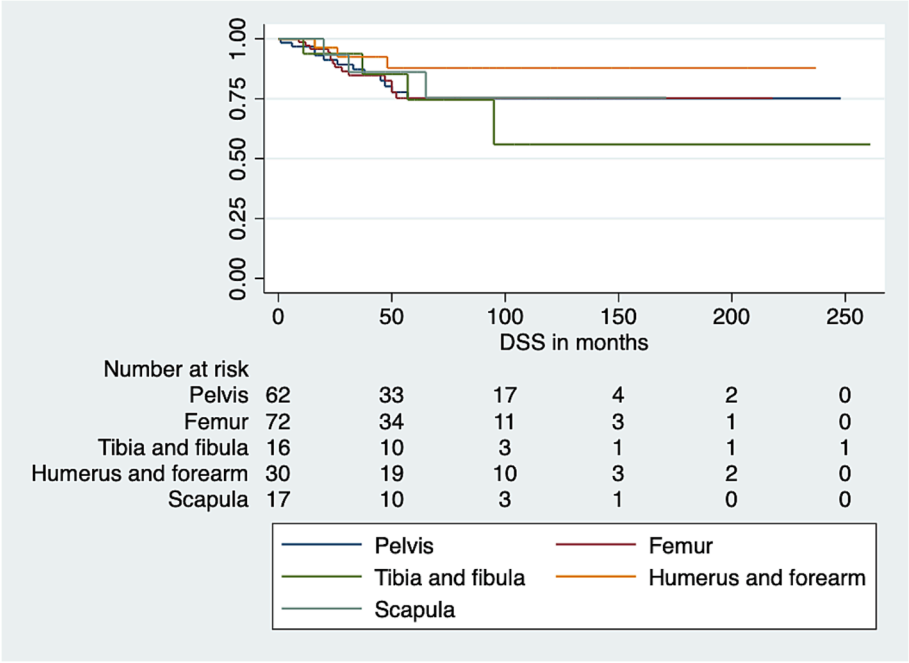

Fig. 2. Disease specific survival in chondrosarcoma tumours with extraosseous soft tissue component stratified by location.

had grade 1 tumours, 149 (44 %) had grade 2, and 76 (23 %) had grade 3 chondrosarcomas. The mean age of the study population was 53 years (8–95 years) and the mean follow-up was 6.0 years (SD ± 50.1). An extraosseous soft tissue component was present in 200 (60 %) of the cases and was present in 76 % (n = 171/225) of high grade compared to 26 % (29/111) of low grade tumours ($p < 0.001$). Of those patients with intraosseous disease the highest grade at definitive surgery was grade 1 in 81 (60 %), grade 2 in 43 (32 %) and grade 3 in 12 (9 %). The patients' characteristics are presented in Table 1.

None of the patients with an intraosseous tumour developed metastases or died of the disease, therefore MFS and DSS were both 100 % at 2, 5 and 10-years. For patients with extraosseous tumour component, the MFS was 92 % (95 % CI, 96–100) at 2-years, 81 % (95 % CI, 75–87) at 5-years and 74 % (95 % CI, 67–81) at 10-years and the DSS was 91 % (95 % CI, 87–95) at 2-years, 78 % (95 % CI, 71–84) at 5-years, 75 % (95 % CI, 68–82) at 10-years. The difference in MFS ($p < 0.001$) and DSS ($p < 0.001$) (Fig. 1) was statistically significant for those with extraosseous chondrosarcoma, irrespective of highest grade at surgery or the anatomical location.

For patients with extraosseous tumour component, stratified by the tumour location, DSS was 85 % (95 % CI, 75–94) at 2-years, 73 % (95 % CI, 60–85) at 5- and 10-years for pelvis, 90 % (95 % CI, 82–97) at 2-

years, 75 % (95 % CI, 68–83) at 5- and 10-years for femur, 94 % (95 % CI, 88–100) at 2-years, 75 % (95 % CI, 49–100) at 5-years and 56 % (95 % CI, 19–93) at 10-years for tibia and fibula, 96 % (95 % CI, 89–100) at 2-years, 88 % (95 % CI, 75–100) at 5- and 10-years for humerus and forearm, and 93 % (95 % CI, 81–100) at 2-years, 86 % (95 % CI, 68–100) at 5-years, 75 % (95 % CI, 50–100) at 10-years for scapula. (Fig. 2). These differences were not statistically different. A higher proportion of tumours with an extraosseous component were seen in the axial skeleton compared to other locations with the pelvis (n = 64/84, 76 %) and scapula (n = 17/24, 70 %) compared to femur (n = 73/127, 58 %), tibia and fibula (n = 16/35, 46 %) and humerus and forearm (n = 30/66, 46 %).

4. Discussion

Conventional central chondrosarcoma, whilst traditionally regarded as a single disease entity, constitutes a broad spectrum of tumour variants that have been thought to behave differently depending on anatomical location, predisposing conditions and clinical features [12,13,14,15]. Historically, histological grade was considered the most important factor in determining metastatic potential of chondrosarcomas [8,13]. We have previously demonstrated a poor correlation between the highest grade seen on preoperative biopsy and the final resection histology, which was only 50 %. This brings into question the role of preoperative biopsy in guiding the planned resection strategy, especially when combined with the dire consequences of intralesional margins in a higher grade chondrosarcoma [8].

In the current study, the authors have shown that if the chondrosarcoma is intraosseous at presentation (approximately 40 % of patients), then no patient suffered from metastatic disease, despite 40 % the intraosseous tumour cases showing high grade chondrosarcoma at resection, which has significant clinical and biological implications. If the tumour being confined to the bone reduces the metastatic potential, basic science investigation of the mechanism of bone destruction, proliferation index and subsequent metastatic potential, may lead to actionable targets for chemotherapy, currently lacking in chondrosarcoma [16]. There has been significant interest in the role of osteoclast mediated bone destruction in sarcomas and their possible inhibition with bisphosphonates or receptor-activator of nuclear kappaB ligand (RANKL) [17,18]. Dysregulation of the bone microenvironment in chondrosarcoma is thought to cause a vicious cycle between resident cells and tumor cells playing a part in bone sarcoma growth and the associated metastatic process [19].

Historically, chondrosarcomas of the pelvis have been shown to have poorer oncological outcomes compared to anatomical locations, with some postulating that they behave in a more aggressive manner. However, this study shows that the pelvis and scapular tumours with extraosseous component have a similar DSS compared to tumours with extraosseous component in other anatomical locations. In axial locations, tumours are more likely to present with an extraosseous component, which in itself was the most important predictor of DSS in this series. This poses a question as to why these sites may have a higher proportion of extraosseous mass compared to other sites. The authors postulate that it may be due to these sites being flat bones, with a thin cortex and narrow medullary cavity which may be less able to resist cortical destruction, allowing the more rapid formation of a soft tissue mass and subsequently increasing the metastatic potential.

The authors propose, that the findings of our study simplifies treatment algorithms for clinicians when combined with radiological classification systems, such as BACTIP, which has been validated to correlated with malignancy in CCTs in certain anatomical locations [9]. The presence of significant deep endosteal scalloping has been shown to be the radiological factor that best correlates with malignancy in ACTs and can be safely monitored on seriel MRIs [20].

The authors postulate that the results suggest that a CCT with an extraosseous mass requires *en bloc* excision with wide surgical margins, whereas an intraosseous CCT can be either safely observed (with the knowledge that the patient is at negligable risk of metastatic disease [21]) or undergo definitive management if symptomatic or there is evidence deteriorating radiology, or significant cortical scalloping which may lead to development of a cortical breach and subsequent extraosseous mass.

The Oslo classification estimated the risk of metastases by taking into account anatomical location and the size of the soft tissue mass [22] and Fiorenza et al showed excellent survival for patient with intracompartmental tumours with small numbers of patients [23], further validating of the results of this study which we believe further simplies management. The results will be discussed at a global consensus meeting, to encourage collaborative studies to validate the results, investigate the safe timing interval for MRI surveillance and basic science studies to better understand the mechanisms of cortical destruction and metastases.

In conclusion, our large multicentre study has shown that the metastatic potential of intraosseous conventional central chondrosarcoma is negligible, irrespective of histological grade or tumour location. The presence of an extraosseous soft tissue component may be used for prognostication and to guide treatment pathways for patients with CCTs.

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6. Author statement

A study of 336 patients treated during a 20-year period between years 2000–2020. Study concepts ML, LJ, Study design ML, JT, LJ, Literature research ML, LJ, Clinical studies ML, JT, LJ, Data acquisition ML, JT, GM, VK, JS, MP, LJ, Data analysis ML, JT, Manuscript preparation ML, JT, Manuscript editing ML, JT, GM, VK, JS, MP, LJ, Manuscript review ML, JT, GM, VK, JS, MP, LJ.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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