RESEARCH ARTICLE

Risk stratification for central conventional chondrosarcoma of bone: A novel system predicting risk of metastasis and death in the Cancer Registry of Norway cohort

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Abstract

Background and Objectives: Interobserver variability in histological grading of central conventional chondrosarcoma (CCCS) limits the quality of patient information and research progression. We aim to quantify known and new prognostic variables and propose a risk stratification model.

Method: We selected 149 cases from the Cancer Registry of Norway. Cox proportional hazard models were estimated. Based on these results a dichotomous risk classification was proposed and presented by Kaplan-Meier estimates for rates of local recurrence, metastasis, and disease-specific survival.

Results: The influence of axial skeletal location (Hazard ratio [HR] = 19.06), a soft tissue component ≥1 cm (HR = 13.45), and histological grade 3 (HR = 16.46) are all significant in predicting the rate of metastasis. The creation of a variable combining axial skeletal location and a soft tissue component ≥1 cm strongly predicts the risk of metastasis (HR = 14.02; \( P < .001 \)) and death (HR = 2.74; \( P = .030 \)) at multivariate analysis, making the histological grade insignificant. Together with metastasis at diagnosis (HR = 285.65; \( P < .001 \)), this forms the basis of our proposed risk stratification, producing a small high-risk group (39 cases with 33% risk of metastasis) and a large low-risk group (103 cases with 2% risk of metastasis) without a histological grade.

Conclusion: Axial skeletal location and a soft tissue component ≥1 cm combined divides a CCCS cohort into low- and high-risk groups without a histological grade.

KEYWORDS  
chondrosarcoma, classification, prognosis, risk

1 | INTRODUCTION

The role of histological grading in the prognosis of chondrosarcoma (CS) of bone was first described over 50 years ago.\(^1\) During the last 10 years, the inter-observer variability of grading between expert pathologists, radiologists, and orthopedic oncologists and its clinical and research implications has been well documented.\(^2,5\)
Despite this, the scientific literature presents results for CS of bone by histological grade. These results are generally in mixed cohorts, and include central, peripheral, and often dedifferentiated CS subtypes together. Though these subtypes have similar features on microscopic examination, they are now recognized as different diseases with varying biology and treatment and as such, the prognostic work should also be performed at a subtype level.

Many cohorts with central conventional chondrosarcoma (CCCS) alone are limited to specific anatomical locations or with multivariate analyses for limited variables in institutional cohorts. Histological grade significantly predicts survival at univariate analysis in two national CCCS cohorts, but has not been proven in multivariate models. Neither does it convey the established importance of anatomical location and soft tissue extension which drives treatment of CCCS. A new system of risk stratification for CS of bone is needed. It should ideally depict differing risk groups with regard to both local and systemic control in as few categories as possible and must be specifically validated for each subtype. The methodology should be simple to ensure low inter-observer variability, thereby establishing common definitions to allow for the pooling of cases vital to rare disease research.

We have previously shown the prognostic importance of a soft tissue component in CCCS of bone. We, therefore, chose to look at whether the soft tissue components’ size by standardized measurement was associated with prognosis.

Our primary aim was to use prognostic analysis from a complete national cohort of CCCS of bone to quantify the influence of anatomical location, presence, and size of a soft tissue component, as well as malignancy grade.

The secondary aim was to propose a risk stratification model for CCCS based on the above and to present results from our cohort by this stratification.

2 MATERIALS AND METHOD

The Cancer Registry of Norway (CRN) cohort of CS of bone from 1990 to 2013 has been previously described, and the same definitions were applied to this study (Supporting Information Material). It is a prospective register, but we have retrospectively quality controlled all data. There were 197 eligible cases of CCCS in the cohort for all anatomical locations excluding head and neck. Radiology was reviewed for 134 cases. Radiology was missing in 63 cases due to the hospitals deleting the images 10 years after diagnosis. Of the 63 cases, 48 had histologically proven soft tissue components. These 48 were therefore excluded since we had no means of measuring the soft tissue component, while the other 15 cases were intramedullary cases and were included in the study. This resulted in 149 cases eligible for analysis (Figure 1).

Thirty-eight of the 149 cases were selected for histological review by set criteria to complement missing or unclear data. All 149 cases are histologically confirmed and have complete data sets and documented follow-up. All information in the register for all cases was quality controlled by the main author from the clinical notes.

FIGURE 1 Flowchart illustrating methodology for inclusion/exclusion of cohort [Color figure can be viewed at wileyonlinelibrary.com]

Borderline malignant lesions have intentionally been excluded under the selection of the original cohort (11 cases). The size of the soft tissue component was measured using radiology software to the nearest mm, perpendicular to the stipulated outer cortex in the plane that best allowed the greatest measurement by coauthor IT, a senior sarcoma radiologist. Examples are illustrated in Figure 2. Edema was not measured. In the case of circumferential tumor, measurement was made where the largest.

Extremity location was defined by the glenohumeral and hip joints, meaning that the pelvis and scapula are denoted as part of the axial skeletal location group.

Grading has been practiced in accordance with WHO criteria in a four-grade system. CCCS is graded 1 to 3, while dedifferentiated CS as grade 4 was not included in this study.

The term “Atypical Cartilaginous Tumor (ACT)” has not been adopted in Norway during the study period and as such was not introduced into the manuscript.

The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) checklist was used as far as the methodology allowed.

2.1 Clinical setting

Investigation, treatment, and follow-up of chondrosarcoma in Norway during the period was highly centralized. Ninety-one percent were referred to as untouched cases, 3% had a biopsy outside a referral center, and 6% had contaminated surgeries. In the early1990s treatment was driven by grade on open biopsy, but this
changed in the mid-90s with the acceptance of skeletal location and soft tissue components role in depicting biology together with the awareness of challenges involved in defining accurate histological grade on biopsy. Since then, curettage has been performed on extremity intramedullary lesions with limited signs of radiological aggressiveness, while all others have been resected. Similarly, needle biopsy has primarily been performed to confirm a radiological chondrosarcoma diagnosis before more extensive surgery (ie resection) and increasingly not at all, in the latter part of the study period. Reporting to the CRN was mandatory by law throughout the period.

2.1.1 | Bias

Possible bias has been addressed by the use of multiple sources. Review of both radiology and pathology where available, or by set criteria, including all cases at risk of wrongful diagnosis or with missing data. The review was partly in a group setting. The cohort is population-based, which should control for random patterns in local or regional referral practices.

There exists a possibility for selection bias since cases with a soft tissue component and missing radiology were excluded (48/197 cases = 25%). Thus, the influence of the soft tissue component on our findings may be underestimated in magnitude in prognostic analysis when compared to intramedullary disease. We have reason to believe that our national cohort is complete.24 A recent national Dutch cohort19 report an overall CS incidence nearly twice that of Norway and clearly highest in the world.25 Their documented incidence increase is driven by ACT’s while ours is for grade 2 disease and as such it seems likely that they define ACT at a lower level of aggressiveness in the Netherlands as opposed to Norway. Since ACT’s are by definition tumor with limited or no metastatic potential this should not effect our results.

2.1.2 | Statistics

Stata 14 software was used for statistical analysis. Significance was set at $P < .05$ and was tested using two-tailed tests.

Descriptive statistics are presented as mean values with range for continuous variables and frequencies and relative frequencies for categorical variables. The Kaplan-Meier estimator was used to establish rates of local recurrence (LR), rate of metastasis (Met), and disease-specific survival (DSS) at 2, 5, and 10 years of follow-up. The log-rank test was used to test for differences in survival curves. Patients were followed from the date of diagnosis to the date of the event of interest, death, or end of clinical follow-up, whichever came first. Death was treated as a censoring mechanism in analyses of LR and Met, but as an event in DSS. We have used the CRN definition “dead from cancer” as depicting DSS with censor date 30 October 2016, linked to the national death registry.
Uni- and multi-variate Cox proportional hazard models were estimated. The following covariates were included in the multivariate model: age (continuous), sex (female/male), size (>8 cm), and histological grade (grade 1-3), and a constructed variable combining axial location with a soft tissue component measuring ≥1 cm against the rest of the cohort. The latter was based on the findings of the univariate analysis of anatomical location (Figure 3A) and size of the soft tissue component (Figure 3B) on rates of metastasis. Metastasis at diagnosis was included in DSS analysis only. Hazard ratios (HR) are reported with 95% confidence intervals. The assumption of proportional hazards was tested by Schoenfeld residuals for all models. The likelihood-ratio test was used to test the significance of each variable.

2.1.3 | Ethics

Retrieval and handling of data is in accordance with the Helsinki declaration. The project is based at the CRN and data retrieval is based on the quality control charter of the cancer registry act of 1967/2014. The regional ethics board (REK) has been consulted and accepts this foundation.

3 | RESULTS

3.1 | Follow-up

Median follow-up based on observed follow-up from diagnosis to death or end follow-up at 10 years was 8.29 years (range, 0.08-10 years). In all, 61 patients completed 10 years of follow-up while 32 died from any cause.

3.2 | Prognostic analysis

Figure 3A-D shows that for Met, the influence of extremity versus axial location was large (Figure 3A). The presence of a soft tissue component ≥1 cm was also statistically significant (Figure 3B), with an influence similar in magnitude to that of histological grade 3 (Figure 3C). Creating a variable with axial location and a soft tissue component ≥1 cm combined against the rest of the cohort identified a high- and a low-risk group with a narrowed confidence interval (Figure 3D).

Multivariate analysis (Tables 1A, 1B, 1C) showed that male sex HR = 3.77 (1.18-12.02) remained a significant independent predictor of LR in this cohort together with Residual tumor classification of...
The combined variable did not reach significance at multivariate level. The combined axial location with ≥1 cm sized soft tissue component variable remained strongly statistically significant for rate of metastasis \((P < .001)\) when corrected for age at diagnosis, size of tumor, sex, and histological grade (Table 1B), while histological grade became insignificant.

The same combined variable remained a significant independent predictor of DSS \((P = .03)\), while histological grade became insignificant at multivariate analysis (Table 1C). In addition, DSS was independently influenced by age \((P = .004)\) and metastasis at diagnosis \((P < .001)\).

Referral status (biopsy or surgery outside a sarcoma center) did not to a significant degree effect either LR; \(HR = 2.3\) (0.7-7.9), Met; \(HR = 0.8\) (0.6-5.5) or DSS; \(HR = 1.9\) (0.6-5.5) in our cohort.

### 3.3 | Stratification system

We propose a risk stratification model for CCCS of bone based on axial versus extremity skeletal location and a size of soft tissue component <≥1 cm together with primary metastatic status.

| Variable name | Cox analysis for metastasis no. 142 |
|---------------|-----------------------------------|
|               | Univariate HR (95% CI) | Multivariate HR (95% CI) |
|               | \(P\) value by \(lr\) test if significant |
| Age at diagnosis | 1.01 (0.97-1.04) | 1.01 (0.97-1.04) |
| Sex female/male | 2.67 (0.84-8.53) | 1.50 (0.48-4.76) |
| Size <≥8 cm by AJCC | 3.17 (1.06-9.45) | 1.43 (0.41-4.99) |
| Rest of cohort/axial location with soft tissue comp. >1 cm | 17.31 (3.87-77.37) | 14.02 (2.98-65.94) \(P < .001\) |

**Table 1B Cox analysis for metastasis no. 142**

Note: Hazard ratio (HR) and 95% confidence interval. Likelihood ratio (lr) test for testing of multivariate significance. \(P\) values given only for significant findings.

### 3.4 | Cohort by risk stratification

The demographic data and tumor characteristics by risk group are presented in Table 2. There was an even distribution by sex with the exception of a higher proportion of female cases in the low-risk type I
TABLE 1C  Cox analysis for disease-specific survival no. 149

| Variable name                                      | Univariate HR (95% CI) | Multivariate HR (95% CI) | P value by lr test if significant |
|----------------------------------------------------|------------------------|--------------------------|----------------------------------|
| Age at diagnosis                                    | 1.04 (1.01-1.06)       | 1.04 (1.01-1.07)         | .004                             |
| Sex female/male                                     | 2.12 (0.91-4.95)       | 1.70 (0.68-4.25)         |                                  |
| Size <8 cm by AJCC                                   | 2.69 (1.18-6.15)       | 1.12 (0.41-3.06)         |                                  |
| Rest of cohort/axial location with soft tissue comp. >1 cm | 3.65 (1.62-8.23)       | 2.74 (1.09-6.91)         | .03                              |
| Malignancy grade                                    | Ref                    | Ref                      |                                  |
| Grade 1                                             | 2.84 (0.77-10.52)      | 1.40 (0.35-5.58)         |                                  |
| Grade 2                                             | 6.72 (1.90-23.83)      | 1.90 (0.45-7.98)         |                                  |
| Grade 3                                             | 49.97 (13.37-186.77)   | 285.65 (26.34-3098.32)   | .001                             |

Note: hazard ratio (HR) and 95% confidence interval. Likelihood ratio (lr) test for testing of multivariate significance. P values given only for significant findings.

Abbreviation: AJCC, American Joint Committee on Cancer.

cohort and a higher proportion of male cases in the high-risk cohort. For both extremity and axial locations, a larger size of soft tissue component was associated with a higher mean age at diagnosis and a larger tumor size. Primary metastatic cases had the highest age, the largest tumors, and the largest soft tissue components of all groups.

Table 3 shows the diagnostic and treatment characteristics of the cohort by risk stratification. A total of 142 cases were operated; 104 (73%) by resection, 7 (5%) by primary amputation, and 31 (22%) by curettage. Of the latter, 25 curettages were performed at a tumor center aimed at treating a known CCCS, while 6 were contaminated surgeries from other hospitals. For the total cohort, the residual tumor margin26,27 was reported as R0, R1, and R2 in 66%, 29%, and 5% of cases. A total of nine reresections were performed, primarily due to R2 margins (seven cases). Radiotherapy and chemotherapy were infrequent treatment modalities, given to only 5% and 3%, respectively.

3.5 Rates of LR, Met, and DSS

Table 4 shows the rates of LR, Met, and DSS by risk stratification. LR increased from 7% to 21% at 10 years from low-risk I to the high-risk group. For all groups, LR was stable from 5 years of follow-up. Met ranged from 0% to 5% for low-risk groups and was stable from 5 years of follow-up. This encompassed 103 patients with a total rate of metastasis at 5 years of 2% or metastasis-free survival (MFS) of 98%. The high-risk cohort included 39 patients with a metastatic rate of 10%, 26%, and 33% at 2, 5, and 10 years of follow-up or MFS of 90%, 74%, and 67%, correspondingly. This was the only group with events after 5 years.

DSS for the cohort overall was 96%, 85% and 82% at 2, 5, and 10 years. For all subgroups, the DSS at 2 years was excellent ranging from 95% to 100%. Low-risk II and III had slightly lower DSS at 5 years (86% and 89%) than low-risk I (97%). The high-risk cohort clearly had lower 5-year DSS at 76%. DSS for the high-risk group continued to fall from 76% to 70% from 5 years to 10 years of follow-up, in line with continued metastatic events in this group.

Figure 4A-D shows the Kaplan-Meier curves for rates of LR, Met, and DSS, as well as overall survival by risk stratification with log-rank testing. All patients with primary metastatic disease died. Overall survival at 5 and 10 years was similar for low-risk I (72% and 66%) and high-risk cohorts (76% and 67%), despite wide differences in the rates of metastasis between these two groups (0% vs 33% at 10 years).

4 DISCUSSION

Prognostic analysis concerning the size of the soft tissue component has not been described previously. This is also the first report from a national cohort which attempts to quantify and organize prognostic analysis for CCCS related to the rate of metastasis, which is likely a more direct outcome measure as compared to survival. This results in a simple and novel tool for presenting systemic outcomes for patients with CCCS without the use of histological grade allowing for improved information of patients at the time of diagnosis before surgery and the pooling of results for the research. This cohort provides further evidence towards the safety of clinical CS management not driven by biopsy28,29 since the overall results are good when compared to other CCCS cohorts.5,7

Our most important finding is the organization of the cohort into a low- vs high-risk group. This dichotomous division creates a large low-risk group and a small high-risk group. Interobserver variability has not been studied for our proposed stratification, but is likely less, since the methodology has fewer elements and is less subjective by nature.

If our findings are confirmed, the clinical implications are numerous. First, the CS community will have a common language essential for cooperation between centers. As opposed to osteosarcoma or Ewing patients; CS patients are seldom included in prospective cohorts and numbers reported are often either small or
TABLE 2  Descriptive statistics of patient and tumor demographics by risk group

| Risk group no. | Sex female/male no. (%) | Age mean years of age (range) | Size in cm mean (range) | Ollier/Maffucci syndrome no. (%) | Soft tissue component present yes/no no. | Size of Soft tissue component present mean cm (range) | Malignancy grade 1/2/3 no. |
|----------------|-------------------------|-----------------------------|------------------------|-------------------------------|----------------------------------------|------------------------------------------|--------------------------|
| **Low risk**   |                         |                             |                        |                               |                                        |                                          |                          |
| Type I         | No. 59                  | 38/21 (64/36)               | 49 (20-81)             | 7.1 (2-31)                    | 5(8)                                   | 0.5 (0.1-0.9)                          | 40/15/4                  |
| Type II        | No. 22                  | 12/10 (55/45)               | 64 (26-95)             | 10.4 (3-29)                   | 0                                      | 2.8 (1-8.3)                            | 3/10/9                   |
| Type III       | No. 22                  | 9/13 (41/59)                | 52 (17-80)             | 6.3 (2-14.5)                  | 0                                      | 0.5 (0.2-0.7)                          | 6/14/2                   |
| Total          | No. 103                 | 59/44 (57/43)               | 52 (17-95)             | 7.7 (2-31)                    | 5(5)                                   | 1.6 (0.1-8.3)                          | 49/39/15                 |
| **High risk**  |                         |                             |                        |                               |                                        |                                          |                          |
| No. 39         | 14/25 (36/64)           | 54 (15-80)                  | 8.7 (3.6-15)            | 2(5)                          | 39/0                                   | 3.5 (1-9.7)                            | 4/19/16                  |
| **Primary metastatic** | 3/4 (43/57)            | 63 (33-82)                  | 11.9 (4.5-18)          | 0                             | 7/0                                    | 6.1 (3.5-7.3)                          | 0/3/4                    |
| **Total**      | No. 149                 | 76/73 (51/49)               | 53 (15-95)             | 8.1 (2-31)                    | 7(5)                                   | 2.7 (0.1-9.7)                          | 53/61/35                 |

*Rounded to nearest decimal point.
This finding underlines that a censor for metastatic events is the most important direct measure of systemic biology for CCCS. Measuring outcomes solely by survival will introduce other confounders and insecurities, particularly in a slow to intermediate growing disease like CS with an overall low rate of metastasis. The accuracy of a diagnosis of lung metastasis in this setting has not been studied to our knowledge, but there is little reason why there should be a discrepancy between the groups.

Our cohort shows increased number of men in the high-risk subcohort and women in the low-risk subcohort and as such and an increased influence of sex on risk of local recurrence. This may be random in a small cohort and rare disease, but could also represent different tumor biology or medical seeking behavior between the sexes. Our proposed system predicts LR at univariate (Figure 4A), but not at multivariate level (Table 1A) and as such should be re-examined in larger cohorts.

The surgical margin independently predicts risk of LR in line with intuitive thinking. Further subgroup analysis is needed, seeking to find whether this is valid for all CCCS or only the high risk group. Although LR has been linked to increased rates of metastasis and death in CS research, 13,32-37 this has been performed in mixed CS cohorts and without considering immortal time bias for time dependent variables.

There are no directly comparable reports. Two institutional reports on CCCS with multivariate analysis use either survival or a combined event-free survival censor for analysis and neither report on extracompartmental status. 6,7 In line with our findings, the German group 6 reports that grade 3 lesions with axial location have the worst prognosis. Another national register study 19 reports on a mixed cohort but with prognostic analysis at a subtype level. Their CCCS cohort is driven by a large and increasing proportion of ACT’s and unfortunately lack information

### TABLE 3  Treatment summary of cohort by risk group

| Risk group no. | Pre-op. biopsy no. (%) | Untouched referral no. (%) | Residual tumor margin no. | No surgery no. | Radio-therapy no. | Chemo-therapy no. |
|----------------|------------------------|-----------------------------|---------------------------|----------------|------------------|------------------|
| **Low risk**   |                         |                             |                           |                |                  |                  |
| Type I         | 59                     | 36 (61%)                    | 57 (97%)                  | 34 21 4 4 0    | 1                | 0                |
| Type II        | 22                     | 14 (64%)                    | 18 (82%)                  | 15 6 1 2 0     | 0                | 0                |
| Type III       | 22                     | 14 (64%)                    | 17 (77%)                  | 15 6 1 1 0     | 2                | 0                |
| **Total**      | 103                    | 64 (62%)                    | 92 (89%)                  | 64 33 6 7 0    | 3                | 0                |
| **High risk**  |                         |                             |                           |                |                  |                  |
| No. 39         |                        | 35 (90%)                    | 36 (97%)                  | 29 7 1 2 2     | 2                | 2                |
| **Primary metastatic** |               |                             |                           |                |                  |                  |
| No. 7          |                        | 7 (100%)                    | 5 (71%)                   | 1 1 0 0 5      | 3                | 2                |
| **Total**      | 149                    | 106 (71%)                   | 128 (90%)                 | 94 41 7 9 7    | 8                | 4                |

Abbreviations: No Surgery, no surgery performed; Pre-op biopsy, pre-operative biopsy performed; Untouched referral, no biopsy or surgery outwith sarcoma center; 2nd surgery, Performed re-resection.

### TABLE 4  Rates of local recurrence, metastasis and disease-specific survival at 2, 5, and 10 y follow-up by Kaplan-Meier estimates according to risk groups

|                     | Local recurrence rate % (95% CI)  | Metastasis rate % (95% CI)  | Disease-specific survival % (95% CI)  |
|---------------------|-----------------------------------|-----------------------------|--------------------------------------|
|                     | 2 y 5 y 10 y                      | 2 y 5 y 10 y                | 2 y 5 y 10 y                         |
| **Low risk**        |                                   |                             |                                      |
| Type I              | No. 59                            | 5 (2-15)                    | 7 (3-18)                             | 0 2 (0-12) 2 (0-12) 100 97 (87-99) 94 (82-98) |
| Type II             | No. 22                            | 10 (2-33)                   | 15 (5-39)                            | 15 (5-39) 0 0 0 95 (72-99) 86 (62-95) 86 (62-95) |
| Type III            | No. 22                            | 14 (5-38)                   | 14 (5-38)                            | 14 (5-38) 5 (7-29) 5 (7-29) 5 (7-29) 100 89 (60-97) 89 (60-97) |
| **Total**           | No. 103                           | 8 (4-15)                    | 10 (6-18)                            | 10 (6-18) 1 (0-7) 2 (1-8) 2 (1-8) 99 (93-100) 93 (85-97) 91 (83-96) |
| **High risk**       |                                   |                             |                                      |
| No. 39              |                                   |                             |                                      |
|                     | 16 (8-33)                         | 21 (12-39)                  | 21 (12-39)                           | 10 (4-25) 26 (15-43) 33 (20-52) 100 76 (60-87) 70 (52-82) |
| **Primary metastatic** |                                   |                             |                                      |
| No. 7               |                                   |                             |                                      |
|                     | 0                                 | Na                          | Na                                    | Na Na Na Na Na 29 (4-61) Na Na |
| **Total**           | No. 149                           | 10 (6-16)                   | 13 (9-20)                            | 13 (9-20) 4 (2-8) 9 (5-15) 11 (7-18) 96 (91-98) 85 (78-90) 82 (74-88) |

Note: Percentages rounded to nearest whole number.

*Seven patients not receiving surgery removed, five of which are primary metastatic.
Though we present a nationwide cohort over nearly 25 years, our numbers are small and the findings should be interpreted accordingly. 25% of patients are excluded from analysis due to missing radiology and as such a degree of selection, bias may be present. It is, however, a larger cohort than Evans’ original, retrospective institutional report of mixed CS subtypes (75 cases). Furthermore, large cohorts have failed to contribute significant new findings in predicting CS biology, even when re-examined with machine learning, likely due to limited variables and data quality. We believe the quality of our data to be unique both with regard to its completeness, range of variables and quality control of every variable with a complete data set for all included at a subtype level. The CRN has a documented 97% completeness for bone sarcoma before our further quality control.

This is a historical prospective analysis of a small national cohort, while most CS literature is retrospective. Only by analysis of other CCCS cohorts and multicenter prospective registration can we truly confirm the study’s external validity. If validated this confers the possibility to provide a simple surrogate measure to histological grade in depicting biological CCCS activity, thereby simplifying real-life CCCS management and research.

5 | CONCLUSION

In summary, the combination of axial location and a soft tissue component ≥1 cm predicted a high risk of metastasis and death in our cohort of CCCS without the use of histological grade.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are in part available from the corresponding author. Restrictions apply to the availability of these data, which were used under license for the current study from the National Cancer Registry, and so are not publicly available. Data are however available from the corresponding author upon
reasonable request and with application to the Cancer Registry of Norway.

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REFERENCES
1. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. Cancer. 1977;40(2):818-831.

2. Skeletal Lesions Interobserver Correlation among Expert Diagnosticians (SLICED) Study Group. Reliability of histopathologic and radiologic grading of cartilaginous neoplasms in long bones. J Bone Joint Surg Am. 2007;89(10):2113-2123.

3. de Andrea CE, Kroon HM, Wolterbeek R, et al. Interobserver reliability in the histopathological diagnosis of cartilaginous tumors in patients with multiple osteochondromas. Mod Pathol. 2012;25(9):1275-1283.

4. Eefting D, Schrage YM, Gerinaerd MJA, et al. Assessment of interobserver variability and histologic parameters to improve reliability in classification and grading of central cartilaginous tumors. Am J Surg Pathol. 2009;33(1):50-57.

5. Zamora T, Urrutia J, Schweitzer D, Amenabar PP, Botello E. Do orthopaedic oncologists agree on the diagnosis and treatment of cartilage tumors of the appendicular skeleton? Clin Orthop Relat Res. 2017;475(9):2176-2186.

6. Andreou D, Ruppin S, Fehlberg S, Pink D, Werner M, Tunn PU. Survival and prognostic factors in chondrosarcoma: results in 115 patients with long-term follow-up. Acta Orthop. 2011;82(6):749-755.

7. Angelini A, Guerra G, Mavrogenis AF, Pala E, Picci P, Ruggieri P. Clinical outcome of central conventional chondrosarcoma. J Surg Oncol. 2012;106(8):929-937.

8. Bjornsson J, McLeod RA, Unni KK, Ilstrup DM, Pritchard DJ. Primary chondrosarcoma of long bones and limb girdles. Cancer. 1998;83(10):2105-2119.

9. Pritchard DJ, Lunke RJ, Taylor WF, Dahlin DC, Medley BE. Chondrosarcoma: a clinicopathologic and statistical analysis. Cancer. 1980;45(1):149-157.

10. Rizzo M, Ghert MA, Harrelson JM, Scully SP. Chondrosarcoma of bone: analysis of 108 cases and evaluation for predictors of outcome. Clin Orthop Relat Res. 2001;391(391):224-233.

11. Giuffrida AY, Burguengo JE, Koniaris LG, Gutierrez JC, Duncan R, Scully SP. Chondrosarcoma in the United States (1973 to 2003): an analysis of 2890 cases from the SEER database. J Bone Joint Surg Am. 2009;91(5):1063-1072.

12. Whelan J, McTiernan A, Cooper N, et al. Incidence and survival of malignant bone sarcomas in England 1979-2007. Int J Cancer. 2012;131(4):E508-E517.

13. Lee FY, Mankin HJ, Fonnren G, et al. Chondrosarcoma of bone: an assessment of outcome. J Bone Joint Surg Am. 1999;81(3):326-338.

14. Thorkildsen J, Taksdal I, Bjerkhagen B, et al. Chondrosarcoma in Norway 1990-2013: an epidemiological and prognostic observational study of a complete national cohort. Acta Oncol. 2019;58:1-10.

15. Aigner T. Towards a new understanding and classification of chondrogenic neoplasias of the skeleton—biochemistry and cell biology of chondrosarcoma and its variants. Virchows Arch. 2002;441(3):219-230.

16. Bovee JV, Cleton-Jansen AM, Kuipers-Dijkstraen NJ, et al. Loss of heterozygosity and DNA ploidy point to a diverging genetic mechanism in the origin of peripheral and central chondrosarcoma. Genes Chromosomes Cancer. 1999;26(3):237-246.

17. ESMO/European Sarcoma Network Working Group. Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii113-iii123.

18. Fromm J, Klein A, Baur-Melnyk A, et al. Survival and prognostic factors in conventional central chondrosarcoma. BMC Cancer. 2018;18(1):849.

19. van Praag (Veroniek) VM, Rueten-Budge AJ, Ho V, et al. Incidence, outcomes and prognostic factors during 25 years of treatment of chondrosarcomas. Surg Oncol. 2018;27(3):402-408.

20. Damron TA. CORR Insights,(RI): do orthopaedic oncologists agree on the diagnosis and treatment of cartilage tumors of the appendicular skeleton? Clin Orthop Relat Res. 2017;475(9):2187-2188.

21. Greene FL, Sobin LH. A worldwide approach to the TNM staging system: collaborative efforts of the AJCC and UICC. J Surg Oncol. 2009;99(5):269-272.

22. Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2013.

23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-349.

24. Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009;45(7):1218-1231.

25. Valery PC, Laversanne M, Bray F. Bone cancer incidence by morphology subtype: a global assessment. Cancer Causes Control. 2015;26(8):1127-1139.

26. Edge SB, American Joint Committee on Cancer, American Cancer Society, AJCC cancer staging handbook; from the AJCC cancer staging manual. 7th ed. New York: Springer; 2009.

27. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. Cancer. 2002;94(9):2511-2516.

28. Berber O, Datta G, Sabharwal S, Wasten W, Saifuddin A, Briggs T. The safety of direct primary excision of low-grade chondral lesions based on radiological diagnosis alone. Acta Orthop Belg. 2012;78(2):254-262.

29. Brown MT, Gikas PD, Bhamra JS, et al. How safe is curettage of low-grade cartilaginous neoplasms diagnosed by imaging with or without pre-operative needle biopsy? Bone Joint J. 2014;96-B(8):1098-1105.

30. Sandberg AA. Genetics of chondrosarcoma and related tumors. Curr Opin Oncol. 2004;16(4):342-354.

31. Bernard SA, Murphey MD, Fleming DJ, Kransdorf MJ. Improved differentiation of benign osteochondromas from secondary chondrosarcomas with standardized measurement of cartilage cap at CT and MR imaging. Radiology. 2010;255(3):857-865.

32. Fiorenza F, Abudu A, Grimer RJ, et al. Risk factors for survival and local control in chondrosarcoma of bone. J Bone Joint Surg Br. 2002;84(1):93-99.

33. Kim HS, Bindiganavile SS, Han I. Oncologic outcome after local recurrence of chondrosarcoma: analysis of prognostic factors. J Surg Oncol. 2011;108(1):957-961.

34. Lin PP, Alfawareh MD, Takeuchi A, Moon BS, Lewis VO. Sixty percent 10-year survival of patients with chondrosarcoma after local recurrence. Clin Orthop Relat Res. 2012;470(3):670-676.

35. Schwab JH, Wenger D, Unni K, Sim FH. Does local recurrence impact survival in low-grade chondrosarcoma of the long bones? Clin Orthop Relat Res. 2007;462:175-180.
36. Stevenson JD, Laitinen MK, Parry MC, Sumathi V, Grimer RJ, Jeys LM. The role of surgical margins in chondrosarcoma. *Eur J Surg Oncol*. 2018;44(9):1412-1418.

37. Streitbuerger A, Ahrens H, Gosheger G, et al. The treatment of locally recurrent chondrosarcoma: is extensive further surgery justified? *J Bone Joint Surg Br*. 2012;94(1):122-127.

38. Thio QCBS, Karhade AV, Ogink PT, et al. Can machine-learning techniques be used for 5-year survival prediction of patients with chondrosarcoma? *Clin Orthop Relat Res*. 2018;476(10):2040-2048.

39. Healey JH. CORR insights(R): can machine-learning techniques be used for 5-year survival prediction of patients with chondrosarcoma? *Clin Orthop Relat Res*. 2018;476(10):2049-2051.

**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section.

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