Research Article

Association of Cartilage Cap Thickness With Tumor Grade and Outcomes in Secondary Chondrosarcoma

Takashi Hirase, MD, MPH
Jessica A. Lavery, MS
Moshe Gertzulin, MD
Dan C. M. Viola, MD, PhD, MBA
Sinchun Hwang, MD
Arianna Rizzo, MD
Carol D. Morris, MD, MS

From the Department of Surgery (Hirase, Gertzulin, Viola, Rizzo, and Morris), the Department of Epidemiology and Biostatistics (Lavery), and the Department of Radiology (Hwang), Memorial Sloan Kettering Cancer Center, New York, NY.

Correspondence to Dr. Morris: MorrisC@mskcc.org

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

Lavery has the following disclosures: salary support paid to her institution from the American Association of Cancer Research Project Genomics Evidence Neoplasia Information Exchange Biopharma Collaborative (GENIE BPC). None of the following authors or any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article: Hirase, Gertzulin, Viola, Hwang, Rizzo, and Morris.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.jaaos.org).

J Am Acad Orthop Surg 2025;00:1-7

DOI: 10.5435/JAAOS-D-25-00803

ABSTRACT

Introduction: Although increased cartilage cap thickness (CCT) is associated with secondary chondrosarcoma in patients with osteochondroma, no studies have assessed its relationship with histologic grade or outcomes after primary resection. Thus, the objectives of this study were to determine whether CCT is associated with (1) histologic grade in secondary chondrosarcoma and (2) oncologic outcomes after primary resection of secondary chondrosarcoma.

Methods: Patients who had a history of osteochondroma and were diagnosed with a biopsy-proven secondary chondrosarcoma at a single institution between January 2000 and December 2023 were included. CCT was measured on T2-weighted imaging or through direct measurement of the resected gross specimen. The primary outcome measure was of histologic grade. Secondary outcome measures were overall survival, local recurrence, distant recurrence, and margin positivity. Grade and margin positivity were evaluated using logistic regression models; time-to-event outcomes were assessed using Kaplan-Meier and cumulative incidence methods and Cox models.

Results: Forty-five patients (30 male; median age, 39 years) were included. Thirty (67%) had grade 1 secondary chondrosarcoma, 12 (27%) had grade 2, and 3 (6.7%) had grade 3. Mean CCT was smaller in grade 1 chondrosarcoma (35 mm; SD, 18 mm) than in grade 2 or 3 disease (76 mm; SD, 30 mm; $P < 0.001$). Thicker cartilage cap was associated with increased odds of high (grade 2 or 3) versus low histologic grade (odds ratio, 1.11; 95% confidence interval, 1.05 to 1.21; $P < 0.001$). No statistically significant associations were observed between CCT and overall survival, local recurrence, distant recurrence, or margin positivity.

Conclusions: Although CCT may be a useful diagnostic marker for secondary chondrosarcoma, thickness itself is not a reliable prognostic marker for predicting long-term patient outcomes. However, its positive association with tumor grade may have implications for surgical planning.

Type of study: Diagnostic Study.
Level of evidence: III

Osteochondroma is the most prevalent benign bone tumor and is characterized by a sessile or pedunculated osseous lesion along the surfaces of bones covered by a cartilage cap.[1] These lesions are most often seen at the sites of tendon insertion in skeletally immature individuals and may be associated with inflammatory, mechanical, or neurovascular compression-related symptoms.[2] Although the diagnosis is benign, these lesions have the potential for malignant transformation to secondary chondrosarcoma; approximate transformation rates of up to 10% among patients with multiple hereditary exostoses and 1% among those with solitary lesions have been reported.[1,3]

Secondary chondrosarcoma originating from solitary or multiple osteochondromas is treated with surgical resection with wide margins for optimal local control and survival.[4] Timely diagnosis of malignant transformation is often difficult because of the clinical and radiologic challenge of distinguishing benign osteochondromas from secondary chondrosarcomas. Historically, cartilage cap thickness (CCT) has been used as a marker for suspected malignant transformation, and thicknesses ranging from 1.5 to 3 cm have been recommended as thresholds for additional workup.[5,6] However, there remains no definitive CCT cutoff value that is pathognomonic for malignancy, and there has been notable debate regarding its use as a suitable marker for assessing malignant potential.[5,7] Previous studies have demonstrated that CCT can be measured with good interobserver reliability using CT imaging, magnetic resonance imaging (MRI), ultrasonography, or direct gross measurement of the histopathologic specimen.[6-9]

Although the value of CCT in diagnosing secondary chondrosarcoma in patients with osteochondromas is well-established, no studies have investigated the clinical utility of measuring CCT for patients with secondary chondrosarcoma. In a radiologic case series of 34 patients with secondary chondrosarcoma, Bernard et al[6] reported a potential relationship between greater CCT and histologic grade, although their findings were not statistically significant. Furthermore, no studies have examined the relationship between CCT and oncologic outcomes after primary resection of secondary chondrosarcoma. Thus, the objectives of this study were to determine whether CCT is associated with (1) histologic grade in secondary chondrosarcoma and (2) oncologic outcomes after primary resection of secondary chondrosarcoma.

Methods

Study Population

We conducted a retrospective analysis of patients who had a history of osteochondroma and were diagnosed with a biopsy-proven secondary chondrosarcoma at a single tertiary cancer center between January 2000 and December 2023. Biopsies were done using a core needle, incisional, or excisional biopsy technique. Patients were excluded if there was no MRI available for direct measurement of the CCT, no MRI radiology read of the CCT, and no documented histopathologic measurement of the CCT, or if the biopsy was not obtained within 6 months of the MRI or histopathologic measurement.

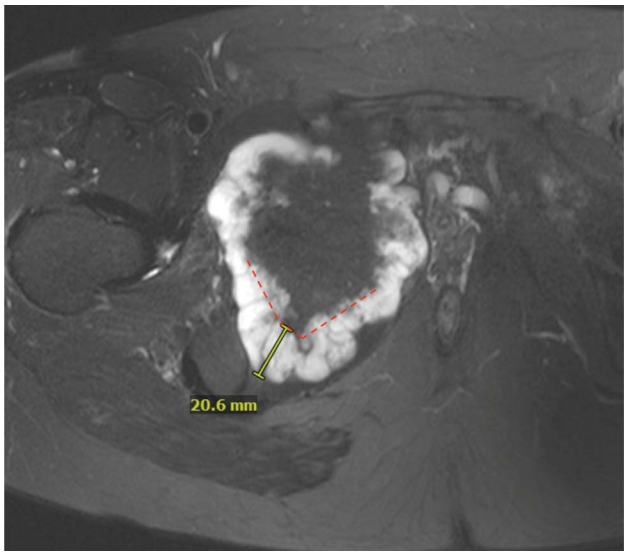
Data Collection

Demographic data were retrospectively retrieved from electronic medical records. Extracted variables included age at biopsy, sex, and anatomic location of tumor. Pathologic and oncologic outcome data were also obtained, including histologic grade, surgical margins, date of local recurrence, and distant recurrence. CCT was measured on T2-weighted imaging using the Visage Imaging software (Visage Imaging Inc.) as described by Bernard et al[6] (Figure 1). For a subset of the samples (n = 20), CCT was measured by three orthopaedic oncology fellows to evaluate interobserver variability. When an MRI file was not available for CCT measurement, a documented radiologist's read of the CCT was included. A direct histopathologic measurement of the resected gross specimen was included if neither an MRI file nor a radiology read was available.

Outcome Measures

The primary outcome measure was histologic grade, which was determined by a musculoskeletal pathologist using a combination of cellularity, nuclear size, atypical mitosis, and the presence of an abundant hyaline cartilage matrix or mucomyxoid matrix as previously described.[10,11] The secondary outcome measures were overall survival, local recurrence, distant recurrence, and margin positivity.

Figure 1



Axial T2-weighted MRI illustrating the measurement technique for the cartilage cap.[6] The cartilage crevasses are excluded by connecting adjacent peaks in the tidemark (dotted red lines), and the measurement is done at the thickest portion of the cartilage cap perpendicular to the tidemark. MRI = magnetic resonance imaging

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study cohort. The interobserver reliability of CCT measurements was assessed using intraclass correlation coefficient (ICC); an ICC below 0.5 implies poor agreement, between 0.5 and 0.75 implies moderate agreement, between 0.75 and 0.90 implies good agreement, and above 0.90 implies excellent agreement.[12] We evaluated the relationship of CCT with histologic grade (2/3 versus 1) and margin status (positive versus negative) using logistic regression models that adjusted for tumor location and age at surgery; results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Kaplan-Meier methods were used to estimate overall survival from biopsy. Patients alive at the end of the study period were censored at their last visit date. We estimated the cumulative incidence of local recurrence treating death as a competing event. Cox proportional hazards models were used to model overall survival, local recurrence, and distant recurrence as a function of CCT; the models of overall survival and local recurrence adjusted for tumor grade and age at surgery, but the small number of distant recurrence events precluded multivariable adjustment. For the Cox models of local recurrence and distant recurrence, we used a cause-specific Cox model and censored individuals without recurrence events. Results are reported as hazard ratios (HRs) for overall survival and as cause-specific HRs for local recurrence and distant recurrence, with 95% CIs. Statistical significance was defined as $P < 0.05$. Data analysis was done using R statistical software (Version 4.3.1).

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and received approval from our institutional review board (#16-1123). Informed consent requirement was waived because of the retrospective and observational nature of the study.

Results

Study Sample

A total of 45 patients (30 male, 15 female) with a median age at biopsy of 39 years (interquartile range [IQR], 30 to 45) were included in the study (Table 1). Thirty-one patients (69%) had MRIs available for direct CCT measurement. Radiology reports with CCT measurements were used for nine patients (20%), and histopathologic measurement of the gross specimen was used for five patients (11%). The median follow-up from biopsy was 5.9 years (IQR, 3.3 to 8.3) among individuals alive at the end of the study period. Eight patients (18%) had tumors in the chest wall, 10 (22%) in the lower extremity, 18 (40%) in the pelvis, four (9%) in the spine, and five (11%) in the upper extremity. The median CCT was highest for tumors in the chest wall (68; IQR, 27 to 83) and pelvis (54; IQR, 30 to 66), followed by those in the spine (38; IQR, 18 to 51), lower extremity (34; IQR, 29 to 50), and upper extremity (26; IQR, 22 to 26). Thirty patients (67%) had grade 1 secondary chondrosarcoma, 12 patients (27%) had grade 2 disease, and three (6.7%) had grade 3. Three patients (6.7%) had dedifferentiated histology. Forty-four patients (98%) underwent primary wide resection at the current institution and were included in the outcomes analyses; negative margins were achieved in 40 of these patients (91%). The remaining patient (2%) was lost to follow-up after the biopsy and was not included in the outcomes analysis.

Cartilage Cap Thickness and Histologic Grade

The interobserver reliability of CCT was excellent, with an ICC of 0.99 (95% CI, 0.98 to 1.00). Mean CCT was smaller in grade 1 chondrosarcoma (35 mm; SD, 18 mm) than in grade 2 or 3 disease (76 mm; SD, 30 mm; $P < 0.001$; Figure 2). Grade 2 and 3 tumors were combined

Table 1. Characteristics of the Study Sample

Variable	Total (n = 45)	Grade 1 (n = 30)	Grade 2 or 3 (n = 15)	*P* Value[a]
Age (yr)	40.5 ± 13.5	36.9 ± 11.9	47.7 ± 14.1	**0.009**
Male	30 (66.7)	20 (66.7)	10 (66.7)	>0.9
Dedifferentiated histology	3 (6.7)	1 (3.3)	2 (13.3)	0.3
Tumor location				0.6
Chest wall	8 (17.8)	4 (13.3)	4 (26.7)	—
Lower extremity	10 (22.2)	8 (26.7)	2 (13.3)	—
Pelvis	18 (40.0)	12 (40.0)	6 (40.0)	—
Spine	4 (8.9)	2 (6.7)	2 (13.3)	—
Upper extremity	5 (11.1)	4 (13.3)	1 (6.7)	—
Location				0.5
Appendicular	18 (40)	13 (43)	5 (33)	—
Axial	27 (60)	17 (57)	10 (67)	—
CCT (mm)	48.4 ± 29.9	34.5 ± 17.9	76.3 ± 30.0	<**0.001**
Positive margins	4 (9.1)	2 (6.9)	2 (13.3)	0.6

CCT = cartilage cap thickness
[a]Comparisons between grade 1 and grade 2/3 are through the Wilcoxon rank sum exact test, Pearson chi-squared test, Fisher exact test, and Wilcoxon rank sum test.
Statistically significant values are expressed in bold.
Values are given as mean ± SD or as n (%).

into a single group due to the small number of grade 3 tumors. Each increase of 1 mm in CCT was associated with an 11% increase in the odds of higher (grade 2 or 3) histologic grade (OR, 1.11; 95% CI, 1.05 to 1.21; $P < 0.001$; Table 2).

Cartilage Cap Thickness and Oncologic Outcomes

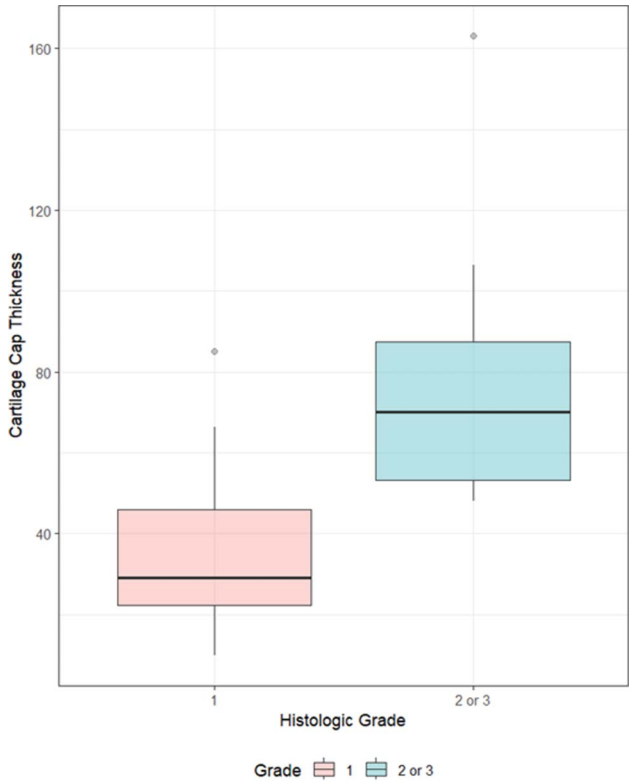
Among the 44 patients who underwent resection at our institution, there were 10 local recurrence events, three distant recurrence events, and 7 deaths. Overall survival was 93% (95% CI, 86% to 100%) at 1 year, 91% (95% CI, 82% to 100%) at 2 years, and 81% (95% CI, 70% to 95%) at 5 years (Figure 3). The appendix presents Kaplan-Meier curves for overall survival by tumor location (Appendix Figure 1, http://links.lww.com/JAAOS/B456), tumor grade (Appendix Figure 2, http://links.lww.com/JAAOS/B457), and both location and grade (Appendix Figure 3, http://links.lww.com/JAAOS/B458).

The cumulative incidence of local recurrence was 9.1% (95% CI, 2.9% to 20%) at 1 year, 14% (95% CI, 5.6% to 26%) at 2 years, and 26% (95% CI, 13% to 40%) at 5 years (Figure 4). By 3 years, the cumulative incidence of distant recurrence was 7.2% (95% CI, 1.8% to 18%). Only four patients had positive margins; their median CCT was 41 (IQR, 27 to 51), compared with 45 (IQR, 26 to 66) among patients with negative margins. In Cox proportional hazards and logistic regression models, CCT was not associated with overall survival (HR, 1.01; 95% CI, 0.98 to 1.04; $P = 0.7$), local recurrence (HR, 0.98; 95% CI, 0.95 to 1.02; $P = 0.3$), distant recurrence (HR, 1.02; 95% CI, 0.99 to 1.05; $P = 0.14$), or margin positivity (OR, 0.98; 95% CI, 0.93 to 1.02; $P = 0.5$). However, higher tumor grade was significantly associated with lower overall survival (i.e., higher mortality: HR, 4.41; 95% CI, 1.33 to 14.7; $P = 0.02$) and higher risk of local recurrence (HR, 5.71; 95% CI, 1.81 to 18.1; $P = 0.003$; Table 3).

Discussion

Secondary chondrosarcoma arising from primary osteochondromas may be challenging to distinguish from benign osteochondromas.[5,7] A thicker cartilage cap is associated with the diagnosis of secondary chondrosarcoma; however, its reliability as a marker for a more aggressive clinical and histologic pathology has not been demonstrated. In this study, we explored the association between CCT and histologic grade in secondary chondrosarcoma and between CCT and oncologic outcomes after primary resection of secondary chondrosarcoma.

Figure 2



Boxplot of the distribution of CCT by histologic grade, depicting larger CCT among high-grade tumors than low-grade tumors ($P < 0.001$, Kruskal-Wallis rank sum). CCT = cartilage cap thickness

Our analysis found that greater CCT is associated with a higher tumor grade in secondary chondrosarcoma. However, no statistically significant associations were evident between CCT and overall survival, local recurrence, or distant recurrence when we adjusted for tumor grade and age (overall survival, local recurrence).

A major finding in this study was that CCT was strongly associated with histologic grade in secondary chondrosarcoma. On average, CCT was more than 40 mm thicker in grades 2 and 3 tumors than in grade 1 tumors. Although a radiologic series by Bernard et al[6] demonstrated a pattern consistent with this result, their study of 34 patients with secondary chondrosarcoma may have been underpowered and did not find a statistically significant association. Thus, the findings from this larger study contribute evidence in support of the long-held clinical suspicions that an unusually thick cap is not merely a marker of malignant transformation but also a surrogate for biologic aggressiveness.

In our study, despite being associated with higher histologic grade, CCT was not markedly associated with overall survival, local recurrence, or distant recurrence, although our analysis is limited by the small number of events. In the models that adjusted for grade, we observed a statistically significant relationship between grade and overall survival and local recurrence, consistent with the finding of Laitinen et al.[5] that grade 2 or higher pathology in secondary pelvic chondrosarcoma is strongly associated with increased local recurrence and decreased overall survival. This is also consistent with reports that patients with low-grade chondrosarcomas in general have markedly lower rates of local recurrence and distant recurrence and longer overall survival than their counterparts with intermediate-grade and high-grade chondrosarcomas.[13-15] This uncoupling suggests that although higher CCT may be a useful diagnostic marker for higher grade tumors in secondary chondrosarcoma, the thickness itself is not a reliable prognostic marker for predicting long-term patient outcomes.

Nevertheless, this study adds an additional datapoint to guide the counseling of patients on the management of secondary chondrosarcoma. Previous research has demonstrated that delayed diagnosis and definitive treatment of higher-grade tumors is associated with increased rates of distant metastasis and poorer overall survival.[15,16] Thus, patients with particularly thick cartilage caps may benefit from prompt discussions regarding

Table 2. Association Between CCT and Histologic Grade From the Multivariable Logistic Regression Model

Characteristic	OR for High (2/3) Versus Low (1) Grade	95% CI	*P* Value
1-unit increase in CCT	1.11	1.05-1.21	**<0.001**
1-yr increase in age	1.08	1.00-1.19	**0.04**
Tumor location			0.5
Lower extremity	Reference	Reference	—
Pelvis	0.47	0.02-13.1	—
Other (chest wall, spine, upper extremity)	1.89	0.08-67	—

CCT = cartilage cap thickness, CI = confidence interval, OR = odds ratio
Statistically significant values are expressed in bold.

Figure 3

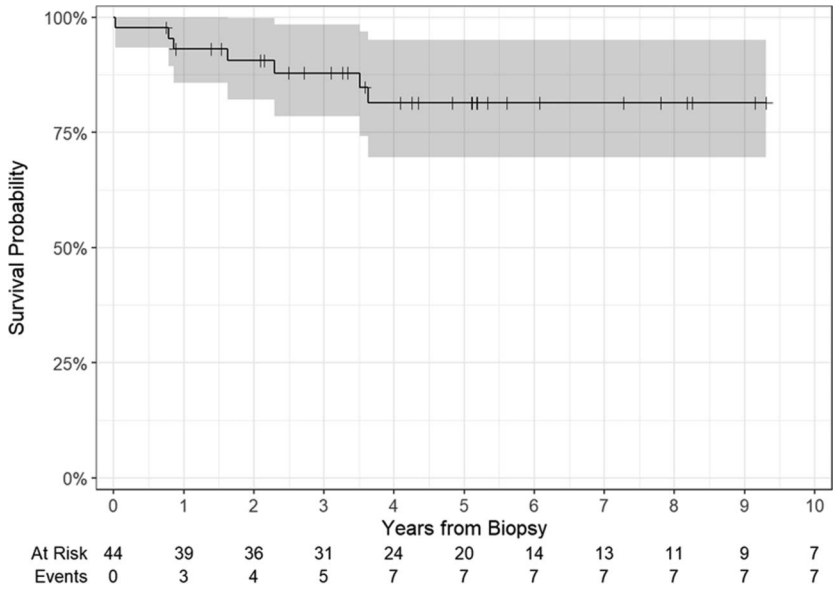


Diagram showing Kaplan-Meier estimates of overall survival.

expedited surgical planning because these cases are more likely to represent higher grade tumors.

This study has several limitations. First, the retrospective single-center design and the referral patterns inherent to a tertiary sarcoma center may have introduced selection bias and overrepresented more complex cases. Second, the sample size and number of events were modest, particularly for grade 3 tumors, which limited our statistical power. Furthermore, although the interobserver reliability for MRI measurements of CCT was excellent, 14 patients required extracting CCT from radiology reports or gross pathology, which introduced heterogeneity in the measurement technique. However, previous data have demonstrated that both MRI and direct measurements are reliable for measuring CCT.[6-8] In addition, this study lacked data on adjuvant systemic therapy or radiation therapy, which may confound outcomes analyses. Finally, although we had a median follow-up of 5.9 years, this still may have been insufficient to capture late recurrences typical of chondrosarcomas.

Figure 4

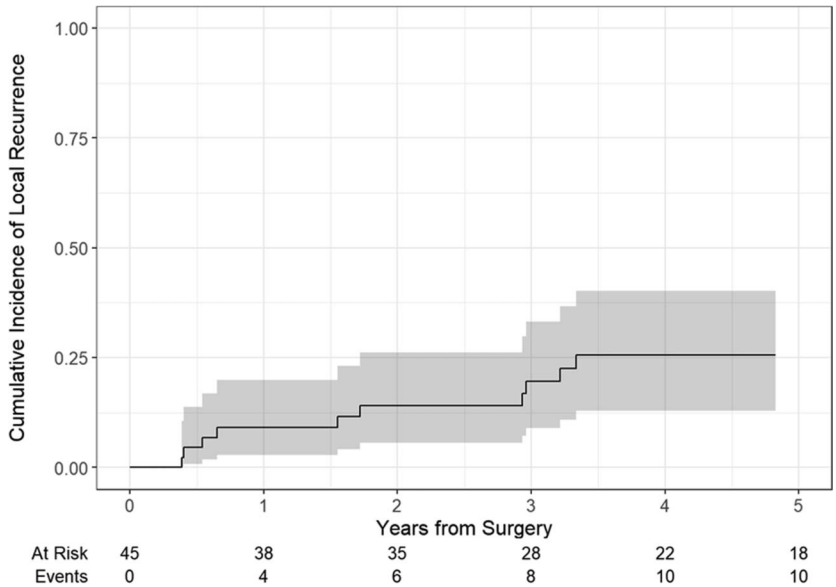


Diagram showing cumulative incidence of local recurrence.

Table 3. **Results of Cox Proportional Hazards Models Examining Associations of CCT With Overall Survival and Local Recurrence**

Characteristic	Univariable			Multivariable		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Overall survival						
CCT	1.02	1.00-1.04	0.069	1.01	0.98-1.04	0.7
Age at biopsy	NA	NA	NA	1.03	0.97-1.09	0.4
Tumor grade	NA	NA	NA	4.41	1.33-14.7	**0.016**
Local recurrence						
CCT	1.01	0.99-1.04	0.4	0.98	0.95-1.02	0.3
Age at biopsy	NA	NA	NA	0.98	0.92-1.04	0.4
Tumor grade	NA	NA	NA	5.71	1.81-18.1	**0.003**

CCT = cartilage cap thickness, CI = confidence interval, HR = hazard ratio, NA = not applicable
Statistically significant values are expressed in bold.

Despite these limitations, to our knowledge, this is the largest study to date that directly evaluated CCT as both a diagnostic and prognostic factor in secondary chondrosarcoma. Although no specific CCT threshold exists that is pathognomonic for malignancy, we found that a larger CCT is associated with a higher histologic grade in secondary chondrosarcoma. Future studies through multicenter collaborations are needed to confirm these findings. In addition, studies that incorporate advanced radiomics and molecular profiling may help refine treatment algorithms and personalize surveillance schedules for patients with secondary chondrosarcoma.

Conclusion

In secondary chondrosarcoma, increased CCT is associated with a higher tumor grade, and a higher tumor grade is associated with decreased overall survival and increased local recurrence. However, there were no statistically significant associations observed between CCT and overall survival, local recurrence, distant recurrence, or margin positivity. Although thickness itself is not a reliable prognostic marker for predicting long-term patient outcome, its positive association with tumor grade may have implications for patient counseling and surgical planning.

References

1. Tepelenis K, Papathanakos G, Kitsouli A, et al: Osteochondromas: An updated review of epidemiology, pathogenesis, clinical presentation, radiological features and treatment options. *In Vivo* 2021;35:681-691.

2. Giudici MA, Moser RP Jr, Kransdorf MJ: Cartilaginous bone tumors. *Radiol Clin North Am* 1993;31:237-259.

3. D'Arienzo A, Andreani L, Sacchetti F, Colangeli S, Capanna R: Hereditary multiple exostoses: Current insights. *Orthop Res Rev* 2019;11:199-211.

4. Lin PP, Moussallem CD, Deavers MT: Secondary chondrosarcoma. *J Am Acad Orthop Surg* 2010;18:608-615.

5. Laitinen MK, Parry MC, Morris GV, Kurisunkal V, Stevenson JD, Jeys LM: Can the cartilaginous thickness determine the risk of malignancy in pelvic cartilaginous tumors, and how accurate is the preoperative biopsy of these tumors?. *Clin Orthop Relat Res* 2024;482:1006-1016.

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

7. Kitsoulis P, Galani V, Stefanaki K, et al: Osteochondromas: Review of the clinical, radiological and pathological features. *In Vivo* 2008;22:633-646.

8. 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;25:1275-1283.

9. Malghem J, Vande Berg B, Noël H, Maldague B: Benign osteochondromas and exostotic chondrosarcomas: Evaluation of cartilage cap thickness by ultrasound. *Skeletal Radiol* 1992;21:33-37.

10. Deloin X, Dumaine V, Biau D, et al: Pelvic chondrosarcomas: Surgical treatment options. *Orthop Traumatol Surg Res* 2009;95:393-401.

11. Kivioja A, Ervasti H, Kinnunen J, Kaitila I, Wolf M, Böhling T: Chondrosarcoma in a family with multiple hereditary exostoses. *J Bone Joint Surg Br* 2000;82:261-266.

12. Koo TK, Li MY: A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 2016;15:155-163.

13. Tsuda Y, Gregory JJ, Fujiwara T, Abudu S: Secondary chondrosarcoma arising from osteochondroma. *Bone Joint J* 2019;101:1313-1320.

14. Weinschenk R, Wang WL, Levis V: Chondrosarcoma. *J Am Acad Orth Surg* 2021;29:553-562.

15. Kinoshita H, Kamoda H, Hagiwara Y, Kinoshita S, Ohtori S, Yonemoto T: Prognostic factors for survival in patients with high-grade chondrosarcoma. *Cancer Diagn Progn* 2022;2:681-685.

16. Ciechanowicz D, Kotrych D, Starszak K, et al: Delay in diagnosis and treatment of bone sarcoma—systematic review. *Cancers (Basel)* 2025;17:981.