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## Correlation between radiograph imaging and degree of chondrosarcoma histopathology



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### ABSTRACT

**Background:** Chondrosarcoma is the second most common primary bone tumor in adults after osteosarcoma. It is difficult to distinguish between low and high-grade chondrosarcoma radiographically, due to its various imaging appearances. Therefore, an imaging analysis method is needed to increase grading accuracy preoperatively. This study aim was to evaluate the correlation between imaging characteristics and degree of chondrosarcoma from histopathology.

**Material and methods:** This study was approved by the ethical clearance and ethics committee in our centre. A cross sectional study was conducted of 22 subjects with histopathology proven diagnosis of chondrosarcoma and had met both inclusion and exclusion criteria. Bone destruction, endosteal scalloping, transitional zone, chondroid matrix calcification, and periosteal reaction were the imaging characteristic that was re-evaluated by two radiologists with hidden identification.

**Result:** Mean age of all subjects was  $43.22 \pm 14.28$  years old, with slight female predominance (54.5%). 21 out of 22 chondrosarcomas (95.55%) were found in appendicular skeleton and the most

frequent site was found in iliac bone (31.82%), followed by femur, humerus, and pubic ramus. Bone destruction and soft tissue mass were the characteristics found on high-grade chondrosarcoma as many as 94% and 100% respectively, in the other hand all low-grade chondrosarcoma none has a picture of endosteal scalloping and periosteal reaction. Still, all low-grade chondrosarcoma has a chondroid matrix. Transitional zone margin 1B and 1C were discovered more on high-grade chondrosarcoma, whereas 1A, 1B, and no 1C were detected on low-grade chondrosarcoma. A radiographic abnormality score  $\geq 3$  has 4.7 times more chance to become a high degree greater than  $<3$  score, with ROC curve 0.96 ( $p < 0.05$ ). The intraobserver and interobserver scores were  $r = 0.630$ .

**Conclusion:** Each abnormality in this plain photo cannot stand alone, but must be combined and produce a total score of radiograph abnormality. A radiograph abnormality score with cut off value 3 can help to determine chondrosarcoma's histopathology degree. Further research with a larger sample and better image quality can be done to increase statistical analysis accuracy.

**Keywords:** Chondrosarcoma, degree of chondrosarcoma, radiology, histopathology

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### INTRODUCTION

Cancer research has experienced rapid development in recent decades, supported by technology-based diagnostic modalities that continue to produce new scientific concepts to improve the effectiveness and efficiency of diagnosis enforcement and determine therapeutic decisions. Chondrosarcoma is the second most giant primary bone tumor after osteosarcoma, which is characterized by the production of chondroid tissue or cartilage matrix by these tumor cells.<sup>1</sup> Globally, the estimated cumulative incidence of chondrosarcoma is 1: 200,000 per year, and covers 20-30% of primary tumours in bone. Data in the United States shows that the prevalence of chondrosarcoma annually is 3.6% of all primary malignancies in bone. Regarding all cases of chondrosarcoma, 85% of them are conventional chondrosarcoma.<sup>2</sup> Primary

chondrosarcoma is usually found in the elderly population, with a peak incidence in the fifth to seventh decade. Until now, the method of diagnosis and determination of therapy from chondrosarcoma is still a debate between clinicians and researchers.

The diagnosis of chondrosarcoma is determined by history taking, physical examination, and two primary investigations, such as radiology and anatomic pathology. Determination of the degree of preoperative malignancy from chondrosarcoma is the primary key to therapeutic decision making. So far, the generally accepted classification of chondrosarcoma is based on pathology examination results from a biopsy of tumor cell samples, which include cellularity, atypia, and pleomorphism. However, research by Eefting et al.<sup>3</sup> shows that biopsy specimens do not always lead to appropriate diagnosis and not all hospitals have

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anatomic pathology laboratory. For this reason, we need a method that can improve the reliability of the determination of the degree of preoperative malignancy by increasing the sensitivity and specificity of the diagnostic modality used, one of which is by radiological examination.

Several recent studies have shown that the use of radiological modalities in chondrosarcoma can be done preoperatively with X-Ray, CT Scan, and MRI modalities. The use of X-rays or plain radiology can accurately evaluate bone destruction, margins, transitional zones, calcification matrices, periosteal reactions, and soft tissue involvement, which are pathological features as a result of the process of molecular pathogenesis that occurs during disease development.<sup>4,5</sup> Therefore, the combination of chondrosarcoma diagnosis methods using radiological imaging and pathological findings is considered important in efforts to optimize the diagnosis of chondrosarcoma in clinical practice. Regarding community-based medical science, the implications of finding more sensitive and specific diagnostic methods are a contributing factor to the four comprehensive components of health care, particularly in the curative and rehabilitative-based service subsystems.<sup>6,7</sup>

As a consideration in Sanglah General Hospital Denpasar is a regional referral center that receives many oncology cases and considers that one of the objectives of plenary service is to improve the quality of life of patients after management efforts, the study to look at the distribution of

chondrosarcoma based on examination radiology and pathology appropriate to do. To the author's knowledge, a similar study has never been carried out in the Province of Bali, in particular, and in Indonesia, in general. This research will assess the relationship between plain photo abnormalities and the degree of histopathology of chondrosarcoma.

## METHOD

This study was a cross sectional study that evaluates the relationship between plain x-ray abnormalities and the degree of histopathology of chondrosarcoma based on radiological databases and anatomic pathology conducted during the period April 2019 to June 2019. The inclusion criteria in this study were patients with proven chondrosarcoma with histopathological examination expressed as low grade (Grade 1) and high grade (Grades 2-3). Exclusion criteria from this study were chondrosarcoma patients who did not have radiological clusters or had plain photographs that were not worth reading. Radiological variables studied were bone destruction, endosteal scalloping, transitional zones, chondroid matrix, periosteal reaction, and soft tissue involvement.

Data analysis was performed with the help of SPSS version 25.0, chi-square test and risk analysis were used to examine the relationship of radiological appearance to the histopathological degree of chondrosarcoma, the conformity of the results of the measurement of plain x-ray abnormalities by radiologists one and two were compared to correlation analysis and Bland Altman limit of agreement analysis. The ROC (Receiver Operating Curve) curve analysis aims to find the cutoff value of the radiograph score. All values are considered significant if  $p < 0.05$ .

## RESULT

The samples obtained were 22 patients consisting of 10 (45.5%) men and 12 (54.5%) women who came to Sanglah Hospital from January 2016 to July 2018 and had been diagnosed with chondrosarcoma from the results of anatomic histopathology examination.

The mean age was  $43.22 \pm 14.28$  years, with an age range of 18 years to 61 years. Most locations were in the appendicular as much as 21 samples (95.55%), only one (4.55%) was located diaxial skeleton (costae). Distribution of long bones 9 samples (40.91%) and flat bones 13 samples (59.09%). The most affected bone was iliac with 7 samples (31.82%), followed by femur as many as 4 samples (18.18%), and 3 samples (13.64%) respectively on the humerus and ramus pubis. There are 2 samples

**Table 1. Study characteristics**

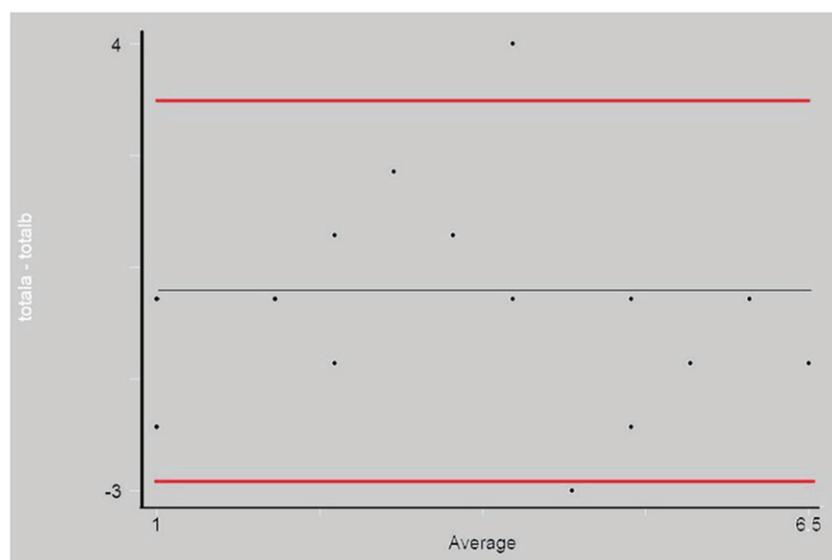
Characteristics	n=22
Age (years) (mean $\pm$ SD)	43.22 $\pm$ 14.28
Gender	
Male	10 (45.5%)
Female	12 (54.5%)
Location	
Axial	1 (4.55%)
Appendicular	21 (95.55%)
Bone type involvement	
Long bone	9 (40.91%)
Flat bone	13 (59.09%)
Bone	
Femur	4 (18.18%)
Humerus	3 (13.64%)
Iliac	7 (31.82%)
Metacarpal	1 (4.55%)
Ramus pubis	3 (13.64%)
Scapula	2 (9.09%)
Sternum	1 (4.55%)
Tibia	1 (4.55%)

of scapula (9.09%), metacarpal, tibia and sternum were found in 1 sample (4.55%) (Table 1).

The distribution of radiographic abnormalities based on chondrosarcoma histopathology is shown in Table 2, where radiographic abnormalities to be assessed include bone destruction, endosteal scalloping, transitional zone, choroidal calcification matrix, periosteal reaction, soft tissue involvement and total online score of each abnormality. Prevalent ratios were assessed using the Fisher exact test.

**Table 2. Distribution of radiographic abnormalities based on the degree of chondrosarcoma histopathology**

Variable dd Derajat	Chondrosarcoma grading		Prevalence Ratio	CI 95%	p-value
	High	Low			
<b>Destruction</b>					
Present	16	3	2.53	0.50-12.66	0.1169
Absent	1	2			
<b>Endosteal scalloping</b>					
Present	7	0	1.50	1.05-2.14	0.1348
Absent	10	5			
<b>Transitional zone</b>					
1A	2	2	1.67	0.61-4.54	0.2098
1B	9	3			
1C	6	0			
<b>Chondroidal matrix</b>					
Present	10	5	1.50	1.05-2.14	0.1348
Absent	7	0			
<b>Periosteal reaction</b>					
Present	3	0	1.36	1.04-1.77	1.0000
Absent	14	5			
<b>Soft tissue involvement</b>					
Present	17	1	NA	-	0.0001
Absent	0	4			



**Figure 1.** Bland Altman limit of agreement chart

Bone destruction assessment, obtained in high-grade chondrosarcoma only 1 sample did not achieve bone destruction, as many as 16 samples (94.12%) experienced bone destruction. Whereas in the low-grade group, there were 2 samples with no destruction and 3 samples with bone destruction (Table 2).

The distribution of endosteal scalloping in all low grade (100%) did not appear to have any endosteal scalloping, whereas in high grade 10 (58.8%) that has no endosteal scalloping, and 7 (41.18%) had endosteal scalloping, in other words, endosteal scalloping was more frequent in high-grade chondrosarcoma (Table 2).

The transitional zone is divided into 3 margins, namely margins 1A, 1B, and 1C. In the low-grade chondrosarcoma there were 2 (40%) samples that had a margin of 1A, 3 (60%) samples that had a margin of 1B, and none had a margin of 1C. Meanwhile, in high-grade chondrosarcoma, there were 2 (40%) samples that had 1A margins, 9 (52.94%) samples had 1B margins, and 6 (35.29%) samples had 1C margins (Table 2).

In high-grade chondrosarcoma, 7 (41.18%) samples did not have a chondroid calcification matrix, 10 (58.82%) samples had. In the low grade of 5 (100%) the example has a chondroidal calcification matrix, and none has no calcification matrix (Table 2).

Periosteal reactions in high-grade chondrosarcoma found 3 (17.65%) samples that contained periosteal reactions and 14 (82.35%) samples that did not have periosteal reactions. Whereas all low-grade chondrosarcoma (100%) did not have a periosteal response (Table 2).

Soft tissue masses were found in all (100%) high-grade chondrosarcoma, whereas in low-grade chondrosarcoma 4 (80%) samples had no mass and 1 (20%) sample had mass (Table 2).

The suitability of the results of radiographic abnormality measurements by radiologists one (A) and two (B) is determined by Bland Altman's correlation analysis and limit of agreement analysis. The maximum difference in the 95% Bland Altman Limits of Agreement between observers A and B is -2.783 to 3.056, with the distribution of plots that can be seen from Figure 1. The scattered plot illustrates the results of a relatively different total score.

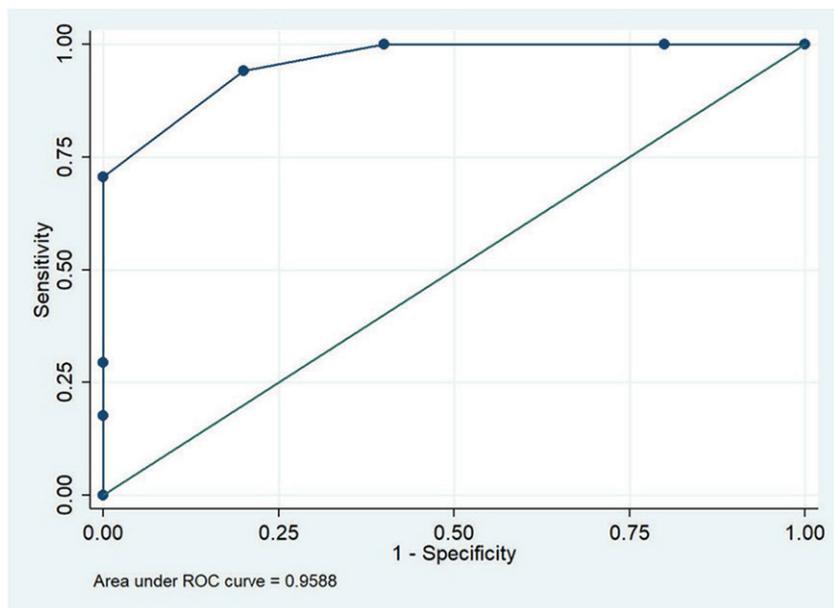
The mean radiographic abnormality score for observer A was  $3.50 \pm 1.63$  with a range of values 0-6 and observer B was  $3.36 \pm 1.84$  with a variety of benefits 1-7, the average difference between the two observers was 0.136 (Table 3).

A ROC (Receiver Operating Characteristic) curve analysis was carried out to determine the cut-

**Table 3. Evaluation of the suitability of radiographic abnormality scores between observers A and B**

Observer	Radiological scoring (mean ± SD, min-max)	r	Mean differences	95% Limits of Agreement
A	3.50 ± 1.63; 0-6	0.630	0.136	-2.783 - 3.056
B	3.36 ± 1.84; 1-7			

r = coefficient correlation



**Figure 2.** ROC curve predictive model

**Table 4. Results of total assessment of radiographic abnormalities score in determining the histopathology level of chondrosarcoma**

Variable	Chondrosarcoma grading		Prevalence ratio	CI 95%	p-value
	High	Low			
≥3	16	1	4.70	0.81-27.28	0.003
<3	1	4			

off point for the radiographic abnormality score. Determination of the cutoff point is important because based on the cutoff point can be assessed the relationship between the radiographic abnormality score with the degree of histopathology of chondrosarcoma.

This cut point is determined using the optimal point where the sensitivity and 1-specificity values are almost the same, in the ROC table above, the optimal cut point is 3 (Figure 1). A radiographic score of more than three was 4.7 times more likely to have Hi grade chondrosarcoma (p = 0.003) (Table 4).

**DISCUSSION**

**Study participant characteristics**

Chondrosarcoma predilection reported tends to be found in male sex compared to female, which is as much as 1.5-2: 1 this is not in accordance with the number of chondrosarcoma samples in this study, were from 22 samples found 10 men and 12 women. This discrepancy is likely to occur because of the insufficient number of samples in this study.<sup>8</sup>

Based on the origin of the formation or appearance of the first tumor cells. Primary chondrosarcoma is a malignancy that arises de novo or is a new lesion that does not originate from the development of other neoplasms, while secondary chondrosarcoma usually grows from benign tumors in the cartilage, such as enchondromas or osteochondromas, this explains the average age range of patient samples from 28 years to 57 years old.

According to Yoshimura et al.<sup>9</sup> the bone most often location of chondrosarcoma is the femur, humerus, pelvic region, and patella which is appendicular skeleton, this is in accordance with the location distribution of the sample were the most localized location in the appendicular bone as much as 21 samples, with the distribution in iliac bone were 7 sample, followed by femur as many as 4 samples, and 3 samples on the humerus, only 1 is in the axial skeleton (sternum).

**The results of the total score assessment of radiographic abnormalities in determining the degree of histopathology in chondrosarcoma**

Assessment of total score in determining the histopathology degree of chondrosarcoma, it was found that the radiographic abnormality score ≥3 had a chance to become a high-grade chondrosarcoma as much as 4.7 times greater than the score <3. The ROC curve also shows that the total radiographic abnormality score gives a good diagnostic rating, because the area under the ROC curve is 0.96.

Although the number of samples in this study is less than the minimum number of samples, but from the results of hypothesis testing there is a relationship between the total radiographic abnormalities score and the degree of histopathology of the chondrosarcoma, so that the radiographic abnormality score has a good predictive ability in determining the degree of histopathology of the chondrosarcoma.

**CONCLUSION**

This study concludes that there is a relationship between the total radiographic abnormalities

score and the degree of histopathology of chondrosarcoma, where if the total radiographic abnormality score is  $\geq 3$  has a chance to become high-grade chondrosarcoma as much as 4.7 times greater than the score  $< 3$ .

### CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding the publication of the current study.

### FUNDING

This study doesn't receive any specific grant from the government or any private sector.

### ETHICAL CONSIDERATION

The current study has been approved by the Ethical Committee Faculty of Medicine, Universitas Udayana/Sanglah General Hospital, Bali-Indonesia.

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