

Giant cell tumor of bone arising in long bones possibly originates from the metaphyseal region

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Received January 7, 2015; Accepted February 4, 2016

DOI: 10.3892/ol.2016.4264

Abstract. Giant cell tumor of bone (GCTB) is a primary benign bone tumor with a locally aggressive character. Definitive descriptions of the site of origin for this type of tumor are not available. The aim of the present study was to evaluate the site of origin of GCTB of long bones with regards to epiphyseal lines by means of radiographic examination. For that purpose, plain X-ray scans of 71 GCTBs arising in long bones were retrospectively reviewed. The tumor locations were the distal femur in 31 cases, proximal femur in 11 cases, proximal tibia in 13 cases, distal radius in 6 cases, proximal humerus in 5 cases and proximal fibula in 5 cases. The vertical center (VC) of the tumor was determined with X-ray anteroposterior view, and the correlation between the VC and the epiphyseal line, and between the distance from the epiphyseal line to the VC and tumor area or volume were analyzed using a regression model equation based on scatter plot diagrams. The VC of the tumor was located in the metaphyseal region in 57 cases, in the epiphyseal line in 11 cases and in the epiphyseal region in 3 cases. In cases of GCTB located in the distal femur or proximal tibia, significant correlations between the distance from the VC to the epiphyseal line and tumor area or volume were identified. The site of origin of GCTB was estimated to be located in the metaphyseal region. GCTB often occurs in mature patients, which renders it challenging to estimate the true site of origin of this lesion, since the metaphyseal line has disappeared in mature patients. The results of the present study suggest that GCTB possibly originates in the metaphyseal region.

Introduction

Giant cell tumor of bone (GCTB) is a relatively uncommon primary bone tumor that exhibits an aggressive character

and a high risk of local recurrence following surgery. GCTB accounts for 4-5% of all primary bone tumors and 13-20% of all benign bone tumors (1,2). These tumors frequently occur in skeletally mature persons, with a peak incidence in the third to fourth decade of life, while rarely arise in patients with an open growth plate. In addition, GCTBs display a slight female preponderance (3). The majority of GCTBs follow a benign course. However, GCTBs often exhibit local recurrence following surgery (3), and a previous study reported that pulmonary metastases develop despite the presence of benign histological features in 3% of patients with GCTB (4). GCTBs may undergo malignant transformation (3). Rock *et al* (5) reported that this may occur as a result of dedifferentiation of the primary tumor, or secondary to prior radiation therapy.

The majority of GCTBs are located at the end of long bones, and ~50~60% of them are located around the knee, distal femur and proximal tibia, being the distal femur the bone most frequently involved (6-8).

A previous study described that GCTB arises in the epiphyseal region of long tubular bones (9). The recent literature states that the majority of GCTBs exhibit a typical metaphyseal/epiphyseal location (10), whereas GCTBs may be centered in the metaphysis in children with open physes (11). However, no studies have ever been conducted to determine precisely the site of origin of GCTB. Thus, the purpose of the present study was to determine the site of origin of GCTB of the extremities and to analyze the pattern of progression in GCTB of long bones.

Materials and methods

A total of 128 patients were diagnosed with GCTB at Nagoya University Graduate School of Medicine (Nagoya, Japan) between October 1977 and September 2011. Of these, GCTB cases with location in the pelvis, vertebrae and small long bones (11 cases), as well as rare sites such as the distal tibia, distal humerus and proximal radius (7 cases) were excluded. Recurrent cases at initial referral (21 cases) and cases with insufficient X-ray data (18 cases) were also excluded. Metabolic bone diseases or brown tumors based on hyperparathyroidism were not included in the study. In total, 71 patients (50 males and 21 females) who were pathologically diagnosed with GCTB and subsequently treated at Nagoya University Graduate School of Medicine were enrolled in the present

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Key words: giant cell tumor of bone, long bones, origin, metaphysis, radiograph

study, which was approved by the Institutional Review Board of Nagoya University Graduate School of Medicine (approval no. 2013-0134). Written informed consent was obtained from each patient for participation in the study. Patients' X-ray scans (RADREX-i; Toshiba Medical Systems Corporation, Otawara, Japan) conducted at the initial referral were subjected to analysis. The mean age of the patients at diagnosis was 35 years (range, 13-71 years). The tumor locations were the distal femur in 31 cases, the proximal femur in 11 cases, the proximal tibia in 13 cases, the distal radius in 6 cases, the proximal humerus in 5 cases and the proximal fibula in 5 cases.

The size and volume of the tumor were estimated according to the method previously described (12). Briefly, the largest dimensions of the tumor (depth, width and height) were measured, and it was assumed that the tumor was spherical in shape. The vertical center (VC) of the tumor was determined as the center of tumor height on anteroposterior (AP) X-ray views. The trace of the growth plate was also determined with AP views (Fig. 1). The accuracy of the observations conducted with AP X-ray was confirmed to be adequate, since the same results were obtained with computed tomography (CT; Aquilion™ ONE; Toshiba Medical Systems Corporation) or magnetic resonance imaging (MRI; MAGNETOM Verio; Siemens Healthcare, Erlangen, Germany) (Fig. 2). The absolute intraobserver and interobserver differences were ≤ 1 mm in $>90\%$ of cases.

In cases where the VC was located in the metaphyseal region, the distance from the epiphyseal line to the VC was represented as a positive value, whereas a negative value was assigned when the VC was located in the epiphyseal region. Joint surface was defined as the roentgenographic border of long bones on X-ray AP views. Using these data, a regression model equation was derived from scatter plot diagrams using commercially available software (Excel version 2013, Microsoft Corporation, Redmond, WA, USA; Ekuseru-Toukei version 2012, Social Survey Research Information Co. Ltd., Tokyo, Japan). Prediction of significant correlations between each pair of variables was determined by the value of the Pearson's correlation coefficient (r). The correlation between the changes of a dependent variable (y) and an independent variable (x) was ascertained by a simple linear regression, using $y=a+bx$ as the equation in the regression model, where $a=y$ intercept when $x=0$, and b is the regression coefficient. $P<0.05$ was considered to indicate a statistically significant difference (13).

Results

The VC of the tumor was located in the metaphyseal region in 57 cases, in the epiphyseal line in 11 cases and in the epiphyseal region in 3 cases (Table I). The mean distance from the epiphyseal line to the VC was 13.1 mm (range, -20.0 to 50.0 mm). The mean tumor area and volume were 17.8 cm² (range, 2.4-62.8 cm²) and 45.7 cm³ (range, 2.4-209.3 cm³), respectively. The mean distance from the joint space to the tumor border of the articular side was 6.2 mm (range, 1.0-35.0 mm) (Table II). In cases of distal femur and proximal tibia, significant associations between the distance from the epiphyseal line to the tumor VC and the tumor area or volume were observed. The distance between the tumor VC and the epiphyseal line increased with increasing tumor area or volume. In cases of distal femur, the

Table I. Distribution of the vertical center of the tumor in patients with giant cell tumor of bone.

Tumor site	Metaphysis	Epiphyseal line	Epiphysis
Distal femur	27	3	1
Proximal femur	8	2	1
Proximal tibia	11	1	1
Distal radius	2	4	0
Proximal humerus	5	0	0
Proximal fibula	4	1	0

r values between the distance from the epiphyseal line to the tumor VC and the tumor area or volume were 0.439 ($P<0.001$) and 0.313 ($P=0.001$), respectively (Fig. 3). Significant correlations were also observed in cases of proximal tibia. The r values between the distance from the epiphyseal line to the tumor VC and the tumor area or volume were 0.332 ($P=0.002$) and 0.276 ($P=0.002$), respectively (Fig. 4). A fitted line corresponding to the regression model equation is represented in the scatter plot diagrams shown in Figs. 3 and 4. The equations obtained for the regression model corresponding to the correlation between the distance from the epiphyseal line to the tumor VC and the tumor area were $y=1.2900+0.4812x$ in the cases of distal femur, and $y=5.5100+0.4825x$ in the cases of proximal tibia, where y is the tumor VC in mm and x is the tumor area in cm². The equations obtained for the regression model evaluating the correlation between the distance from the epiphyseal line to the tumor VC and the tumor volume were $y=4.4200+0.1209x$ for distal femur and $y=7.800+0.1339x$ for proximal tibia, where y is the tumor VC in mm and x is the tumor volume in cm³. If the tumor volume in the distal femur is hypothesized to be 0 cm³, the tumor VC is assumed to be located in the metaphyseal region, at 4.4 mm distance from the growth plate. If the tumor volume in the proximal tibia is hypothesized to be 0 cm³, the tumor VC is assumed to be located in the metaphyseal region, at 7.8 mm distance from the growth plate. These findings suggest the site of origin of GCTB to be the metaphyseal region. No significant associations between the distance from the epiphyseal line to the tumor VC and the tumor area or volume were observed in cases of GCBT located in the proximal femur ($P=0.309$ and $P=0.32$), distal radius ($P=0.512$ and $P=0.506$), proximal humerus ($P=0.089$ and $P=0.172$) or proximal fibula ($P=0.505$ and $P=0.505$). Regarding the distance from the joint space to the tumor border, no associations between the distance from the joint surface to the tumor border and the tumor area or volume were observed in cases of distal femur ($P=0.536$ and $P=0.903$, respectively, Fig. 5). Similarly, no associations were observed in cases of proximal tibia (tumor area, $P=0.526$; tumor volume, $P=0.555$, Fig. 6). No associations were observed either in cases of proximal femur ($P=0.785$ and $P=0.636$), distal radius ($P=0.414$ and $P=0.543$), proximal humerus ($P=0.182$ and $P=0.559$) or proximal fibula ($P=0.559$ and $P=0.559$).

In addition, a significant association between patients' age and tumor area or volume was observed only in cases of proximal tibia, whereas no association was observed in any of the other cases.

Table II. Mean distance from the epiphyseal line to the tumor VC, tumor area, tumor volume and distance from the joint surface to the tumor border in patients with giant cell tumor of bone.

Tumor site	Epiphyseal line to VC, mm (range)	Tumor area, cm ² (range)	Tumor volume, cm ³ (range)	Joint surface to tumor border, mm (range)
Distal femur	11.7 (-5.0 to 25.0)	21.6 (5.9-62.8)	60.3 (11.8-209.3)	4.9 (1.0-10.0)
Proximal femur	19.0 (-20.0 to 50.0)	17.8 (4.7-42.4)	37.8 (11.0-84.8)	12.8 (1.0-35.0)
Proximal tibia	13.6 (-10.0 to 40.0)	16.8 (3.1-56.5)	43.3 (5.2-169.6)	5.2 (1.0-10.0)
Distal radius	1.3 (0.0-5.0)	4.6 (2.4-9.6)	6.6 (2.4-16.0)	1.7 (1.0-3.0)
Proximal humerus	23.6 (20.0-30.0)	18.0 (7.9-31.4)	48.6 (13.1-91.6)	10.6 (10.0-13.0)
Proximal fibula	12.0 (0.0-25.0)	12.3 (7.9-20.4)	22.9 (10.5-40.8)	2.8 (1.0-10.0)
All cases	13.1 (-20.0 to 50.0)	17.8 (2.4-62.8)	45.7 (2.4-209.3)	6.2 (1.0-35.0)

VC, vertical center.

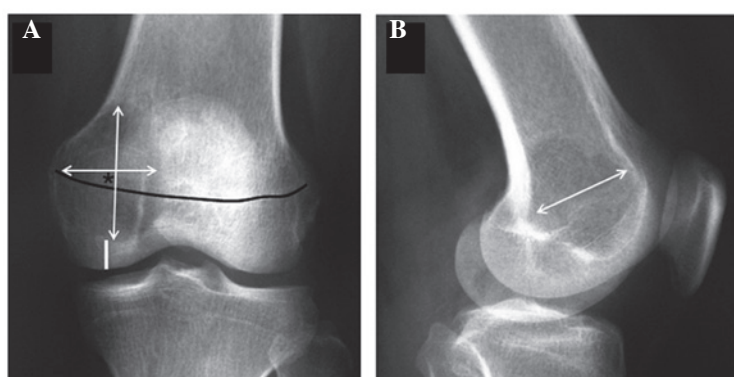


Figure 1. Schematic illustration of tumor measurement using X-rays. (A) Anteroposterior and (B) lateral views were used for measuring the largest dimensions of the tumor (depth, width and height) (white lines with arrows), distance from the joint surface to the tumor border (white thick line), vertical center of the tumor (°) and trace of growth plate (black line).

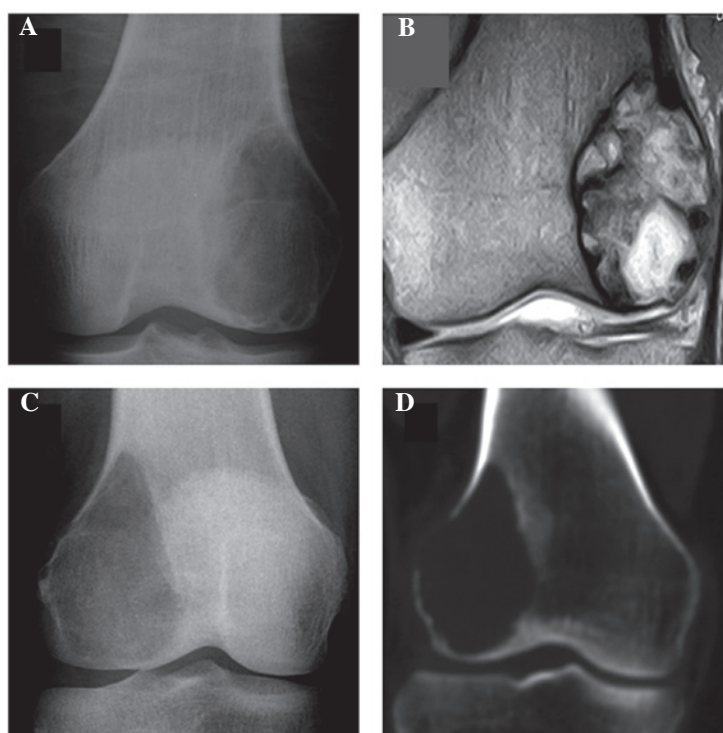


Figure 2. Representative images of two cases of giant cell tumor of bone arising in the distal femur. (A) AP X-ray and (B) coronal view of T2-weighted magnetic resonance image of a 20-year-old male patient. (C) AP X-ray and (D) coronal view of computed tomography image of a 33-year-old female patient. AP, anteroposterior.

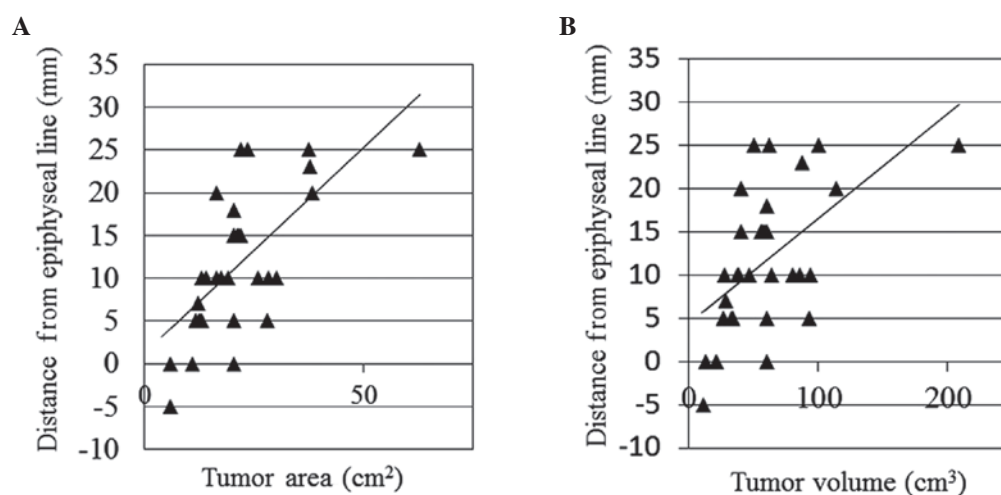


Figure 3. Scatter plot diagrams and regression analysis of tumors arising in the distal femur. (A) Correlation between the tumor area and the distance from the epiphyseal line to the tumor VC (model equation, $y=1.2900+0.4812x$; $r=0.439$; $P<0.001$). (B) Correlation between the tumor volume and the distance from the epiphyseal line to the tumor VC (model equation, $y=4.4200+0.1209x$; $r=0.313$; $P=0.001$). VC, vertical center.

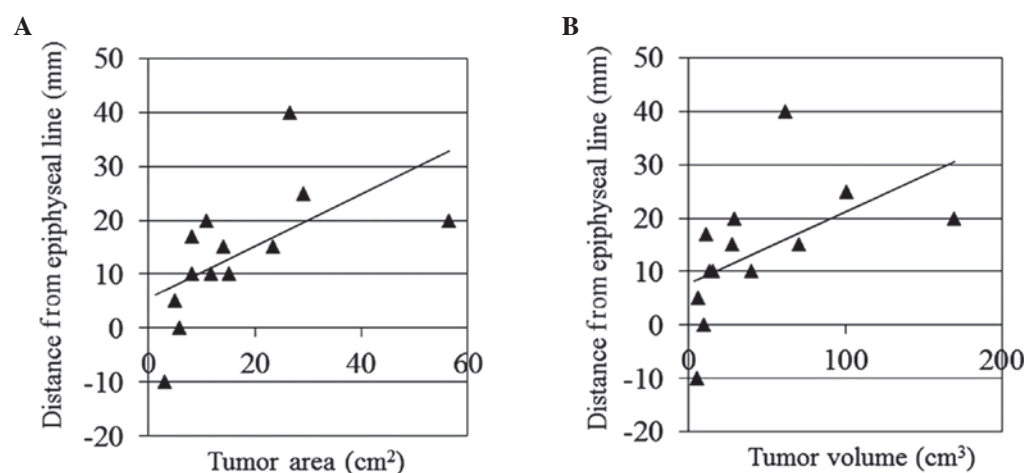


Figure 4. Scatter plot diagrams and regression analysis of tumors arising in the proximal tibia. (A) Correlation between the tumor area and the distance from the epiphyseal line to the tumor VC (model equation, $y=5.5100+0.4825x$; $r=0.332$; $P=0.002$). (B) Correlation between the tumor volume and the distance from the epiphyseal line to the tumor VC (model equation, $y=7.8000+0.1339x$; $r=0.276$; $P=0.002$). VC, vertical center.

Discussion

To the best of our knowledge, the results of the present study suggest for the first time the site of origin of GCTB to be the metaphyseal region, using equations fitted to regression models. The exact site of origin of GCT remains controversial. Murphey *et al* (14) reported that in skeletally immature patients, GCTBs were located in metaphyseal rather than meta-epiphyseal bone, with an open epiphyseal plate acting as a barrier to tumor growth. Fain *et al* (15) reported non-epiphyseal GCTB of long bones. Of 1,682 cases of GCTB reported by the authors, only 14 (0.8%) were located in exclusively metaphyseal or diaphyseal regions. A notable finding of that study was the fact that the majority of patients with non-epiphyseal GCTB were <15 year-old (15). These unusual cases raised debate as to whether GCTB is capable of developing in the epiphysis (6,9) or in the metaphysis, with subsequent extension to the epiphysis following growth plate closure (16-18). Gandhe *et al* (19) reported cases of epiphyseal GCTB. However, considering that

GCTB is occasionally misdiagnosed or confused with other giant cell-rich tumors, other giant cell-containing tumors such as giant cell-rich osteosarcoma and chondroblastoma should be strictly differentiated from epiphyseal GCTB by experienced pathologists (3).

The current study revealed that the distance between the joint surface and the tumor border of the articular side is short, even in cases of small tumors. These results are consistent with those reported by Murphey *et al* (14), whereby 84-99% of lesions extended to locations within 1 cm of subarticular bone (14). Suzuki *et al* (20) reported that less residual thickness of subarticular bone correlated with higher recurrence following surgery for GCTB, and tended to be associated with secondary osteoarthritis. Thus, it may be hypothesized that early diagnosis may lead to preservation of a sufficient quantity of subchondral bone, and as a result, the rate of local recurrence may decrease and the functional outcome may improve. However, the biological character of GCTB, which easily extends to the articular side (epiphyseal region) of the

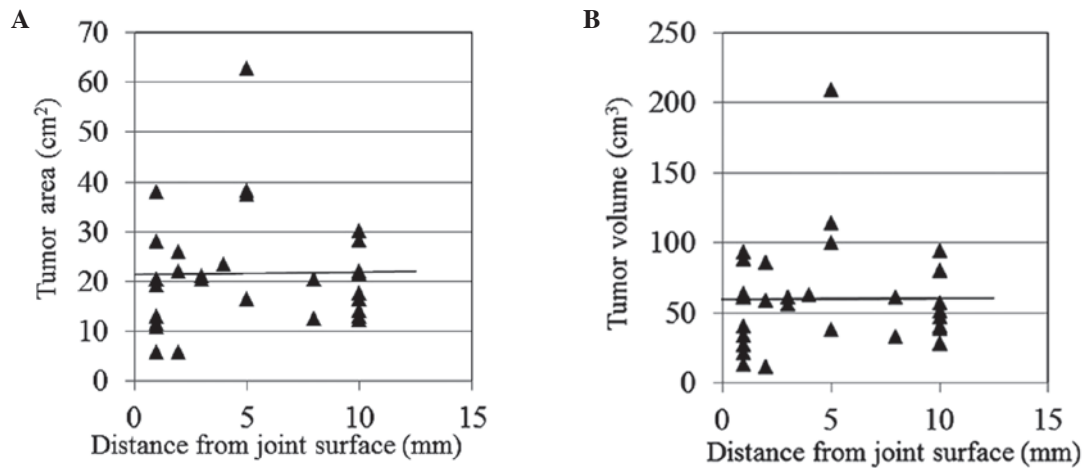


Figure 5. Scatter plot diagrams and regression analysis of tumors arising in the distal femur. (A) Correlation between the tumor area and the distance from the joint surface to the tumor border (model equation, $y = 4.5900 + 0.0090x$; $r = 0.001$; $P = 0.536$). (B) Correlation between the tumor volume and the distance from the joint surface to the tumor border (model equation, $y = 4.9000 + 0.0001x$; $r = 0.000$; $P = 0.903$).

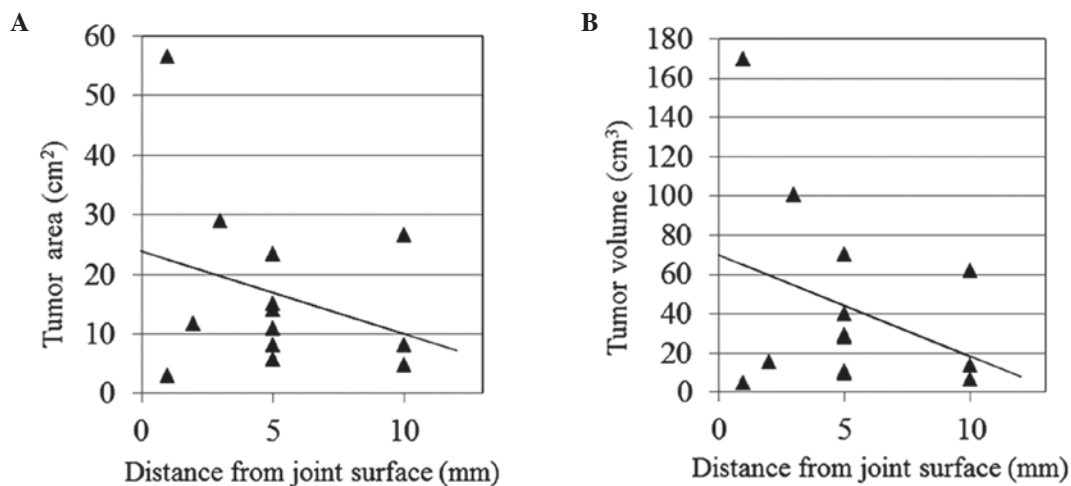


Figure 6. Scatter plot diagrams and regression analysis of tumors arising in the proximal tibia. (A) Correlation between the tumor area and the distance from the joint surface to the tumor border (model equation, $y = 6.2600 - 0.0660x$; $r = 0.092$; $P = 0.526$). (B) Correlation between the tumor volume and the distance from the joint surface to the tumor border (model equation, $y = 6.1400 - 0.0227x$; $r = 0.120$; $P = 0.555$).

affected long bones, difficulties the reduction of the recurrence rate and induces the development of postoperative osteoarthritic changes.

Gandhe *et al* (19) and Kransdorf *et al* (21) reported that GCTB lesions involve the metaphysis rather than the epiphysis in skeletally immature patients, since the open epiphyseal plate acts as a barrier to tumor growth. Puri *et al* (22) noted that an open physis did not prevent GCTBs from penetrating the epiphyseal cartilage. Campanacci *et al* (23) observed invasion of the joint in only 5% of GCTB cases. Based on these previous reports, it may be proposed that the expansion of GCTBs is partly inhibited by the presence of articular cartilage or an open growth plate. As indicated in the current study, GCTB appears to arise at a metaphyseal site and extend in a diaphyseal and epiphyseal direction. There was observed to be no barrier in the diaphysis against tumor extension, whereas tumor growth was inhibited by articular cartilage. As a result, the tumor VC may shift slowly in a diaphyseal direction. However, the site of origin of GCTB is suggested to be the

metaphyseal region, according to the regression model equations discussed in the present study.

There are a number of limitations affecting the current study. First, a relatively small number of patients were included in the study, which may be underpowered to obtain more meaningful results regarding the original site of GCTBs. Second, it is not possible to analyze or explain the site-specific differences observed in the present study, since the location of GCTBs in the proximal femur, distal radius and proximal fibula should be analyzed in a larger number of cases, based on multicenter analyses. Third, other radiological modalities including CT or MRI may evaluate more precisely the VC of GCTBs than X-rays, although, as demonstrated in the present study, AP X-rays were able to evaluate the center of tumor as adequately as CT or MRI. Fourth, a tumor is unable to extend to the articular side once it reaches the subchondral region, possibly biasing the results of the current analyses. However, the significant correlations obtained with the regression model equations suggest the reliability of the present results.

In conclusion, the findings of the present study indicate that the site of origin of GCTB is possibly the metaphyseal region. The results of the current study provide useful information regarding the clinical course of GCTB for physicians, and suggest that early detection may be crucial to cure this refractory benign tumor.

Acknowledgements

The authors would like to thank Miss Eri Ishihara (Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine) for her secretarial assistance during the present study, and Dr Satoshi Yamashita (Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine) for his support with statistical analyses. The present study was partly funded by the Ministry of Education, Culture, Sports, Science and Technology of Japan [Tokyo, Japan; grant-in-aid no. 262933341 for Scientific Research (B)] and partly by the National Cancer Center Research and Development Fund (Tokyo, Japan; grant no. 26-A-4).

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