Giant cell tumor of bone – Analysis of 213 cases involving extra-craniofacial bones

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Abstract

We elucidated clinicopathological characteristics of giant cell tumor of bone (GCTB) in Japan, and significant clinicopathological factors for predicting local recurrence. Clinicopathological profiles of 213 patients with GCTB (100 male, 113 female) involving extra-craniofacial bones were retrieved. Pathological slides obtained at the initial surgery were reviewed. Fourteen pathological and five clinical features were statistically analyzed to disclose prognostic significance. Patient age ranged from 12–80 years (Average 38.7). Long bones were most frequently affected (86.4%), especially around the knee (62.9%). Histological features are basically similar to those previously reported. Within a follow-up period (24–316 months, average 106.1 months), the local recurrence rate is 29.1%. Metastasis has occurred in 9 patients. Cox regression analysis of representative clinicopathological features shows that younger age, higher mitotic count, smaller zones of stromal hemorrhage, considerable vascular invasion and absence of ischemic necrosis are significant predictors for local recurrence. Initial operative method (curettage) is a significant risk factor in univariate analysis but not by multivariate analysis (\(P = 0.053\)). Denosumab administration increases risk but not significantly (\(P = 0.053\)). Histone 3.3 G34W immunopositivity is not significant for predicting local recurrence.

KEYWORDS
bone, denosumab, extra-craniofacial bone, G34W, giant cell tumor of bone, local recurrence, mitosis, prognosis, risk factor, statistical analysis
INTRODUCTION

Giant cell tumor of bone (GCTB) is a locally aggressive and rarely metastasizing intermediate tumor,\(^1\) with incidence of about 6% of all primary bone tumors in one institutional review.\(^2\) In Japan, it is about 8% in the bone tumor registry.\(^3\) Recent reviews from China and Europe estimated the incidence rate as 1.2 to 1.7 cases per 1 million person-years.\(^4,5\) GCTB usually affects the epi-metaphysis of long bones in young adults with a mild female preponderance.\(^3,4,6\)–\(^15\) Long bones around the knee, sacrum and vertebral body are frequently affected.\(^3,6\)–\(^8,11,13,16\)–\(^18\) Local recurrence has been reported between 5–49%\(^4,6–19\) and pulmonary metastasis 2 to 7%.\(^7,10,11,20\) Recently, H3F3A mutant gene expression is linked to GCTB.\(^21\) Histone 3.3 G34W immunopositivity was most frequently observed (about 90%).\(^22,23\)

Useful clinicopathological features for predicting local recurrence and/or pulmonary metastases have been documented, but morphological features alone have not been found.\(^8–10,15,18,24–26\)

In this study, we describe clinicopathological characteristics of GCTB involving extra-craniofacial bones in Japan, and analyze statistically significant factors for predicting local recurrence.

This study was conducted with the approval of the institutional review board for ethics of each institution.

MATERIALS AND METHODS

Clinicopathological profiles of 306 cases of histologically proven GCTB, affecting extra-craniofacial bones were retrieved within the Kansai Musculoskeletal Oncology Group, Japan. For 263 cases, initial surgeries for primary lesions were performed within the Group and pathological slides were available for review. Of 263 cases, we analyzed 213 cases who had follow-up periods for twenty-four months or more after initial surgeries (Figure 1), performed between February 1989 and April 2017. The follow-up period ranged 24–316 months (average 106.1 months, median 80.0 months). Pathological slides obtained from the surgical specimens were reviewed by three expert pathologists (EK, MM, SN). Immunohistochemistry for histone 3.3 G34W (clone RM263, x1000, RevMAb Biosciences, South San Francisco, CA, USA) was performed for 135 cases. We evaluated 14 pathological features for each case, as listed Table 1. Because each reviewer used a personal microscope for counting mitoses, the counts were adjusted by area of view calculated by field number and objective lens magnification of microscope [baseline: 0.3447 mm\(^2\) (field number: 26.5, objective lens: x40)].

The 14 features and clinical profiles, such as age, gender, administration of denosumab,\(^27,28\) were analyzed statistically. Statistical analyses were performed with SPSS Statistics 26 (IBM, Armonk, NY, USA), in order to elucidate outcomes, including predictive features for the local recurrence. Cox regression analysis, Kaplan–Meier analysis, t-test and \(\chi^2\) test were used. Significant level was set at 0.05 (two sided).

RESULTS

Epidemiologic characteristics (Figure 1)

Of 213 Japanese patients, 113 were female and 100 were male (Female: Male = 1.13:1). Age of the patients at initial presentation ranged from 12 to 80 years (average 38.7 years, median 35.2 years) and the peak age was between 25 to 34 years (62 cases) (Figure 1a). 65% of the patients who were younger than 25 years of age, were female (male 14 cases, female 26 cases). GCTB most often affected long bones (184 cases, 86.4%) [femur (88 cases, 41.3%), tibia (51 cases, 23.9%), radius (20 cases, 9.4%), fibula (11 cases, 5.2%), humerus (11 cases, 5.2%)]. Axial bones were involved less frequently [vertebrae (6 cases, 2.8%), rib (5 cases, 2.3%) and sacrum (5 cases, 2.3%)]. Flat bones, for example, pelvic bones (8 cases, 3.8%) and scapula (1 case, 0.5%) were rarely affected. Long bones around the knee were the most frequent primary site (133 cases, 62.9%) (Figure 1b). None of the 213 cases were multicentric. Chief complaint at initial presentation was pain (99%), swelling (7.4%), numbness (2.8%), and discomfort (0.9%).
Pathological features (Table 1 and Figure 2)

Histological material was available in all 213 cases. Diffuse mononuclear cell proliferation, often with spindle cells (99.5%) was observed. Percent spindle cell proliferation was variable, but in 58.0% of the cases, spindle cell zones occupied more than half the lesion. Stromal hemorrhage was quite common (94.8%).

Secondary aneurysmal bone cyst was often identified (77.8%). Storiform pattern (60.3%), foam cell infiltrates (51.9%) and tumoral ossification (49.5%) were common. Ischemic necrosis was also observed (46.5%). Vascular invasion was noted in 15.6% of cases.

Mitotic figures were counted in 172 cases (80.8%), ranging 1 to 26.1 per 10 high-power fields (HPF) (average 4.342/10 HPF, median 2.90/10 HPF). Atypical mitosis was not observed. Pleomorphic cells with nuclei
more than three times that seen in adjacent tumor cells were found in 10.8% of cases.

Because surgical curettage was the most common initial operative method (mentioned below), the submitted specimens were usually fragmented. It was not easy to detect a permeative growth pattern, such as entrapment, or extramedullary extension, histologically. Entrapment was only rarely observed (5.6%, 3/54 cases). Extramedullary extension was present in 38 of 61 cases (61.3%). An ossified rim was noted in 7 of 38 cases (20.6%).

A total of 124 of 135 cases (91.9%) expressed histone 3.3 G34W-positive immunostaining.

Therapy and prognosis (Table 1, Figure 3)

Information about operative methods was available in 206 cases. Curettage (with or without adjuvant agents) was usually selected for the initial surgery (171 cases, 83.0%) and resection (surgical method other than curettage: total or en bloc resection, amputation, joint replacement, etc.) was performed in 35 cases (17.0%). Local recurrence developed in 62 cases (29.1%, male: 32%, female: 26.5%). Time to recurrence after initial surgery ranged from 3 to 161 months (average: 29.8 months, median: 18.5 months). The rate of recurrence was 33.9% (58/171 cases) when treated by curettage, and was 11.4% (4/35 cases) following resection. 48 cases (78.4%) recurred within 36 months after surgery. Three cases (4.8%) appeared after 120 months. By Kaplan–Meier curve, 5-year and 10-year local recurrence free survival rates were 72.7% and 68.8%, respectively (Figure 3).

Recurrent sites were femur (39 cases, 62.9%), tibia (18 cases, 29.0%), axial skeletons (5 cases, 8.0%), radius (4 cases, 6.5%), humerus (3 cases, 4.8%), limb-girdles (2 cases, 3.2%) and fibula (1 case, 1.6%) (Figure 1b). Forty-one cases (66.1%) were observed around the knee. Three of four recurrent cases with resection as initial surgery affected spine and one affected proximal radius. Age of the patients with
recurrence ranged from 16–80 years (average 34.6 years, median 31.0 years), and those without recurrence ranged from 12–79 years (average 40.3 years, median 38.0 years). Information about therapy for initial local recurrent lesions was available in 61 of 62 cases. Twenty-five had curettage alone, seven had curettage and denosumab administration, one had curettage with radiotherapy, nine had resection, two had resection with anti-cancer drug, three had denosumab administration alone, and thirteen were just observed. 14 patients had a second recurrence (22.6%). Its rate is lower than that of an initial recurrence but not significant ($\chi^2$ test, $P = 0.312$).

In this series, nine patients had lung metastases (4.2%, male 6, female 3). One female patient had lung metastasis at the first visit and is still alive with persistent neoplasm and no local recurrence (follow-up 111 months). Four of the remaining eight who did not have lung metastases at their first visits, developed local recurrence at primary sites. Primary sites of the cases with metastases were femur (proximal 1, distal 3), proximal tibia (1), proximal humerus (1), distal radius (1), thoracic vertebra (1) and ileum (1). No cases with lung metastasis were fatal. Unfortunately, two patients died during the follow-up periods. One patient died with peritoneal dissemination from pelvic bone GCTB, 24 months after the first surgery. The other developed fatal esophageal cancer. Disease-specific mortality rate of GCTB was 0.47% (1/213 cases). Administration of denosumab at the time of initial surgery was identified in 10 cases (4.7%), and local recurrence appeared in 4. Patients who received denosumab after the detection of local recurrence and/or metastasis were not included. Transformation to a higher grade neoplasm was observed in a case without radiotherapy, diagnosed histologically at the second recurrence (79 months after the initial surgery). The tumor was immune-positive for histone 3.3 G34W antibody. The patient was alive with disease (4 months since the last surgery).

Statistical analyses

Univariate analyses (Table 1 and Figure 3)

Univariate analyses (Cox regression, t-test, Kaplan–Meier) were performed in order to isolate predictive factors for local recurrence. Within clinical features, the average age of the patients with local recurrence (34.6 years) was statistically younger than that of the patients without local recurrence (40.3 years) (t-test, $P = 0.013$). Younger age increases risk of local recurrence statistically (Cox regression, $P = 0.004$). Considering treatment, curettage increases risk significantly compared to resection (Cox regression: $P = 0.019$). Male gender, tumor locations (long bone, bones around the knee), denosumab administration did not significantly increase risk for recurrence. Initial surgeries in between 2006 to 2017 increased risk to those in between 1989 to 2005, but not significantly.

![Figure 3](image-url)
### TABLE 1 Summary of clinical and histological findings, and results of statistical analyses (Cox regression, Kaplan–Meier, and t-test) for each finding between non-recurrent and recurrent cases.

| Clinical Features | Total | CDF | REC | \(P\)-value | Hazard ratio (95% CI) | Test |
|-------------------|-------|-----|-----|-------------|----------------------|------|
| **Sex**           | 213   |     |     | 0.591      | 0.872 (0.530–1.436)  | Cox: ratio of female to male |
| **Age (years)**   | 213   | 40.3| 38.0| 0.013*     | 0.974 (0.956–0.991)  | Cox: ratio of female to male |
| **Operative method** | 206   |     |     | 0.019*     | 0.298 (0.108–0.823)  | Cox: ratio of resection to curettage |
| **Location (long vs non-long)** | 213   |     |     |             |                      | Cox: ratio of long bone to non-long bone |
| **(knee vs non-knee)** | 213   |     |     |             |                      | Cox: ratio of bones around knee to extra-knee |
| **Year of initial surgery** | 213   |     |     |             |                      | Cox: ratio of 2006–2017 to 1989–2005 |
| **Denosumab administration** | 213   |     |     |             |                      | Cox: ratio of present to absent |
| **Histological Features** |       |     |     |             |                      | Cox: ratio of 2006–2017 vs 1989–2005 |
| **Stromal hemorrhage** | 211   | 63  | 87  | 0.014*     | 0.523 (0.312–0.875)  | Cox: ratio of area ≥25% to <25% |
| **Vascular invasion** | 212   | 149 | 2   | 0.005**    | 5.402 (1.677–17.398) | Cox: ratio of occasional or frequent to absent or rare |

(Continues)
| Condition                                | Total | CDF | REC  | P-value | Hazard ratio (95% CI) | Test          |
|------------------------------------------|-------|-----|------|---------|-----------------------|---------------|
| **Ischemic necrosis**                    | 213   | 72  | 79   | Present:| Absent: 42 Present: 20 | **0.009**     |
| **Osteoid/Ossification**                 | 212   | 79  | 72   | Absent: | Present: 28           | 0.492 (0.289-0.838) Cox: ratio of present to absent |
| **Pleomorphic cells**                    | 212   | 134 | 17   | Absent: | Present: 55           | 0.921 (0.396-2.140) Cox: ratio of present to absent |
| **Mitotic figure mitotic count/10 HPF**  | 213   | 3.88| 2.9  | Average:| Median: 5.47          | 0.055*** t-test (Welch, unequal variance) |
| **Aneurysmal bone cyst**                 | 212   | 30  | 121  | Absent: | Present: 17           | 0.775 (0.443-1.357) Cox: ratio of present to absent |
| **Foamy cell infiltrate**                | 212   | 73  | 78   | Absent: | Present: 29           | 0.991 (0.599-1.639) Cox: ratio of present to absent |
| **Spindle cell proliferation**           | 212   | 62  | 89   | >50%:   | 27 >50%:             | 0.856 (0.517-1.419) Cox: ratio of area >50% to 0-50% |
| **Storiform pattern**                    | 209   | 56  | 93   | Absent: | Present: 27           | 0.812 (0.488-1.350) Cox: ratio of present to absent |
| **Extramedullary extension**             | 61    | 20  | 30   | Absent: | Present: 3            | 1.761 (0.467-6.642) Cox: ratio of present to absent |
| **Ossified rim at extramedullary tumor** | 34    | 22  | 5    | Absent: | Present: 5            | 1.829 (0.354-9.459) Cox: ratio of present to absent |
Among histological features, the average number of mitoses in locally recurrent cases (5.47/10 HPF) was higher than those in non-recurrent cases (3.88/10 HPF) (t-test, \( P = 0.055 \), a significant trend \( 0.05 \leq P < 0.10 \)). By Cox regression analysis, higher mitotic count increases risk for local recurrence statistically \( (P = 0.014) \). Other pathological features were analyzed by numerical scoring methods using categories as shown in Table 1. Stromal hemorrhage less than 25% in area, occasional to frequent vascular invasion, and absence of ischemic necrosis increase risk significantly as well \( (P < 0.05) \). Osteoid formation/ossification, extramedullary extension, ossified rim at the surface of extramedullary extension, and histone 3.3 G34W immunopositivity also increased risk, but not significantly. Pleomorphic cells, secondary aneurysmal bone cyst, foamy cell infiltrate, storiform pattern and spindle cell proliferation more than 50% in area decreased risk for local recurrence, but also not significantly.

**Multivariate analysis (Table 2)**

We performed Cox regression analysis on the selected features in which around 200 cases were available for evaluation (Table 1), using forced entry method in order to isolate predictive factors for local recurrence. The model included all clinical information (age, sex, operative method, location, denosumab administration), and selected histological information (area of stromal hemorrhage, frequency of vascular invasion, ischemic necrosis, osteoid formation/ossification, pleomorphic cells, mitotic count, secondary aneurysmal bone cyst, foamy cell infiltrate, storiform pattern and spindle cell proliferation).

We analyzed 201 cases, and \( P \)-value of the equation was 2.2E-05. Significant \( (P < 0.05) \) factors for local recurrence are age, mitotic count, stromal hemorrhage, vascular invasion, and ischemic necrosis. Hazard ratios of these are 0.975, 1.070, 0.548, 8.711, and 0.423, respectively. Younger age, higher mitotic count, smaller zone (<25%) of stromal hemorrhage, considerable (occasional to frequent) vascular invasion and absence of ischemic necrosis each significantly increased risk. Other features were not significant, while denosumab administration and curettage increased risk as a significant trend \( (P = 0.053, \text{ each}) \).

**DISCUSSION**

In this study, demographical features of giant cell tumor of bone (GCTB), such as gender, age distribution, frequent location, chief complaint etc., are basically similar to those of the previous reports.\(^6\)\(^-\)\(^1\)\(^5\) Interestingly, a male predominance was reported from China\(^5\) a result different from other studies\(^6\)\(^-\)\(^1\)\(^5\) including a single-year registry.
TABLE 2 Results of Cox regression analysis (multivariate, forced entry method) of selected clinicopathological features.

| Feature                                      | P-value | Hazard ratio | 95.0% Confidence interval for hazard ratio | Lower | Upper |
|----------------------------------------------|---------|--------------|-------------------------------------------|-------|-------|
| Age (years)                                  | 0.014*  | 0.975        | 0.956                                     | 0.995 |
| Sex (female vs male)                         | 0.869   | 0.956        | 0.558                                     | 1.637 |
| Operative method (resection vs curettage)    | 0.053***| 0.310        | 0.094                                     | 1.016 |
| Location (around knee vs except knee)        | 0.793   | 1.096        | 0.553                                     | 2.174 |
| (long bone vs non-long bone)                 | 0.822   | 0.885        | 0.305                                     | 2.566 |
| Denosumab administration (adjuvant and/or neoadjuvant) | 0.053***| 2.957        | 0.985                                     | 8.876 |
| Stromal hemorrhage (area ≥25% vs <25%)       | 0.039*  | 0.548        | 0.310                                     | 0.971 |
| Vascular invasion (absent or rare vs occasional or frequent) | 0.002** | 8.711        | 2.238                                     | 33.908 |
| Ischemic necrosis (absent vs present)        | 0.008** | 0.423        | 0.223                                     | 0.803 |
| Osteoid/Ossification (absent vs present)     | 0.307   | 1.372        | 0.748                                     | 2.516 |
| Pleomorphic cells† (absent vs present)       | 0.229   | 1.716        | 0.712                                     | 4.135 |
| Mitotic figure (mitotic count/10HPF)         | 0.010*  | 1.070        | 1.016                                     | 1.127 |
| Aneurysmal bone cyst including microscopic (absent vs present) | 0.861   | 1.056        | 0.575                                     | 1.938 |
| Foamy cell infiltrate (absent vs present)    | 0.991   | 1.003        | 0.545                                     | 1.847 |
| Spindle cell proliferation (area 0-50% vs >50%) | 0.280   | 0.700        | 0.367                                     | 1.336 |
| Storiform pattern (absent vs present)        | 0.615   | 0.850        | 0.451                                     | 1.601 |

P-value of the equation: 2.2E-05.
Abbreviation: HPF, high-power field.
* P < 0.05.; ** P < 0.01.
*** 0.05 ≤ P < 0.10.
† nuclear size variation in diameter (>3 times).

(2016) in Japan. While a multi-year registry (2006–2016) in Japan revealed a male preponderance (female to male ratio: 0.81). Environmental conditions may be responsible. Also, accuracy in pathology reporting of skeletal tumors may be a factor, due to the diagnostic challenges surrounding GCTB. Patients younger than 25 years old showed a more distinct female preponderance (ratio: 1.85) in our series, the same as documented previously (ratio: 2.15).29

Histopathological features observed in this study are also similar to those reported previously. Vascular invasion and extramedullary extension affirm the locally aggressive nature of GCTB. Immunopositivity for histone 3.3 G34W mutant, a specific marker for GCTB, is expressed in 91.9% of cases, similar to previous reports. GCTB is not categorized as a “bone producing tumor”, but we found bone/osteoid production by tumor cells in 49%. Murata et al.31 suggested that mononuclear cells in GCTB could differentiate into osteoblast and Yamamoto et al.32 reported that GCTB cells show bone production following denosumab therapy.

In our series, the local recurrence rate is 29.1%. The 5-year and 10-year local recurrence free survival rates are 72.7% and 68.8%. These results were not different from previous reports. Local recurrence developed within 24 months after surgery in 97% of all recurrent cases previously reported. Later relapse is rare, but even a 30-year interval may occur. In our study, 78.4% of recurrent cases were observed within 36 months after initial surgery, and one patient had first recurrence 161 months later. A second recurrence has been reported as 21.7–29.9%, the same in our result (22.6%).
We found nine cases of lung metastasis (4.7%), similar to previous reports (2–7%).

Previous studies draw attention to local recurrence associated with lung metastasis. Only four (44.4%) such cases were observed in our series, where the metastatic rate is not significantly different from that of patients without local recurrence ($\chi^2$ test, $P = 0.301$). Gender difference in the patients with lung metastasis (male: female = 6:3, $\chi^2$ test, $P = 0.226$), confirmed with previous report. Cases involving the distal radius or bones around the knee were reported to have lung metastasis frequently (30% and 71%), In our series, only one case with lung metastasis originated from the distal radius (11.1%) and four from bones around the knee (44.4%). One patient in our study had pulmonary involvement at initial presentation (11.1%) similar to that previously reported (14.3%). Lung metastasis in GCTB patients is usually a chronic condition clinically, but ultimately cause for demise. In our study, there were no fatalities among patients with lung metastasis. Disease-specific mortality rate was only 0.47% (1 of 213 cases), lower than reported in previous studies. Secondary malignant transformation to a higher grade neoplasm was observed in our series (1/213 cases, 0.47%, 79 months after the initial surgery). Cases of secondary malignant GCTB are frequently sarcomas appearing an average of 19 years after radiotherapy. Our patient did not receive radiotherapy. We excluded cases of malignant GCTB from this study when it was diagnosed before or at the initial surgery.

By univariate analysis, we elucidated six (out of 20) significant features for predicting GCTB local recurrence: patient age, operative method, stromal hemorrhage, vascular invasion, ischemic necrosis, and mitotic count (Table 1). By multivariate analysis using 16 features, the operative method disappeared from the list of significant features elucidated by univariate analysis (Table 2). Many trials to determine risk factors for predicting local recurrence have been performed, but results are still indeterminate. Patient age as a risk factor has been controversial. In our study, older age significantly decreases risk for local recurrence, by 2.5% annually. Local recurrence has been reported not to be gender-dependent. We confirmed it statistically, even when cases under 25 years old were examined (male 5/14, female 10/26, $\chi^2$ test, $P = 0.864$).

Skeletal location may influence local recurrent rate. High recurrence (80%) was documented at the distal radius. In our series, recurrent rate at this site is 15.8% (3/19 cases) and is lower than that at other locations (30.4%, 59/194 cases, $\chi^2$ test, $P = 0.181$). Proximal tibia has also been reported as a frequent site but our data fail to confirm it (34.1%, 15/44 cases; $\chi^2$ test comparing to other location, $P = 0.414$).

The initial surgical operation was considered a significant clinical determinant of outcomes. Prognosis after initial curettage even when combined with adjuvant agents was less favorable than that following resection. Using univariate analysis, our data support reports about outcomes related to the initial surgical method but multivariate analysis does not confirm our univariate analytical results (significant trend level, $P = 0.053$). Interestingly, initial surgery in between 2006–2017 increases risk, comparing to that in between 1989–2005, but not significantly. Because rate of curettage as initial surgery is not significantly different between both periods ($\chi^2$ test, $P = 0.918$), further detailed analysis should be done.

Clinical grading systems including radiological evaluation, such as Campanacci grading and Enneking staging, are reported to be unreliable for predicting GCTB outcome. Image analysis alluded to several risk factors, such as tumor size, soft tissue extension, cortical destruction and pathological fracture. However, these features are also controversial for predicting local recurrence.

Denosumab, a RANK ligand inhibitor, is frequently used now in the treatment of GCTB, especially for unresectable tumors. Favorable outcome following its use have been reported but some recent studies reported otherwise. By multivariate analysis, our study shows that denosumab therapy increases the risk for local recurrence as a significant trend level ($P = 0.053$). Our series includes only ten patients receiving Denosumab, and we did not analyze the details of its administration, such as dose or duration.

Histological grading systems have been advocated, but none have been significantly helpful in forecasting outcomes. Mitotic count and Ki67 index have also been unreliable indicators. Dahlin et al. concluded that no histological features predicted recurrence. However, we find four significant factors useful for predicting local recurrence: mitotic count, vascular invasion, stromal hemorrhage, and ischemic necrosis. The first two gauge proliferation or local aggression and the latter two assess degenerative changes in the tumor. Vascular invasion has not been reported as a risk of pulmonary metastasis, but successfully predicts local recurrence in this study.

We did not find prognostic value for histone 3.3 G34W immunostaining. The majority of histone 3.3 peptide variants in GCTB occur at G34W and the minority occur at G34L, G34M, G34R, and G34V. The effects of peptide variant expression, such as invasiveness or metastatic potential are unclear. Expression of minor variants is rare. Future investigation may be useful.
In conclusion, using statistical analysis, we analyzed clinical and pathological features of GCTB in order to elucidate factors for predicting local recurrence. Significant risk factors for local recurrence are younger age, higher mitotic count, considerable vascular invasion and less extensive secondary changes in tumor itself (stromal hemorrhage and ischemic necrosis). Initial surgical curettage is a significant risk factor by univariate analysis but not by multivariate analysis. Other parameters were not reliable for predicting local recurrence, including gender, skeletal location, denosumab administration, osteoid/bone formation, pleomorphic cells, secondary aneurysmal bone cyst, foamy cell infiltration, storiform pattern, extramedullary extension, ossified rim at extramedullary mass, permissive growth pattern and histone 3.3 G34W immunopositivity. Based on our results, we recommend incorporating information about the above-mentioned risk factors in GCTB pathology reports. GCTB is categorized as intermediate tumor, showing metastasis in less than 2% of cases. Determining definite prognosis for GCTB awaits genomic information available in the future.

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CONFLICT OF INTERESTS
None declared.

AUTHOR CONTRIBUTIONS
EK, HO, MM, SN and YN designed the study, and drafted the manuscript. EK, MM, SN, YH, HH, YK and TI participated in pathology data analysis including IHC. HO, TS, NN, ST, JT, SK, MH and MA participated in clinical data analysis. EK and YM performed statistical analysis. YN helped to draft the manuscript.

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