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Clinical outcome of primary giant cell tumor of bone after curettage with or without perioperative denosumab in Japan: from a questionnaire for JCOG 1610 study

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Abstract

Background: Giant cell tumor of bone (GCTB) is an intermediate tumor known to be locally aggressive, but rarely metastasizing. To plan a prospective study of GCTB, we performed a questionnaire survey for institutions participating in the Bone and Soft Tissue Tumor Study Group (BSTTSG) in the Japan Clinical Oncology Group (JCOG) in 2015.

Methods: We reviewed 158 consecutive patients with primary GCTB treated with curettage without perioperative denosumab from 2008 to 2010 in Japan. We investigated local and distant recurrence rates after definitive curettage. We also investigated the recurrence rate after treatment with preoperative and/or postoperative denosumab with curettage in recent years. There were 40 patients treated with perioperative denosumab, and the factors affecting recurrence in them were investigated.

Results: Answers were available from 24 of 30 institutions (80.0%) participating in JCOG BSTTSG. Thirty (19.0%) and 4 (2.5%) of 158 patients developed local and distant recurrence after curettage without perioperative denosumab from 2008 to 2010, respectively. Campanacci grade and embolization before surgery were significantly associated with increasing incidence of local recurrence after curettage (p = 0.034 and p = 0.022, respectively). In patients treated with perioperative denosumab, 120 mg denosumab was administered subcutaneously for a median 6 (2–41) and 6 (1–14) times in preoperative and postoperative settings, respectively. The recurrence rates were 6 of 21 (28.6%), 2 of 9 (22.2%), and 0 of 10 (0.0%) in the preoperative, postoperative, and both pre- and postoperative denosumab treatment groups, respectively. With all of the preoperative treatments, administration exceeding five times was significantly associated with a decreased incidence of local recurrence after curettage (p < 0.001).

Conclusion: The recurrence rate of GCTB was still high after curettage, especially in Campanacci grade III, and improvements in the therapeutic strategy are needed in this cohort. There is a possibility that a sufficient dose of preoperative denosumab can reduce recurrence after curettage. Recently, we have started a clinical trial, JCOG1610, to investigate the efficacy of preoperative denosumab in patients who can be treated with curettage in GCTB.

Keywords: Giant cell tumor of bone, Outcome, Denosumab, Japan

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Background
Giant cell tumor of bone (GCTB) is an intermediate tumor known to be locally aggressive, but rarely metastasizing in the WHO classification [1]. GCTB possibly originates from the metaphyseal region [2], and accounts for 4–5% of all skeletal neoplasms in Japan. Local and distant recurrence rates were reported in 24.8–30.8% [3–6] and 2% [7, 8] of the patients after curettage, respectively. To reduce local recurrence and preserve the adjacent joint, adjuvant treatments such as high-speed burr [3], phenol [5, 9], ethanol, liquid nitrogen [5], and polymethyl methacrylate (PMMA) [3, 5, 9] have been reported. Even though there were some reports of GCTB in Japan [7, 10, 11], the recent clinical results of GCTB after curettage in multiple institutions in Japan have not been well documented.

Denosumab is a fully human monoclonal antibody that inhibits the receptor activator of NF-κB (RANK) ligand (RANKL) and then interrupts RANK-RANKL interactions. In GCTB, the stromal cells and osteoclast-like giant cells express RANKL and RANK, respectively, and the RANK-RANKL interaction is considered to be necessary for the differentiation and activation of osteoclasts [12]. Therefore, the RANK-RANKL interaction has a critical role for bone destruction in GCTB, and dramatic change was observed after treatment of denosumab in GCTB. Multinucleated osteoclast-like giant cells and stromal cells were decreased after denosumab treatment for GCTB [13]. A recent phase 2 study demonstrated the effects of denosumab for patients with unresectable GCTB and salvageable GCTB whose surgery was associated with severe morbidity [14]. Denosumab was accepted for health insurance coverage in Japan in 2014. However, the role of denosumab in patients with GCTB who can be treated by curettage has not been well defined.

We performed a questionnaire survey for institutions participating in the BSTTSG in JCOG in April and June 2015. This questionnaire survey was performed for planning a clinical trial of JCOG 1610 (UMIN000029451), a randomized phase III study of preoperative denosumab with curettage for GCTB. We retrospectively reviewed clinical records and filled out the questionnaire. The questionnaire included standard treatments (e.g., local adjuvant, reconstruction) of curettage for GCTB in each institution, details (e.g., number of extremities, Campanacci grade, pathological fracture at presentation, and embolization before surgery) of GCTB treated with curettage from 2008 to 2010, and clinical results (e.g., number of local recurrences, distant recurrences, and death) after the curettage, and details (e.g., sites, Campanacci grade, pathological fracture at presentation, and embolization before surgery) of the patients with local recurrence. We also asked about perioperative use of denosumab for GCTB. The questionnaire included the indications of denosumab for GCTB in each institution, the number of patients treated with preoperative, postoperative, and both pre- and postoperative denosumab, respectively, number of times of perioperative denosumab administration, and clinical results of local recurrence after the perioperative denosumab with curettage. This study was approved by the ethics committee of Nagoya University Graduate School and School of Medicine (Nagoya, Japan) and a waiver of informed consent was provided.

Statistics
A chi-square test was used to analyze the correlation of various clinical factors with recurrence. Clinical factors such as sites (extremity, trunk), Campanacci grade (I, II, III), pathological fracture at presentation (yes, no), timing of denosumab (preoperative only vs postoperative only, both preoperative and postoperative vs preoperative or postoperative, preoperative only vs both preoperative and postoperative, postoperative only vs both preoperative and postoperative), and number of times of denosumab administration (5>, 5≤) were analyzed as related to the frequency of recurrence. p values of <0.05 were considered significant. Statistical analysis was done using IBM SPSS Statistics 24.0 software (IBM, Armonk, NY, USA).

Results
Responses to the questionnaire were available from 24 of 30 institutions (80.0%) participating to JCOG BSTTSG. Standard treatments of curettage for GCTB in the 24 institutions are summarized in Table 1. As a local adjuvant
therapy, high-speed burr was used after curettage in 22 of 24 (92%) institutions followed by ethanol (8 of 24 institutions, 33%), liquid nitrogen (6 of 24 institutions, 25%), and phenol (3 of 24 institutions, 13%). Autologous bone graft and polymethyl methacrylate (PMMA) were used for reconstruction after curettage in 18 (75%) and 17 (71%) of 24 institutions, respectively. Characteristics of the patients with GCTB were summarized in Table 2. Primary tumor sites were in an extremity in 151 of 158 (96%) patients and trunk in 7 of 158 (4%). Sixteen of 158 (10%) evaluated as Campanacci grade I, 97 of 158 (61%) as Campanacci grade II, and 45 of 158 (29%) as Campanacci grade III.

Thirty of 158 (19.0%) developed local recurrence, and 4 of 158 (2.5%) developed distant recurrence after curettage without perioperative denosumab. In extremities, 29 of 151 (19.2%) developed local recurrence, and 4 of 151 (2.6%) developed distant recurrence after curettage. There were no deaths after curettage. Campanacci grade and embolization before surgery were significantly associated with an increased incidence of local recurrence after curettage ($p = 0.034$ and $p = 0.022$, respectively) (Table 3). Demographics of local recurrent patients after curettage for GCTB were summarized in Table 4. Local recurrence occurred in 1 of 16 (6.2%) in Campanacci grade I, 15 of 97 (15.5%) in Campanacci grade II, and 45 of 45 (31.1%) in Campanacci grade III. Median time to local recurrence was 15.5 months (5–69 months) after curettage, and joint preservation was achieved in 26 of 30 patients (86.7%).

The indications of denosumab for GCTB at the 24 institutions are summarized in Table 5. As a general policy, denosumab was used perioperatively at 6 of 24 (25%) institutions. Actually, 40 patients were treated with perioperative denosumab in 16 institutions. The number of GCTB patients treated with perioperative denosumab and that of the institutions where they were treated were listed in Table 6. Denosumab was administered subcutaneously

### Table 1 Standard treatments with curettage for GCTB in 24 institutions

| Treatments                  | No. of institutions (%) |
|-----------------------------|-------------------------|
| **Local adjuvants**         |                         |
| High-speed burr             | 22 (92%)                |
| Ethanol                     | 8 (33%)                 |
| Liquid nitrogen             | 6 (25%)                 |
| Phenol                      | 3 (13%)                 |
| **Reconstruction after curettage** |                   |
| Autologous bone graft       | 18 (75%)                |
| PMMA$^b$                    | 17 (71%)                |
| $\beta$-TCP$^c$             | 11 (46%)                |
| Hydroxyapatite              | 10 (42%)                |
| Allogeneic bone graft       | 2 (8%)                  |

$^a$GCTB giant cell tumor of bone

$^b$PMMA, polymethyl methacrylate

$^c$$\beta$-TCP, $\beta$ tricalcium phosphate; some of the replies by responded institutions are overlapped

### Table 2 Characteristics of patients of GCTB treated with curettage from 2008 to 2010

| Characteristics                                      | No. of patients (%) |
|------------------------------------------------------|---------------------|
| **Primary tumor site**                               |                     |
| Extremity                                            | 151 (96%)           |
| Trunk                                                | 7 (4%)              |
| **Campanacci grade**                                |                     |
| Grade I                                              | 16 (10%)            |
| Grade II                                             | 97 (61%)            |
| Grade III                                            | 45 (29%)            |
| **Pathological fracture at presentation**            |                     |
| Yes                                                  | 26 (16%)            |
| No                                                   | 132 (84%)           |
| **Do you use denosumab for this case now?**          |                     |
| Yes                                                  | 83 (52%)            |
| No                                                   | 75 (48%)            |
| **Embolization before surgery**                       |                     |
| Yes                                                  | 8 (5%)              |
| No                                                   | 150 (95%)           |

$^a$GCTB, giant cell tumor of bone

### Table 3 Univariate analysis of local recurrence in patients with GCTB treated with curettage from 2008 to 2010 ($n = 158$)

| Clinical factors                                      | No. of local recurrence (%) | Univariate analysis $p$ value$^b$ |
|-------------------------------------------------------|-----------------------------|----------------------------------|
| **Site**                                              |                             |                                  |
| Extremity                                             | 29/151 (19.2%)              | $p = 0.746$                      |
| Trunk                                                 | 1/7 (14.3%)                 |                                  |
| **Campanacci grade**                                 |                             |                                  |
| Grade I                                               | 1/16 (6.3%)                 | $p = 0.034$                      |
| Grade II                                              | 15/97 (15.5%)               |                                  |
| Grade III                                             | 14/45 (31.1%)               |                                  |
| **Pathological fracture at presentation**             |                             |                                  |
| Yes                                                   | 5/26 (16.7%)                | $p = 0.972$                      |
| No                                                    | 25/132 (18.9%)              |                                  |
| **Do you use denosumab for this case now?**           |                             |                                  |
| Yes                                                   | 15/83 (18.1%)               | $p = 0.758$                      |
| No                                                    | 15/75 (20.0%)               |                                  |
| **Embolization before surgery**                       |                             |                                  |
| Yes                                                   | 4/8 (50%)                   | $p = 0.022$                      |
| No                                                    | 26/150 (17.3%)              |                                  |

$^a$GCTB, giant cell tumor of bone

$^b$Chi-square test
at 120 mg, but the dosing interval was not included in the questionnaire. Median number of times of denosumab administration were 6 (2–41) and 6 (1–14) in the preoperative and postoperative settings, respectively. The local recurrences were observed in 6 of 21 (28.6%), 2 of 9 (22.2%), and 0 of 10 (0.0%) patients treated with the preoperative, postoperative, and both preoperative and postoperative denosumab, respectively. In 31 patients treated with any preoperative denosumab, administration exceeding 5 times was significantly associated with a decreased incidence of local recurrence after curettage \( (p < 0.001) \) (Table 7). Question for toxicity or side effects during perioperative denosumab were not included in the questionnaire survey.

Table 4 Characteristics of local recurrent patients after curettage for GCTB* from 2008 to 2010

| Sites          | Campanacci grade | Pathological fracture at presentation | Time to recurrence (months) | Final joint preservation | Embolization before curettage |
|----------------|------------------|----------------------------------------|----------------------------|--------------------------|-------------------------------|
| Tibia          | II               | No                                     | 25                         | Possible                 | No                            |
| Femur          | II               | No                                     | 60                         | Possible                 | Yes                           |
| Metatarsal bone| II               | No                                     | 60                         | Impossible               | Yes                           |
| Femur          | III              | No                                     | 6                          | Impossible               | No                            |
| Tibia          | III              | No                                     | 36                         | Possible                 | Yes                           |
| Tibia          | II               | No                                     | 27                         | Possible                 | No                            |
| Fibula         | II               | No                                     | 6                          | Possible                 | No                            |
| Femur          | III              | No                                     | 11                         | Possible                 | No                            |
| Femur          | II               | No                                     | 28                         | Possible                 | No                            |
| Ulna           | III              | No                                     | 6                          | Possible                 | No                            |
| Femur          | II               | No                                     | 9                          | Possible                 | No                            |
| Tibia          | II               | No                                     | 21                         | Possible                 | No                            |
| Femur          | II               | No                                     | 24                         | Impossible               | No                            |
| Femur          | III              | No                                     | 6                          | Possible                 | No                            |
| Radius         | II               | No                                     | 6                          | Impossible               | No                            |
| Tibia          | III              | Yes                                    | 24                         | Possible                 | Yes                           |
| Tibia          | III              | Yes                                    | 14                         | Possible                 | No                            |
| Fibula         | II               | No                                     | 35                         | Possible                 | No                            |
| Femur          | III              | Yes                                    | 21                         | Possible                 | No                            |
| Lumbar spine   | III              | No                                     | 60                         | Not available            | No                            |
| Femur          | II               | No                                     | 12                         | Possible                 | No                            |
| Femur          | III              | Yes                                    | 5                          | Possible                 | No                            |
| Femur          | II               | No                                     | 6                          | Possible                 | No                            |
| Talus          | II               | No                                     | 12                         | Possible                 | No                            |
| Femur          | III              | Yes                                    | 30                         | Possible                 | No                            |
| Femur          | III              | No                                     | 6                          | Possible                 | No                            |
| Femur          | III              | No                                     | 22                         | Possible                 | No                            |
| Femur          | III              | No                                     | 7                          | Possible                 | No                            |
| Femur          | II               | No                                     | 17                         | Possible                 | No                            |
| Femur          | I                | No                                     | 7                          | Possible                 | No                            |

*GCTB, giant cell tumor of bone

Table 5 Indication of denosumab for GCTB* in 24 institutions

| Indications of denosumab                           | No. of institutions (%) |
|----------------------------------------------------|-------------------------|
| Unresectable                                       | 21 (88%)                |
| Difficult to joint preservation                    | 17 (71%)                |
| Expanding to soft tissue                           | 11 (46%)                |
| Adjusting the time of operation                    | 7 (29%)                 |
| Perioperative use with curettage                   | 6 (25%)                 |
| No experience of denosumab use                     | 3 (13%)                 |

*GCTB, giant cell tumor of bone; some of the replies by responded institutions are overlapped
Timing of perioperative denosumab & No. of patients & No. of institutions 

| Timing of perioperative denosumab | No. of patients (%) | No. of institutions (%) |
|----------------------------------|---------------------|-------------------------|
| Preoperative only                | 21 (53%)            | 10 (63%)                |
| Postoperative only               | 9 (23%)             | 5 (31%)                 |
| Both pre- and postoperative      | 10 (25%)            | 5 (31%)                 |
| Total                            | 40                  | 16                      |

*aGCTB, giant cell tumor of bone
*Some institutions performed denosumab at different timing

Discussion

To plan a clinical trial JCOG 1610, a randomized phase III study of preoperative denosumab with curettage for GCTB, we conducted a questionnaire survey to comprehend the historical clinical results after curettage of GCTB without perioperative denosumab. Although the clinical outcomes after curettage of GCTB have been reported sporadically in Japan [7, 10, 11], the more recent clinical results of GCTB after curettage in multiple institutions in Japan are not as clear. To determine the recent perioperative use in Japan, we also reviewed patients with GCTB treated with curettage and perioperative denosumab. Even though denosumab was accepted for health insurance coverage in Japan in 2014, the risk/benefit ratio of denosumab when used for patients with GCTB who are treatable by curettage is not well defined.

There are some limitations in our study. First, because of its questionnaire format, we did not have data regarding the follow-up period after curettage. We investigated GCTB patients treated from 2008 to 2010 and performed this questionnaire survey in 2015, meaning that the follow-up period can be considered adequate given that most recurrences in GCTB occur within 5 years [3–6] and recurrent GCTB is usually treated at the same institution where the first surgery was performed. Second, there was a lack of important data such as size of tumor, detailed sites, and Campanacci grade of GCTB treated with perioperative denosumab, which could act as confounding factors. Because our study is a questionnaire survey, we could not conduct an additional survey due to unlinkable anonymizing of our data. Third, we could not perform multivariate analysis because of the small number of recurrences and lack of information regarding other important clinical factors. Finally, we could not determine whether the patients treated with preoperative denosumab were all suitable for curettage from the time of their initial consultation.

As a local adjuvant therapy, a high-speed burr was used after curettage in 92% of institutions followed by ethanol (33%), liquid nitrogen (25%), and phenol (13%) in our study. Clinical results of these local adjuvant therapies have been reported [3, 5, 9], but it is difficult to determine the advantage of each treatment. Generally, the high-speed burr is easier to use than drug therapies such as ethanol, liquid nitrogen, and phenol, accounting for its extensive use in Japan.

In our study, autologous bone graft and PMMA were used for reconstruction after curettage in 75% and 71% of institutions, respectively. Some reports demonstrated the clinical benefit of PMMA for decreasing local recurrence after curettage of GCTB [3, 4, 6, 9]. Autologous bone graft is widely used in Japan because the lack of a bone bank precludes routine use of allogenic bone.

In our study, the local recurrence rate after curettage was 19.0%. Previous reports showed local recurrence of GCTB in 24.8–30.8% after curettage [3-6], and so our local recurrence rate is slightly better than that documented in these previous reports. Past reports have shown some clinical factors affecting local recurrence such as tumor extension, surgical margin, local adjuvant therapy, Campanacci grade, use of PMMA, and soft tissue progression on multivariate analyses [4, 5, 9]. In our study, Campanacci grade was well balanced similar to previous studies [9, 15], and we ascribe the better local recurrence rate achieved in our study to the wide use of

Table 6 No. of patients and institutions treated with perioperative denosumab for GCTB

Table 7 Univariate analysis of local recurrence in patients treated with perioperative denosumab and curettage for GCTB

Comparison of factors & No. of local recurrence (%) & Univariate analysis p value

All patients (n = 40)

Timing of denosumab

Preoperative only & 6/21 (28.6%) & p = 0.719

Postoperative only & 2/9 (22.2%) &

Timing of denosumab

Both pre- and postoperative & 0/10 (0.0%) & p = 0.068

Pre- or postoperative only & 8/30 (26.7%) &

Preoperative (n = 31)

Times of denosumab administration

8> & 5/7 (71.4%) & p < 0.001

5≤ & 1/24 (4.2%) &

Timing of denosumab

Preoperative only & 6/21 (28.6%) & p = 0.060

Both pre- and postoperative & 0/10 (0.0%) &

Postoperative (n = 19)

Times of denosumab administration

8> & 0/7 (0.0%) & p = 0.253

5≤ & 2/12 (16.7%) &

Embolization before surgery

Postoperative only & 2/9 (22.2%) & p = 0.115

Both pre- and postoperative & 0/10 (0.0%) &

*aGCTB, giant cell tumor of bone
*Chi-square test
local adjuvant treatments as well as PMMA in many institutions.

In our study, Campanacci grade was significantly associated with increasing incidence of local recurrence after curettage, and this result was similar to that noted in previous studies [4]. Embolization before surgery was also significantly associated with the increasing incidence of local recurrence after curettage, but it was difficult to interpret. Since the embolization is usually used for patients with GCTB which is large and expected bleeding, there was a possibility that these factors affected the result. However, in the present study, one of the recurrent cases after embolization had GCTB in metatarsal bone (Table 4). Our study included only a small number of cases of GCTB in the trunk and a previous report showed a high local recurrence rate of 43.3% in axial cases after curettage [4]. However, there was no difference in the local recurrence rate between location in the trunk (1 of 7 patients, 14.3%) and extremity (29 of 151 patients, 19.2%) in our study. There was no significant relation between pathological fracture at first visit and local recurrence in our study. A past report also could not demonstrate an effect of pathological fracture on local recurrence in a meta-analysis [16].

Our study included no patients after recurrence, and our analysis was limited to primary tumors. Distant recurrence rate was 2.6% after curettage in our study, and this result was similar to that noted in previous studies [7, 8].

In our study, 16 of 24 (67%) institutions actually performed perioperative use of denosumab with curettage, and the recurrence rates were 6 of 21 (28.6%), 2 of 9 (22.2%), and 0 of 10 (0.0%) with preoperative, postoperative, and both pre- and postoperative treatments with curettage, respectively. One study on the perioperative use of denosumab for GCTB with curettage demonstrated local recurrence in 17 of 116 patients (15%) with a median follow-up period of 13.0 months [19]. However, the study included patients with unresectable GCTB and salvageable GCTB whose surgery was associated with severe morbidity, and the effect of denosumab for patients with GCTB who can be treated by curettage at the first visit was not clear. Our study may have also included some patients who could not be treated by curettage at first, but we could not identify those patients due to the questionnaire format used.

Median numbers of administration times of denosumab were 6 (2–41) and 6 (1–14) in the preoperative and postoperative settings, respectively in our study. Some reports demonstrated histopathological changes after 6 months treatment with denosumab [20, 21], but 6 months are thought to be too long to use it as a post- and/or preoperative treatment in patients with GCTB which can be treated by curettage. In our study, more than five administration times was significantly associated with a decreased incidence of local recurrence after curettage in 31 patients treated with preoperative or both pre- and postoperative denosumab, meaning that a sufficiently high dose of preoperative denosumab can suppress local recurrence after curettage. When used as a running dose, five times administration of denosumab takes 3 months. This relatively short administration period is associated with major benefits, both economic and social, for patients, and this dose is specified in JCOG1610.

The clinical use of perioperative denosumab is complicated by various issues such as economic problem, side effects, and pregnancy. The cost of one-shot denosumab (120 mg) for GCTB is 46,685 yen (approximately 420 dollar) in Japan as of October 2017. In the previous phase 2 trial of GCTB, denosumab caused diverse side effects such as arthralgia (20%), headache (18%), nausea (17%), fatigue (16%), back pain (15%), extremity pain (15%), hypocalcemia (5%), and osteonecrosis of jaw (1%) of any grade [14]. The use of denosumab for pregnant women should be avoided because it was reported to increase postnatal mortality, decreased body weight gain, and decreased growth development in a study of infants exposed in utero in cynomolgus monkeys [22]. This may affect the clinical use of denosumab for premenopausal women. In addition, there is a report that denosumab treatment in postmenopausal women with osteoporosis did not interfere with fracture healing [23], but the effects of denosumab on pathological fracture healing and final joint preservation have not been well understood in GCTB patients. Malignant transformation occurs in less than 1% of GCTB [1], and recently, malignant transformation was reported after treatment with denosumab [24] and requires particular caution. In addition, recent study showed a higher rate of recurrence in the GCTB treated with denosumab and curettage compared to historical control without denosumab in retrospective study [25]. For these reasons, perioperative treatment of denosumab should not be done unless an advantage is considered or proved in GCTB which can be treated by curettage.

At present, we have started a clinical trial, JCOG1610 (UMIN000029451), to investigate the efficacy of preoperative denosumab in patients with GCTB which can be treated with curettage. The primary aim of JCOG1610 is to confirm the effects of preoperative denosumab on recurrence after curettage. A previous report demonstrated that proliferation of stromal cells cultured from clinical specimens following denosumab treatment was approximately 50% slower than that of specimens from untreated patients [20]. Even though denosumab did not completely
prevent proliferation of stromal cells which have been considered as genuine tumor cells [20], there is a possibility that preoperative denosumab may decrease local and distant recurrences after the curettage of the tumor stromal cells biologically suppressed by denosumab. Secondary endpoints of JCOG1610 include overall survival, joint-preserved survival, local relapse-free survival, metastasis-free survival, adverse events, serious adverse events, surgical and postoperative complications, and discontinuation of denosumab. Systemic denosumab treatment can affect joint-preserved survival, and both local and distant recurrence.

Conclusions
In conclusion, the recurrence rate of GCTB after curettage was 19.0% in Japan and especially high in Campagnacci grade III; therefore, improvements in the therapeutic strategy are needed in this cohort. There is a possibility that a sufficient dose of preoperative denosumab can reduce recurrence after curettage. Recently, we have started JCOG1610 to investigate the efficacy of preoperative denosumab in patients with GCTB which can be treated with curettage.

Abbreviations
BSTTSG: Bone and Soft Tissue Tumor Study Group; GCTB: Giant cell tumor of bone; JCOG: Japan clinical oncology group; PMMA: Polymethyl methacrylate; RANK: Receptor activator of NF-κB; RANKL: Receptor activator of NF-κB ligand

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Availability of data and materials
The datasets supporting the conclusions of the article are included within the article.

Authors’ contributions
HU was involved in the conception and design of the study. TY, SM, TT, KA, MW, AT, NN, YM, AK, TK, TK, ME, HH, HH, ST, YN, TA, TM, MT, AN, HY, KS, MK, and KH were responsible in the acquisition of data and HU in the analysis of data. HU drafted the article, and all authors edited and revised it for important intellectual content. HU, KT, HY, YI, and TO take responsibility for the integrity of the work as a whole, from inception to finished article. All authors approved the final version to be published.

Ethics approval and consent to participate
This study was approved by the ethics committee of Nagoya University Graduate School and School of Medicine (Nagoya, Japan) and a waiver of informed consent was provided.

Consent for publication
Not applicable.

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