International Orthopaedics
https://doi.org/10.1007/s00264-022-05613-9

ORIGINAL PAPER

Outcome of re-operation for local recurrence following pre-operative denosumab administration and curettage for giant cell tumour of bone with difficult joint preservation

Shinji Tsukamoto[1] · Suraj Hindiskere[2,3] · Kanya Honoki[1] · Andreas F. Mavrogenis[4] · Yasuhito Tanaka[1] · Pramod S. Chinder[2,3] · Davide Maria Donati[5] · Costantino Errani[5]

Received: 28 July 2022 / Accepted: 13 October 2022

Abstract

Purpose Denosumab enables joint-sparing surgery (curettage) and surgical downstaging in patients with giant cell tumour of bone (GCTB), where joint preservation is not possible. However, denosumab treatment causes osteosclerosis of the lesion, making it difficult to curet the lesion, leaving the tumour behind, and increasing the local recurrence rate. We performed a three-centre retrospective study to investigate the postoperative local re-recurrence rate, joint preservation status, and functional outcomes of locally recurrent lesions after preoperative denosumab treatment and curettage in patients with difficult joint preservation.

Methods We included 38 of 142 patients with primary GCTB of the extremities who underwent preoperative denosumab and curettage between 2009 and 2021 with local recurrence. Preoperative denosumab was indicated in patients with minimal residual periarticular and subchondral bones, large extraosseous lesions (Campanacci stage 3), and pathological fractures that made joint preservation difficult.

Results Local re-recurrence occurred in 6 (15.8%) of the 38 patients. In 29 patients who underwent re-curettage, local re-recurrence occurred in six patients (20.7%); however, in nine patients who underwent en bloc resection, no local re-recurrence was observed. The joint preservation rate was 63.2% (24 of 38 patients), with a median Musculoskeletal Tumor Society score of 28 (interquartile range: 26.8–29.0). The median follow-up period after surgery for local recurrence was 63.5 months (interquartile range: 42.5–82.4).

Conclusion Since the local re-recurrence rate after re-curettage for local recurrence was low, and the joint preservation rate and affected limb function were good, preoperative denosumab administration may be considered in patients who require downstaging to maintain good limb function (joint preservation).

Keywords Giant cell tumour of bone · Curettage · Denosumab · Local recurrence · Joint preservation · MSTS score

Introduction

Giant cell tumour of bone (GCTB) is an intermediate-grade primary bone tumour [1]. The main treatment is surgery, with curettage providing joint preservation and good post-operative function but with a high local recurrence rate [2, 3]. En bloc resection followed by reconstruction with a prosthesis or allograft reduces the local recurrence rate but results in poor post-operative function [2, 3]. Curettage is recommended whenever possible in GCTBs to maintain good function of the affected extremity [2, 3]. The re-recurrence rate after re-curettage for recurrent GCTBs has been reported to be 18–36% [4–9]. Therefore, it is recommended that recurrent GCTBs should be treated with curettage rather than en bloc resection [4–9].

Following reports of its efficacy and safety, denosumab, a fully human monoclonal antibody that inhibits receptor activator of the nuclear factor-kappa β ligand, was approved for the treatment of GCTB in 2013 by the US Food and Drug Administration [10]. It was also reported that denosumab has the effect of switching to less invasive surgery, allowing joint-sparing surgery "curettage" in patients for whom joint preservation is not

✉ Shinji Tsukamoto
shinji104@mail.goo.ne.jp

Extended author information available on the last page of the article

Published online: 25 October 2022

possible [11]. Currently, denosumab is indicated for the treatment of unresectable GCTB or in cases of significant functional impairment after resection [10]. However, recent studies have shown that denosumab administered prior to curettage is associated with an increased rate of local recurrence [12–17]. This is because pre-operative administration of denosumab causes osteosclerosis, which makes curettage more difficult and makes it more difficult to identify the extent of the tumour, leading to some sections of the tumour being left behind and reactivation of giant cell tumour cells in the osteosclerotic lesion after discontinuation of denosumab [12, 13, 18, 19]. However, there are few reports on the course of treatment of recurrent lesions after pre-operative denosumab treatment and curettage. We performed a three-centre retrospective study to investigate post-operative local re-recurrence rates, joint preservation rates, and affected limb function of recurrent lesions after pre-operative denosumab treatment and curettage in patients with minimal residual periarticular and subchondral bone, large extraskeletal lesions, and pathologic fractures that precluded joint preservation. We hypothesised that local recurrence after pre-operative denosumab administration and curettage would be difficult to re-operate, have a high re-recurrence rate, and have poor functional outcomes.

Materials and methods

Of the 279 patients with histologically diagnosed GCTB of the extremities who underwent surgery at the authors' institutions between January 2009 and December 2021, 41 patients treated with en bloc resection were excluded. The remaining 238 patients underwent curettage. Patients ($n = 55$) who had not received denosumab prior to curettage were further excluded. The remaining 183 patients received pre-operative ± post-operative denosumab and curettage. Of these, we excluded one patient who developed malignant transformation, 13 patients who experienced local recurrence after initial treatment at another hospital, 22 patients with a post-operative follow-up of less than 24 months, three patients who were lost to follow-up, and two patients with insufficient data. Among the remaining 142 patients, 38 patients with local recurrence were analysed in this retrospective study (Fig. 1). From 2017, we have also investigated the mutation in histone 3.3 (H3.3) gene H3F3A using immunohistochemical and/or allele-locked nucleic acid quantitative polymerase chain reaction assays [20–22]. We retrospectively investigated 102 cases of GCTB; the H3F3 mutation was confirmed in 13 (34.2%) of the 38 patients included in this study. The following information was extracted from the medical records: sex, age, tumour location, Campanacci stage at presentation [23], lung metastasis

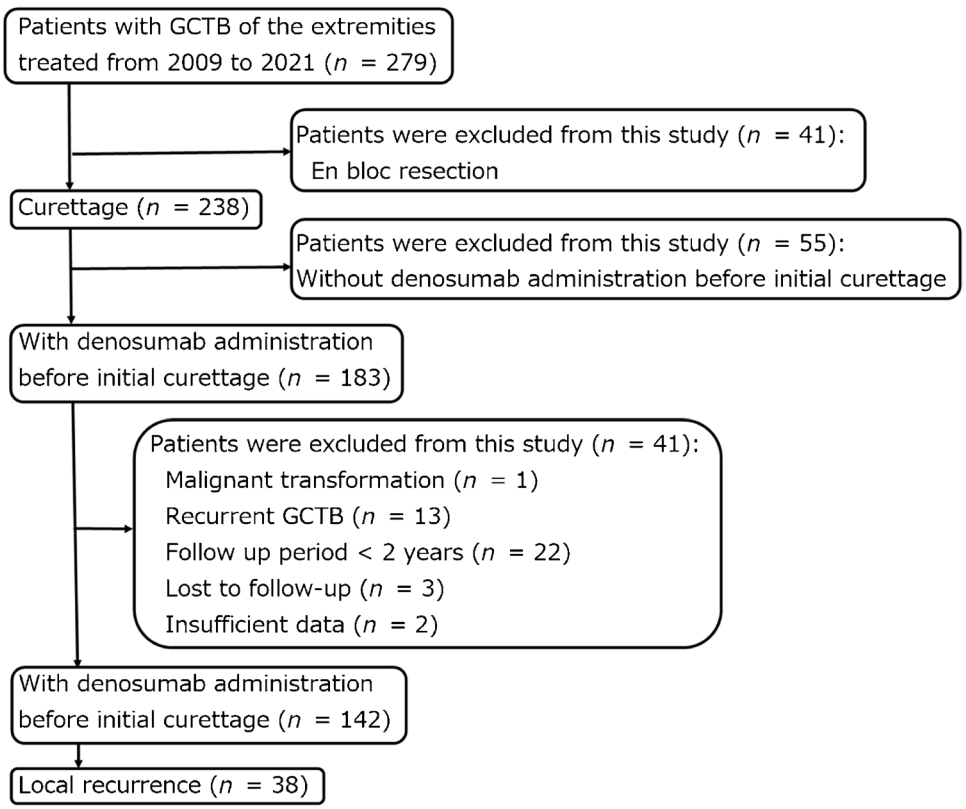

Fig. 1 Flow diagram of patients with giant cell tumour of bone of the extremity treated at three institutions between 2009 and 2021

at presentation, pathological fracture at presentation, material used to fill the bone defect at initial curettage, radiological evaluation of denosumab treatment before initial curettage (Modified inverse Choi criteria) [24], time from initial curettage to local recurrence, site of local recurrence (bone or soft tissue), surgery for local recurrence, denosumab administration prior to surgery for local recurrence, local re-recurrence, post-operative follow-up period, lung metastasis, oncological outcomes, status of joint preservation at the last follow-up, Musculoskeletal Tumor Society (MSTS) score [25], surgery-related complications, and denosumab-related complications according to the Common Terminology Criteria for Adverse Events, volume 4.03 [26] (Tables 1 and 2). The median age was 32 years (interquartile range (IQR), 26–39.5). The median time from initial curettage to local recurrence was 16.7 months (IQR, 12.8–23). Approval was obtained from the institutional review board/ethics committee of each institution.

Curettage was indicated for GCTBs with moderate cortical thinning, well-maintained bony architecture, and simple pathological fractures [27–29]. The curettage was performed through a large cortical bone window using a sharp

Table 1 Patients' characteristics

Variable ($N=38$)	No. of patients	Denosumab administration after initial curettage	
		Yes ($N=15$)	No ($N=23$)
Median age (years)	32 (IQR, 26–39.5)	35.1 (IQR, 28–43.3)	31 (IQR, 24–38)
Sex			
Male	20 (52.6%)	8 (53.3%)	12 (52.2%)
Female	18 (47.4%)	7 (46.7%)	11 (47.8%)
Site			
Distal radius	12 (31.6%)	5 (33.3%)	7 (30.4%)
Proximal femur	0	0	0
Hand and foot	4 (10.5%)	0	4 (17.4%)
Distal femur	6 (15.8%)	1 (6.7%)	5 (21.7%)
Proximal tibia	11 (28.9%)	5 (33.3%)	6 (26.1%)
Proximal humerus	4 (10.5%)	3 (20.0%)	1 (4.3%)
Others	1 (2.6%)	1 (6.7%)	0
Campanacci classification at presentation			
Stage II	19 (50.0%)	8 (53.3%)	11 (47.8%)
Stage III	19 (50.0%)	7 (46.7%)	12 (52.2%)
Lung metastases at presentation			
No	36 (94.7%)	15 (100%)	21 (91.3%)
Yes	2 (5.3%)	0	2 (8.7%)
Pathological fracture at presentation			
No	28 (73.7%)	12 (80.0%)	16 (69.6%)
Yes	10 (26.3%)	3 (20.0%)	7 (30.4%)
Cement use at initial curettage			
No	17 (44.7%)	5 (33.3%)	12 (52.2%)
Yes	21 (55.3%)	10 (66.7%)	11 (47.8%)
Median period from initial curettage to local recurrence (months)	16.7 (IQR, 12.8–23)	13.8 (IQR, 11.5–23.5)	19 (IQR, 14–23)
Site of local recurrence			
Bone	38 (100%)	15 (100%)	23 (100%)
Soft tissue	0	0	0
Surgery for local recurrence			
Curettage	29 (76.3%)	12 (80.0%)	17 (73.9%)
Resection	9 (23.7%)	3 (20.0%)	6 (26.1%)
Denosumab administration before surgery for local recurrence			
No	26 (68.4%)	12 (80.0%)	14 (60.9%)
Yes	12 (31.6%)	3 (20.0%)	9 (39.1%)

IQR interquartile range

Table 2 Patients' outcomes

Variable ($N=38$)	No. of patients	Denosumab administration after initial curettage	
		Yes ($N=15$)	No ($N=23$)
Local re-recurrence			
No	32 (84.2%)	11 (73.3%)	21 (91.3%)
Yes	6 (15.8%)	4 (26.7%)	2 (8.7%)
Lung metastases			
No	35 (92.1%)	14 (93.3%)	21 (91.3%)
Yes	3 (7.9%)	1 (6.7%)	2 (8.7%)
Median follow-up period from initial curettage (months)	84 (IQR, 56.9–98.3)	98 (IQR, 57.2–102)	81 (IQR, 56–92)
Median follow-up period from surgery for local recurrence (months)	63.5 (IQR, 42.5–82.4)	76.5 (IQR, 41–90.0)	57 (IQR, 43–71)
Oncological outcome			
NED (Local recurrence)	35 (92.1%)	14 (93.3%)	21 (91.3%)
NED (Metastasis)	1 (2.6%)	0	1 (4.3%)
AWD (Metastasis)	2 (5.3%)	1 (6.7%)	1 (4.3%)
Joint preservation			
No	14 (36.8%)	6 (40.0%)	8 (34.8%)
Yes	24 (63.2%)	9 (60.0%)	15 (65.2%)
Median MSTS score	28 (IQR, 26.8–29.0)	27 (IQR, 25–29)	28 (IQR, 27–29)
Surgery related complication			
Infection	2 (5.1%)	0	2 (8.7%)
Wrist subluxation	2 (5.1%)	0	2 (8.7%)
Denosumab related complication			
Fatigue (grade II)	1 (2.6%)	0	1 (4.3%)
Periodontal disease (grade III)	1 (2.6%)	1 (6.7%)	0

IQR interquartile range, *MSTS* Musculoskeletal Tumor Society, *NED* no evidence of disease, *AWD* alive with disease

curette and all visible regions of the tumour were removed [27–29]. Subsequently, the cavity was curetted using a high-speed burr, followed by saline washout to remove all tumour tissues [27–29]. During the initial curettage in 31 patients, phenol was applied to the cavity border with a cotton-tipped applicator and neutralised with alcohol. The tumour cavity was then filled with polymethylmethacrylate (PMMA) bone cement alone (18 patients), bone cement and bone allograft (three patients), bone allograft only (16 patients), or hydroxyapatite graft only (one patient). The subchondral region was filled with allograft bone chips when bone cement was used and when the remaining subchondral bone was thin after tumour curettage. In a patient with high fracture risk, prophylactic internal fixation was performed. Re-curettage for local recurrence was performed in 29 patients by using the same method as the initial curettage (Table 1). The tumour cavity was filled with PMMA bone cement only (24 patients), bone cement and bone allograft (one patient), bone allograft only (three patients), or hydroxyapatite grafts only (one patient). Prophylactic internal fixation was performed in one patient (2.6%) with a high fracture risk.

En bloc resection has been indicated for large tumours with soft tissue extension, pathological fractures with joint involvement, or complex fractures [28, 30]. En bloc resection for local recurrence was performed in nine patients (Table 1). Four patients who underwent en bloc resection for recurrent lesions in the bone were reconstructed using modular prostheses. Reconstruction following en bloc resection for local recurrence of the distal radius was performed by arthrodesis translocating the ipsilateral ulna as a vascularised graft in five patients [31].

Denosumab was indicated in patients with minimal residual periarticular and subchondral bones, large extraskeletal lesions (Campanacci stage 3), and pathological fractures that made joint preservation difficult. Denosumab was used to downstage tumours by causing osteosclerosis in the periarticular and subchondral bones or healing pathological fractures (Table 1). It was used relatively frequently in patients with GCTB of the distal radius (Table 1) because tumours in this region are particularly aggressive [6]. Pre-operatively, 38 patients received denosumab (120 mg) subcutaneously every week for one month, followed by monthly doses. Cumulatively, one to 11 doses (median, six doses; IQR,

2–8) were administered depending on the treating physician's recommendation for discontinuation, the occurrence of adverse events, clinical benefit, surgical planning, and clinical trial protocol (6 months). Radiological evaluation of denosumab treatment before the initial curettage (modified inverse Choi criteria) [24] showed a partial response in 34 patients and stable disease in four patients. Post-operatively, 15 patients received denosumab (120 mg) monthly at two to six doses (median, 5; IQR, 4–6) depending on the aforementioned factors (Table 1). In addition to denosumab, patients were administered calcium (500 mg/day) and vitamin D (≥ 400 IU/day) supplements. Prior to surgery for local recurrence, 12 patients received one or two doses of denosumab. After denosumab administration, re-curettage was performed in five patients, and en bloc resection was performed in seven patients.

Routine follow-up examinations were performed every four months for the first two years, every six months for the next three years, and annually thereafter. Follow-up evaluations included radiography of the tumour area and computed tomography of the chest. Local recurrence, lung metastasis, and treatment-related complications were recorded.

Statistical analysis

Local re-recurrence-free survival was defined as the interval between surgery for local recurrence and local re-recurrence or last follow-up. Local re-recurrence-free survival was evaluated using Kaplan–Meier survival analysis. Analyses were performed using JMP 14 software (SAS Institute Inc., Cary, NC, USA).

Results

Local re-recurrence occurred in 6 (15.8%) of the 38 patients included in this study. Local re-recurrence occurred in six (20.7%) of the 29 patients who underwent curettage, but not in the nine patients who underwent en bloc resection. The median time between surgery for local recurrence and local re-recurrence was 11 months (IQR, 10.8–20.0) (Table 2). Five-year local re-recurrence-free survival from surgery for local recurrence was 83.7% (95% confidence interval (CI): 68.2–92.5) (Fig. 2). Five-year local re-recurrence-free survival from surgery for local recurrence was 73.3% (95% CI: 46.7–89.6) in 15 patients who received denosumab after initial curettage and 90.7% (95% CI: 69.4–97.7) in 23 patients who did not. Curettage for local re-recurrence was performed in one patient, and the tumour cavity was filled with bone cement only. En bloc resection for local re-recurrence was performed in five patients. One patient with local re-recurrence in the distal ulna did not require reconstruction after en bloc resection. Patients who underwent en bloc resection for re-recurrent lesions within the bone underwent reconstruction using modular prostheses (three patients) and large bone allografts (one patient). None of the patients had a third local recurrence. The median follow-up period after the first curettage was 84 months (IQR, 56.9–98.3). The median follow-up period after surgery for local recurrence was 63.5 months (IQR, 42.5–82.4) (Table 2).

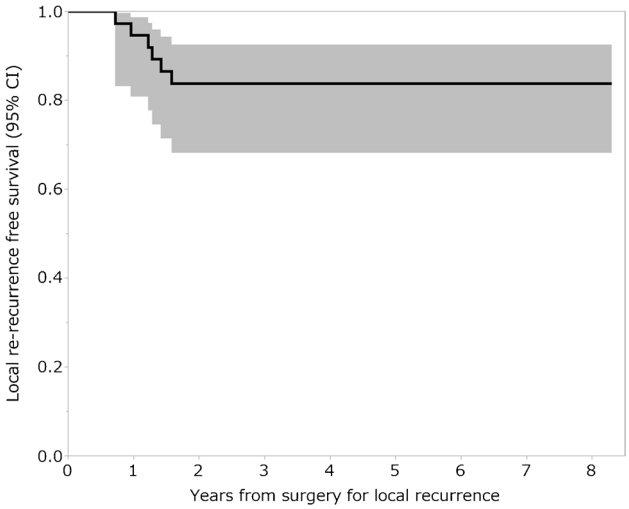

Fig. 2 Local re-recurrence-free survival rates of patients who underwent reoperation for local recurrence after preoperative denosumab administration and curettage for giant cell tumour of bone with difficult joint preservation. Shading around the curves represents the 95% confidence intervals (CI)

The joint preservation rate was 63.2% (24 of 38 patients), with a median MSTS score of 28 (IQR: 26.8–29.0) (Table 2). Surgical complications included infection in two patients (5.1%), which required debridement and antibiotics. Wrist subluxation was observed in two patients (5.1%); one patient required external fixation for two months and the other required orthosis. Two patients (5.1%) had denosumab-related complications, one of whom had periodontal disease (grade 3) and required discontinuation of denosumab. Another patient experienced fatigue (grade 2) and required postponement of denosumab treatment (Table 2).

Discussion

Denosumab can be used to downstage patients with GCTB and enable joint-sparing surgery (curettage) in patients for whom the surgery is otherwise impossible [11]. Rutkowski et al. reported that in an open-label phase II trial of denosumab in patients with GCTB, native joint preservation was 96% ($n = 24/25$) in patients with planned joint/prosthesis replacement and 86% ($n = 30/35$) in patients with planned joint resection/fusion [11]. However, subsequent studies have reported that denosumab administration before

curettage causes osteosclerosis of the lesion, making curettage difficult. Furthermore, discontinuation of denosumab reactivates the remaining tumour and increases the local recurrence rate [12, 13, 18, 19]. Since few reports exist on clinical outcomes after re-operation for recurrent lesions following pre-operative denosumab treatment and curettage, the success of this approach is unknown. In this study, denosumab treatment before initial curettage was performed for patients with minimal residual periarticular and subchondral bone, large extraskeletal lesions (Campanacci stage 3), and pathological fractures that make joint preservation difficult. After a median follow-up of 63.5 months after surgery for local recurrence, the local re-recurrence rate after re-curettage (20.7%) was low, and the joint preservation rate (63.2%) and limb function (median MSTS score, 28) were good. Although the local recurrence rate may increase after denosumab administration [12], pre-operative denosumab treatment may enable curettage in some patients for whom joint preservation is difficult. Furthermore, maximum repeated curettage after local recurrence can maintain good function of the affected limb (joint preservation) (Fig. 3).

Other recent studies have reported the local re-recurrence risk after re-operation for local recurrence following pre-operative denosumab administration and surgery. Muller et al. reported that one patient with a patellar GCTB that recurred after pre-operative denosumab and curettage underwent re-curettage with no subsequent local recurrence [32]. Rehki et al. reported that four patients with GCTB of the extremities, who had local recurrence after pre-operative denosumab and surgery, underwent re-operation and were followed up for 0–14 months after the re-operation with no subsequent local recurrence [33]. Niu et al. reported that four patients with GCTB who experienced recurrence after pre-operative denosumab and curettage underwent re-operation with no subsequent local recurrence [34].

Subsequent studies have reported the risk of local re-recurrence after re-operation for local recurrence following curettage without pre-operative denosumab administration. O'Donnel et al. found that in 15 patients with recurrent GCTB of the extremities after curettage, local re-recurrence occurred in one (20%) of the five patients who had undergone curettage, but none of the ten patients who underwent en bloc resection experienced local re-recurrence [6]. According to previous reports, the local re-recurrence rate after re-curettage for local recurrence following curettage alone without pre-operative denosumab ranged from 17.6 to 35.7% [4–9], and joint preservation rates ranged from 56.5 to 79.1% [4, 5, 7, 35]. These findings are similar to our results.

In this study, denosumab treatment was administered before the initial curettage in patients with difficult joint preservation. After a median follow-up of 63.5 months after surgery for local recurrence, the median MSTS score was 28, with a joint preservation rate of 63.2%. In a related study, Perrin et al. performed pre-operative denosumab treatment

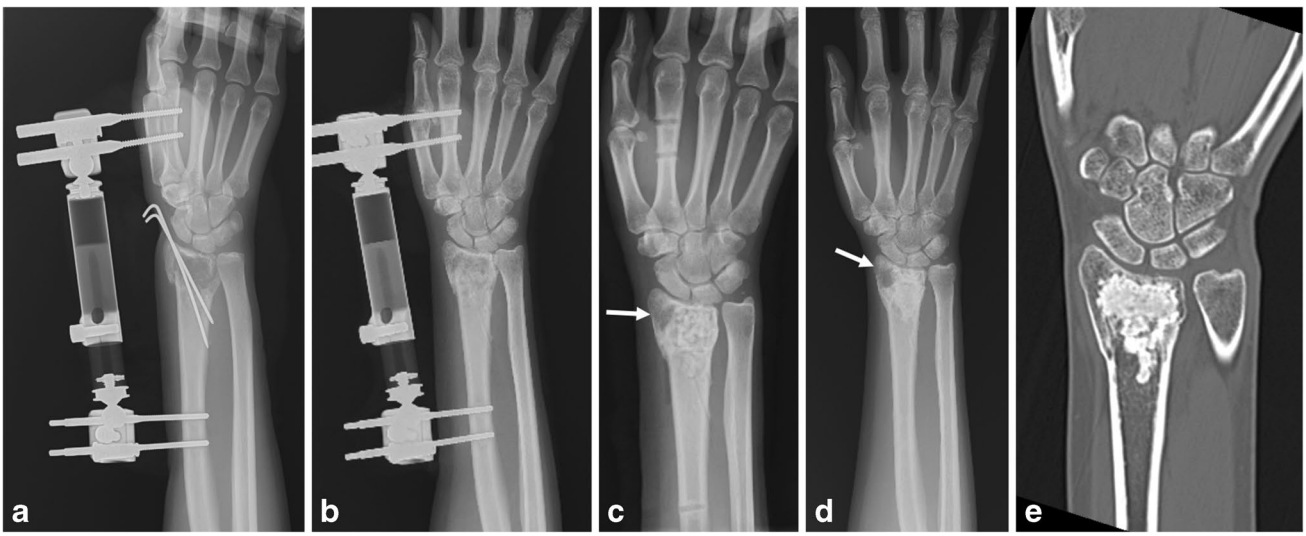

Fig. 3 A 28-year-old female patient with giant cell tumour of the bone of the distal radius. **A** Pathological fracture was found at presentation; therefore, external fixation and the Kirschner wire fixation were performed. Additionally, the subchondral bone was thin. Needle biopsy revealed a giant cell tumour of the bone. **B** Radiograph after 7 doses of pre-operative denosumab. The pathological fracture healed, and osteosclerosis was formed in and around the lesion. **C** Radiograph immediately after curettage, cryosurgery, and hydroxyapatite grafting. A typical soft tissue tumour found within a lytic defect of GCTB changed to a gritty, fibro-osseous matrix after denosumab administration, which made it difficult to determine the true extent of the tumour and the junction between the edges of the transformed tumour tissue and the normal, uninvolved bone. This led to insufficient curettage and tumour cells were left behind in this thick new bone (arrow). **D** Local recurrence was observed at the same site 14 months after surgery (arrow). **E** Thirty-eight months after re-curettage, cryosurgery, and hydroxyapatite grafting, no local recurrence was observed in computed tomography, and the joint was preserved

and curettage in 25 patients with GCTB of the extremities with minimal subchondral bone, large extraskeletal lesions, and pathological fractures, who were unlikely to have joint preservation [36]. After a median follow-up of 57 months, local recurrence occurred in 11 patients (44%), among which four patients underwent repeated curettage to preserve the joint. They observed a joint preservation rate of 37% in a group with local recurrence. The overall joint preservation rate was 92% (23 of 25 patients) [36]. Denosumab reduces the size of extraskeletal lesions and hardens bone lesions [37], allowing for joint preservation (curettage) in patients in whom joint preservation is not possible [11]. However, it has been reported that denosumab does not induce apoptosis of giant cell tumour cells [38, 39]. Denosumab-induced osteosclerosis increases the rate of local recurrence by making curettage difficult and leaving the tumour behind [12–17]. According to a systematic review, the recurrence rate was 20–100% in patients treated with pre-operative denosumab and curettage compared to 0–50% in patients treated with curettage alone [13]. In contrast, Perrin et al. found that half of the patients who received pre-operative denosumab treatment and curettage did not have the local recurrence of lesions for which joint preservation was not possible [36]. A systematic review found that the use of one or two of the following therapies, that is, high-speed burr, bone cement, or phenol adjuvant therapy, reduced the recurrence rate by 50% compared to simple curettage [40]. Local adjuvant therapy with phenol or other agents may kill tumour cells in osteosclerotic lesions formed by pre-operative denosumab administration. Even if GCTB recurs, repeated curettage and local adjuvant therapy may achieve joint preservation and maintain good function of the affected limb, even in cases wherein the joint cannot be preserved because of the small subchondral bone, large extraosseous lesion, and pathological fracture.

This study has a limitation. Only 13 (34.2%) of 38 patients were able to confirm the presence of an H3F3A mutation. However, the patients included in this study were diagnosed by an experienced pathologist specialising in bone tumours.

Conclusion

Denosumab treatment before initial curettage was performed in patients with minimal residual periarticular and subchondral bone, large extraskeletal lesions (Campanacci stage 3), and pathological fractures that made joint preservation difficult. Following re-curettage for local recurrence, the local re-recurrence and joint preservation rates were similar to the published data of patients without pre-operative denosumab treatment. Therefore, pre-operative denosumab administration may be considered in patients who require downstaging to maintain good limb function or joint preservation.

Acknowledgements The authors thank all the patients and their families.

Author contribution S. Tsukamoto: collected and analysed the data and wrote the manuscript.

S. Hindiskere: collected the data and wrote the manuscript.

K. Honoki: conceptualised the study, developed the methodology, and revised manuscript.

A. F. Mavrogenis: conceptualised the study, developed the methodology and revised the manuscript.

Y. Tanaka: conceptualised the study, developed the methodology, and revised the manuscript.

P. S. Chinder: conceptualised the study, developed the methodology, and revised the manuscript.

D. M. Donati: conceptualised the study, developed the methodology, and revised the manuscript.

C. Errani: chief supervisor, collected the data and wrote the manuscript.

Funding This work was supported by the Grant of Japan Orthopaedics and Traumatology Research Foundation (Grant number (No. 495)).

Data availability The datasets generated, analysed, or both during the present study are not publicly available because of privacy issues but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the individual Institutional Review Board (or Ethics Committee) of IRCCS Istituto Ortopedico Rizzoli, Nara Medical University, and HCG hospital.

Consent to participate Informed consent was obtained from all individual participants in IRCCS Istituto Ortopedico Rizzoli and HCG hospital, and the requirement for written consent from participants in Nara Medical University was waived, because an "opt-out" process was used and the study has the retrospective nature.

Competing interests The authors declare no competing interests.

References

1. Flanagan AM, Larousserie F, O'Donnell PG, Yoshida A (2020) Giant cell tumour of bone. In: The WHO classification of tumours editorial board. WHO classification of tumours, 5th ed.: Soft tissue and bone tumours. Lyon, IARC, pp440–446
2. Tsukamoto S, Mavrogenis AF, Kido A, Errani C (2021) Current concepts in the treatment of giant cell tumors of bone. Cancers (Basel) 13:3647. https://doi.org/10.3390/cancers13153647
3. Errani C, Tsukamoto S, Ciani G, Donati DM (2019) Present day controversies and consensus in curettage for giant cell tumor of bone. J Clin Orthop Trauma 10:1015–1020. https://doi.org/10.1016/j.jcot.2019.09.017
4. Balke M, Ahrens H, Streitbuerger A et al (2009) Treatment options for recurrent giant cell tumors of bone. J Cancer Res Clin Oncol 135:149–158. https://doi.org/10.1007/s00432-008-0427-x

5. Vult von Steyern F, Bauer HCF, Trovik C et al (2006) Treatment of local recurrences of giant cell tumour in long bones after curettage and cementing. A Scandinavian Sarcoma Group Study. J Bone Joint Surg Br 88:531–535. https://doi.org/10.1302/0301-620X.88B4.17407
6. O'Donnell RJ, Springfield DS, Motwani HK et al (1994) Recurrence of giant-cell tumors of the long bones after curettage and packing with cement. J Bone Joint Surg Am 76:1827–1833
7. Prosser GH, Baloch KG, Tillman RM, et al (2005) Does curettage without adjuvant therapy provide low recurrence rates in giant-cell tumors of bone? Clin Orthop Relat Res 211–218
8. Wan R, Zhang W, Xu J et al (2012) The outcome of surgical treatment for recurrent giant cell tumor in the appendicular skeleton. J Orthop Sci 17:464–469. https://doi.org/10.1007/s00776-012-0228-6
9. Klenke FM, Wenger DE, Inwards CY et al (2011) Recurrent giant cell tumor of long bones: analysis of surgical management. Clin Orthop Relat Res 469:1181–1187. https://doi.org/10.1007/s11999-010-1560-9
10. Chawla S, Henshaw R, Seeger L et al (2013) Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 14:901–908. https://doi.org/10.1016/S1470-2045(13)70277-8
11. Rutkowski P, Ferrari S, Grimer RJ et al (2015) Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. Ann Surg Oncol 22:2860–2868. https://doi.org/10.1245/s10434-015-4634-9
12. Errani C, Tsukamoto S, Leone G et al (2018) Denosumab may increase the risk of local recurrence in patients with giant-cell tumor of bone treated with curettage. J Bone Joint Surg Am 100:496–504. https://doi.org/10.2106/JBJS.17.00057
13. Tsukamoto S, Tanaka Y, Mavrogenis AF et al (2020) Is treatment with denosumab associated with local recurrence in patients with giant cell tumor of bone treated with curettage? a systematic review. Clin Orthop Relat Res 478:1076–1085. https://doi.org/10.1097/CORR.0000000000001074
14. Agarwal MG, Gundavda MK, Gupta R, Reddy R (2018) Does denosumab change the giant cell tumor treatment strategy? Lessons learned from early experience. Clin Orthop Relat Res 476:1773–1782. https://doi.org/10.1007/s11999.0000000000000243
15. Scoccianti G, Totti F, Scorianz M et al (2018) Preoperative denosumab with curettage and cryotherapy in giant cell tumor of bone: is there an increased risk of local recurrence? Clin Orthop Relat Res 476:1783–1790. https://doi.org/10.1007/s11999.0000000000000104
16. Yang Y, Li Y, Liu W et al (2018) A nonrandomized controlled study of sacral giant cell tumors with preoperative treatment of denosumab. Medicine (Baltimore) 97:e13139. https://doi.org/10.1097/MD.0000000000013139
17. Medellin MR, Fujiwara T, Tillman RM et al (2018) Prognostic factors for local recurrence in extremity-located giant cell tumours of bone with pathological fracture. Bone Joint J 100-B:1626–1632. https://doi.org/10.1302/0301-620X.100B12.BJJ-2018-0189.R2
18. Mak IWY, Evaniew N, Popovic S et al (2014) A translational study of the neoplastic cells of giant cell tumor of bone following neoadjuvant denosumab. J Bone Joint Surg Am 96:e127. https://doi.org/10.2106/JBJS.M.01332
19. Traub F, Singh J, Dickson BC et al (2016) Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. Eur J Cancer 59:1–12. https://doi.org/10.1016/j.ejca.2016.01.006
20. Righi A, Mancini I, Gambarotti M et al (2017) Histone 3.3 mutations in giant cell tumor and giant cell-rich sarcomas of bone. Hum Pathol 68:128–135. https://doi.org/10.1016/j.humpath.2017.08.033
21. Mancini I, Righi A, Gambarotti M et al (2017) Phenotypic and molecular differences between giant-cell tumour of soft tissue and its bone counterpart. Histopathology 71:453–460. https://doi.org/10.1111/his.13249
22. Gamberi G, Morandi L, Benini S et al (2018) Detection of H3F3A p. G35W and p.G35R in giant cell tumor of bone by allele specific locked nucleic acid quantitative PCR (ASLNAqPCR). Pathol Res Pract 214:89–94. https://doi.org/10.1016/j.prp.2017.10.023
23. Campanacci M, Baldini N, Boriani S, Sudanese A (1987) Giant-cell tumor of bone. J Bone Joint Surg Am 69:106–114
24. Choi H, Charnsangavej C, Faria SC et al (2007) Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 25:1753–1759. https://doi.org/10.1200/JCO.2006.07.3049
25 Enneking WF, Dunham W, Gebhardt MC et al (1993) A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. Clin Orthop Relat Res 286:241–246
26 Basch E, Reeve BB, Mitchell SA et al (2014) Development of the national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 106:dju244. https://doi.org/10.1093/jnci/dju244
27. Tsukamoto S, Mavrogenis AF, Tanzi P et al (2020) Curettage as first surgery for bone giant cell tumor: adequate surgery is more important than oncology training or surgical management by high volume specialized teams. Eur J Orthop Surg Traumatol 30:3–9. https://doi.org/10.1007/s00590-019-02535-y
28. Tsukamoto S, Mavrogenis AF, Tanzi P et al (2020) Denosumab for bone giant cell tumor of the distal radius. Orthopedics 43:284–291. https://doi.org/10.3928/01477447-20200721-03
29. Errani C, Tsukamoto S, Leone G et al (2017) Higher local recurrence rates after intralesional surgery for giant cell tumor of the proximal femur compared to other sites. Eur J Orthop Surg Traumatol 27:813–819. https://doi.org/10.1007/s00590-017-1983-z
30. Errani C, Ruggieri P, Asenzio MAN et al (2010) Giant cell tumor of the extremity: a review of 349 cases from a single institution. Cancer Treat Rev 36:1–7. https://doi.org/10.1016/j.ctrv.2009.09.002
31. Puri A, Gulia A, Agarwal MG, Reddy K (2010) Ulnar translocation after excision of a Campanacci grade-3 giant-cell tumour of the distal radius: an effective method of reconstruction. J Bone Joint Surg Br 92:875–879. https://doi.org/10.1302/0301-620X.92B6.23194
32. Müller DA, Beltrami G, Scoccianti G et al (2016) Risks and benefits of combining denosumab and surgery in giant cell tumor of bone-a case series. World J Surg Oncol 14:281. https://doi.org/10.1186/s12957-016-1034-y
33. Rekhi B, Verma V, Gulia A et al (2017) Clinicopathological features of a series of 27 cases of post-denosumab treated giant cell tumors of bones: a single institutional experience at a tertiary cancer referral centre, India. Pathol Oncol Res 23:157–164. https://doi.org/10.1007/s12253-016-0123-0
34. Niu X, Yang Y, Wong KC et al (2019) Giant cell tumour of the bone treated with denosumab: how has the blood supply and oncological prognosis of the tumour changed? J Orthop Translat 18:100–108. https://doi.org/10.1016/j.jot.2018.10.003
35. McGough RL, Rutledge J, Lewis VO et al (2005) Impact severity of local recurrence in giant cell tumor of bone. Clin Orthop Relat Res 438:116–122. https://doi.org/10.1097/01.blo.0000180055.76969.08

36 Perrin DL, Visgauss JD, Wilson DA et al (2021) The role of denosumab in joint preservation for patients with giant cell tumour of bone. Bone Joint J 103-B:184–191. https://doi.org/10.1302/0301-620X.103B1.BJJ-2020-0274.R1
37. Engellau J, Seeger L, Grimer R et al (2018) Assessment of denosumab treatment effects and imaging response in patients with giant cell tumor of bone. World J Surg Oncol 16:191. https://doi.org/10.1186/s12957-018-1478-3
38. Lau CPY, Huang L, Wong KC, Kumta SM (2013) Comparison of the anti-tumor effects of denosumab and zoledronic acid on the neoplastic stromal cells of giant cell tumor of bone. Connect Tissue Res 54:439–449. https://doi.org/10.3109/03008207.2013.848202
39. Shibuya I, Takami M, Miyamoto A et al (2019) In vitro study of the effects of denosumab on giant cell tumor of bone: comparison with zoledronic acid. Pathol Oncol Res 25:409–419. https://doi.org/10.1007/s12253-017-0362-8
40. Machak GN, Snetkov AI (2021) The impact of curettage technique on local control in giant cell tumour of bone. Int Orthop 45:779–789. https://doi.org/10.1007/s00264-020-04860-y

Authors and Affiliations

Shinji Tsukamoto[1] · Suraj Hindiskere[2,3] · Kanya Honoki[1] · Andreas F. Mavrogenis[4] · Yasuhito Tanaka[1] · Pramod S. Chinder[2,3] · Davide Maria Donati[5] · Costantino Errani[5]

Suraj Hindiskere
suraj.ortho@gmail.com

Kanya Honoki
kahonoki@naramed-u.ac.jp

Andreas F. Mavrogenis
afm@otenet.gr

Yasuhito Tanaka
yatanaka@naramed-u.ac.jp

Pramod S. Chinder
drpramods@gmail.com

Davide Maria Donati
davide.donati@ior.it

Costantino Errani
costantino.errani@ior.it

[1] Department of Orthopaedic Surgery, Nara Medical University, 840, Shijo-cho, Kashihara-City, Nara 634-8521, Japan

[2] Department of Musculoskeletal Oncology, HCG Hospital, No. 8, P. Kalingarao Road, Sampangiramnagar, Bangalore, Karnataka 560027, India

[3] The Yellow Ribbon, #805, 2nd floor, 9th Main, 4th Block, Jayanagar, Bangalore 560011, India

[4] First Department of Orthopaedics, School of Medicine, National and Kapodistrian University of Athens, 41 Ventouri Street, 15562 Holargos, Athens, Greece

[5] Department of Orthopaedic Oncology, IRCCS Istituto Ortopedico Rizzoli, Via Pupilli 1, 40136 Bologna, Italy