Clin Orthop Relat Res (2020) 478:2522-2533
DOI 10.1097/CORR.0000000000001285

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Selected Proceedings of the 2019 International Society of Limb Salvage Meeting (Guest Editor: John H. Healey MD)

Is a Short-course of Preoperative Denosumab as Effective as Prolonged Therapy for Giant Cell Tumor of Bone?

Suraj Hindiskere MBBS, MS (Ortho), DNB (Ortho), Costantino Errani MD, PhD, Srinath Doddarangappa MBBS, MS (Ortho), Veena Ramaswamy MBBS, MD (Pathology), Mayur Rai MBBS, MS (Ortho), Pramod S. Chinder MBBS, MS (Ortho)

Received: 21 November 2019 / Accepted: 14 April 2020 / Published online: 6 May 2020

Abstract

Background Denosumab is an inhibitor of monoclonal receptor activator of nuclear factor-κB ligand, approved to treat giant cell tumors of bone (GCTB). It is commonly used for unresectable tumors and for downstaging the tumor to perform less-morbid procedures. Although denosumab has been used extensively for GCTBs, there are no recommendations regarding the duration of therapy. The risk factors associated with local recurrence (LR) in patients receiving preoperative denosumab for GCTB also are unknown.

Questions/purposes (1) Is short-course (three doses or fewer) preoperative denosumab treatment as effective as longer course (more than three doses) of treatment in terms of achieving a clinical, radiologic, and histologic response in patients with GCTB? (2) Is there an increased risk of LR after short-course denosumab therapy compared with long-course denosumab therapy; and after controlling for confounding variables, what factors were associated with LR after surgery for GCTB in patients receiving preoperative denosumab?

Methods A retrospective study was performed using an institutional database of 161 skeletally mature patients with a histologic diagnosis of GCTB who received denosumab between November 2010 and July 2019 to downstage the tumor before surgery. In general, we used denosumab when we thought it would facilitate either resection or curettage (by formation of a sclerotic rim around the osteolytic lesion), when a less-morbid procedure than initially planned might be performed, and in patients with complex presentations like cortical breech and soft tissue extension, pathological fracture, thinning of more than three cortices of the extremity. From 2010 to late 2015, denosumab was administered for approximately 4 to 6 months; starting in late 2015 through 2020, the number of denosumab doses has been reduced. We divided patients into two groups: Those who received three or fewer doses of denosumab (short-course, n = 98) and those who received more than three doses of denosumab (long-course,

Each author certifies that neither he or she, nor any member of his or her immediate family, has funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.
Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.
All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.
This work was performed at the Department of Orthopaedic Oncology, HCG Hospital, Bangalore, India.

S. Hindiskere, S. Doddarangappa, P. S. Chinder, Department of Musculoskeletal Oncology, HCG Hospital, Bangalore, Karnataka, India

C. Errani, Orthopaedic Service, Department of Musculoskeletal Oncology, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

V. Ramaswamy, Department of Pathology, HCG Hospital, Bangalore, Karnataka, India

M. Rai, Department of Orthopaedic Surgery, A. J. Shetty Medical College and Hospital, Mangalore, Karnataka, India

Suraj Hindiskere ✉, Department of Musculoskeletal Oncology, HCG Hospital, No. 8, P. Kalingarao Road, Sampangiramnagar, Bangalore, Karnataka 560027 India, Email: suraj.ortho@gmail.com

Wolters Kluwer

n = 63). Comparing those in the long-course group with those in the short-course group whose procedures were performed at least 2 years ago, there were no differences in loss to follow-up before 2 years (3% [3 of 98] versus. 3% [2 of 63]). The mean patient age was 30 years (± 6.1) and the mean number of denosumab doses was 4.4 (range 1 to 14). Overall, 77% (37 of 48) of patients taking short-course denosumab and 75% (27 of 36) of patients on long-course denosumab underwent curettage, and the remaining patients with an inadequate bony shell around the tumor or destruction of articular cartilage in both groups underwent tumor resection. With the numbers available, the patients with short- and long-course denosumab were not different in terms of age, sex, MSTS score on presentation, lesion size, lesion location, Campanacci grade, presence of pathological fracture and pulmonary metastasis on presentation, and the type of surgery performed (curettage versus resection). We analyzed the change in the Musculoskeletal Tumor Society score, change in Campanacci grade, radiologic objective tumor response (defined as a partial or complete response, per the modified inverse Choi criteria), and histologic response (defined as reduction of more than 90% of osteoclast-like giant cells or a reduction of more than 50% of mesenchymal spindle-like stromal cells, along with evidence of lamellar or woven bone formation, when compared with the biopsy sample) between the two groups (short- and long-course denosumab). LR rates were compared between the two groups, and after controlling for confounding variables, factors associated with LR in all operated patients were analyzed with a Cox proportional hazards regression analysis.

Results With the numbers available, there was no difference between the short- and long-course denosumab groups in terms of mean percentage improvement in MSTS score (20 [± 18.5] versus 24 [± 12.6]; p = 0.37), radiologic objective tumor response (90% [43 of 48] versus 81% [29 of 36]; p = 0.24) and histologic response (79% [38 of 48] versus 83% [30 of 36]; p = 0.81). With the numbers available, there was no difference between the short- and long-course denosumab groups in terms of Kaplan-Meier survivorship free from LR at 5 years after surgery (73% [95% confidence interval, 68 to 76] versus 64% [95% CI 59 to 68]; log-rank p = 0.50). After controlling for potential confounding variables like age, sex, Campanacci grade and MSTS score on presentation, number of denosumab doses administered before surgery, clinical, radiologic and histologic response to denosumab, and time duration between denosumab therapy and surgery, we found that tumors involving the bones of the hand and the foot (hazard ratio 7.4 [95% CI 2.0 to 27.3]; p = 0.009) and curettage (HR 6.4 [95% CI 2.8 to 23.0]; p = 0.037) were independently associated with a higher risk of LR.

Conclusions In this preliminary, single-center study, we found that a short-course of preoperative denosumab (three or fewer doses) was associated with no differences in clinical scores, histological and radiological response, or LR-free survivorship, compared with longer-course of denosumab (more than three doses). Fewer preoperative doses can reduce the complications and costs associated with more-prolonged therapy. Denosumab must be used cautiously before curettage for GCTB, and only if the benefit of joint salvage outweighs the possibility of LR. However, given the small number of patients, potentially clinically important differences might have been missed, and so our findings need to be confirmed by larger, multicenter, prospective trials.

Level of Evidence Level III, therapeutic study.

Introduction

Giant cell tumor of bone (GCTB) is a benign but locally aggressive tumor [3]. Currently, surgery is the main form of management for GCTB, and it usually is performed with an intent to cure [30]. Depending on the type of surgery and local presentation of the tumor, the incidence of local recurrence (LR) has varied widely, from 0% to 65% [20]. En bloc resection has shown substantially better local control than curettage, but at the cost of an inferior functional outcome because the joint is not preserved [35].

GCTB has characteristic large, multinucleated osteoclast-like giant cells expressing receptor activator of nuclear factor-κB and mesenchymal spindle-like stromal cells expressing receptor activator of nuclear factor-κB ligand; this cell interaction leads to bone resorption [3]. Denosumab is a human monoclonal antibody that inhibits receptor activator of nuclear factor-κB ligand and prevents destruction of osteoclast-mediated bone [32]. Denosumab was approved for treating metastatic GCTB, unresectable tumors, and tumors that would otherwise be treated with morbid surgical procedures [9, 18, 33]. Besides being an option in surgically unsalvageable tumors, denosumab may help in facilitating surgery or decrease the extent and morbidity of the surgical procedure in selected patients [26].

However, recent reports have expressed concern regarding increased LR and the possibility of malignant transformation with the use of denosumab [3, 15, 16]. In addition, the number of denosumab doses to treat GCTB has not been standardized, and the duration of treatment ranges from 4 months to 55 months [22]. In 2007, the results of a randomized Phase II trial in which breast cancer-related bone metastases were treated with denosumab indicated that 120 mg to 180 mg of denosumab every 4 weeks provided the most reliable and consistent suppression of urinary N-terminal telopeptide (a potent marker for bone resorption) [21]; as a result, 120 mg once every 4 weeks was chosen as the standard regimen in the

subsequent studies to prove the efficacy of denosumab in GCTB [38]. However, the trial did not evaluate the change in the characteristics of the bone lesion with denosumab, which is more important for a surgeon treating a GCTB [21].

To our knowledge, the response of GCTB to a short-course of denosumab has not been studied. The best duration of therapy and long-term safety profile also remain undefined [17]. A previous study reported increased LR after surgery with preoperative denosumab for GCTB compared with no denosumab among a subset of patients included in the current study, but the duration of therapy was not investigated [10].

We therefore asked: (1) Is a short-course (three doses or fewer) preoperative denosumab therapy as effective as longer course (more than three doses) of treatment in terms of achieving a clinical, radiologic, and histologic response in patients with GCTB? (2) Is there an increased risk of LR after short-course denosumab therapy compared with long-course denosumab therapy, and after controlling for confounding variables, what factors were associated with LR after surgery for GCTB in patients receiving preoperative denosumab?

Patients and Methods

Study Design, Setting, and Participants

We performed a retrospective study using an institutional database of 266 patients who received a histologic diagnosis of GCTB between November 2010 and July 2019. During the study period, 70% (186 of 266) of patients diagnosed with GCTB in our institution were administered denosumab for the following indications after confirming skeletal maturity: (1) neoadjuvant therapy to downstage the tumor before surgery, (2) adjuvant therapy after surgery to prevent LR, (3) monotherapy for inoperable lesions or patients declining to have surgery, (4) pulmonary metastasis, and (5) combination of the above. Among these 186 patients, 161 received denosumab to downstage the tumor before surgery was planned (Fig. 1).

At our institution, after a clinical and radiologic evaluation of a patient with GCTB, preoperative denosumab was given when the provider believed it would facilitate either en bloc resection or curettage (by formation of a sclerotic rim around the osteolytic lesion), when a less-morbid procedure than initially planned could be performed, and in patients with complex presentations like cortical breech and soft tissue extension, pathological fracture, fungating mass and thinning of more than three cortices of the extremity. This was decided on a patient-by-patient basis [26]. All patients were counseled regarding the advantages, disadvantages, and possible complications of denosumab, and informed consent was obtained before therapy.

Until late 2015, before surgery for GCTB, 120 mg of denosumab was administered once every 28 days, with additional loading doses on Days 8 and 15 of the first month, for 3 to 6 months. Denosumab was stopped when there was a substantial reduction in pain and swelling, with radiologic regression of osteolysis and evidence of sclerosis in or surrounding the tumor, and then patients underwent surgery. As we gained experience, we reduced the number of denosumab doses because the desired clinical and radiologic benefits were observed with fewer doses. We thought that a reduced number of doses would prevent possible complications and the economic burden of multiple doses [4, 19, 37]. Thus, since late 2015 until the current day, 120 mg of denosumab is administered once every 2 weeks for 1 or 2 months, depending upon the response, in all patients being planned for surgery after downstaging with denosumab. Further doses are continued only if adequate clinical and radiologic responses are not observed. The present dosing regimen does not depend upon the location, lesion size, or any other tumor characteristics. In some patients, denosumab therapy is terminated if they cannot afford further doses and if an adequate response is not observed, despite multiple doses.

Based on our experience and recent studies, we divided patients into two groups: those who received three or fewer doses of denosumab (short-course, n = 98) and those who received more than three doses of denosumab (long-course, n = 63). Comparing those in the long-course group with those in the short-course group whose procedures were performed at least 2 years ago, there were no differences in loss to follow-up before 2 years (3% [3 of 98] versus 3% [2 of 63]). Since the short-course therapy was started more recently in our institution, many patients did not have a minimum follow-up of 2 years, which is the average time to local recurrence of GCTB after surgery. Of the patients with follow-up of less than 2 years, neither of the two patients in the long-course group developed LR and one of 19 patients in the short-course group developed LR. Forty-eight patients receiving short-course denosumab were analyzed after we excluded the following: 19% (19 of 98) with follow-up of less than 2 years after surgery as mentioned above, 16% (16 of 98) with a recurrent GCTB at presentation, 7% (seven of 98) who received additional denosumab treatment after surgery, 3% (three of 98) who were lost to follow-up, 2% (two of 98) with history of surgery, radiotherapy, or any other form of management of GCTB and 3% (three of 98) with insufficient data. Thirty-six patients receiving long-course denosumab were analyzed after we excluded the following: 13% (eight of 63) with a recurrent GCTB at presentation, 8% (five of 63) who received additional denosumab treatment after surgery, 6% (four of 63) with history of surgery, radiotherapy, or any other form of management of GCTB, 6% (four of 63) who did not undergo surgery after denosumab therapy, 3% (two of 63) with follow-

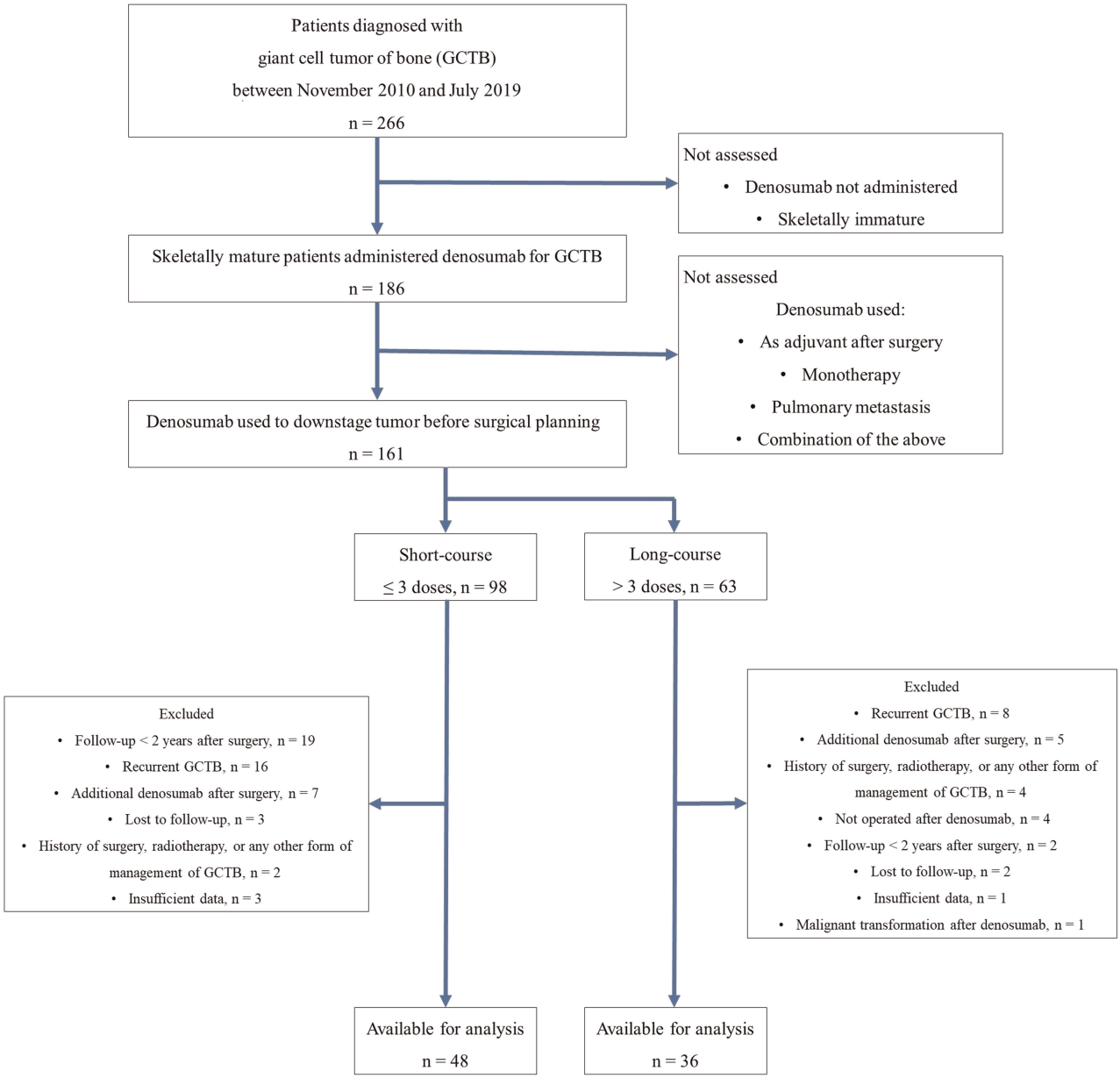

Fig. 1 Flow diagram demonstrating selection of patients for final analysis

up of less than 2 years after surgery (as mentioned above), 3% (two of 63) who were lost to follow-up, 2% (one of 63) with insufficient data and 2% (one of 63) with malignant transformation after denosumab therapy.

With the numbers available, the patients with short- and long-course denosumab were comparable in terms of age, sex, MSTS score on presentation, size of lesion, location of the lesion, Campanacci grade, presence of pathological fracture and pulmonary metastasis on presentation and the type of surgery performed (curettage versus resection) (Table 1). However, since the short-course denosumab was started more recently (late 2015 onwards), the duration of follow-up was shorter when compared with the long-course group (37 months [± 11.4 months] versus 64 months [± 15.7 months]; $p < 0.001$). Approval for this study was obtained from the ethical review board of our institution.

Description of the Treatment

After a response to denosumab, patients underwent curettage along with local adjuvant or en bloc

Table 1. Characteristics of patients with three or fewer than three doses of denosumab and those with more than three doses of denosumab

Characteristics	All patients (n = 84)	Three or fewer doses (n = 48)	More than three doses (n = 36)	p value
Age (years)	30 (± 6.1)	30 (± 6.3)	30 (± 5.9)	0.73
Sex				0.26
Male	51% (43)	46% (22)	58% (21)	
Female	49% (41)	54% (26)	42% (15)	
MSTS score at presentation	18 (± 3.0)	18 (± 3.2)	17 (± 2.5)	0.06
Size of lesion (maximal cross-sectional area) (cm^2)	4 (± 1.5)	4 (± 1.7)	4 (± 1.4)	0.23
Site of lesion				0.25
Proximal tibia	24% (20)	19% (9)	31% (11)	
Distal femur	21% (18)	25% (12)	17% (6)	
Pelvis	12% (10)	4% (2)	22% (8)	
Distal radius	10% (8)	10% (5)	8% (3)	
Spine	10% (8)	8% (4)	11% (4)	
Proximal humerus	7% (6)	10% (5)	3% (1)	
Hand	4% (3)	4% (2)	3% (1)	
Foot	4% (3)	4% (2)	3% (1)	
Distal ulna	2% (2)	4% (2)	0% (0)	
Distal tibia	2% (2)	2% (1)	3% (1)	
Talus	2% (2)	2% (1)	3% (1)	
Proximal femur	1% (1)	2% (1)	0% (0)	
Proximal radius	1% (1)	2% (1)	0% (0)	
Campanacci grade at presentation				0.13
2	51% (43)	58% (28)	42% (15)	
3	49% (41)	42% (20)	58% (21)	
Fracture at presentation				0.08
Yes	17% (14)	10% (5)	25% (9)	
No	70 (83.3%)	90% (43)	75% (27)	
Pulmonary metastasis at presentation	5% (4)	4% (2)	6% (2)	0.73
Surgery performed				0.82
Curettage	76% (64)	77% (37)	75% (27)	
En bloc resection	24% (20)	23% (11)	25% (9)	
Local recurrence	31% (26)	27% (13)	36% (13)	0.38
Time to local recurrence (months)	18 (± 6.7)	18 (± 7.0)	18 (± 6.7)	0.87
Follow-up (months)	48 (± 18.9)	37 (± 11.4)	64 (± 15.7)	< 0.001
Systemic complications (CTCAE v4.03 Grade 2 or higher)	6% (5)	0% (0)	14% (5)	0.008

Categorical variables are presented as frequencies and percentages and continuous variables are presented as the mean and SD.

resection for the tumor. An inadequate bony shell around the tumor and destruction of articular cartilage were indications for en bloc resection. Irrespective of the tumor location, the number of denosumab doses administered, and the Campanacci grade of the lesion, the indications for resection as opposed to curettage did not change. Thirty-seven patients with short-course denosumab (77%) and 27 patients with long-course denosumab (75%) underwent curettage, and the remaining patients in both groups underwent en bloc resection ($p = 0.82$). During curettage, a high-speed burr and phenol were used as adjuvants for all patients. After curettage, the cavity was filled with a bone allograft or polymethylmethacrylate bone cement. Prophylactic internal fixation and stabilization were performed if there was a risk of fracture.

Data Sources, Variables, and Outcome Measures

Demographic details on presentation, tumor characteristics on plain radiographs, CT images, and MRI, details of denosumab therapy, clinical and tumor characteristics after denosumab therapy, associated complications of therapy, details of the procedure, and postoperative details were retrieved from the database.

We compared the change in the Musculoskeletal Tumor Society (MSTS) score, change in the Campanacci grade, and the radiological objective tumor response (defined as partial or complete response, per the modified inverse Choi criteria) between patients with short- and long-course therapy [8, 9, 11, 13, 34]. The histologic response to denosumab was evaluated by comparing specimens obtained during surgery with biopsy samples. Based on our institutional review, a good histologic response was defined as a reduction of more than 90% of osteoclast-like giant cells or a reduction of more than 50% of mesenchymal spindle-like stromal cells, along with evidence of lamellar or woven bone formation. We compared the incidence of Grade 2 or higher complications as per the Common Terminology Criteria for Adverse Events, volume 4.03 [5], and the LR free survivorship at 5 years after surgery between the two groups.

After controlling for confounding variables, we analyzed factors associated with LR in all operated patients (both groups) with a Cox proportional hazards regression analysis. For patients in both groups, factors that have been previously reported to influence LR in GCTB such as the age and sex of the patient, type of surgery, location of the tumor, fracture at presentation, and Campanacci grade [15], and other factors with a possible association with LR like functional status at presentation (MSTS score), duration of preoperative denosumab therapy, duration between the end of therapy and surgery, and the tumor's response to denosumab were entered in the univariable analysis for association with LR. The following factors were then advanced to a multivariable analysis to estimate the hazard ratio as p value was less than 0.05 in the univariable analysis: (1) location of the tumor, (2) histological response to denosumab and (3) type of surgery performed (curettage vs. resection).

Statistical Analysis

Pearson's chi-square test or Fisher's exact test was used for categorical variables (presented as frequencies and percentages), and an independent-samples T test was used for continuous variables (presented as the mean and SD) to evaluate associations between the two groups. Significance was defined as p less than 0.05. LR-free survival was estimated using the Kaplan-Meier method, and the log-rank test was used to evaluate differences between the survival curves of the two groups. To estimate the hazard ratio of risk factors for LR, we used a Cox proportional hazards regression analysis, and factors with a significant association in the univariate analysis ($p < 0.05$) were included in a multivariate analysis to identify independent risk factors for LR. Post hoc analysis was performed to estimate the power of the study, with percentage improvement in MSTS score in both groups as the end point. With the numbers available and level of significance at 5%, we achieved a power of 21% with an effect size of 0.252. Statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp, Armonk, NY, USA).

Results

Long- versus Short-course Denosumab: Clinical, Radiologic, and Histologic Responses, and Complications

With the numbers available, there was no difference between short- and long-course denosumab groups in terms of mean percentage improvement in MSTS score (20 [± 18.5] versus 24 [± 12.6]; p = 0.37), radiological objective tumor response (90% [43 of 46] versus 81% [29 of 36]; p = 0.24) (Fig. 2) and histological response (79% [38 of 48] versus 83% [30 of 36]; p = 0.81) (Fig. 3).

However, patients with long-course denosumab were more likely to improve by at least one Campanacci grade than patients in the short-course group (83.3% [30 of 36] versus 60.4% [29 of 48]; p = 0.02).

There were more Grade 2 or higher systemic complications in patients with long-course therapy (14% [5 of 36] versus 0%, p = 0.008). With denosumab therapy, 2% (one of 48) with short-course therapy had asymptomatic hypocalcemia (Grade 1). In the long-course therapy group, 3% (one of 36) had asymptomatic hypocalcemia (Grade 1), 6% (two of 36) reported fatigue (Grade 2) that improved without active intervention, and 6% (two of 36) developed hypocalcemia tetany (Grade 3) which required intravenous calcium and supportive care.

LR after Long- and Short-course Denosumab Treatment and Factors Associated with LR

With the numbers available, there was no difference between short- and long-course denosumab treatment in terms of Kaplan-Meier survivorship free from LR at 5 years after surgery (73% [95% confidence interval, 68 to 76] versus 64% [95% CI 59 to 68], log-rank p = 0.50) (Fig. 4). No difference was found between the two groups in terms of mean time to LR after surgery (18 months [± 7.0] versus 18 months [± 6.7]; p = 0.87).

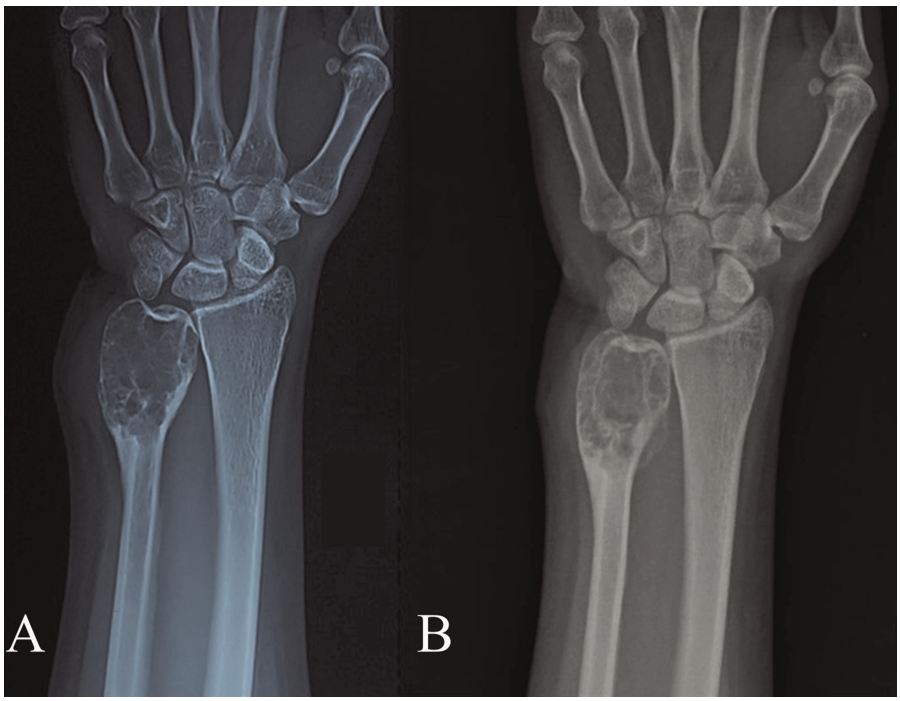

Fig. 2 Plain radiographs were taken of a 27-year-old patient with a histologic diagnosis of giant cell tumor of the distal ulna (**A**) before denosumab and (**B**) 2 weeks after one 120-mg dose of denosumab.

After controlling for potential confounding variables like age, sex, Campanacci grade and MSTS score on presentation; the number of denosumab doses administered before surgery; the clinical, radiological and histological response to denosumab; and the time duration between denosumab therapy and surgery, we found that the tumors involving the bones of hand and foot (hazard ratio 7.4 [95% CI 2.0 to 27.3]; p = 0.009) and curettage (HR 6.4 [95% CI 2.8 to 23.0]; p = 0.037) were independently associated with higher LR (Table 2).

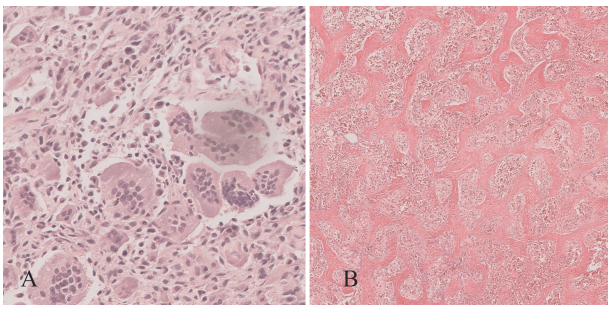

Fig. 3 Hematoxylin and eosin-stained histopathology images show (**A**) a biopsy sample with osteoclast-like giant cells, bland spindle-shaped stromal cells, and a collagenous matrix consistant with GCTB (200 x magnification) and (**B**) ovoid-to-spindle-shaped stromal cells with few capillaries, occasional areas of hemorrhage, and extensive areas of woven bone with no evidence of osteoclast-like giant cells (100 x magnification) after two doses of denosumab. A color image accompanies the online version of this article.

Other Findings

Of the 26 patients who developed LR, 88% (23 of 26) underwent repeat surgery by curettage (n = 17; 73.9%) or en bloc resection (n = 6; 26.1%). The remaining 12% (three of 26) were treated only by adjuvant denosumab, without surgery. Preoperative denosumab was used again in 44% (10

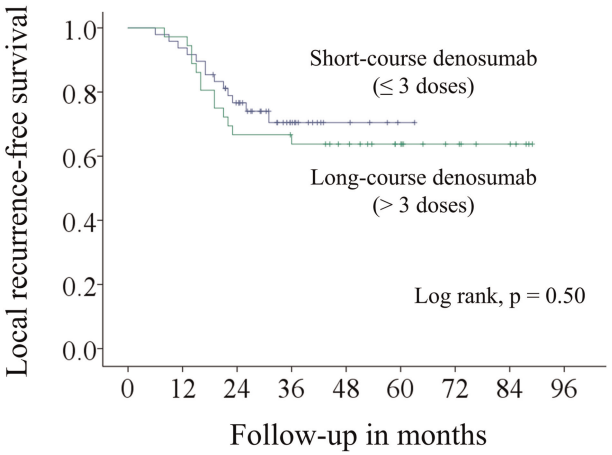

Fig. 4 This Kaplan-Meier survival curve depicts there was no difference LR-free survival between patients who had three or fewer doses of denosumab and those with more than three doses of denosumab.

Table 2. Multivariate Cox proportional hazards regression analysis of risk factors with a significant association with local recurrence in the univariate analysis in patients with GCTB who underwent surgery after preoperative denosumab treatment

		Multivariate analysis		
Factor	**Number (%) (n = 84)**	**HR**	**95% CI**	**p value**
Site of tumor				0.009
Distal femur and proximal tibia	45% (38)	1.5	0.5 to 4.0	
Distal radius	10% (8)	3.6	1.0 to 12.7	
Hand and foot	7% (6)	7.4	2.0 to 27.3	
Other bones	38% (32)			
Histologic response to denosumab				0.07
Good[a]	81% (68)	1		
Not good	19% (16)	2.3	0.9 to 5.8	
Surgery performed				0.037
Curettage	76% (64)	6.4	2.8 to 23.0	
En bloc resection	24% (20)	1		

[a]Good histological response: reduction of more than 90% of osteoclast-like giant cells or reduction of more than 50% of mesenchymal spindle-like stromal cells, along with evidence of lamellar or woven bone formation.

of 26) undergoing repeat surgery. At the final follow-up examination, all patients included in the analysis were alive, and none of the patients treated for LR had re-recurrence.

Discussion

Denosumab to treat GCTB was greeted with interest by the orthopaedic community, with hopes of avoiding morbid procedures and complex reconstructions [30]. Most patients have reduced pain and increased function after denosumab therapy, with evidence of radiologic shrinkage and calcification of the lesion, facilitating surgery [17]. However, because of recent reports of increased LR and possibility of malignant transformation, there has been dampened enthusiasm for using denosumab to treat GCTB [1, 2, 4, 10, 15]. There are no regulations for the duration of therapy and patients often receive multiple doses before surgery. Although recent studies suggested that a short-course of preoperative denosumab should be used to treat GCTB, to our knowledge, the response to limited doses of denosumab has not been studied before [1, 26]. With the numbers available, we found no differences between short- and long-course preoperative denosumab therapy in terms of clinical, radiologic and histologic benefits, of LR-free survivorship, and we found that patients treated with a shorter course had fewer complications.

Limitations

This study had several limitations. A relatively limited number of patients in each group and low statistical power are the major limitations of this study, which could have led to missing potentially clinically important differences between the two groups. However, since the point estimates in terms of endpoints like MSTS scores and LR-free survivorship were close, and since the CIs were relatively narrow and overlapped broadly, we believe our findings likely are valid. By contrast, sparse-data bias with wide CIs in our multivariable analysis may restrict the readers to clinically interpret the factors associated with LR. This is due to the presence of only a small number of events of interest (LR).

Secondly, this was a retrospective analysis of patients who received a varied number of denosumab doses who were arbitrarily categorized into two groups. The categorization was made for statistical purposes, based on recent reports and the experience of the authors observing that GCTBs had an adequate clinical and radiologic response to three doses of denosumab [1, 26]. We believe there was no selection bias because since late 2015, most patients in our institution received short-course denosumab irrespective of the tumor or patient characteristics on presentation; more than three doses were administered only if adequate clinical or radiologic benefits were not seen. Although there was no difference in LR between the long- and short-course groups, we are concerned that this may have been a function of Type-II error (insufficient statistical power to detect a difference that may have been present); the fact that the groups also differed in terms of the proportion of patients with pathological fractures and Campanacci grade 3 lesions (both of which were more common in the long-course group) also should cause some caution in interpreting our findings. Future, multicenter collaborations may be needed to provide some clarity on these important

points. Although the patient and tumor characteristics were not different between the two groups, a randomized cohort of patients matched by tumor characteristics is a better way to compare responses to a therapy. Thirdly, this was a single-institution study in which the number of denosumab doses to be administered, duration of therapy, and surgical procedure were determined by a single team of surgeons. But during the period of study duration, although the practice of reducing the frequency of denosumab changed with time, the indications to start/stop denosumab and the indications for the type of surgery to be performed did not change. Fourthly, the study aimed to evaluate the clinical, radiologic, and histologic responses to denosumab, and the parameters chosen to report these outcomes are susceptible to assessment bias. The criteria for the histologic response were purely based on a review of institutional data, as standard criteria were not available. Even though the reporters were blinded, using parameters with a definitive cutoff would have been more robust, and future studies should try to do this. Lastly, vast number of patients were excluded from both groups from the final analysis (51% [50 of 98] in short-course and 43% [27 of 63] in long-course group). Most patients who were not analyzed were excluded because they had follow-up of less than 2 years after surgery (19% [19 of 98] in short-course and 3% [2 of 63] in the long-course group). Since this study aimed at determining the factors associated with LR, and because most LRs after surgery for GCTB occur within 2 years, the authors felt that including only patients who have completed 2 years follow-up would be appropriate; however, it is important to realize that a larger proportion of patients in the short-course group have not yet achieved 2 years of follow-up, and so we may learn more (both about local recurrences and complications) as their follow-up period increases in duration. This difference in follow-up duration could make the short-course group appear to be doing better than it actually is. More patients in the short-course group had shorter follow-up as the practice of limited dosing was more recently started in our institution, and so it is possible that this, too, may have led to an underestimate of complications in this group.

Long- versus Short-course Denosumab: Clinical, Radiologic, and Histologic Responses

Our study demonstrated that patients with GCTBs treated with more than three doses of preoperative denosumab experienced no benefits in clinical, radiologic, or histologic responses when compared with patients receiving three or fewer doses. To our knowledge, no previous studies demonstrating such findings are available. A few case reports and one study on five patients with GCTB have reported favorable clinical and radiologic responses of primary, metastatic and recurrent GCTB to a few doses of denosumab, but extensive data with strong evidence are lacking [13, 19, 23, 36].

A recent systematic review of studies on denosumab for GCTB reported that the duration of treatment with denosumab varied substantially between different studies and between participants in the same study, and ranged from 4 months to 55 months [22]. Long duration of denosumab for GCTB might not be needed when the main purpose is to downstage the disease. A phase II study demonstrating the therapeutic benefits of denosumab has shown that serum levels of markers of bone resorption fall rapidly within 2 months of the start of therapy [33]. It has also been demonstrated that denosumab's pharmacokinetics do not change with multiple doses, and prolonged duration of therapy maintains a sustained concentration in the body that may be beneficial when denosumab is being used for unresectable GCTBs or in standalone therapies but not for surgical downstaging of the tumor [7, 33].

Recent studies have suggested that a short-course of preoperative denosumab may benefit patients with GCTB, as only three doses is enough to form a stiff shell around the lesion, which is beneficial for the intralesional procedure and resection [1, 26]. Consistent with these preliminary reports, our results confirm that a short-course of denosumab may be adequate to obtain the desired clinical and radiologic benefits in patients with GCTB before planning surgery.

The long-term safety profile of denosumab for GCTB is not well-defined [3]. The incidence of Grade 2 or higher complications in our study was seen only in patients with long-course denosumab. Similarly, a study evaluating toxicity of denosumab in 97 patients with GCTB reported complications such as osteonecrosis of the jaw, mild peripheral neuropathy, skin rash, hypophosphatemia, and atypical femur fracture in patients receiving prolonged treatment (median duration of therapy 54 months), and only one patient with a shorter duration of therapy (median of 12 months) had osteonecrosis of the jaw [25]. Limiting the number of preoperative denosumab doses may reduce the potential complications associated with the therapy.

LR after Long- and Short-course Denosumab Treatment and Factors Associated with LR

We found no advantage in terms of LR-free survivorship for longer-course denosumab treatment in patients with GCTB. Preoperative denosumab has not been shown to reduce the risk of LR after surgery [30] and a few recent reports have in fact reported increased LR in patients operated after denosumab therapy [10, 15]. But there is no

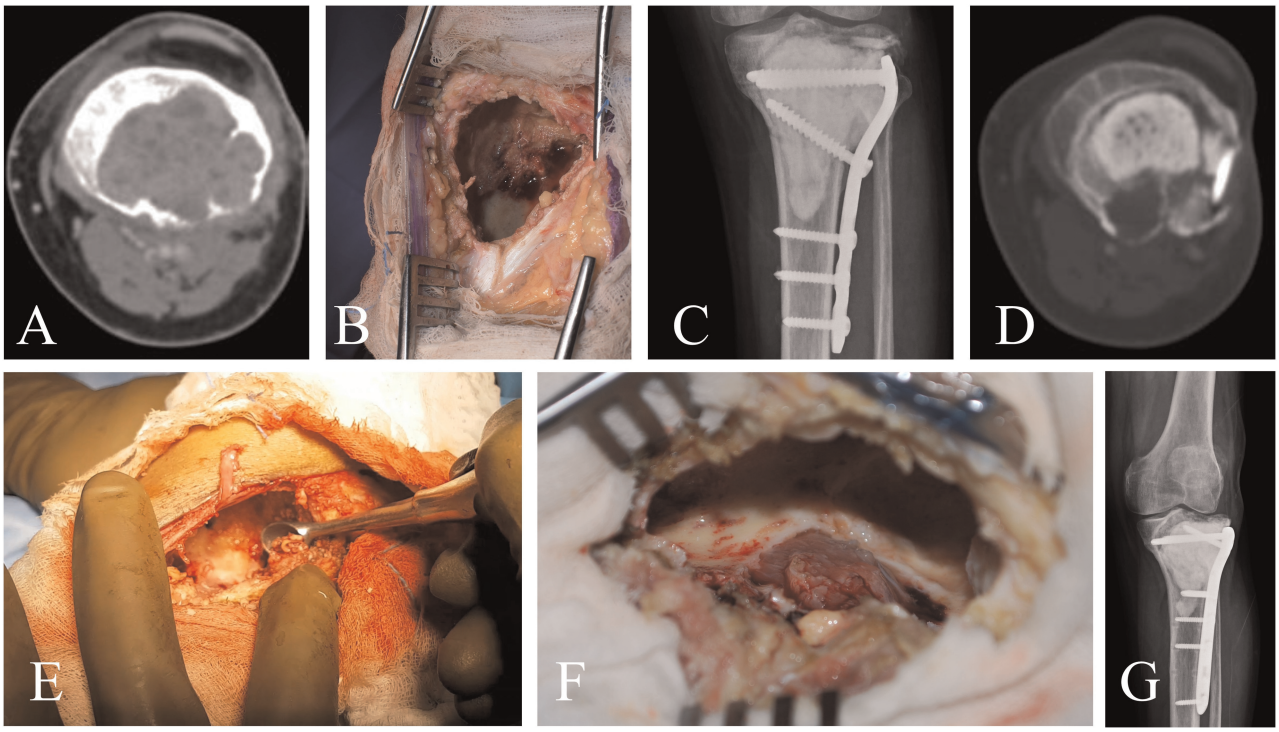

Fig. 5 A-G A patient with a giant cell tumor of the proximal tibia was administered two doses of denosumab. (**A**) An expansile osteolytic lesion was seen on a CT image. (**B**) After the patient responded to treatment, curettage was performed until a hard bony shell was identified. (**C**) The cavity was filled with bone cement, and prophylactic internal fixation was performed. (**D**) LR was evident on a CT image at 14 months. (**E**) The patient underwent repeat curettage, and a recurrent tumor in the tissue was confined to the posterior cortex, near where rigid bone was felt during the first procedure. (**F**) Aggressive repeat curettage was performed, the posterior cortex was nibbled to prevent further recurrence, and the cavity was filled with a bone graft in the subchondral region and bone cement. The joint was salvaged. (**G**) There was no recurrence at 42 months of follow-up. A color image accompanies the online version of this article.

data from prospective studies evaluating the role of denosumab on LR of GCTB; also, there is no study demonstrating the effect of duration of denosumab therapy on LR of GCTB.

Curettage was independently associated with higher likelihood of LR. Tumor cells can hide in the thickened cortex or densely formed bone in the subchondral region or walls of the lesion, which form as a response to denosumab [15]. This may prevent the surgeon from delineating the true extent of the tumor, resulting in incomplete curettage and increased LR [15]. Some authors recommended more aggressive curettage, completely covering the pre-denosumab tumor margin to reduce LR [1, 24] (Fig. 5A-G). Similar to our results, recent studies have reported increased LR after curettage (versus resection) for GCTB after preoperative denosumab therapy, with an incidence of up to 60%, but studies with long-term follow-up are limited [10, 15, 30]. Curettage in patients who were treated with denosumab should be performed cautiously if the benefit of joint salvage substantially outweighs the possibility of LR. The reconstituted peripheral rim around the tumor after denosumab therapy may prevent tumor spillage and allow for easier resection, explaining the low LR incidence of 5% in our series after resection, similar to previous reports [1, 6, 20, 39, 40].

In our study, GCTB of the hand and foot was independently associated with higher LR. An incidence of LR of more than 50% has been reported for intralesional procedures for GCTB of the small bones; this is a more anatomically challenging location and this tumor has more aggressive behavior [27]. Some studies attribute the increased LR not to the aggressive behavior of the tumor but to a delayed presentation and diagnosis apart from the location [12, 27, 31]. However, we feel that the main reason for increased LR is anatomic constraints that prevent adequate curettage. A large cortical window is not always possible in the bones of the hand and foot, and microscopic disease may remain, especially after denosumab therapy because of the formation of reactive bony trabeculae shielding the tumor cells. Adequate exposure and confirming the extent of curettage with intraoperative radiographs may help to reduce LR, not only in the bone of hand and foot but also in all patients undergoing curettage after denosumab treatment [1].

Conclusions

In this preliminary, single-center study, we found no differences between short- and long-course preoperative denosumab therapy in terms of clinical, radiologic and histologic benefits, of LR-free survivorship, and we found that patients treated with a shorter course had fewer complications. Fewer preoperative doses of denosumab may reduce the complications and costs associated with more prolonged therapy. Denosumab must be used cautiously before curettage for GCTB, and only if the benefit of joint salvage outweighs the possibility of LR. Special attention must be given when treating GCTB of the hand and foot in view of higher LR rates. However, given the small number of patients, potentially clinically important differences might have been missed, and so our findings need to be confirmed by larger, multicenter, and ideally prospective trials.

References

1. Agarwal MG, Gundavda MK, Gupta R, Reddy R. Does Denosumab Change the Giant Cell Tumor Treatment Strategy? Lessons Learned From Early Experience. *Clin Orthop Relat Res*. 2018;476:1773-1782.
2. Alaqaili SI, Abduljabbar AM, Altaho AJ, Khan AA, Alherabi JA. Malignant Sarcomatous Transformation of Benign Giant Cell Tumor of Bone after Treatment with Denosumab Therapy: A Literature Review of Reported Cases. *Cureus*. 2018;10:e3792.
3. Aponte-Tinao LA, Piuzzi NS, Roitman P, Farfalli GL. A High-grade Sarcoma Arising in a Patient With Recurrent Benign Giant Cell Tumor of the Proximal Tibia While Receiving Treatment With Denosumab. *Clin Orthop Relat Res*. 2015;473:3050-3055.
4. Balke M. Denosumab treatment of giant cell tumor of bone. *Lancet Oncol*. 2013;14:801-802.
5. Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC, Mendoza TR, Hay J, Atkinson TM, Abernethy AP, Bruner DW, Cleeland CS, Sloan JA, Chilukuri R, Baumgartner P, Denicoff A, St Germain D, O'Mara AM, Chen A, Kelaghan J, Bennett AV, Sit L, Rogak L, Barz A, Paul DB, Schrag D. 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.* 2014;106.
6. Becker WT, Dohle J, Bernd L, Braun A, Cserhati M, Enderle A, Hovy L, Matejovsky Z, Szendroi M, Trieb K, Tunn PU. Local recurrence of giant cell tumor of bone after intralesional treatment with and without adjuvant therapy. *J Bone Joint Surg Am*. 2008; 90:1060-1067.
7. Boriani S, Cecchinato R, Cuzzocrea F, Bandiera S, Gambarotti M, Gasbarrini A. Denosumab in the treatment of giant cell tumor of the spine. Preliminary report, review of the literature and protocol proposal. *Eur Spine J*. 2020;29:257-271.
8. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. *J Bone Joint Surg Am*. 1987;69:106-114.
9. Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, Kroep J, Grimer R, Reichardt P, Rutkowski P, Schuetze S, Skubitz K, Staddon A, Thomas D, Qian Y, Jacobs I. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumor of bone: interim analysis of an open-label, parallel-group, phase 2 study. *Lancet Oncol*. 2013;14: 901-908.
10. Chinder PS, Hindiskere S, Doddarangappa S, Pal U. Evaluation of Local recurrence in Giant-Cell Tumor of Bone Treated by Neoadjuvant Denosumab. *Clin Orthop Surg*. 2019; 11:352-360.
11. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, Benjamin RS. 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*. 2007;25: 1753-1759.
12. Co HL, Wang EH. Giant cell tumor of the small bones of the foot. *J Orthop Surg (Hong Kong)*. 2018;26:2309499018801168.
13. Demirsoy U, Karadogan M, Selek Ö, Anik Y, Aksu G, Müezzinoglu B, Corapcioglu F. Golden Bullet—Denosumab: Early Rapid Response of Metastatic Giant Cell Tumor of the Bone. *J Pediatr Hematol Oncol*. 2014;36:156-158.
14. Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. *Clin Orthop Relat Res*. 1993:241-246.
15. Errani C, Tsukamoto S, Leone G, Righi A, Akahane M, Tanaka Y, Donati DM. Denosumab May Increase the Risk of Local Recurrence in Patients with Giant-Cell Tumor of Bone Treated with Curettage. *J Bone Joint Surg Am*. 2018;100:496-504.
16. Errani C, Tsukamoto S, Mavrogenis AF. How safe and effective is denosumab for bone giant cell tumor? *Int Orthop*. 2017;41: 2397-2400.
17. Gaston CL, Grimer RJ, Parry M, Stacchiotti S, Dei Tos AP, Gelderblom H, Ferrari S, Baldi GG, Jones RL, Chawla S, Casali P, LeCesne A, Blay JY, Dijkstra SP, Thomas DM, Rutkowski P. Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. *Clin Sarcoma Res*. 2016; 6:15.
18. Goldenberg MM. Pharmaceutical Approval Update. *Pharmacy and Therapeutics*. 2013;38:518-524.
19. Kajiwara D, Kamoda H, Yonemoto T, Iwata S, Ishii T, Tsukanishi T, Ohtori S, Yamazaki M, Okawa A. Denosumab for Treatment of a Recurrent Cervical Giant-Cell Tumor. *Asian Spine J*. 2016;10:553-557.
20. Klenke FM, Wenger DE, Inwards CY, Rose PS, Sim FH. Giant cell tumor of bone: risk factors for recurrence. *Clin Orthop Relat Res*. 2011;469:591-599.
21. Lipton A, Steger GG, Figueroa J, Alvarado C, Solal-Celigny P, Body JJ, de Boer R, Berardi R, Gascon P, Tonkin KS, Coleman R, Paterson AH, Peterson MC, Fan M, Kinsey A, Jun S. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol*. 2007;25:4431-4437.
22. Luengo-Alonso G, Mellado-Romero M, Shemesh S, Ramos-Pascua L, Pretell-Mazzini J. Denosumab treatment for giant-cell tumor of bone: a systematic review of the literature. *Arch Orthop Trauma Surg*. 2019;130:1339-1349.
23. McCarthy CL, Gibbons C, Bradley KM, Hassan AB, Giele H, Athanasou NA. Giant cell tumor of the distal radius/ulna: response to pre-operative treatment with short-term denosumab. *Clin Sarcoma Res*. 2017;7:19.
24. Muller DA, Beltrami G, Scoccianti G, Campanacci DA, Franchi A, Capanna R. Risks and benefits of combining denosumab and surgery in giant cell tumor of bone-a case series. *World J Surg Oncol*. 2016;14:281.
25. Palmerini E, Chawla NS, Ferrari S, Sudan M, Picci P, Marchesi E, Leopardi MP, Syed I, Sankhala KK, Parthasarathy P, Mendanha WE, Pierini M, Paioli A, Chawla SP. Denosumab in

advanced/unresectable giant-cell tumor of bone (GCTB): For how long? *Eur J Cancer*. 2017;76:118-124.
26. Puri A, Gulia A, Hegde P, Verma V, Rekhi B. Neoadjuvant denosumab: its role and results in operable cases of giant cell tumor of bone. *Bone Joint J*. 2019;101-B:170-177.
27. Rajani R, Schaefer L, Scarborough MT, Gibbs CP. Giant Cell Tumors of the Foot and Ankle Bones: High Recurrence Rates After Surgical Treatment. *J Foot Ankle Surg*. 2015;54:1141-1145.
28. Rekhi B, Verma V, Gulia A, Jambhekar NA, Desai S, Juvekar SL, Bajpai J, Puri A. 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*. 2017;23:157-164.
29. Rutkowski P, Ferrari S, Grimer RJ, Stalley PD, Dijkstra SP, Pienkowski A, Vaz G, Wunder JS, Seeger LL, Feng A, Roberts ZJ, Bach BA. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. *Ann Surg Oncol*. 2015;22:2860-2868.
30. Scoccianti G, Totti F, Scorianz M, Baldi G, Roselli G, Beltrami G, Franchi A, Capanna R, Campanacci DA. Preoperative Denosumab With Curettage and Cryotherapy in Giant Cell Tumor of Bone: Is There an Increased Risk of Local Recurrence? *Clin Orthop Relat Res*. 2018;476:1783-1790.
31. Shigematsu K, Kobata Y, Yajima H, Kawamura K, Maegawa N, Takakura Y. Giant-cell tumors of the carpus. *J Hand Surg Am*. 2006;31:1214-1219.
32. Suehara Y, Okubo T, Kurihara T, Hayashi T, Kohsaka S, Kazuno S, Sano K, Hasegawa N, Miura Y, Akaike K, Kim Y, Takamochi K, Takahashi F, Ueno T, Kaneko K, Saito T. Protein Expression Profiles Corresponding to Histological Changes with Denosumab Treatment in Giant Cell Tumors of Bone. *Proteomics Clin Appl*. 2019;13:e1800147.
33. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, Roudier M, Smith J, Ye Z, Sohn W, Dansey R, Jun S. Denosumab in patients with giant-cell tumor of bone: an open-label, phase 2 study. *Lancet Oncol*. 2010;11:275-280.
34. Ueda T, Morioka H, Nishida Y, Kakunaga S, Tsuchiya H, Matsumoto Y, Asami Y, Inoue T, Yoneda T. Objective tumor response to denosumab in patients with giant cell tumor of bone: a multicenter phase II trial. *Ann Oncol*. 2015;26: 2149-2154.
35. Urakawa H, Mizusawa J, Tanaka K, Eba J, Hiraga H, Kawai A, Nishida Y, Hosaka M, Iwamoto Y, Fukuda H, Ozaki T. A randomized phase III trial of denosumab before curettage for giant cell tumor of bone: Japan Clinical Oncology Group Study JCOG1610. *Jpn J Clin Oncol*. 2019;49:379-382.
36. von Borstel D, Taguibao A R, Strle A N, Burns E J. Giant cell tumor of the bone: aggressive case initially treated with denosumab and intralesional surgery. *Skeletal Radiol*. 2017;46: 571-578.
37. Xie J, Diener M, Sorg R, Wu EQ, Namjoshi M. Cost-Effectiveness of Denosumab Compared With Zoledronic Acid in Patients With Breast Cancer and Bone Metastases. *Clin Breast Cancer*. 2012;12:247-258.
38. Xu SF, Adams B, Yu XC, Xu M. Denosumab and giant cell tumor of bone-a review and future management considerations. *Curr Oncol*. 2013;20:e442-447.
39. Yacob O, Umer M, Gul M, Qadir I. Segmental excision versus intralesional curettage with adjuvant therapy for giant cell tumor of bone. *J Orthop Surg (Hong Kong)*. 2016;24:88-91.
40. Yin ZC, Liu BG, Pang QJ, Chen XJ, Yu X. [Intralesional curettage and wide excision for treatment of giant cell tumors (GCTs) of the distal radius: A Meta-analysis] [in Chinese]. *Zhongguo Gu Shang*. 2016;29:58-64.