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ORIGINAL RESEARCH

Clinical Outcome of Extended Curettage with Postoperative Denosumab Administration for the Treatment of Campanacci Grade III Giant Cell Tumors of the Extremities

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Purpose: To investigate the local recurrence rate, joint preservation status, and functional outcomes after extended curettage and postoperative denosumab treatment for Campanacci Grade III giant cell tumors of the extremities.

Methods: We retrospectively reviewed 23 patients with Campanacci Grade III GCTB of the extremities in our hospital between January 2017 and June 2023 who underwent extended curettage and postoperative denosumab administration alone, without preoperative denosumab treatment. Patients were followed-up for adverse events of denosumab, surgical outcomes, limb function of lesions, and local recurrence following extended curettage with postoperative denosumab.

Results: All incisions healed without deep infections or internal fixation failure. The mean age of the patients at surgery was 36.6 years, and the mean follow-up was 35.8 months (range, 6–72 months). There of the 3 patients experienced a postoperative local recurrence. The recurrence rate was found to be 13.0%. Two patients were treated with repeat intralesional surgery with no additional recurrence two years later, and the other was treated with en bloc resection and reconstruction with a vascularized fibular graft. One patient experienced knee osteoarthritis without oral analgesics. No patient developed pulmonary metastases or malignant transformation of the GCTB. The mean Musculoskeletal Tumor Society functional score at the last follow up was 27.3 30 (range, 25–29). No serious adverse events were observed after the denosumab treatment.

Conclusion: Our observations suggest that extended curettage with postoperative denosumab administration is a reasonable option for treating Campanacci Grade III giant cell tumors of the extremities. Extended curettage with adjuvant denosumab therapy results in beneficial surgical downstaging, including a less morbid surgical procedure or delayed en bloc resection. Resection should be considered when the structural integrity cannot be regained after bone grafting or bone cement filling combined with internal fixation.

Keywords: giant cell tumor of bone, curettage, denosumab, outcome

Introduction

Giant cell tumor of the bone (GCTB) is an intermediate primary bone tumor that is locally aggressive, but rarely metastasizes. It is most commonly found in the metaphyseal-epiphyseal region of long bones, especially around the knee.[1] The primary treatment is surgery, which includes curettage with adjuvants, and en bloc resection. Currently, Campanacci grade I and II GCTB, which are defined as having no extraosseous extension,[2] are routinely treated with curettage with adjuvants. Grade III lesions are often treated with en bloc resection owing to obliteration of the cortical bone and extension into the soft tissue to prevent local recurrence.[3–5] The use of curettage with adjuvants is reportedly associated with relatively high local recurrence rates but with joint preservation and good postoperative function.[3,6] En bloc resection reduces the local recurrence rate but results in poor functional outcomes in the anatomic location.[3,6]

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In GCTB, stromal cells and osteoclast-like giant cells express receptor activation of the nuclear factor-kappa ß (RANK) ligand and induce receptor activation of RANK-positive osteoclast-like giant cells and their precursors,[7] VEGFR has been described in involving in and supporting this process.[8] Denosumab is a human monoclonal antibody that inhibits RANK ligand (RANKL) and interrupts RANK-RANKL interactions, thereby preventing bone-induced bone destruction in giant cell tumors.[9] Early evidence suggests that preoperative denosumab treatment was associated with a reduction in local recurrence and resulted in beneficial surgical downstaging; however, some studies found an increase in the proportion of patients experiencing local recurrence, thereby questioning this premise.[9–15] Therefore, we did not use preoperative denosumab therapy for most of patients with giant cell tumor of the extremities. For Campanacci Grade III giant cell tumors of the extremities, although the local recurrence rate is generally low after en bloc resection, it is not necessarily the most favorable primary treatment. Considering the benign nature of GCTB, complications, long-term survival, and need for multiple revision surgeries.

Thus, the aim of joint preservation is justified. The preferred surgical treatment for Campanacci grade III GCTB of the extremities remains controversial.

Therefore, we performed a retrospective study to investigate the local recurrence rate, joint preservation status, and functional outcomes after extended curettage and postoperative denosumab treatment for Campanacci Grade III giant cell tumors of the extremities. We attempt to answer the questions,: (1): Is the use of extended curettage with adjuvants and postoperative denosumab treatment would provide adequate local control? (2) Is extended curettage with adjuvants and postoperative denosumab treatment associated with good postoperative function? (3) Does the use of extended curettage with adjuvants and postoperative denosumab treatment result in beneficial surgical downstaging in patients with Campanacci Grade III giant cell tumors of the extremities?

Patients and Methods

We retrospectively reviewed 23 patients with Campanacci Grade III GCTB of the extremities in our hospital between January 2017 and June 2023 who underwent extended curettage surgery with adjuvants and postoperative denosumab administration alone. Patients who received preoperative denosumab were excluded from the study. Patients without sufficient clinical information and those diagnosed with malignant GCTB were excluded from this study. This study was approved by the ethics committee of Southwest Hospital, Army Military Medical University.

We collected data from the medical records and included patient demographics, radiographic evaluations, and histopathological evaluations.

Tumor localization, soft tissue extension, date and type of surgical intervention, reconstruction method, surgery-related complications, revisions, reasons for revisions, local recurrence, and metastasis. Functional outcomes (evaluated using the Musculoskeletal Tumor Society (MSTS) score[16]) and denosumab-related adverse events (evaluated by the Common Terminology Criteria for Adverse Events, volume 4.03[17]) were assessed at the latest follow-up.

All patients were surgically treated by a senior oncological orthopedic surgeon (Shuai Zhang). Soft tissue extension and extent of bone involvement were assessed on preoperative plain radiographs and magnetic resonance imaging (MRI), occasionally with a computed tomography (CT) scan or emission computed tomography (ECT) bone scan of the lesion, depending on the presentation. The tumor mass in the surrounding soft tissues was resected with a safe margin (0.5–1 cm, except for the areas connected to cortical destruction. Fracture hematoma is also considered a soft tissue extension. Important blood vessels and nerves must be protected during the resection of soft tissue masses to avoid limb ischemic necrosis or severe neurological dysfunction of the extremities. A large bone window was then made to facilitate the observation and evaluation of the tumor under direct view. Curettage was performed through a large cortical bone window using curettes of different sizes and bending angles, and all the visible regions of the tumor were removed. Subsequently, the cavity was cauterized using a high-frequency electric knife (Figure 1) and alcohol was used in the remaining cavity for more than 15 min, followed by saline washout to remove all tumor tissues. The subchondral region was filled with autologous or allogeneic cancellous bone graft when the remaining subchondral bone was thin after tumor curettage to ensure that the thickness of the subchondral bone exceeded 1 centimeter (cm) (Figure 2). The tumor cavity was filled with polymethyl methacrylate (PMMA) bone cement. Subsequently, internal fixation was performed after

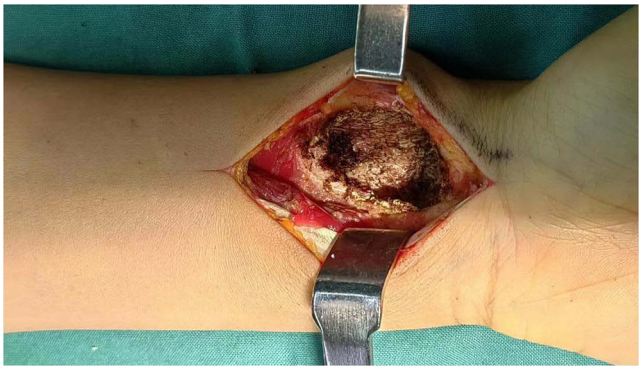

Figure 1 Intraoperative photo showing a case of giant cell tumor of the distal radius after removing all tumor tissues and the cavity was cauterized by high-frequency electric knife.

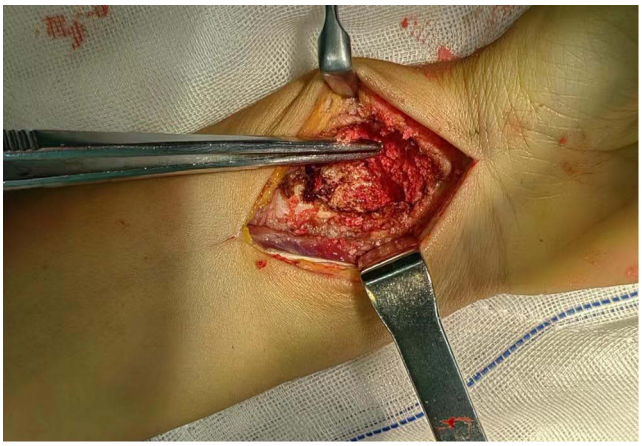

Figure 2 Intraoperative photo showing that the subchondral region was filled with allogeneic cancellous bone graft.

curettage to maintain structural integrity and allow early functional exercises despite the size of the bone defects. The wound was closed with deep drains.

Each patient was managed using a standard perioperative protocol, including intravenous antibiotics until all drains were removed, prophylaxis against venous thrombosis, and pain control. Some patients were immobilized in a brace for the first 4–-6 weeks to maintain joint stability and protect implants. Postoperatively, the patients received subcutaneous denosumab (120 mg) monthly for half a year. All patients were advised to receive denosumab every six months until disease progression, serious adverse drug reactions, withdrawal of patient consent, pregnancy, or absence of clinical benefit, according to the doctor's judgment. All patients were strongly advised to take daily supplements of ≥500 mg of calcium and ≥400 IU of vitamin D during denosumab therapy.

Our follow-up protocol consisted of radiography at 1, 3, and 6 months postoperatively, followed by half-yearly radiographs until 2 years postoperatively, and annually thereafter until the last follow-up. Chest computed tomography (CT) and ECT were performed at 1, 2, 3, and 5 years postoperatively. MRI of the tumor area was performed if recurrence was suspected. Local recurrence, lung metastasis, surgical and denosumab-related complications, graft union, and final joint preservation were recorded. At the final follow-up, functional results and pain in the affected extremity were evaluated using the Musculoskeletal Tumor Society (MSTS) system, which is based on six parameters: walking ability, pain, emotional acceptance, functional activities, use of external support, and gait. The results were excellent for MSTS scores ≥90%, good for 80–90%, satisfactory for 60–80%, and poor for≤60%.

Results

The details and functional outcomes of the patients in the present study are shown in Table 1, including the notable incidences of complications and problems. There were 15 men and eight women, with a mean age of 36.6 years (range, 20–63 years). The involved bone was the distal femur in 8 patients, proximal tibia in 4 patients, proximal humerus in 3 patients, distal radius in 7 patients, and scapula in 1 patient. Four patients had a pathological fracture, and six patients experienced recurrence before extended curettage surgery. At the final follow-up, all patients were alive and had a mean follow-up time of 35.8 months (range, 6–72 months), measured from the date of surgery. None of the 23 patients included in the present study had tumor metastasis. However, one (patient 20) experienced recurrence in the soft tissue and bone 14 months postoperatively, which was subsequently treated with en bloc resection and reconstruction with a vascularized fibular graft. Two patients (patients 9 and 12) had local recurrence in the bone 12 and 18 months later, respectively, and were treated with repeat intralesional surgery with adjuvants. These two patients had no additional recurrence at follow-up. The local recurrence rate after extended curettage with adjuvant therapy was 13.0% (three of 23). The relationship between local recurrence-free rate and follow-up time is shown in Figure 3.

The joint preservation rate was 95.7%. Only one patient received en bloc resection and reconstruction with a vascularized fibular graft due to recurrence. The mean overall MSTS score was 27.3 30 (range,25–29)., with 17 being excellent and 6 good. Joint function can meet the needs of daily life, with the exception of heavy labor. The detailed clinical data are presented in Table 1. One patient showed radiographic evidence of osteoarthritis, with experienced pain (especially physical activity). However, the pain can persist without the need for analgesics. X ray showed the healing of bone graft were satisfactory, no signs of subchondral collapse. Perioperative and 24-months' follow-up images of patient 22 are shown in Figures 4–7.

There were no major surgery-related complications, and one patient developed a superficial wound infection, which resolved after a 4-week course of antibiotics. Neuropraxia of the peroneal nerve was observed in one patient, potentially caused by stretching during surgery, and the function of the affected extremity recovered within six months. None of the patients experienced immune rejection, fractures, failure of internal fixation, or significant graft bone resorption. No serious adverse events, malignant progression, or positively adjudicated osteonecrosis of the jaw due to denosumab treatment were detected. Five patients had at least one denosumab-related adverse event, most frequently headache, nausea, fatigue, back pain, or musculoskeletal pain. None of the patients discontinued denosumab treatment owing to adverse events. Only one patient discontinued denosumab treatment for 12 months because of cost constraints.

Discussion

Campanacci Grade III GCTB of the extremities is also considered an intermediate primary bone tumor despite being more aggressive and easier to recur and metastasize. The rate of metastasis is approximately 1% in patients without recurrence and 6% in those with recurrence.[18] This unique behavior of GCTB has led to controversy regarding optimal surgical treatment. Grade III lesions are often treated with en bloc resection owing to obliteration of the cortical bone and extension into the soft tissue to prevent local recurrence.[3–5] However, wide resection results in poor functional outcomes in the anatomic location,[3,6] especially in the context of the proximal humerus and distal radius. Intralesional surgery with adjuvants tends to have better functional results with joint preservation but has been associated with relatively higher local recurrence rates.[3,6] A retrospective study involving 408 patients with GCTB of the extremities reported a local recurrence rate of 16% in those treated with curettage alone compared to 60% in those treated with curettage after preoperative deno-sumab therapy.[12] Asano et al[15] performed a retrospective study and found that among patients with Campanacci grade 3 tumors, 53 patients underwent curettage, and 21 (39.6%) had local recurrence. However, the recurrence rate in our study was only 13.0%, significantly lower than that reported in the previous literature in patients treated with curettage of patients with Campanacci Grade III tumors. We believe that this lower recurrence rate is due to the following reasons: (1) the tumor mass in the surrounding soft tissues was resected with a safe margin (0.5–1 cm, a large bone window was created to facilitate observation and evaluation of the tumor under direct view, and curettage with adjuvants was performed through the large cortical bone window. All patients underwent extended curettage to obtain a safe surgical margin. (2) When structural integrity could not be regained after bone grafting or bone cement

Table 1 Characteristics and Results of the 23 Patients

Case	Sex	Age	Site	Pathological Fracture at Presentation	Local Recurrence at Extended Curettage Surgery	Follow-up, Months	Duration of Postoperative Denosumab Therapy (Months)	Surgery-Related Complication	Denosumab-Related Complication	Recurrence and Treatment	MSTS Score*
1	Male	33	Proximal humerus	No	Yes	66	60	None	Fatigue, musculoskeletal pain	None	93.3 (28)
2	Female	28	Distal tibia	No	No	67	66	None	None	None	96.7 (29)
3	Male	51	Scapula	No	No	60	60	None	nausea, fatigue	None	86.7 (26)
4	Male	36	Distal radius	No	No	26	24	None	None	None	86.7 (26)
5	Male	20	Proximal humerus	Yes	No	32	30	None	None	None	83.3 (25)
6	Female	49	Distal femur	No	Yes	26	24	Neuropraxia of the peroneal nerve	None	None	90.0 (27)
7	Male	26	Distal radius	No	No	35	30	None	None	None	93.3 (28)
8	Male	41	Proximal tibia	No	No	39	36	Superficial wound infection	None	None	96.7 (29)
9	Male	29	Distal radius	Yes	No	62	60	None	Back pain, headache	Once (12 months), repeat extended curettage and bone cement	86.7 (26)
10	Female	33	Distal radius	Yes	No	45	42	None	None	None	93.3 (28)
11	Male	31	Distal femur	No	No	48	48	None	None	None	96.7 (29)
12	Male	63	Distal femur	No	No	50	48	None	None	Once (18 months), repeat extended curettage and bone cement	90.0 (27)
13	Male	23	Distal radius	No	No	52	48	None	Fatigue	None	93.3 (28)
14	Male	35	Proximal humerus	No	No	8	6	None	None	None	96.7 (29)

(*Continued*)

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Table 1 (Continued).

Case	Sex	Age	Site	Pathological Fracture at Presentation	Local Recurrence at Extended Curettage Surgery	Follow-up, Months	Duration of Postoperative Denosumab Therapy (Months)	Surgery-Related Complication	Denosumab-Related Complication	Recurrence and Treatment	MSTS Score*
15	Male	23	Distal femur	No	No	12	12	None	None	None	96.7 (29)
16	Female	47	Distal femur	No	Yes	6	6	None	None	None	90.0 (27)
17	Male	51	Distal femur	Yes	Yes	9	6	None	None	None	83.3 (25)
18	Male	37	Distal femur	No	No	18	18	None	None	None	90.0 (27)
19	Female	29	Proximal tibia	No	Yes	12	12	None	None	None	93.3 (28)
20	Female	34	Distal radius	No	No	39	36	None	None	Once (14 months), en bloc resection and reconstruction with vascularised fibular graft	83.3 (25)
21	Male	40	Proximal tibia	No	No	16	12	None	None	None	96.7 (29)
22	Female	54	Distal radius	No	No	24	24	None	None	None	90.0 (27)
23	Female	29	Distal femur	No	Yes	72	60	None	Musculoskeletal pain, fatigue, back pain	None	90.0 (27)

Note: *Musculoskeletal Tumor Society (MSTS) score calculated as the percentage of the maximum possible score of 30.

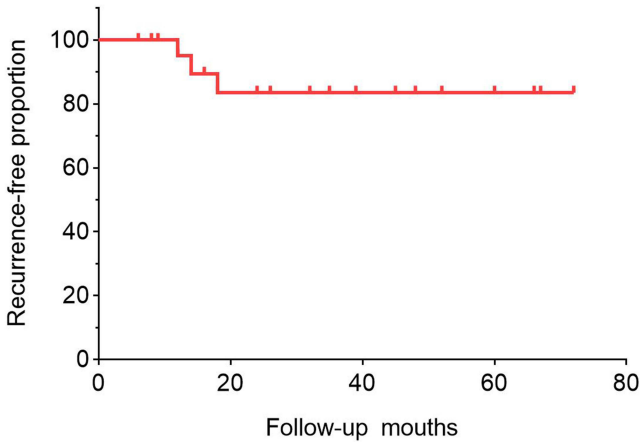

Figure 3 Local recurrence-free survival and follow-up time.

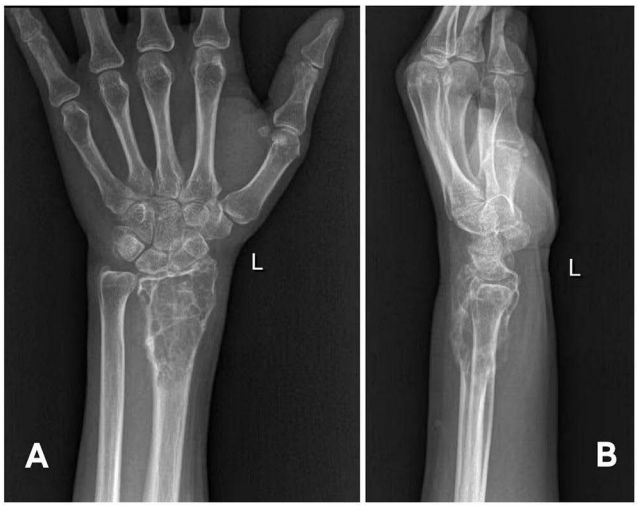

Figure 4 Preoperative X-ray, (**A**) anteroposterior and (**B**) lateral views of patient 22 showing Campanacci grade III giant cell tumor (GCT) of the distal radius.

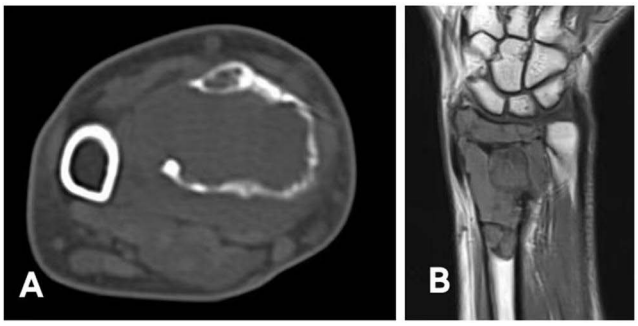

Figure 5 (**A**) A CT image and (**B**) a MR image of patient 22 show cortical destruction and soft tissue extension of the GCT.

filling combined with internal fixation, resection was performed. We excluded patients whose recurrence rates were higher when curettage was performed. This may be another reason for the finding. (3) The application of postoperative denosumab therapy maybe delay the local recurrence, then reduce the recurrence rate at the last follow up.

The subchondral bone at the joint is destroyed by tumor destruction and extended curettage. This leads to irregularity of the articular surface and instability of the lower limbs, which, in turn, leads to further wear of the articular surface. In

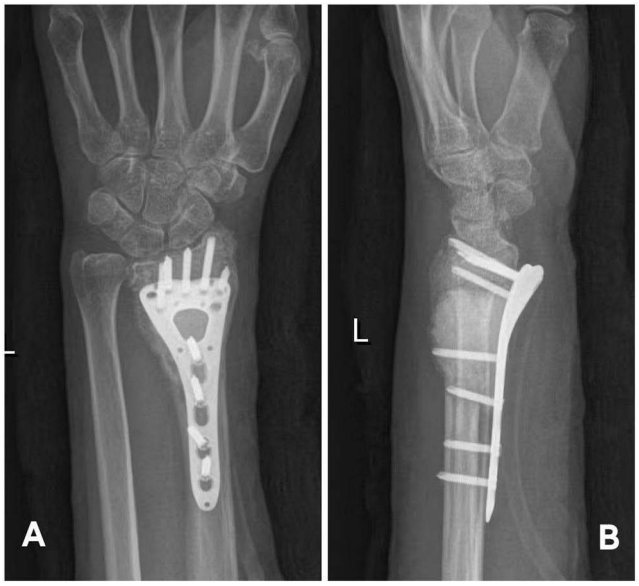

Figure 6 Postoperative X-ray, (**A**) anteroposterior and (**B**) lateral views of patient 22 after surgery.

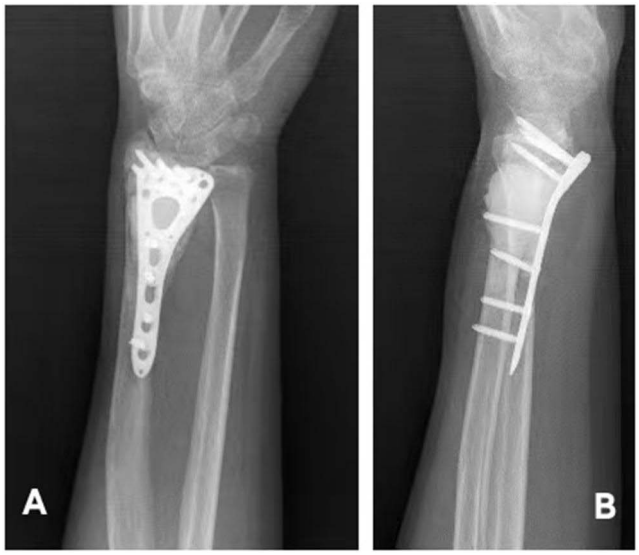

Figure 7 Postoperative X-ray, (**A**) anteroposterior and (**B**) lateral views of patient 22 after 24 months follow-up.

addition, the filled bone cement cannot be integrated into the host bone, and the elastic moduli of the two materials are different. When the patient walks, the bone cement rolls slightly, causing damage to the subchondral and articular cartilage, which in turn results in mechanical wear of the joint. Abdelrahman et al[19] reported that when the tumor was less than 1 cm from the articular surface, the incidence of degenerative changes in the articular cartilage after the use of cement alone was more than 2.5 times greater than that when the tumor was more than 1 cm away. Studies have also shown that cement constructs are less rigid than normal subchondral bone and successful bone graft.[20] Therefore, we believe that more attention should be paid to the preservation of subchondral bone, and the thickness of the subchondral bone should be greater than 1 cm. At the last follow-up, most of our patients showed bone graft fusion, normal contour of the articular surface, and no stenosis of the articular space. Only one patient with radiographic evidence of osteoarthritis showed early degenerative joint changes.

The joint preservation rate was 95.6%, and joint function, evaluated using the American Musculoskeletal Tumor Society system, was well preserved in all patients in the current series. Functional outcomes in our patients were improved compared with reported outcomes of en bloc resection, especially in studies of proximal humerus and distal radius resections and reconstructions for GCTB.[21,22] Except for excellent functioning, no major surgery-related complications were observed in our patients. Only one patient developed a superficial wound infection, and neuropraxia of the peroneal nerve was observed in one patient. Surgery-related complications can easily be resolved. Fewer surgery-related complications and better functional results support the use of extended curettage with adjuvants and postoperative denosumab treatment to defer or downstage the planned surgical procedure in patients with Campanacci Grade III cell tumors of the extremities.

Denosumab, which is highly effective in suppressing the progression of GCTB, has been used in many cases for the treatment of GCTB for more than a decade, although studies shown that the combination of denosumab and lenvatinib in the treatment of GCTB is a promising therapeutic strategy compared to single-agent chemotherapy.[23] However, the role of denosumab in patients with GCTB who can be treated with curettage is not well-defined. An increasing number of studies[13,15,22] have observed potentially increased risk of local recurrence after surgery following the preoperative application of denosumab, raising concerns regarding the use of this agent against GCTB in combination with surgery. Chawla et al[24] found that preoperative denosumab therapy in combination with curettage surgery was significantly associated with an increased risk of local recurrence in Campanacci Grade 3 tumors in a multi-institutional retrospective study involving 234 patients. Chinder et al reported the following: The use of preoperative denosumab for GCTB was the only significant risk factor for local recurrence.[25] Both previous reports and our patients have found that preoperative denosumab treatment causes irregular ossification within the GCTB and new bone on the periphery of the tumor. New bone formation makes it difficult to recognize the true margins to be removed during curettage, and neoplastic cells may remain. This may be the main cause of tumor recurrence. Therefore, we abandoned the preoperative use of denosumab and chose only postoperative application after extended curettage for Campanacci Grade III tumors.

Furthermore, there is no consensus on the management of postoperative denosumab use after curettage. Further investigation is required to determine the optimal interval and duration of postoperative denosumab treatment. Postoperatively, our patients received subcutaneous denosumab monthly for half a year. All patients were advised to receive denosumab every six months until disease progression, serious adverse drug reactions, withdrawal of patient consent, pregnancy, or absence of clinical benefit, according to the doctor's judgment. The reasons for choosing this strategy are as follows: First, some patients cannot bear high financial pressures due to the long-term application of denosumab after undergoing surgery, especially in the underdeveloped areas of western China. Second, all patients underwent extended curettage to obtain safe surgical margins. This might have reduced the frequency of denosumab use. Third, we were concerned about the side effects and resistance to denosumab, making the patient unable to benefit from denosumab treatment. Fourth, the potential malignant transformation after denosumab use, which has been reported in previous studies,[16,26] was concerning, especially for long-term use.

We recognize the following significant limitations of our results: the number of patients was small, the follow-up was not yet sufficient to report long-term results, there was a lack of a control group, and it was retrospective. However, this is a relatively uncommon tumor and large numbers cannot be readily obtained from a single institution. By reporting the results of this initial study, we hope to encourage the appropriate use of this promising strategy for Campanacci grade III GCTB to obtain better clinical results. A larger series, multicenter study, and longer follow-up are needed to further verify long-term efficacy. A future randomized clinical trial would be desirable to clear up this issue.

Conclusion

Based on the current follow-up results, except for some limitations, extended curettage with postoperative denosumab administration can achieve adequate local control, obtain good postoperative function, and result in beneficial surgical downstaging, including either a less morbid surgical procedure or delayed en bloc resection for patients with Campanacci Grade III giant cell tumors of the extremities. Resection should be considered when the structural integrity cannot be regained after bone grafting or bone cement filling combined with internal fixation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of the Army Medical University in accordance with the Declaration of Helsinki and relevant policies in China. And the publication of the details of the cases involved in this study has been approved by the First Affiliated Hospital of the Army Medical University. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Consent for Publication

Written informed consent was obtained from all participants.

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Disclosure

The authors declare that they have no conflicts of interest.

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