

## ORIGINAL ARTICLE

# Therapeutic benefits of neoadjuvant and post-operative denosumab on sacral giant cell tumor: a retrospective cohort study of 30 cases

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## Summary

**Purpose:** Denosumab, a new monoclonal antibody that inhibits receptor activator for nuclear factor  $\kappa$ B ligand (RANKL), has recently been approved by FDA for the treatment of aggressive giant cell tumor of bone (GCTB). So we initiated this study to evaluate the clinical benefits of denosumab used preoperatively or postoperatively.

**Methods:** Patients diagnosed with classic sacral GCT without metastasis were included in this study. Patients were assigned into 3 groups according to the use of denosumab: control group 1, post-operative group 2 and neoadjuvant group 3. The latter two groups were treated with 120 mg of subcutaneous denosumab every 4 weeks with loading doses on days 8 and 15 of the first cycle. The primary endpoints were event-free-survival (EFS) and objective response rate (OPR) based on RECIST criteria. A system (MUD system) proposed by our center was applied to score the sacral nerve deficit changes before surgery in group 3.

**Results:** A total 30 patients (13 men and 17 women, mean age 34.7 years, range 15-56) were enrolled from April 2014 to July 2016. Group 1 included 10 patients, group 2 9 and group 3 11. The study ended in March 01, 2017, and follow-up ranged from 3 to 36 months (mean 18.3). Two patients with PET-CT showed SUV max uptake down to muscle tissue level. In the neoadjuvant group 3 7 patients had partial responses and 4 stable disease (ORR 63.6%; 95% CI 35-92). Most (80%) patients achieved significant improvement in pain and great relief in the bladder and bowel functions. In 4 patients the uro catheter was removed after neoadjuvant denosumab.

**Conclusion:** Neoadjuvant therapy with denosumab can significantly relieve the symptoms and neurologic deficits.

**Key words:** denosumab, giant cell tumor of bone, neoadjuvant, RANKL, sacrum

## Introduction

GCTB, a kind of borderline primary bone tumor mainly occurring in people aged 20-40 and those from East Asia, is characterized by osteolytic lesions of mild aggressiveness. Some cases of GCTB have the potential of metastasizing and truly malignant transformation. Surgery is the main therapeutic approach of GCTB. Taking up about 2.5% of lesions in the whole body, sacral giant cell tumor

(sacral GCT) is a kind of GCTB being adjacent to important organs, vessels and nerves. Its complex anatomical structure makes the surgery very difficult, leading to large amount of intraoperative blood loss and very high postoperative recurrence rate [1]. A previous study conducted in our hospital has shown that intralesional curettage aided by tumor-feeding artery embolization (DSA) and

balloon occlusion of abdominal aorta can increase the 5-year recurrence-free survival rate of sacral GCT to 69.6% [2]. However, how to further reduce the local recurrence rate of sacral GCT is a problem demanding prompt solution.

Osteoclast-like giant cells and mononuclear stromal cells are the two main components of GCTB, and the receptor activator of nuclear factor- $\kappa$ B ligand RANKL expressed by the latter is a key factor starting osteoclast differentiation [3]. Recently, denosumab, a fully human monoclonal antibody that can inhibit RANKL, has been approved by FDA as an adjuvant therapy for progressive GCTB. Two phase 2 clinical studies verifying the efficacy of denosumab in controlling the progress of GCTB have been published in Lancet [4,5], and previous clinical observations conducted in our hospital have indicated that the safety and efficacy of denosumab in Chinese GCTB patients is similar to that in Caucasians [6]. Considering the significant efficacy of denosumab in treating GCTB, researchers have suggested that drugs should be administered to control lesions in body parts with high risk of surgery, such as the sacrum [4-6]. However, there is still no study analyzing the effect of postoperative use of denosumab on the prognosis of sacral GCT and the effect of preoperative neoadjuvant use of denosumab on the function of sacral nerves. Therefore, this retrospective study was conducted to evaluate the clinical significance of postoperative and preoperative denosumab combined with surgery.

## Methods

### Research design

As a retrospective cohort study, this study only included patients who met all the following criteria: (1) with treatment-naïve sacral GCT firstly treated in our center (for referral patients, only those with definite diagnosis were included); (2) with only lesion in sacrum without metastasis, which can involve bilateral sacroiliac joints but not beyond the IV region of pelvis; (3) being diagnosed with classic GCTB by puncture pathology prior to treatment (for referral patients, definite diagnosis should be made by the Pathology Department in our center through pathology consultation on tissue sections); (4) previously denosumab-naïve. According to the administration time of denosumab, patients included in this study were classified into 3 groups: (1) the control group, including patients who never received denosumab in the whole process; (2) the postoperative denosumab group, including patients receiving denosumab after intralesional curettage aided by digital subtraction angiography (DSA) and balloon occlusion of abdominal aorta; (3) the neoadjuvant denosumab group, including patients receiving denosumab prior

to surgery. Denosumab 120 mg was administered to patients by subcutaneous injection every four weeks, with loading doses on days 8 and 15 of the first cycle. Patients were instructed to take calcium supplements orally every day and avoid any oral operation during treatment [4]. The following patient data included in this study were collected: (1) basic information: age, gender; (2) pathological data: puncture pathological diagnosis, and postoperative pathological findings; (3) the imaging findings (including X-ray, CT, MRI, PET-CT) and functional assessment of patients in the neoadjuvant denosumab group before and after the use of denosumab; (4) intraoperative blood loss and duration of operation; (5) imaging findings in postoperative follow-up re-examination and outcome.

### Efficacy and functional assessment

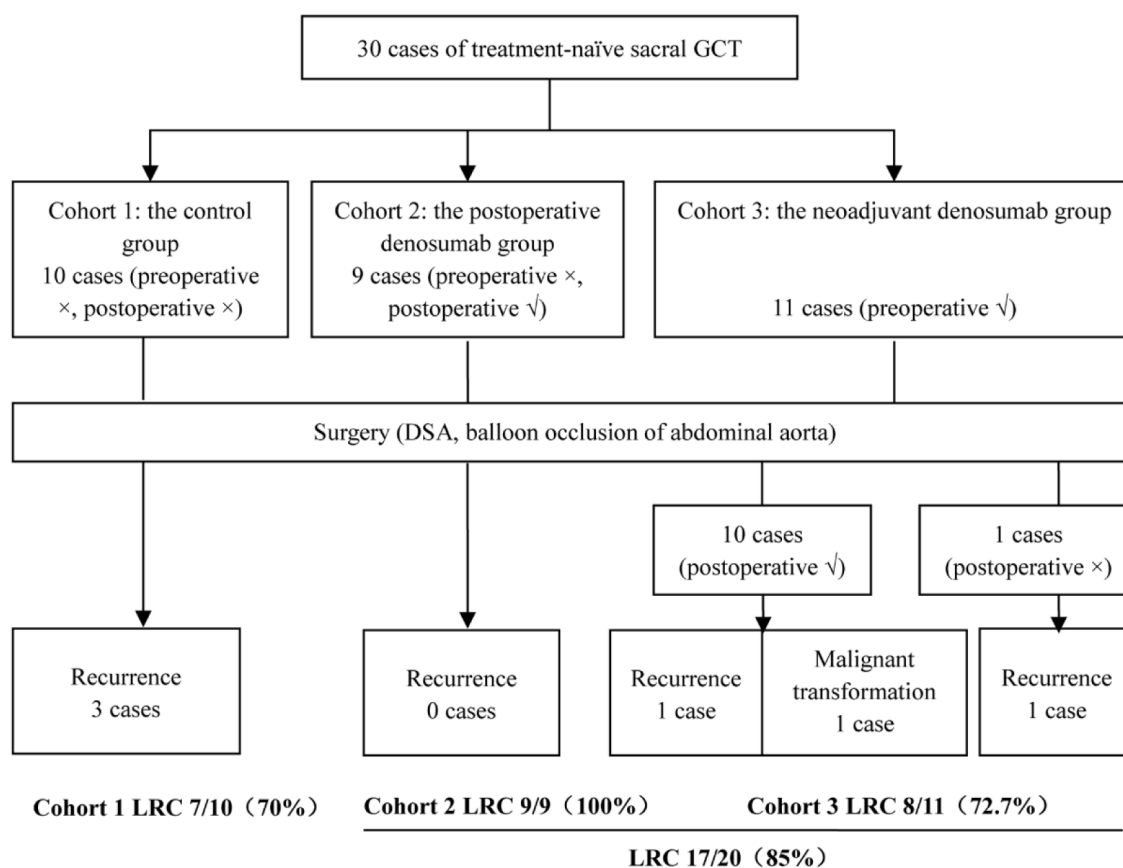
Safety assessment indicators mainly included adverse drug reactions (clinical symptoms and laboratory abnormalities). The RECIST criteria and the histologically clearance of giant cells were used to estimate the efficacy of denosumab in the neoadjuvant denosumab group [7]. The MUD scoring system published on Spine by our center in 2016 [8], which included three domains (motor function and sensation of lower limbs [M], urination and uriesthesia [U], and defecation and rectal sensation [D]) with three items in each domain (each item can be scored by 0, 1, 2 or 3, and with maximum score 27), was applied in the functional assessment of sacral nerves. The effect of preoperative medication on intraoperative blood loss and duration of operation were analyzed. The locoregional control (LRC) rate was compared among the three groups.

### Statistics

SPSS 20.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. The Kaplan-Meier method was used to evaluate event-free survival. All quantitative data were expressed as mean  $\pm$  standard deviation. Comparison between groups was done using One-Way ANOVA test, followed by *post hoc* test (least significant difference). P values  $<0.05$  were considered statistically significant.

## Results

Thirty patients with sacral GCT (13 males and 17 females) were enrolled in this study between April 2014 and July 2016. The mean age of patients was 34.7 years (range: 15-56; median 36). Among the 30 patients, 10 were enrolled in the control group 1, 9 in the postoperative denosumab group 2, and 11 in the neoadjuvant denosumab group 3 (Figure 1). Patients in the neoadjuvant denosumab group started treatment with denosumab before surgery, with a range of 1-11 doses of preoperative denosumab received (mean 4.1). Ten of these patients went on to receive denosumab after surgery, but one aged 14 did not. Patients in



**Figure 1.** Flow chart of grouping and the locoregional control rate (LRC) in each group.

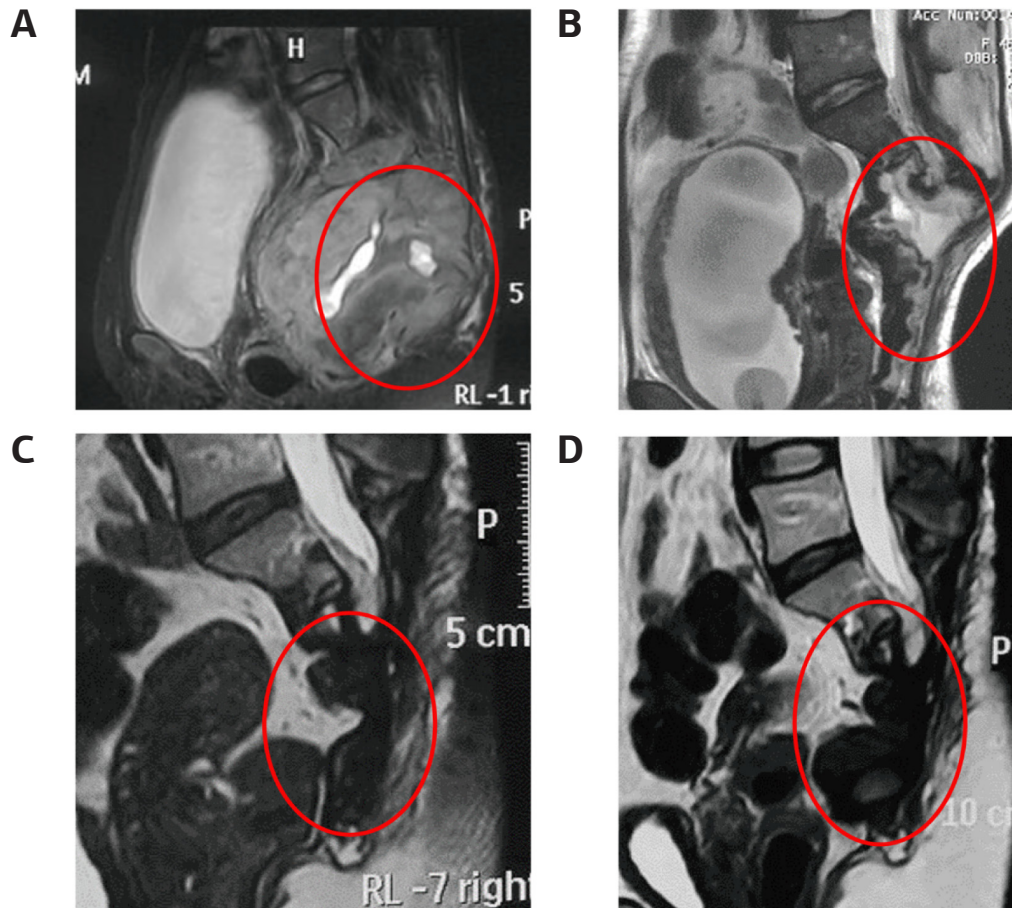


**Figure 2.** CT images of a 14-year-old female patient with sacral GCT: **A:** before surgery; **B:** after 4 doses of denosumab treatment; **C:** tumor recurrence was observed 9 months after surgery (red arrows indicate the tumors).

the postoperative denosumab group received 4-24 (mean=12) doses of denosumab. Follow-up started from surgery, and the last visit was on March 1, 2017. The duration of follow-up lasted for 3-36 months (mean 18.3). As of the end of follow-up, recurrence was observed in 3 cases in the control group (3/10), 0 in the postoperative denosumab group (0/9), and 3 in the neoadjuvant denosumab group (3/11). Of the 3 recurrence cases in the neoadjuvant denosumab group, a male patient aged 43 was shown to have secondary malignant GCT by postoperative pathological examination, which progressed rapidly after surgery and showed no response to continuing use of denosumab. This patient died six months later. Another patient was

the above-mentioned one aged 14 who did not use denosumab after surgery in consideration of skeletal development and experienced recurrence 9 months later (Figure 2). The third patient was a female aged 46 who received denosumab for 12 months after surgery and experienced local recurrence when denosumab had been discontinued for 12 months (Figure 3).

In event-free survival, there was no significant difference between the control group and the treatment group (groups 2+3) ( $p=0.149$ ) as well as among group 1, 2 and 3 ( $p=0.133$ ) (Figure 4). With regard to the duration of surgery and intraoperative blood loss, there was no difference between the control group and the neoadjuvant denosumab

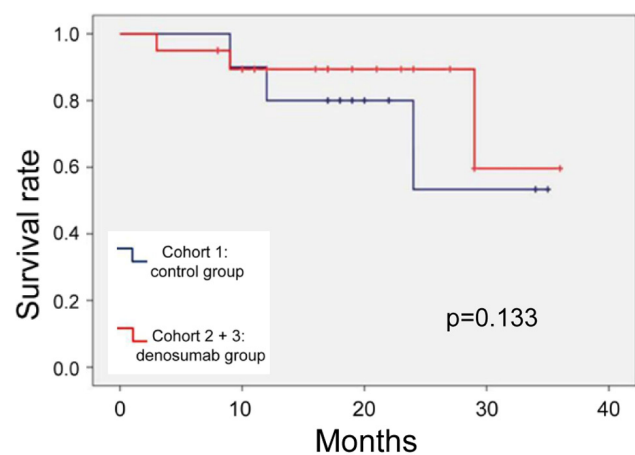


**Figure 3.** MRI images of a 46-year-old female patient with sacral GCT who received 4 doses of denosumab before surgery and 12 doses of denosumab after surgery and experienced tumor recurrence when denosumab had been discontinued for 12 months. **A:** 1 month after preoperative denosumab treatment; **B:** 12 months after postoperative denosumab treatment; **C:** 12 months after postoperative denosumab withdrawal; **D:** 18 months after postoperative denosumab withdrawal (the red circles indicate tumors).

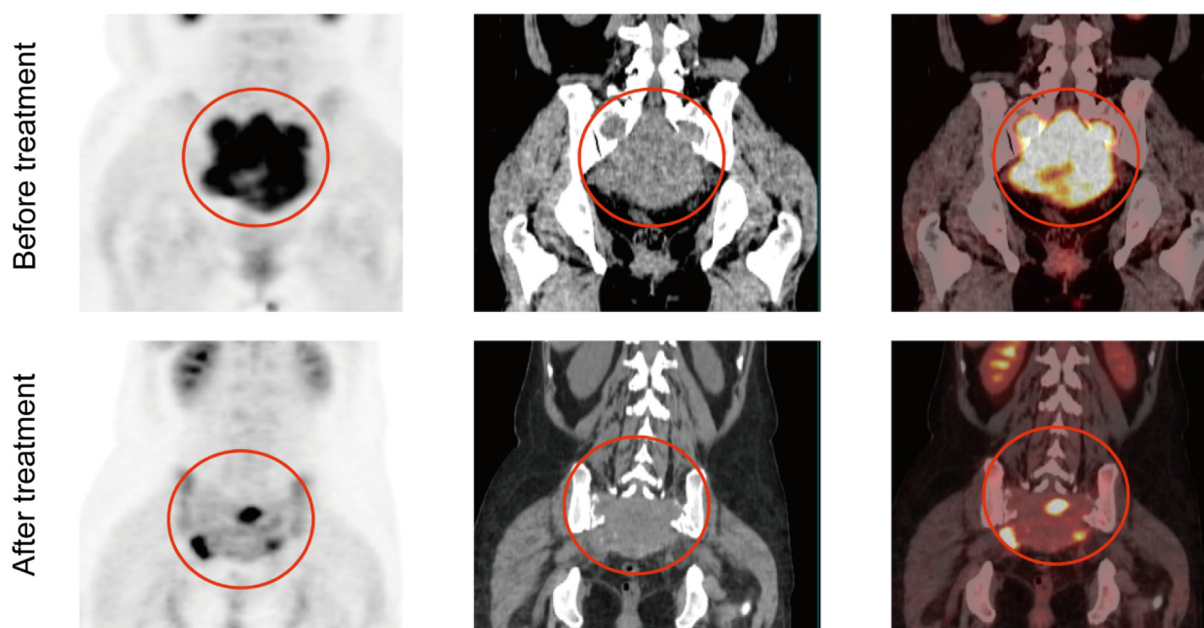
group. No osteonecrosis of the jaw (ONJ) was observed in all patients treated with denosumab. A patient in the neoadjuvant denosumab group was shown to have sarcomatous transformation by postoperative pathological examination, and died of tumor progression three months after surgery.

After drug administration, the RECIST evaluation conducted for the neoadjuvant denosumab group showed 7 cases of partial response (PR), 4 cases of stable disease (SD), an objective response rate (ORR) of 63.6% (7/11), and a histologically clearance rate of giant cells of 100% (10/10). Except for one patient who experienced malignant transformation, no residual giant cell tumor was observed by postoperative histological examination in any other patients. In 2 patients PET-CT was performed before and after being treated with preoperative denosumab, and their SUV values at the latter time point decreased significantly as compared to that at the former one (7.7 to 4.9; 8.1 to 2; Figure 5). In 80% of the patients from the neoadjuvant denosumab group pain was significantly relieved. Symptoms

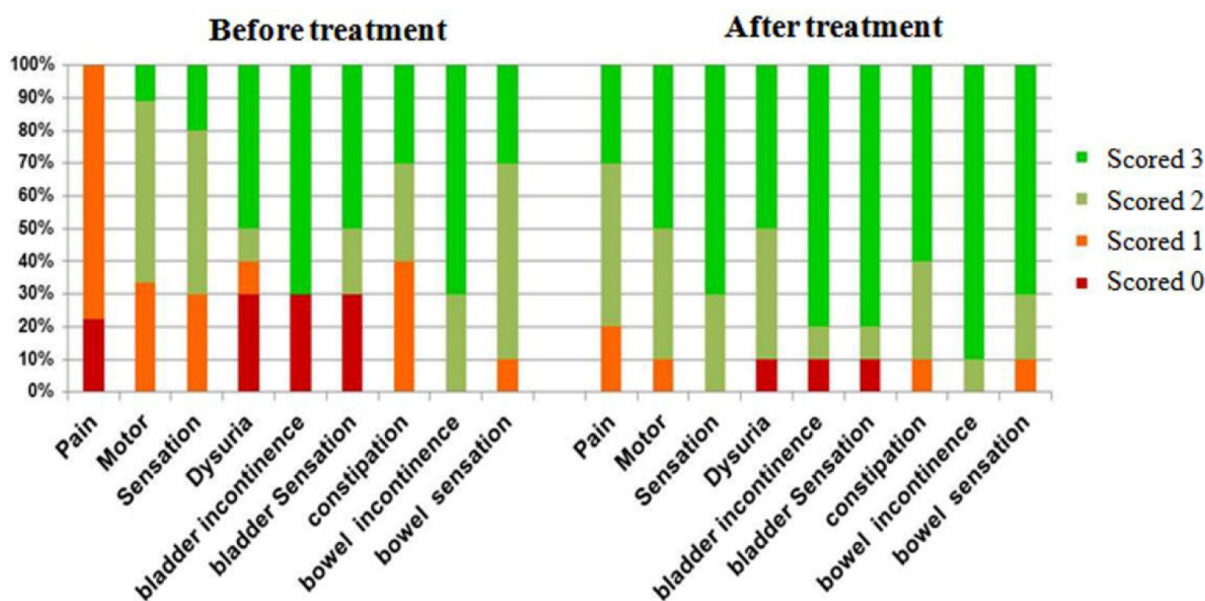
including difficulty in bowel movement or urination, bladder and bowel incontinence, and feeling of numbness were relieved and ruinous catheter could be pulled out in 2 of 4 patients (Figure 6).



**Figure 4.** Kaplan-Meier survival of control and denosumab groups.  $p=0.133$



**Figure 5.** Change in PET-CT imaging (including functional, anatomical and fusion images) before and after denosumab treatment (the red circles indicate the tumors).



**Figure 6.** The recovery status of sacral nerve function evaluated by the MUD scoring system with preoperative use of denosumab.

**Discussion**

Before denosumab was developed, only radiotherapy was used traditionally for GCTBs that were unresectable and highly risky (i.e. with lesions located in body parts with complex anatomical structure such as spine, pelvis and sacrum, or repeatedly recurrent) [9]. Interferon  $\alpha$  was reported to have some effect on GCTB in several reports [10]. However, results from follow-up visits showed that patients treated with denosumab for a long time

may develop some serious complications, such as ONJ. What’s more, patients with unresectable disease or without satisfactory surgical margin were faced with high risk of recurrence. This retrospective study was conducted to evaluate the safety and efficacy of denosumab combined with surgery and the prognosis of disease.

*Safety of denosumab*

Denosumab is a fully human biological agent with very high safety. Perioperative use of deno-

sumab did not lead to serious adverse reactions or operative complications. ONJ is a serious complication [11], but no case of ONJ was observed in this study, which might be related to the fact that patients had been told by the investigators to avoid oral operation (tooth extraction and filling) during treatment. Patients shall be told to take 500 mg calcium everyday during treatment to prevent hypocalcemia. In this study, a patient diagnosed with classic GCTB by preoperative pathological examination was shown to have secondary malignant GCTB by postoperative pathological examination. This patient received 4 doses of denosumab before surgery, with significant pain relief and significant tumor volume reduction. However, drug resistance occurred after surgery and the tumor progressed rapidly, which led to his death after 6 months. The pathologic morphology of GCTB changed a lot with the use of denosumab, with some cases being histologically highly similar to high-grade malignant osteosarcoma (short-term use) or low-grade malignant central osteosarcoma (long-term use). In 2015, Aponte-Tinao et al. [12] firstly reported a case of true sarcomatous transformation induced by denosumab, after which many similar cases have been reported [13,14]. But no plausible biologic evidence has been identified to support a causal association of malignant transformation with denosumab treatment. The patient with sarcomatous transformation in this study had been previously treated for 2 years with selective arterial embolization, therefore, the relationship between sarcomatous transformation and denosumab use in this case needs to be further investigated.

#### *The effect of perioperative use of denosumab on the recurrence rate of tumor*

In this retrospective study we tried to evaluate the effect of preoperative and postoperative use of denosumab on GCTB and the prognosis of disease, but its nonrandomized design may lead to selection bias. No significant difference in LRC rate was observed between the treatment groups using denosumab and the control group never using denosumab ( $p=0.149$ ). Cases of local recurrence were mainly from the neoadjuvant denosumab group, while no case of recurrence was observed in the postoperative denosumab group. The higher rate of recurrence in the neoadjuvant denosumab group might be attributed to the residual neoplastic stromal cells in GCTB caused by the preoperative use of denosumab made the surgery in the complex anatomical structure of sacrum more difficult, leading to a higher risk of intraoperative

tumor residue and postoperative recurrence [13]. The intralesional curettage aided by DSA and balloon occlusion of the abdominal aorta conducted in our hospital can remove the lesions relatively completely, and with the postoperative use of denosumab to remove residual disease, a better LRC rate was achieved.

#### *Discussion on preoperative use of denosumab*

This study has shown that the preoperative use of denosumab can effectively relieve patients' pain and disorders in defecation and urination. In most patients, the volume of tumor was reduced, the metabolic activity of tumor detected by PET-CT was lowered significantly, and the blood supply of tumor detected by enhanced scanning was also decreased. What's more, in some patients, the duration of the operation was shorter and the intraoperative blood loss was less as compared to the control group. These facts indicated that the preoperative use of denosumab can lower the level of difficulty in surgery, thus benefiting patients with GCTB. However, the duration of medication should be shortened to the greatest extent so as to avoid the formation of thick rim of new bone formed after denosumab administration. We hold the idea that 3-4 doses of denosumab [15] and no longer than 4 weeks of medication is appropriate before surgery. At present, strictly randomized controlled trials are urgently needed in this topic.

#### *Withdrawal and rebound*

According to the medication experience of 97 patients with GCTB from Rizzoli center reported by Palmerini et al. [16], patients with satisfactory surgical margin could withdraw the medication and be monitored after having received postoperative denosumab for a period of time, while those with unresectable disease were suggested to take denosumab for a long time, because the recurrence rate of them could be as high as 40% if denosumab was discontinued. Of the two patients experiencing recurrence without malignant transformation in this study, one did not take postoperative denosumab in consideration of age, and the other took postoperative denosumab for one year but experienced recurrence after the medication had been discontinued for one year. Thus, it can be preliminarily inferred that postoperative use of denosumab can lower the risk or delay the time to recurrence, but the prerequisite is achieving satisfactory surgical margin. Long-term postoperative use of denosumab may increase the risk of ONJ. Therefore, the treatment of denosumab alone is not an ideal therapeutic strategy.

## Limitations and conclusions

Limitations of this study are its retrospective design and its small sample size that weakened the accuracy of the statistical analysis to some extent. Even so our study still provided a proof that denosumab is an effective therapy for sacral GCT that can relieve pain and disorders in defecation and urination caused by sacral nerve compression. The neoadjuvant use of denosumab can reduce patient's intraoperative blood loss by shrinking the tumor size which facilitate the surgeon. The effect

of neoadjuvant use of denosumab combined with surgery on long-term recurrence rate of disease needs to be further investigated. Patients receiving prolonged treatment with denosumab should be monitored for complications, especially ONJ. In a word, as a systemic therapy, denosumab combined with surgery wins a place in the multidisciplinary treatment of sacral GCT.

## Conflict of interests

The authors declare no conflict of interests.

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