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Denosumab combined with en bloc resection and arthrodesis for recurrent grade 3 giant cell tumor of bone in distal radius

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Abstract

Purpose This study aimed to analyse the clinical outcomes of preoperative adjuvant denosumab therapy (PADT) combined with resection and arthrodesis for recurrent grade 3 giant cell tumor of bone (GCTB) in the distal radius.

Methods A retrospective study was conducted on twenty-three patients (8 males, 15 females) who were treated with the adjuvant denosumab combined with en bloc resection (EBR) and arthrodesis for biopsy confirmed recurrent Campanacci III giant cell tumor of bone in the distal radius between January 2015 and December 2022. All 23 patients were treated with wrist arthrodesis reconstruction using autogenous free iliac crest bone graft (ICBG), bridging plate and screws. The local control, metastasis and overall survival were evaluated during the follow-up period. Functional outcomes were evaluated using the Disabilities of the Arm, Shoulder and Hand (DASH) score, Musculoskeletal Tumor Society Score (MSTS-87 and MSTS-93), and grip strength in the follow-up period. Additionally, all surgical or denosumab-related complications that occurred were recorded in this study.

Results Twenty-three patients were included in this retrospective study and no patients were lost in the follow-up period. The average patient age was 32.5 ± 10.2 years (range, 19–53 years) and the mean follow-up time was 35.5 ± 18.4 months (range, 13–72 months). The average tumor length was 71.7 ± 8.7 mm (range, 50 to 85 mm) and bone reconstruction length was 78.5 ± 8.5 mm (range, 60 to 90 mm). Four patients (17.4%) had secondary local recurrence after reoperation and two patients had (8.7%) multiple recurrences. One patient (4.3%) was deceased in the last follow-up due to multiple metastases. The estimated 5-year recurrence-free survival rate was 81.3% and 5-year metastasis-free survival rate was 95.7%. The mean union time was 8.5 ± 1.9 (6–12) months and the overall survivorship of the allograft was 82.7% (21/23) at an average 35 month follow-up. The average MSTS-87 and MSTS-93 scores were 27.8 ± 1.6 (range, from 23 to 30) and 91.5 ± 5.0 (range, from 76 to 100), and the average DASH score was 8.9 ± 3.2 (range, from 3 to 15), respectively. The average grip strength was 64.6 ± 15.7% (range, from 30 to 95%) of the uninvolved side. Eight patients (34.7%) had at least one complication in the follow-up time. Two autografts (8.7%) were removed due to local recurrence and bone nonunion, and the average autograft survival time was 32.8 ± 18.5 months (range, 12 to 72 months).

Conclusions Preoperative adjuvant denosumab therapy (PADT) combined with en bloc resection and arthrodesis is a promising method for the treatment of recurrent Campanacci III GCTB in distal radius with acceptable short-term local control and functional satisfaction.

Level of evidence: level IV Therapeutic.

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Keywords Denosumab, Recurrent GCTB, Arthrodesis, Distal radiusl Campanacci III

Introduction

Giant cell tumor of bone (GCTB) is a histologically benign but clinically aggressive bone tumor, and a high local recurrence rate has been the main cause of unsatisfactory clinical outcomes [1–3]. The former studies have reported a local recurrence (LR) rate ranging from 3 to 65% in GCTB [4–7]. Despite curettage combined with adjuvant local therapy has been the most widely used surgical technique in the treatment of Campanacci I or II GCTB, the high local recurrence rate in Campanacci III tumors remains a challenging clinical problem. Among all surgical techniques in the treatment of GCTB, en bloc resection has the lowest recurrence rate from 3 to 25% [8, 9]. The most common lesion locations of GCTB are the distal femur, proximal tibia, and distal radius. The distal radius is associated with a higher risk of local recurrence especially in Campanacci III tumors [10–12]. Therefore, en bloc resection followed by reconstructions as a primary treatment has been supported by many studies [13–16].

Denosumab is a human monoclonal antibody that inhibits the RANK-RANKL (receptor activation of nuclear factor-kappa β ligand) pathway and osteoclast-mediated bone destruction, and was approved for the treatment of operable, unresectable and metastatic GCTB [17–19]. However, there are still some controversies in the preoperative use of denosumab. In recent reports, denosumab has been reported as a risk factor for increased local recurrence rate. A study involving 25 patients with GCTB who underwent curettage following denosumab had a local recurrence rate of 60% [20]. What's more, some authors have reported that the short course of preoperative denosumab administration (≤6 doses) has similar oncological, functional outcomes, histological, and radiological responses as longer courses of therapy (>6 doses).

To our knowledge, few studies reported the clinical outcomes of preoperative adjuvant denosumab therapy (PADT) combined with en bloc resection and wrist arthrodesis using ICBG for the treatment of distal radius recurrent Campanacci III GCTB in former English literature. Therefore, we attempted to answer the following questions: (1) What's the local recurrence rate of combination therapy of preoperative adjuvant denosumab therapy and en bloc resection in recurrent Campanacci grade III giant cell tumor of bone? (2) What are the functional outcomes of wrist arthrodesis using an iliac crest bone graft (ICBG) to reconstruct the bone defect in the distal radius? (3) What are the complications of preoperative short-course denosumab (≤6 doses) administration in the distal radius giant cell tumor of bone? (4) What's the radiological and histological response to adjuvant denosumab therapy of recurrent giant cell tumor of bone?

Patients and methods

This was a retrospective cohort study including patients who accepted preoperative adjuvant denosumab combined with en bloc resection and arthrodesis for recurrent Campanacci III giant cell tumor of bone in the distal radius and the human protocol for this study was approved by the institutional review board (IRB) in our hospital. Among 111 cases that underwent resection for distal radius GCTB in our institution from 2015 to 2022, we included 23 cases treated with PADT combined with en bloc resection and arthrodesis (Fig. 1). The minimal follow-up time was ≥12 months. All patients were diagnosed as recurrent Campanacci III GCTB by percutaneous core needle biopsy and reconstructed by en bloc resection and wrist arthrodesis using autogenous free iliac crest bone graft (ICBG) in the reoperation.

All patients accepted preoperative evaluations including plain films of the wrist, hand, forearm, and pelvis (bone graft donor site); CT scan of the wrist and chest; MRI of the wrist, whole body scan (WBS), and PET-CT if necessary. Denosumab was approved for surgically salvageable GCTB with planned surgery expected to result in severe morbidity and all patients used denosumab to control the local progression of GCTB before reoperation [21, 22]. Considering the higher occurrence rate of systemic complications in patients with long-course therapy (14–20%) than short-course therapy (0–5%), we recommend short-course denosumab therapy for preoperative treatment [23]. Patients received 120 mg subcutaneous denosumab once every 4 weeks for 3 months with loading doses (120 mg subcutaneously) administered on days 8 and 15 in the first month. Calcium and vitamin D supplements were used for all patients to prevent denosumab-related complications. We assessed the complete blood count technique, calcium and phosphorus before each dose of preoperative denosumab treatment. Oral examination is mandatory at each visit. Adverse events and laboratory abnormalities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0).

All patients included in this study underwent distal radius recurrent tumor reoperation, autogenous non-vascularized structural ICBG reconstruction and arthrodesis. A dorsal approach was used to expose the tumor

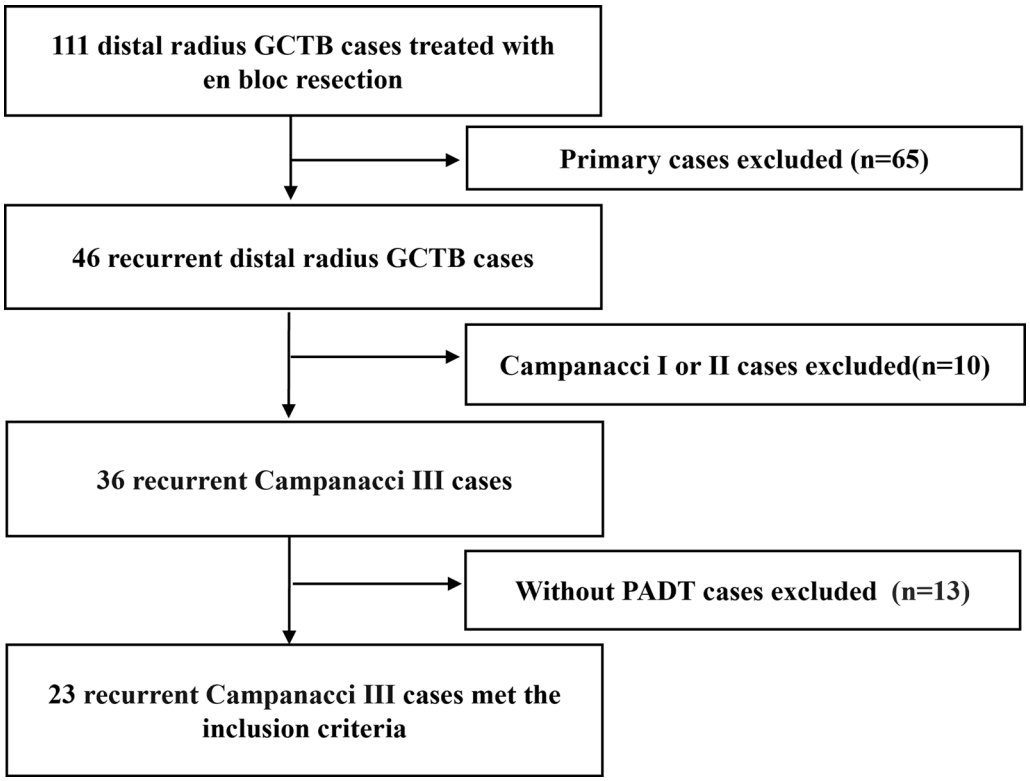

Fig. 1 Flow chart of distal radius recurrent Campanacci III GCTB treated with PADT and en bloc resection in our institution from 2015 to 2022

lesions and en bloc resection for at least marginal margin was performed. Autografts were harvested from the iliac crest donor site and a reconstruction plate was used for internal fixation. The remaining radius, structural ICBG, the carpals, and the middle finger metacarpal were fixed from proximal to distal and the wrist joint was fixed at 15°-20°dorsal extension (functional position) (Fig. 2).

The radiological evaluation was based on the enhanced CT scan and analyzed the enhanced CT value before and after PADT, which was introduced in our former studies [24]. The average tumor enhancement rates were defined as the ratio of the enhanced CT value to the plain CT value and used to evaluate the tumor blood supply at diagnosis, one month after PADT and three months after PADT. All specimens were evaluated by two senior pathologists at our institution. The histological evaluation included the preoperative biopsy and postoperative resected specimens after denosumab administrations of all 23 patients.

All patients accepted at least 1-year follow-up and postoperative follow-up included radiological and functional evaluation including AP and lateral plain radiographs of the wrist, CT scan of wrist and chest, MRI scan

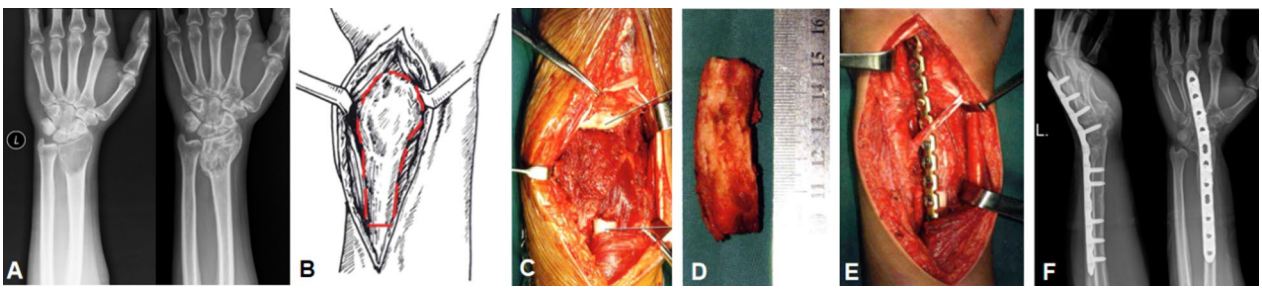

Fig. 2 A 48-year-old male with left distal radius recurrent Campanacci III GCTB treated with inadequate curettage as initial treatment. This figure shows procedures for tumor resection and reconstruction. **A** The distal radial X-ray before and after the denosumab therapy. **B–C** A dorsal approach was used to expose the tumor location. **D**–**E** The structural ICBG was harvested and reconstructed by autografts and a reconstruction plate. **F** The X-ray showed that the wrist was fixed at 15°-20°dorsal extension

and whole-body scan (WBS) if necessary. The host-autograft bone union evaluation was based on the conventional radiographs and the bone nonunion was defined as the lack of continuity in three cortices at the junction one year after surgery. Autograft failures were defined as the removal or replacement of an iliac crest bone graft. Recurrence, metastasis, progression-free survival, and overall survival rate were used to evaluate the oncological outcomes. The functional outcomes were evaluated by the Musculoskeletal Tumor Society Score (MSTS-87 and 93), the Disabilities of the Arm, Shoulder and Hand (DASH) score, and grip strength [11, 25]. The functional results were reported at the latest follow-up only.

Statistical analysis

The Student *t*-test was used for bivariate analysis. The recurrence-free survival and overall survival were measured from the time of reoperation for recurrent tumors. Survival was analyzed with Kaplan–Meier curves and the log-rank test. All tests were two-sided and a p-value < 0.05 was considered significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 26.0 (USA) and GraphPad Prism software version 10 (USA).

Results

Twenty-three patients were included in this retrospective study, in which eight patients were male and fifteen were female with an average age of 32.5 ± 10.2 years (range, 19–53). The mean follow-up time was 35.5 ± 18.4 months (range, 13–72). No patient was lost in the follow-up. The average interval between the initial surgery and first recurrence was 16.7 ± 9.7 months (range, 4 to 36 months) and 78.2% of all these patients had local recurrence two years after the initial surgery. The demographics of all patients are shown in Table 1.

Oncological outcomes

Local re-recurrence occurred in four patients (17.4%) after the preoperative adjuvant denosumab combined with en-bloc resection and arthrodesis. Of all 4 patients who had a second recurrence, two patients (8.7%) had soft tissue recurrences and two patients (8.7%) had bone

Table 1 Demographics of patients

Case	Age (yrs)/gender	Dominance hand /Tumor size (mm)	Initial treatment	Time to recurrence (mths)	Site of local recurrence	Pathological fracture	Cement use at initial curettage	Distant metastasis at presentation
1	24/female	No/75	IC	9	Bone	No	Yes	No
2	40/female	Yes/80	IC	17	Bone	No	Yes	No
3	53/male	Yes/70	IC	21	Soft tissue; Bone	No	Yes	No
4	24/male	Yes/50	IC	17	Bone	No	No	No
5	46/male	No/80	IC	32	Bone	No	No	No
6	24/female	Yes/70	IC	33	Bone	No	Yes	No
7	36/female	No/70	IC	8	Bone	No	Yes	No
8	30/male	No/75	IC	12	Bone	No	No	No
9	40/male	No/55	IC	12	Bone	No	No	No
10	40/female	No/70	IC	15	Bone	No	No	No
11	26/male	No/70	IC	16	Bone	Yes	Yes	Yes
12	23/female	Yes/70	EBR	4	Bone	No	NA	No
13	23/female	Yes/70	IC	7	Soft tissue; Bone	No	Yes	No
14	49/male	Yes/85	IC	26	Bone	No	Yes	No
15	48/female	No/70	IC	2	Bone	No	Yes	No
16	28/female	Yes/80	IC	6	Bone	No	No	No
17	29/male	Yes/80	IC	24	Soft tissue; Bone	No	No	No
18	19/male	Yes/60	IC	28	Bone	No	Yes	No
19	23/male	Yes/60	IC	4	Bone	No	Yes	No
20	23/female	No/80	IC	11	Bone	No	Yes	No
21	38/female	No/80	IC	3	Soft tissue; Bone	No	No	No
22	22/female	Yes/75	IC	8	Bone	No	No	No
23	33/male	Yes/75	IC	5	Bone	No	No	No

IC intralesional curettage, *EBR* en bloc resection

recurrences. Two patients accepted soft tissue extended resections and two patients accepted recurrent tumor resections and reconstruction. In 4 patients who underwent reoperations, two cases had the third recurrence. The average duration from the reoperation to the third recurrence was 14.5 months (range, 5 to 24 months). In these 2 patients, one patient (case 11) had multiple pulmonary metastases 8 months after reoperation and accepted long-term denosumab administration (120 mg/month) and died in the 57 months after reoperation. Another patient accepted extended resection and did not have further recurrences after the third surgery. The estimated 5-year recurrence-free survival rate was 81.3% and 5-year metastasis-free survival rate was 95.7%, respectively (Fig. 2).

Functional outcomes

We achieved good functional outcomes using this technique in our patients. The average MSTS-87 and MSTS-93 scores were 27.8 ± 1.6 (range, from 23 to 30) and 91.5 ± 5.0% (range, from 76 to 100%), respectively. What's more, the average DASH score was 8.9 ± 3.2 (range, from 3 to 15) (value range, from 0 to 100%, with higher scores representing better function). Regarding the postoperative grip strength, the involved hand had an average of 64.6 ± 15.7% (range, from 30 to 95%) on the contralateral side (Table 2; Fig. 3).

Radiological and histopathological evaluation

The average post-treatment enhancement rates at diagnosis, 1 month and 3 months were 2.10 ± 0.25, 1.45 ± 0.15 and 1.26 ± 0.11, respectively (Fig. 4). With the prolonged administration of denosumab, the enhancement rates declined but the reduction of the absolute CT enhancement value and the degree of reduction reduced. The average reduction was 0.61 (29.3%) at one month of denosumab treatment and 0.83 (39.5%) at three months of denosumab treatment, which had a significant difference in CT enhancement rates among the diagnosis, one month, and three months of treatment ($p < 0.001$). However, the average reduction was 0.22 (10.2%) from one month to three months of treatment.

Table 2 Outcomes of patients

Case	Resected length (mm)	Resection margin	Autograft union time (mths) / status	Complications	Grip strength (percent uninvolved)	MSTS-87	MSTS-93	DASH score	Status/ follow-up (mths)
1	80	Marginal	9/preserved		40	26	86	11	ANED, 28
2	90	Wide	8/preserved		67	29	94	5	ANED, 28
3	80	Marginal	6/preserved	Recurrence	51	27	89	10	ANED, 25
4	60	Wide	10/preserved	Recurrence	67	28	90	9	ANED, 25
5	80	Marginal	12/preserved	Limb pain	70	28	92	9	ANED, 22
6	80	Wide	7/preserved		95	30	100	3	ANED, 19
7	70	Marginal	6/preserved		66	29	100	3	ANED, 14
8	90	Wide	8/preserved		55	26	85	13	ANED, 24
9	65	Wide	9/preserved		64	28	90	10	ANED, 14
10	70	Marginal	20/removed	Bone nonunion	52	27	90	10	ANED, 59
11	80	Wide	10/preserved	Recurrence; metastasis	51	26	85	12	D,57
12	70	Marginal	10/Removed	Recurrence	30	23	76	11	AWED, 34
13	80	Wide	8/preserved		63	26	82	15	ANED, 21
14	90	Marginal	7/preserved	Donor site pain	65	29	96	7	ANED, 23
15	80	Wide	6/preserved		69	29	93	8	ANED, 72
16	90	Marginal	9/preserved		85	29	100	4	ANED, 71
17	80	Marginal	9/preserved		90	29	96	7	ANED, 61
18	70	Wide	8/preserved	Asymptomatic hypocalcemia	51	28	95	7	ANED, 51
19	70	Wide	7/preserved		59	28	93	9	ANED, 45
20	80	Marginal	6/preserved		69	28	91	14	ANED, 47
21	90	Wide	9/preserved		60	28	93	9	ANED, 29
22	80	Marginal	8/preserved		82	29	95	10	ANED, 27
23	80	Marginal	12/preserved		85	29	96	9	ANED, 32

ANED alive with no evidence of disease, *AWED* alive with evidence of disease, *D* Dead, *MSTS* musculoskeletal Tumor Society scoring system

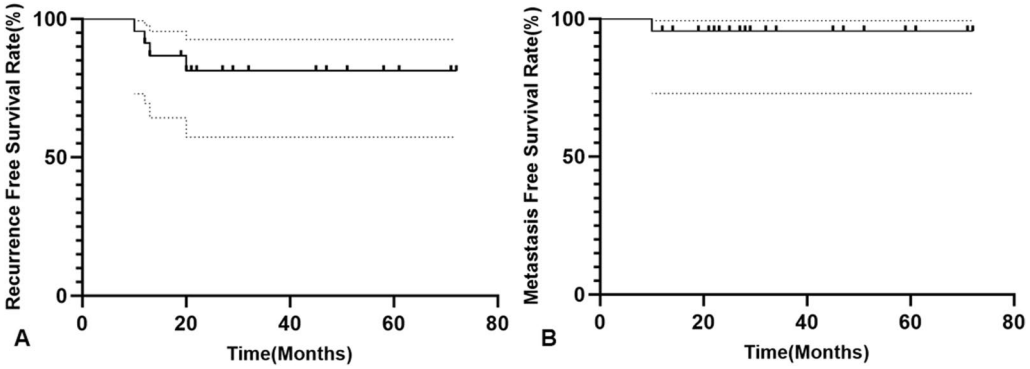

Fig. 3 The Kaplan–Meier survival curve showed recurrence-free survival and metastasis-free survival for the treatment of distal radius recurrent Campanacci III GCTB. (**A**) The 5-year recurrence-free survival of patients who underwent PADT combined with EBR for distal radius GCTB. (The dotted line showed a 95% confidence interval.) (**B**) The 5-year metastasis-free survival of patients who underwent PADT combined with EBR for distal radius GCTB. (The dotted line showed a 95% confidence interval)

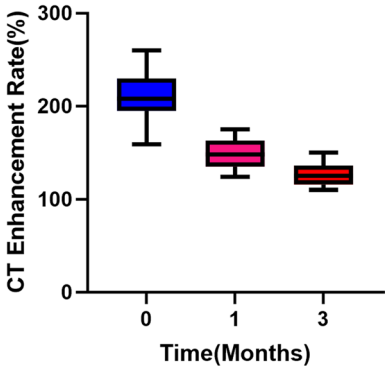

Fig. 4 The CT enhancement rate in different PADT treatment periods (diagnosis, 1 month, and 3 months after PADT). There is a significant difference between the CT enhancement rate at diagnosis and 3 months after PADT ($p < 0.001$, $F = 131.2$), and between 1 and 3 months after PADT ($p = 0.0004$, $F = 18.2$)

Twenty-three cases accepted preoperative diagnostic biopsy. Histopathological examinations and typical GCTB morphology were seen in all cases (Fig. 5A-B. After denosumab treatment, all samples showed significant pathological changes: osteoclast-like giant cells had almost disappeared. Other areas were characterized by fibrillary extracellular matrices organized in trabecular structures or with increased honeycomb-pattern bone (Fig. 5C-D).

Complications

A total of eight patients (34.7%) had complications in the follow-up period. Four patients with oncological complications had been described in oncological outcomes. Two patients (8.7%) had mechanical complications related to wrist arthrodesis and ICBG. One patient accepted revision with free vascularized fibular grafting (FVFG) and had bone union 6 months after the secondary surgery. Another patient had long-term donor site pain (>1 year) and accepted oral non-steroidal anti-inflammatory drugs (NSAIDs). Moreover, two patients (8.7%) had denosumab-related complications in this cohort. Limb pain occurred in one patient during the denosumab treatment period which was relieved soon after stopping the denosumab. Asymptomatic hypocalcemia occurred in one patient but improved without medical intervention (Table 2).

Discussion

The diagnosis and treatment of recurrent Campanacci III GCTB of the distal radius are challenging due to the special anatomical structure and histological characteristics [4,6–9,26,]. Recent studies have reported a range of 69–96% H3F3A mutations in GCTB [27, 28], and Luo et al. demonstrated that H3F3A mutations may contribute to the differential diagnosis of GCTB in non-long bones [29]. H3F3A hotspot mutations were not highly expressed in other giant cell tumor-rich lesions including chondroblastoma, osteosarcoma, aneurysmal bone cysts and cartilaginous mucinous fibroma, which helped us to identify giant cell tumors of bone and other giant cell-rich lesions (Figs. 6, 7).

Intralesional curettage combined with local adjuvant therapy had been recommended as an optimal treatment method for primary or recurrent Campanacci I or II giant cell tumor of bone in the distal radius because the patients got more clinical benefits despite the slightly higher local recurrence rates compared to en bloc resection [30]. However, the high recurrence rate was the most significant risk in the treatment of distal radius Campanacci III GCTB and there was uncertainty regarding the best treatment strategy [31]. Aoude et al. reported curettage and distal radius location were independent

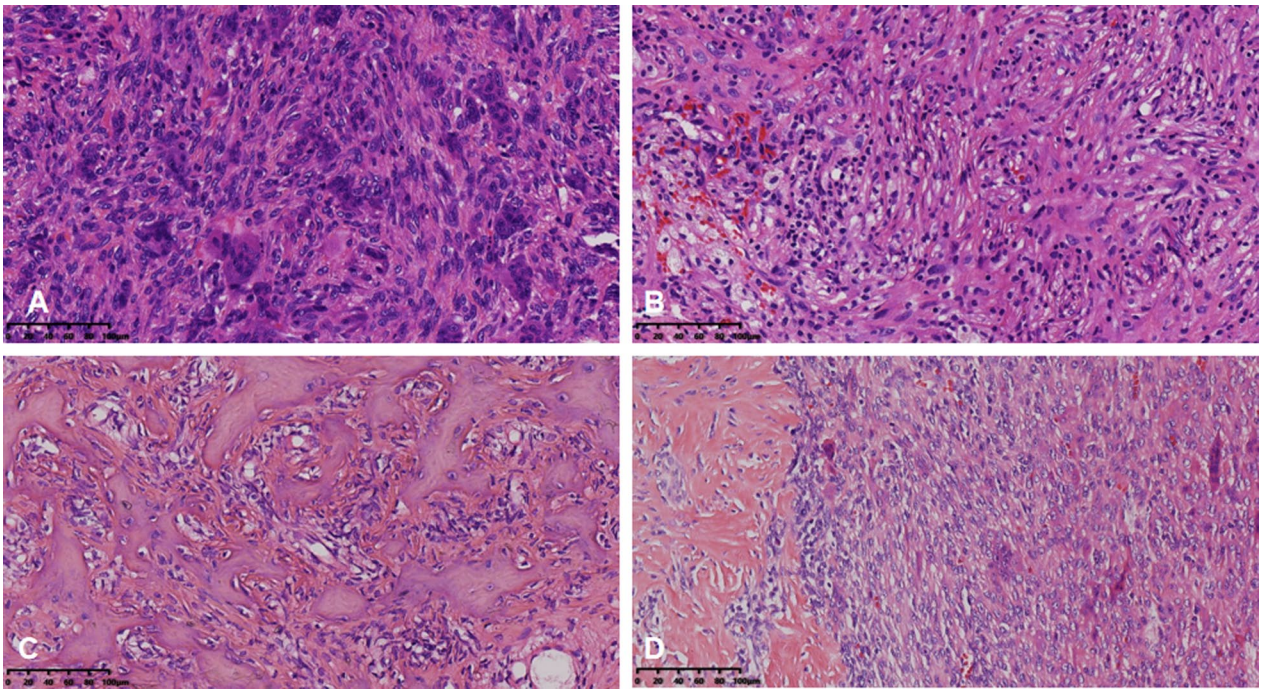

Fig. 5 Hematoxylin and eosin staining of GCTB before and after denosumab treatment. **A–B** Biopsy specimens revealed an admixture of neoplastic mononuclear cells and osteoclast-type giant cells. (Magnification, × 20). **C–D** The post-treatment specimens revealed storiform-pattern bland-appearing spindle cells, associated with collagen matrix production. (Magnification, × 20)

risk factors for local recurrence (LR) of GCTB [32]. Furthermore, all patients were recurrent cases in this cohort and the special anatomical structures in the distal radius may contribute to further recurrences. Therefore, en bloc resection was deemed as a primary choice to receive satisfactory local control. The standard reconstructive approach after the resection of a tumor of the distal radius remained uncertain because of the extremely high functional demands of the wrist.

The commonly used reconstructive modalities included: arthrodesis, allograft reconstruction, ulnar transposition, non-vascularized or vascularized autologous fibula implantation, and endoprosthetic replacement [33]. Despite acceptable postoperative function, allograft reconstruction was associated with a high rate of complications, including fractures, bone nonunion, and infection [34, 35]. The ulnar transposition technique reduced the incidence of allograft bone complications (infection and bone nonunion), but its most common complication remained proximal radio-ulnar junction nonunion. this might require autologous cancellous bone grafting and internal fixation revision [36, 37].

Autogenous non-vascularized structural ICBG had been a favourable reconstruction technique that provided simple autograft harvest, ample cancellous bone, robust wrist stability, consistent graft union, and wrist fusion. 95.6% (22/23) patients had bone union in both osteosynthesis sites 12 months after surgery and the proximal osteosynthesis site had a prolonged union time (8.5 ± 1.9 months) than the distal osteosynthesis site (4.5 ± 1.4 months). However, this result may be caused by the use of reconstruction plates and was still acceptable compared with former studies using arthrodesis reconstruction [38–41]. Clarkson et al. compared the functional results between vascularized (80, median MSTS-93 score) versus non-vascularized (90, median MSTS-93 score) autografts for wrist arthrodesis in distal radius GCTB, and non-vascularized autografts were deemed as a more convenient reconstruction technique which had comparable functional scores [42]. In our study, the MSTS-93 scores (91.5% ± 5.0%) were slightly better than the former study without statistical difference ($p > 0.05$) and we hypothesized that may be a result of the ceiling effect in distal radius bone defect reconstruction. One patient in our study had a revision with free vascularized fibular grafting (FVFG) because of bone nonunion, and the FVFG technique still had non-negligible advantages in prompting bony union and larger bone defects.

The denosumab use brought revolutionary changes and has been proven to improve tumor response and reduce surgical morbidity in the treatment of giant cell tumor of bone, especially in recurrent or unresectable

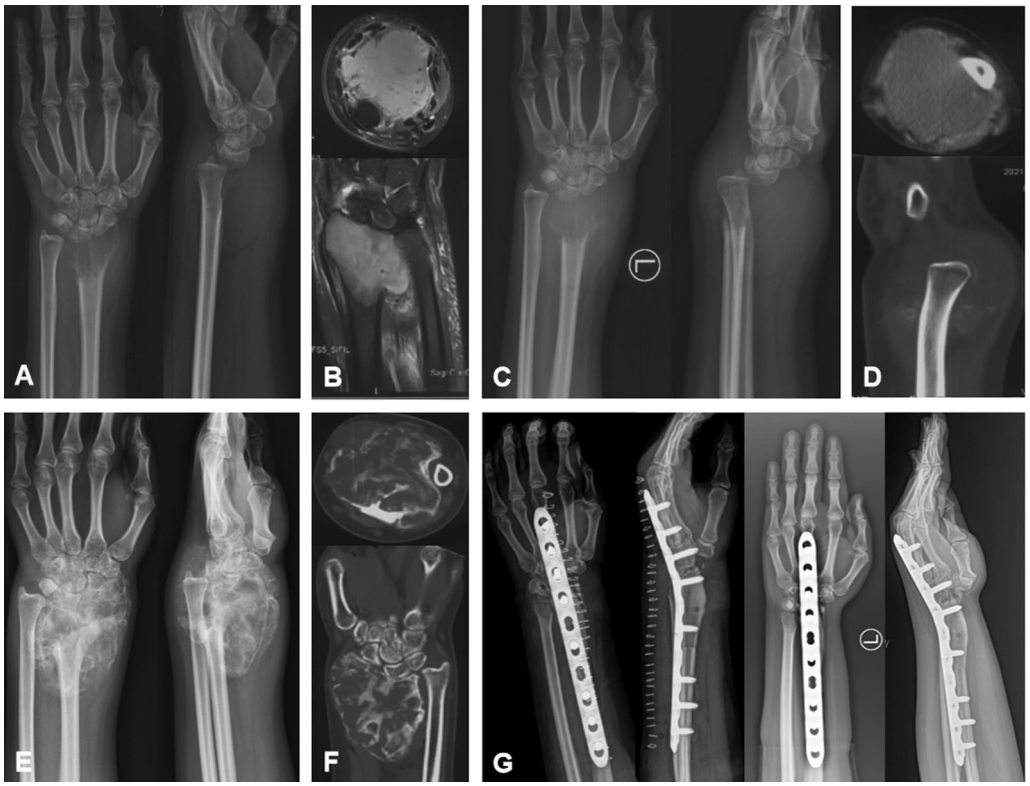

Fig. 6 A 22-year-old female with left distal radius GCTB. **A–B** The AP and lateral plain films of the wrist and MRI revealed a Campanacci III GCT at first diagnosis. **C**–**D** Postoperative AP and lateral plain films and CT scan of the wrist showed local recurrence 2 months after initial curettage. **E–F** After 3 months of PADT, perilesional new bone formation eggshell-like mineralization layer occurred at recurrent site as shown on AP and lateral radiographs and CT scan of the wrist. **G** This patient underwent en bloc resection combined with arthrodesis for the treatment of recurrent GCTB and got bony union six months after autograft reconstruction

GCTB [43, 44, 46]. However, Errani et al. reported a high local recurrence rate (60%, 15/25) in extremities GCTB treated with preoperative denosumab and intralesional curettage with long-term denosumab administration courses (>6 months). All 25 patients with preoperative denosumab therapy were diagnosed with remaining GCTB after pathological specimen examinations [16]. Moreover, the perioperative administration doses and duration of denosumab have been controversial in different indications. In former studies, Hindiskere et al. reported that short-term PADT (≤3 doses) was associated with no differences in clinical outcomes compared to long-term PADT and Liang et al. Reported that short-term PADT could elicit tumor responses and reduce the perilesional fibrosis and ossification to facilitate nerve-sparing surgeries in sacral GCTB [45]. Moreover, Zhang et al. used short-term PADT (≤6 doses) to treat unresectable or recurrent GCTB in axial and appendicular bones and had a total recurrence rate of 27% (3/11) after reoperation [47]. Our studies indicated that the denosumab administration could decrease the CT enhancement rate of GTCB, which proved that the blood supply of tumor lesions was reduced by the denosumab therapy. Moreover, the effect of three-month courses of denosumab administration decreased gradually compared with one-month courses, which indicated that the short-term denosumab courses had the most evident effects on reducing tumor blood supply. Yang et al. reported longer denosumab administration (6 months) had no significant difference with 3 months of denosumab administration in axial and appendicular bones and PET-CT results indicated the average SUV max values of the tumors decreased significantly, which showed the biological activity of tumor declined [24]. In our cases, patients who accepted 3 months of denosumab treatment had significant CT enhancement rate and blood supply decrease and we recommended 3 months of denosumab treatment.

To our knowledge, there have been few studies concerning PADT therapy combined with en bloc resection and arthrodesis in the treatment of distal radius recurrent Campanacci III GCTB. Because long-term denosumab had been proven to increase the local recurrence rate in curettage surgery and the distal radius adjoined

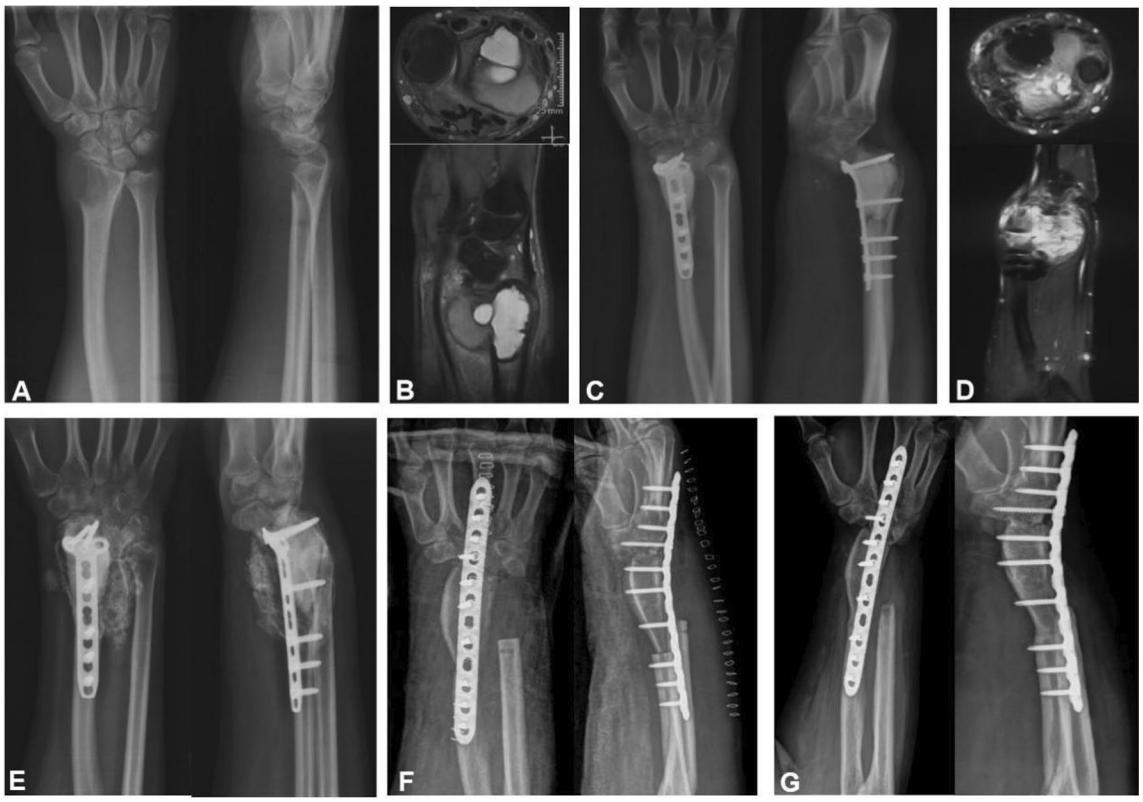

Fig. 7 A 24-year-old male with right distal radius GCTB. **A**–**B** The AP and lateral plain films of the wrist and MRI revealed a Campanacci III GCT at first diagnosis. **C**–**D** Postoperative AP and lateral plain films and MRI of the wrist showed local recurrence involving distal ulna 21 months after initial curettage and cement reconstruction. **E** After 3 months of PADT, perilesional new bone formation eggshell-like mineralization layer occurred at recurrent site as shown on AP and lateral radiographs of the wrist. **F**–**G** This patient underwent en bloc resection combined with arthrodesis for the treatment of recurrent GCTB and got bony union six months after autograft reconstruction

the neurovascular structures, tendons, and distal radial ulnar joint (DRUJ), we believed that achieving a safe surgical margin was extremely important. Soft tissue extension was also common in distal radius recurrent GCTB, therefore a clear demarcation between tumor and healthy tissues was necessary. PADT could result in extensive perilesional new bone formation and sclerosis which was conducive to lesion resection and reduced the risk of tumor cell extravasation, and this layer became thicker when the denosumab administration period was prolonged. En bloc resection (EBR) could resect the eggshell-like mineralization layer with remaining tumor cells and help to achieve a clear surgical margin. Tsukamoto et al. reported a local recurrence rate in distal radial GCTB of 30.6% with preoperative denosumab therapy and no LR difference was found between the curettage group and the EBR group [48]. However, this study did not consider the denosumab usage in different Campanacci grade GCTB and the denosumab administration in Campanacci I or II GCTB may increase the local recurrence rate treated with preoperative denosumab and curettage therapy. Tsukamoto et al. also reported clinical outcomes of reoperation for recurrent GCTB in extremities following en bloc resection with a second recurrence rate of 41.4% (12/29) and a third recurrence rate of 17.2% (5/29) [49]. A meta-analysis showed that recurrent GCTB patients had a 20.5% secondary recurrence rate and a 23.4% third recurrence rate after reoperation [4]. In our study, the second recurrence rate was 17.4% (4/23) after reoperation and the third recurrence rate was 8.7% (2/23) after the third operation, which was fairly low in the treatment of distal radius recurrent Campanacci III GCTB.

Recent studies have also reported some complications associated with denosumab administration including jaw osteonecrosis, atypical femoral fracture, hypercalcemia, arthralgia, headache, nausea, fatigue, and anaemia [14, 43, 44]. The long-term denosumab safety profile had not been determined in recent studies, however, former studies reported fewer complications, especially Grade 2 or higher complications, in the short-term compared with long-term denosumab

administration. Palmerini et al. reported 54 cases that accepted long-term denosumab therapy (median duration of 54 months) had 37% complications in total and 13% Grade 2 or higher complications and 43 cases accepted short-term denosumab therapy (median duration of 12 months) had 2% complications (one case of osteonecrosis of the jaw) [44]. Moreover, Hindiskere et al. also reported no Grade 2 or higher complications in the short-term denosumab courses (≤ 3 doses) [45]. In our study, 8.7% (2/23) patients had denosumab-related Grade 1 complications (1 case of asymptomatic hypocalcemia and 1 case of limb pain) and no Grade 2 or higher complications were found in this cohort.

There were also some limitations in our study. Firstly, the retrospective cohort had selection bias and confounding bias due to the lack of randomization. Secondly, the sample size was still limited in this study, because the recurrent Campanacci III giant cell tumor of bone was a quite rare disease in a single institution, even in a referral cancer center. And to our knowledge, this is the largest case series regarding the adjuvant preoperative denosumab and en bloc resection therapy for recurrent Campanacci III GCTB in the distal radius. Because of the limited sample size and non-randomization nature of our study, we cannot conclude that adjuvant denosumab combined with en bloc resection will significantly improve the local control in distal radius recurrent Campanacci III GCTB. Therefore, a prospective, randomized study is necessary to determine the efficacy and safety of denosumab in the treatment of recurrent Campanacci III GCTB in the distal radius.

Nevertheless, this study introduced a possible method for the treatment of distal radius recurrent Campanacci III GCTB with preoperative short-course denosumab therapy, en bloc resection and arthrodesis, which has few mentions in the former literature. Although there are many options for reconstruction after resection of giant cell tumours of the distal radius, this technique avoids the need for microsurgical techniques and bone banking, and the complication rate is comparable to other described techniques [50, 51]. Because the technique was not compared with other reconstruction techniques, we cannot claim that this reconstruction is superior to other methods. However, in our preliminary report, we obtained satisfactory oncological and functional results and we believe that this technique is a reasonable alternative to resection and reconstruction of recurrent Campanacci III GCT tumours of the distal radius. Further future studies comparing the advantages and disadvantages of arthrodesis with other reconstructive methods, such as vascularised fibula grafts and carpal prostheses, are necessary to assess the potential advantages of one technique over the other.

Author contributions
Concept and design: Weifeng Liu; data collection: ZD, YY; drafting of the article: ZL; critical revision of the article for important intellectual content: QZ and XN. ZL and ZD contributed equally to this paper.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Review Board of Beijing Jishuitan Hospital. All methods were performed in accordance with the 1964 Declaration of Helsinki and its later amendments, and the ethical standards of the institutional research committee.

Consent for publication
Written informed consent for publication was obtained from all participants.

Competing interests
The authors declare no competing interests.

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