

# Successful limb salvage in progressive proximal tibia osteosarcoma following denosumab chemotherapy

## A case report

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### Abstract

**Rationale:** Osteosarcoma (OS) is a primary malignant bone tumor that originates in the mesenchymal tissue. It is the most common type of pleomorphic tumor occurring in children and adolescents. Currently, there is no established systematic treatment for OS that progresses during standard preoperative chemotherapy.

**Patient concerns and diagnoses:** We describe a 14-year-old male patient with a 4-month history of pain in the upper right leg. Based on the results of percutaneous biopsy, a diagnosis of OS was made. After admission, the patient was treated with first-line chemotherapy agents. After a single course of treatment, the tumor progressed locally and no limb salvage was feasible.

**Interventions and outcomes:** Intervention with denosumab combined with chemotherapy led to a significant reduction in tumor volume and ossification of soft tissue, which successfully resulted in limb salvage rather than amputation. The patient showed no evidence of recurrent or distant metastasis at 6-month follow-up.

**Lessons:** Treatment with receptor activator of nuclear factor- $\kappa$ B ligand inhibitor denosumab combined with standard chemotherapy is effective for advanced OS progressing after chemotherapy. We recommend denosumab therapy for successful limb salvage in patients with high-grade OS associated with osteolytic bone destruction and refractory to preoperative neoadjuvant chemotherapy.

**Abbreviations:** CT = computed tomography, OS = osteosarcoma, RANK = receptor activator of nuclear factor- $\kappa$ B, RANKL = receptor activator of nuclear factor- $\kappa$ B ligand

**Keywords:** chemotherapy, denosumab, osteosarcoma, RANK, RANKL

## 1. Introduction

Osteosarcoma (OS) is the most common type of primary malignant bone tumor in younger individuals. The pathophysiology of OS is characterized by inactivation of retinoblastoma and/or p53 tumor suppressor genes.<sup>[1]</sup> Curative treatment for high-grade OS entails surgery of the primary tumor and chemotherapy in order to facilitate limb salvage and extend disease-free survival.<sup>[2]</sup> Doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide are considered the most active agents against OS. Several studies reported that the combination of chemotherapy and surgery increase the long-term survival rates above 70% and is widely accepted by physicians and patients.<sup>[3]</sup> It is crucial to identify and validate new agents that might be administered alone or as adjuvants to conventional chemotherapy to improve not only patients' chances of survival and cure but also their quality of life.<sup>[4]</sup>

In recent years, some primary bone tumors have been identified as new therapeutic targets for denosumab, particularly those expressing the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) and those involving osteoclast-mediated bone resorption. We report a 14-year-old male with proximal tibia OS who achieved successful limb salvage following treatment with denosumab combined with neoadjuvant chemotherapy. Also, we discuss the relevant clinicopathology, diagnosis, and treatment following the patient's informed consent.

## 2. Case presentation

A 14-year-old healthy male reported no obvious cause of pain involving his upper right leg in March 2021. At first, the pain was aggravated during activity and relieved at rest,

Written informed consent for publication was obtained from the patient. All patient information was obtained from the 960th Hospital of the People's Liberation Army. The datasets generated during and/or analyzed during the current study are available from the first author on reasonable request.

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All data generated or analyzed during this study are included in this published article.

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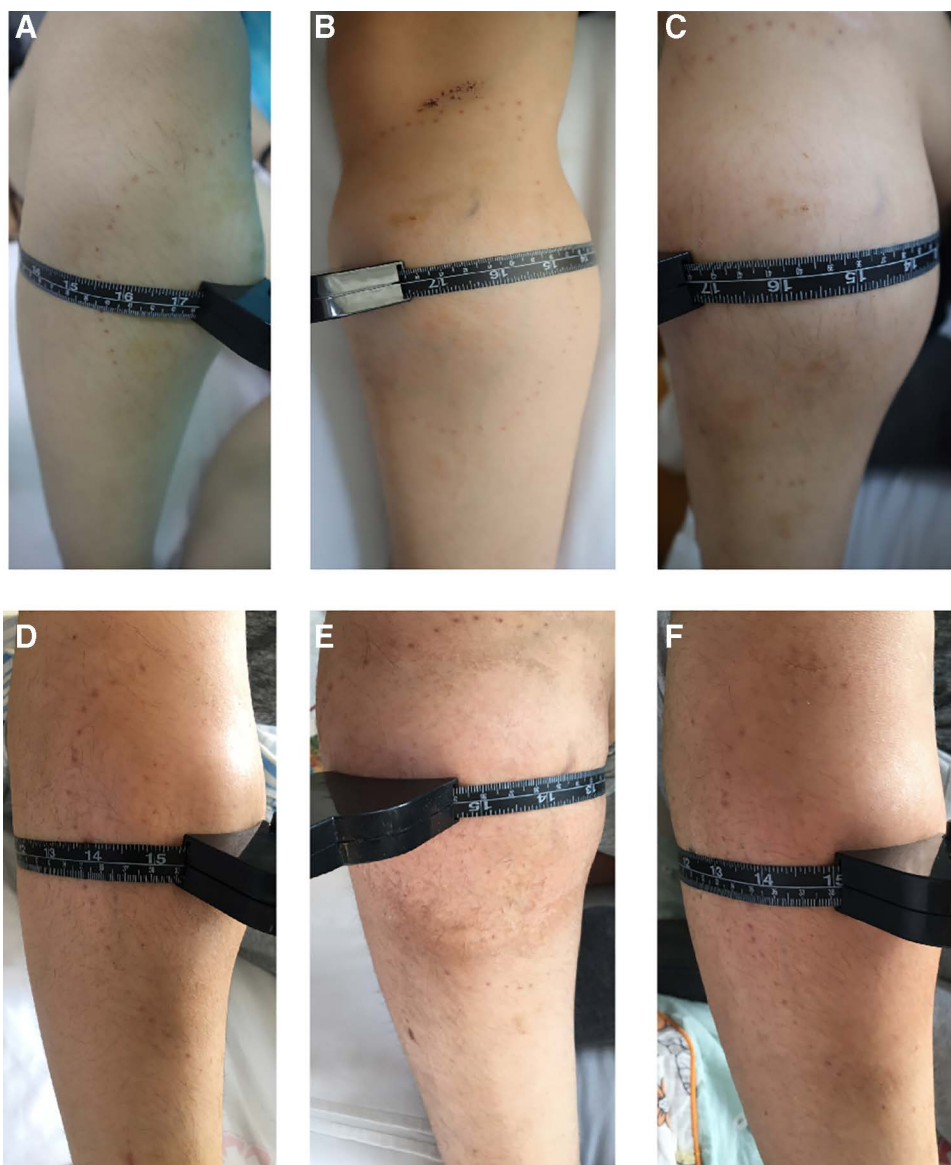
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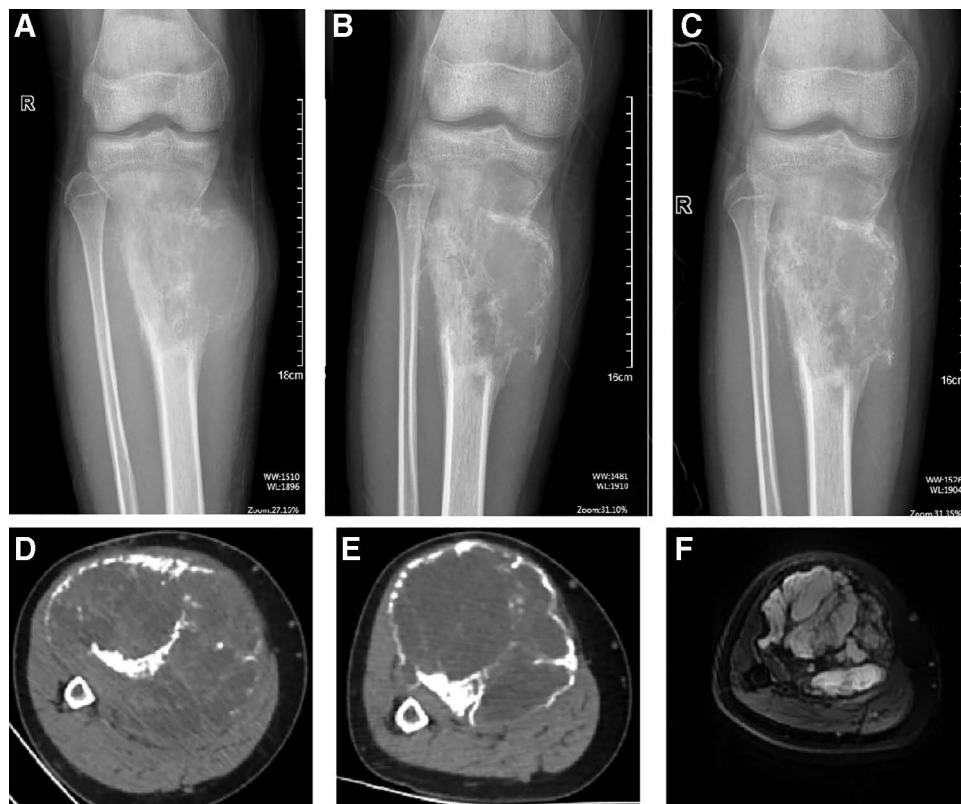


**Figure 1.** The maximum diameter of right leg tumor measured before chemotherapy was 44.2 cm (A), increasing to 44.5 cm after the first course of neoadjuvant chemotherapy (B). The diameter after the first dose of denosumab was 44.1 cm (C), 39.3 cm after the second dose of denosumab (D), and 39.0 cm after the third dose of denosumab (E). The circumference measured again before operation was 38.3 cm (F).

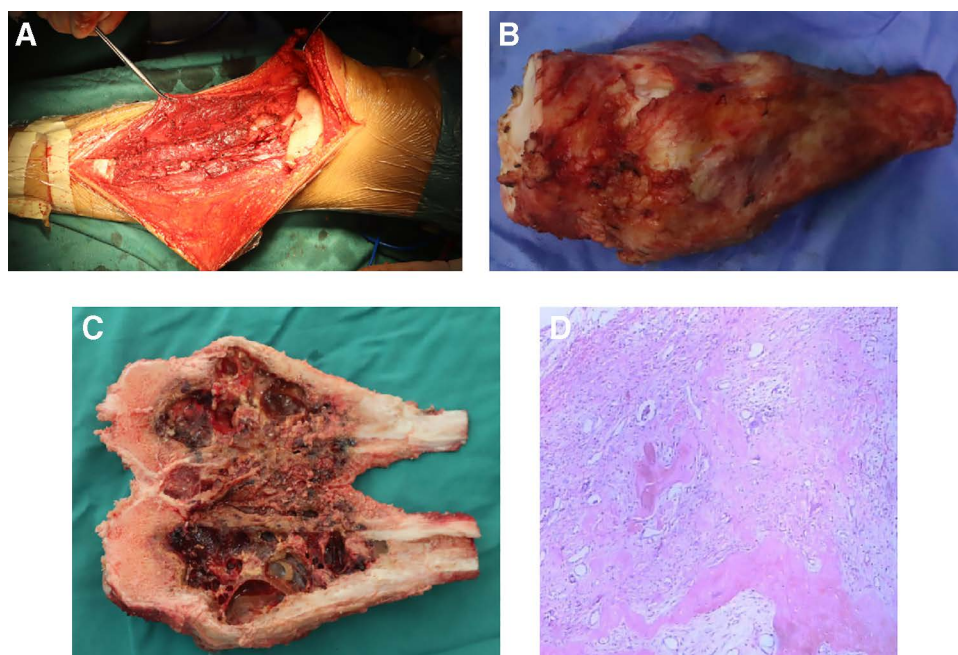
accompanied by local swelling. After discussion with his family, imaging procedures and percutaneous biopsy were performed in April 2021. The pathology report showed telangiectatic OS. The patient refused surgical treatment and instead managed with traditional Chinese medicine and needles, without any efficacy. The tumor volume increased gradually. The patient was referred to our hospital for systematic treatment. Physical examination revealed a swollen proximal right leg. The eye of the puncture needle was visible; however, no change in skin color or superficial veins was seen. A palpable  $10 \times 8 \times 3$  cm firm mass was detected on his right leg, with elevation in local skin temperature, obvious tenderness, and no range of motion. Flexion and extension of the right knee joint were obviously limited by pain, and the maximum circumference of the tumor surface on the right was thicker than on the left side (Fig. 1A). Plain radiography of the right tibia and fibula showed swelling, irregular osteolytic bone destruction and soft tissue mass, uneven density, scattered irregular strips of tumor bone shadow, with associated bone cortical interruption and obvious periosteal reaction (Fig. 2A). Because of the pain and the large size

of the tumor, the patient maintained a forced flexion position after admission and was not screened via magnetic resonance imaging. Computed tomography (CT) of the chest showed no evidence of pulmonary metastasis.

The patient was diagnosed with stage II B OS based on surgical staging system recommended for bone and soft tissue tumors. Overcoming chemotherapy taboos, the patient received a single neoadjuvant chemotherapy DIA regimen comprising cisplatin  $120 \text{ mg/m}^2$  for 1 day, doxorubicin liposome  $60 \text{ mg/m}^2$  for 1 day, and ifosfamide  $2 \text{ g/m}^2$  for 5 days. The maximum circumference of the tumor surface on the right proximal tibia was thicker than before chemotherapy (Fig. 1B). The tumor showed progression and no limb salvage was possible. Based on the imaging findings of osteolytic bone destruction, denosumab therapy was considered as it inhibits osteolysis and has been cleared by FDA for use in various conditions. Two weeks later, a decision was made to try DIA regimen combined with denosumab ( $120 \text{ mg}$ , days 1, 8, and 15), in an effort to achieve limb salvage. Medications were routinely supplemented with vitamin D3 ( $600 \text{ }\mu\text{g}$  daily). The patient had no side effects or complications.



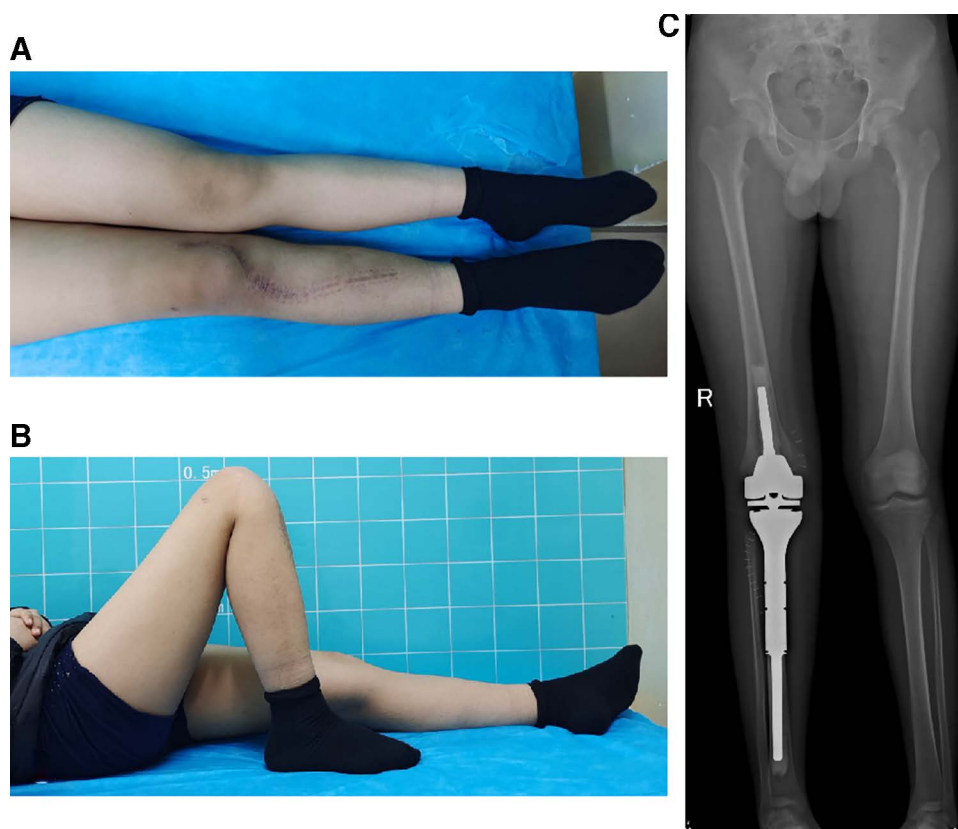
**Figure 2.** Plain radiograph: Before chemotherapy, the density of the proximal right tibia decreased, with a huge soft tissue mass surrounding it and an unclear boundary (A). The soft tissue volume was significantly reduced and the calcification was obvious after the addition of denosumab (B and C). Computed tomography images before (D) and 3 times after the administration of denosumab combined with chemotherapy (E).



**Figure 3.** Intraoperatively, the tumor tissue was completely resected and the major neuro-vascular bundles and muscles were preserved, and no amputation was performed (A). Completely resected tumor tissue (B). Incised specimen tissue (C). The pathology results showed the presence of degenerative malignant tumor cells in all the tissues (D) (HE,  $\times 100$ ).

The maximum circumference of the right tumor measured again after each denosumab administration was smaller than that after the first course of neoadjuvant chemotherapy (Fig. 1C through F). Preoperative plain radiographs (Fig. 2B, C) and CT

(Fig. 2E) showed that the volume of soft tissue mass was significantly reduced. Soft tissue and medullary calcification and ossification were found. Magnetic resonance imaging (Fig. 2F) revealed irregular polycystic expansive bone destruction in the



**Figure 4.** The incision healed well after operation (A). The function and activity of the right knee joint are basically normal (B). The postoperative plain radiograph showed good prosthesis location without loosening; the small head of the right fibula was absent, and the length of both lower limbs was basically the same (C).

metaphysis of the right tibia, without breaking through the epiphyseal plate. Excluding invasion of the surrounding soft tissue and capsule formation, a clear boundary and absence of adhesion to peripheral nerves and vessels were detected, which facilitated limb salvage surgery. In the junction area, the images showed circular and flaky isometry on T1 images and slightly longer on T2. On September 14, 2021, resection of the tumor and prosthesis reconstruction in the right proximal tibia was performed (Fig. 3A). The surgery was successful and the incision healed well (Fig. 4A). Postoperative pathology confirmed OS and a large necrotic tumor, along with degenerative malignant tumor cells in medullary cavity tissue, bone cortex, and extraosseous soft tissues. No tumor was found at the broken end (Fig. 3D). After 3 weeks, postoperative chemotherapy was performed sequentially (the dose and regime of chemotherapeutic drugs were the same as before operation) and functional exercise of the right lower limb was performed. Notably, denosumab was not added again during postoperative chemotherapy.

Six months after the operation, a total of 6 courses of adjuvant chemotherapy with DIA regimen were completed at an interval of 3 weeks. The patient's Musculoskeletal Tumor Society score was 27 (Fig. 4B). The patient had no evidence of recurrent or distant metastasis based on CT of the chest. The postoperative plain radiography showed that the prosthesis was in good position (Fig. 4C).

### 3. Discussion

According to the 2020 NCCN classical OS diagnosis and treatment guidelines, successful limb salvage surgery is based on safe surgical boundaries and good chemical reactions. Amputation is recommended (level 1) for patients undergoing preoperative neoadjuvant chemotherapy with unclear tumor boundaries and invasion of blood vessels and nerves. Studies have reported that the expression of RANKL in OS ranges

from 8.8% to 75%.<sup>[5-7]</sup> In the study of Bago-Horvath et al and Mori et al,<sup>[7,8]</sup> a positive expression of RANK in OS was detected in 57% and 69% of patients, respectively. RANKL is a key factor that is required for osteoclast differentiation and activation.<sup>[9]</sup> Some studies involving OS animal models<sup>[10]</sup> have shown that anti-RANKL agents can effectively decrease tumor growth, improve survival and inhibit lung metastasis. Branstetter et al<sup>[5]</sup> reported that anti-RANKL therapy may prevent osteolytic bone destruction in OS. A phase II study investigated denosumab alone in patients with relapsing/refractory OS was inadequate in this setting.<sup>[9]</sup> In patients who are nonresponders to conventional chemotherapy, combining neoadjuvant chemotherapy regimens with targeted agents, such as RANKL-directed antibodies might improve survival.<sup>[9]</sup> Denosumab is a human monoclonal antibody that inhibits bone resorption, increases new bone formation and delays tumor progression by binding to RANKL and preventing its interaction with RANK, thus mimicking the action of osteoprotegerin.

Punzo et al<sup>[11]</sup> discouraged the use of denosumab in addition to conventional chemotherapy in OS, when used in combination with doxorubicin, since it reduces its activity and probably inhibits the efficacy of the chemotherapy drug. However, the study did not classify the cases of standard OS based on imaging criteria, suggesting obvious limitations.

The imaging examination of the 14-year-old patient reported in our study showed that the lesion area of the proximal tibia was dominated by osteolytic bone destruction, which was mediated by the combination of RANKL and RANK. The binding of RANKL to RANK triggers osteoclast activation, which disrupts the balance of ecological environment in bone, and consequently prevents bone resorption and osteolysis. The results of preoperative plain radiograph reveal a time lag in osteogenesis after the application of denosumab. Given the limitations of a

case report, a large number of clinical trials are needed to validate this phenomenon.

To our knowledge, no published reports are available to demonstrate successful limb salvage in OS with the addition of denosumab combined with first-line chemotherapy to achieve tumor progression during neoadjuvant chemotherapy. Therefore, for patients with high-grade OS associated with mainly osteolytic bone destruction based on imaging findings and the progress of preoperative neoadjuvant chemotherapy, denosumab can be used as a new agent in limb salvage surgery.

### Author contributions

Q.C. did the study, analyzed the data, and wrote the manuscript.

J.W. measured the tumor circumference, K.Z., M.X., Z.H., and X.Y. were involved in the design, data management, and analysis of the study. All authors read and approved the final manuscript.

Investigation: Q.C. and J.W.

Supervision: K.Z., M.X., Z.H., and X.Y.

Writing—original draft: Q.C.

Writing—review and editing: Q.C.

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