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ORIGINAL ARTICLE

The efficacy and safety of short-course neoadjuvant denosumab for en bloc spondylectomy in spinal giant cell tumor of bone: a preliminary report

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Abstract

Purpose This study aimed to investigate whether short course of neoadjuvant denosumab treatment for spinal GCTB could (1) Induce radiological and histological response? (2) Facilitate en bloc resection? (3) Achieve satisfactory oncological and functional outcomes?

Methods The clinical information of ten consecutive patients between 2018 and 2022 with spinal GCTB treated with short course of neoadjuvant denosumab (≤ 5 doses) and en bloc spondylectomy was retrospectively reviewed. The radiological and histological response, operative data, oncological and functional outcomes were analyzed.

Results The mean doses of neoadjuvant denosumab were 4.2 (range 3–5 doses). After neoadjuvant denosumab, there were 9 cases showing new ossification and 5 cases with reappearance of cortical integrity. The values of Hounsfield units (HU) of the soft tissue component were increased by > 50% in 7 cases. The signal intensity (SI) ratios of tumor/muscle in T2WI of plain MRI were decreased by > 10% in 60% of the cases. Shrinkage of soft tissue mass by > 10% was observed in 4 cases. The mean duration of operation was 575 ± 174 min, and the mean estimated blood loss (EBL) was 2790 ± 1934 ml. No obvious adhesion to dura mater or major vessels was encounter intraoperatively. There is no tumor collapse or breakage during surgery. Multinucleated giant cells were decreased in 6 cases (60%) with the remaining 4 cases showing absence of multinucleated giant cells. Mononuclear stromal cells existed in most of the cases (8 cases, 80%). New bone formation was noticed in 8 cases (80%). No patient had a worsening of neurologic function after surgery. No tumor recurrence was noticed within the mean follow-up of 24 ± 20 months.

Conclusion Short-term neoadjuvant denosumab could yield radiological and histological responses and might facilitate en bloc spondylectomy by hardening the tumor and causing less adhesion to segmental vessels, major vessels and nerve roots, which was beneficial to achieve the optimal oncological and functional outcomes.

Keywords Spinal giant cell tumor of bone · Denosumab · En bloc resection · Clinical outcome

Introduction

Giant cell tumor of bone (GCTB) is a primary intermediate neoplasm with local aggressiveness [1, 2]. Most tumor commonly occurs at extremity, where only 1.4–9.4% of the cases occur in the spine [3, 4]. Spinal GCTB represents a special entity, and the standard treatment is surgical removal. The surgery for spinal GCTB is challenging and usually technically difficult [5, 6]. Whenever feasible, en bloc resection with negative margins should be always considered [6–9].

Histologically, GCTBs are composed of mononuclear stromal cells and multinucleated giant cells [10, 11]. Nuclear factor-κB ligand (RANKL) is highly expressed by mononuclear stromal cells and promotes osteoclast activation [12,

Qinglian Tang, Jinchang Lu and Xiaojun Zhu have contributed equally to this study and therefore share first authorship.

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13]. Denosumab, a fully human monoclonal antibody that binds to RANKL, blocks activation of osteoclastogenesis [14–16].

Denosumab can elicit objective clinical, radiological and histological response in spinal GCTB [17–19]. Denosumab is useful as a neoadjuvant treatment for planned total spondylectomy [20, 21]. However, the optimal duration of neoadjuvant denosumab treatment is controversial. Studies indicated that median time to the best tumor response was within 1–3 months [22, 23]. A neoadjuvant treatment protocol proposed by Boriani et al. includes ≥ 6 months of neoadjuvant treatment [17]. Here, we defined the neoadjuvant treatment with ≥ 6 months of denosumab as long-term treatment and the neoadjuvant treatment with ≤ 3 months of denosumab as short-term treatment. Though reduced soft tissue mass and firmer tumor are helpful in lowering the difficulty of resection, adhesion or ossified encasement of segmental vessels, major vessels, dura mater, nerve roots or vertebral artery can be encountered after 6 months of denosumab therapy, which bring additional risk to total spondylectomy. Indeed, Yonezawa et al. found that it was difficult to dissect the segmental arteries from the vertebral body owing to bridging callus formation after 10 courses of denosumab [21]. Besides, possible complications and economic burden of long-term doses are also issues which should be considered.

We therefore asked whether short-term neoadjuvant denosumab (≤ 5 doses) for en bloc spondylectomy can: (1) Induce radiological and histological response? (2) Facilitate en bloc resection? (3) Achieve satisfactory oncological and functional outcomes?

Materials and methods

Data collection

This study was approved by the institutional review board (IRB) of our institute, and informed consents were obtained from the patients. We retrospectively reviewed the cases of spinal GCTB treated with neoadjuvant denosumab and en bloc spondylectomy in our center between 2018 and 2022. After searching the surgical data base, 10 cases (6 females and 4 males) met the criteria and were included. The mean age is 30.3 ± 6.1 years (Table 1). The duration from symptom onset to medical consulting was 2.4 ± 1.4 months. The locations of the lesion were thoracic (5 cases, 50%), lumbar (4 cases, 40%) and thoracolumbar spine (1 case, 10%). 80% of the cases had a soft tissue mass with the mean size of 6.1 cm (range 2.7–10.2 cm). A mean 4.2 doses of denosumab (range 3–5 doses) were used preoperatively, and the duration from 1st dose to operation was 60 ± 22 days. Neurological status was assessed and classified according to the Frankel score [24].The authenticity of this article has been validated by uploading the key raw data onto the Research Data Deposit public platform (https://www.researchdata.org.cn), with the approval RDD number as RDDA2023464372.

Table 1 Baseline data of patients with spinal GCTB treated with short course of neoadjuvant denosumab

Variables	
Gender [N (%)]	
Male	4 (40)
Female	6 (60)
Age (year, mean ± SD)	30.3 ± 6.1
Onset Duration (month, mean ± SD)	2.4 ± 1.4
Location [N (%)]	
Thoracic	5 (50)
Thoracolumbar	1 (10)
Lumbar	4 (40)
Frankel score [N (%)]	
A	1 (10)
C	1 (10)
D	1 (10)
E	7 (70)
Soft tissue mass [*N* (%)]	4 (40)
Size of soft tissue mass (cm, mean ± SD)	6.1 ± 2.6
Vertebral fracture [*N* (%)]	4 (40)
Doses of denosumab [N (%)]	
3	1 (10)
4	6 (60)
5	3 (30)

Application of denosumab

All spinal GCTB cases were pathologically confirmed. The patients received neoadjuvant denosumab treatment (120 mg, subcutaneously, D1, D8, D15, D28 and monthly thereafter) with supplement of calcium and vitamin daily. Serum calcium and phosphate levels were monitored monthly.

Radiological evaluation of the response to denosumab

Spine X-ray, computerized tomography (CT) and magnetic resonance image (MRI) examinations before and after neoadjuvant denosumab treatment were performed. The location of spinal lesion and the presence and extension of soft tissue mass were documented. New ossification within the tumor, reappearance of cortical integrity and change of the diameter of soft tissue mass after denosumab treatment were evaluated. The values of Hounsfield units (HU) of the soft

tissue component were measured. Signal intensity (SI) ratios of the tumor and the erector spinae in T2WI on plain MRI were calculated.

Histological evaluation of the response to denosumab

Specimens from biopsy and spondylectomy were routinely examined. The presence of mononuclear stromal cells and multinucleated giant cells, and reactive bone formation or fibrosis, was evaluated. H3F3A mutation (H3.3G34W or H3.3G34L) was also tested by immunohistochemistry or/and Sanger sequencing.

Assessments of the effects of short-term neoadjuvant denosumab on spondylectomy

Surgical data were collected to access the effects of neoadjuvant denosumab on spondylectomy, including adhesion or encasement of segmental vessels, major vessels, dura mater, nerve roots, duration of the operation and the estimated blood loss (EBL). Tumor collapse or breakage during surgery was documented.

Follow-up schedule

Patients were followed up every 3–4 months during the first two years, then six monthly until five years after spondylectomy and thereafter yearly. Routine physical examination was performed during each follow-up. X-ray of spine, CT scan of the spine and the lung were also performed. The status of local control and lung metastasis was documented by each follow-up. Local recurrence and death were endpoints.

Statistical analysis

Continuous variables were presented as the mean and standard deviation (SD).

Statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline data

There were 10 patients (6 females and 4 males) included in this study (Table 1). The mean doses of neoadjuvant denosumab were 4.2 (range 3–5 doses), with 6 patients receiving 4 doses before surgery.

At first examination, 7 patients (70%) presented with a Frankel score of E. Frankel score was improved from C to D after 4 doses of denosumab in one patient. One patient with Frankel D remained the same neurological function after 3 doses of denosumab.

The thoracic spine (5 cases) is the most commonly involved location, followed by lumbar spine (4 cases) and thoracolumbar region (1 case). Pathological fractures were presented in 40% of the patients. Eight cases have soft tissue mass extension to spinal canal. In one case, the soft tissue mass was encasing half diameter of the thoracic aorta (180° encasement) (Table 1 and Fig. 2).

Radiological and histological response

After neoadjuvant denosumab, there were 9 cases showing new ossification and 5 cases with reappearance of cortical integrity determined by CT scan (Table 2). The values of Hounsfield units (HU) of the soft tissue component were increased by > 50% in 7 cases (Figs. 1 and 2). The SI ratios of tumor/muscle in T2WI of plain MRI were decreased by > 10% in 60% of the cases. Shrinkage of soft tissue mass by > 10% was observed in 4 cases (Figs. 1, 2 and 3).

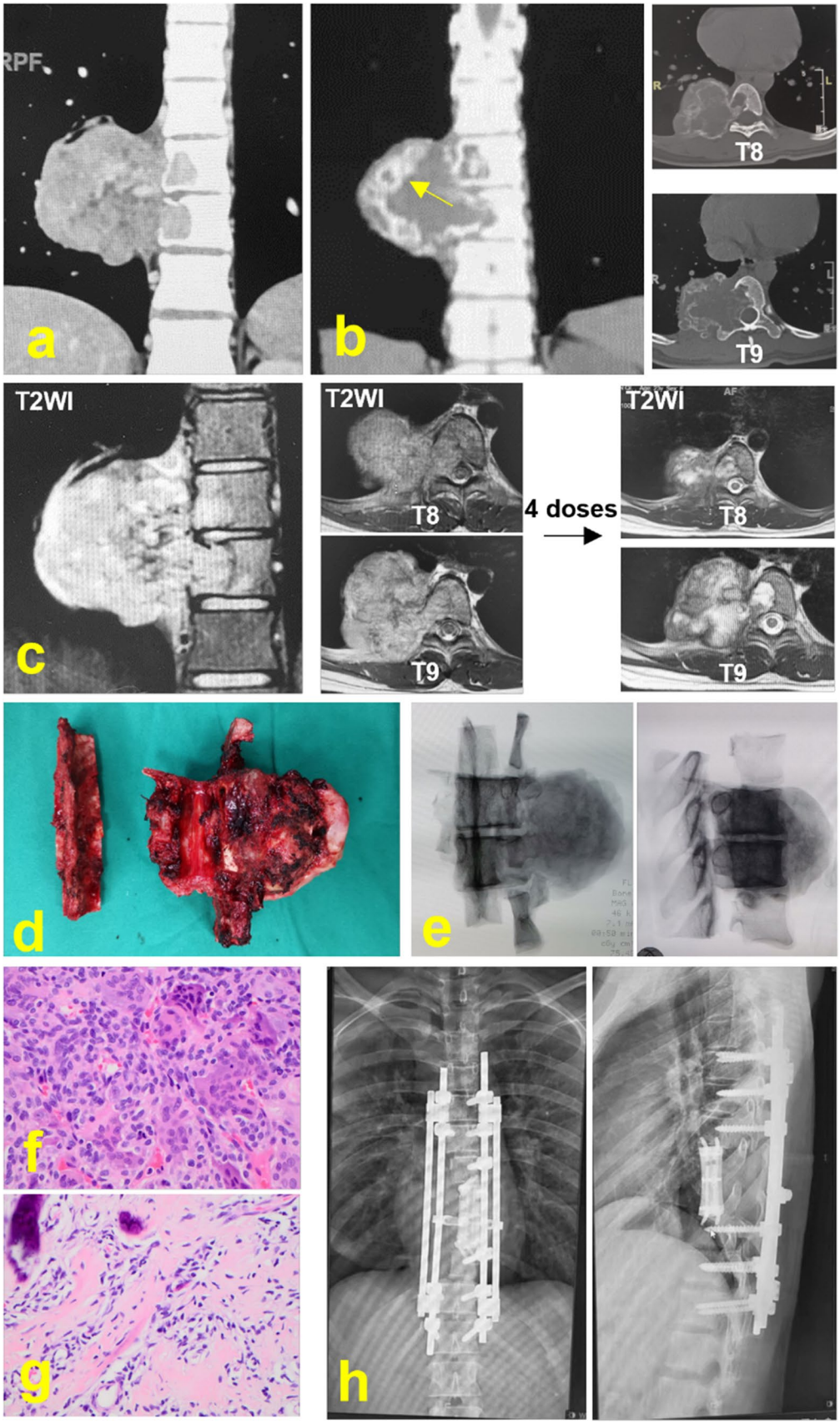
Histological evaluation revealed that multinucleated giant cells were decreased in 6 cases (60%) with the remaining 4 cases showing absence of multinucleated giant cells (Figs. 1, 2 and 3). However, mononuclear stromal cells existed in most of the cases (8 cases, 80%). New bone formation was noticed in 8 cases (80%). Six cases (60%) were positive for H3.3G34W, and 1 case presented H3.3G34L mutation (Table 2).

Operative data

The mean doses of neoadjuvant denosumab were 4.2 (range 3–5 doses). Preoperative embolization was not performed in our cases. The mean duration of operation was

Table 2 Radiological and histological response of patients with spinal GCTB treated with short course of neoadjuvant denosumab

Variables [*N* (%)]	
New ossification	9 (90)
Reappearance of cortical integrity	5 (50)
Increased HU value	7 (70)
Decreased SI ratios of tumor/muscle in T2WI	6 (60)
Shrinkage of soft tissue mass	4 (40)
Number of multinucleated giant cells	
Decreased	6 (60)
Absent	4 (40)
Present mononuclear stromal cells	8 (80)
New bone formation	8 (80)
Histone variant	
H3.3G34W	6 (60)
H3.3G34L	1 (10)


RPF
a
b
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4 doses
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◂**Fig. 1** Thoracic GCTB treated by en bloc spondylectomy after short course of neoadjuvant denosumab. **a** A 23-year-old female presented with right back pain. Coronal CT showed lytic lesion in T8-9 with obvious soft tissue mass. She was diagnosed as thoracic GCTB by core needle biopsy. **b** The patient received 4 doses of neoadjuvant denosumab. Thoracic CT revealed a shrinkage of soft tissue mass and new ossification (arrow) of the lesion. **c** MRI (T2WI) showed bone destruction at T8-9 with soft tissue mass extending to spinal canal with dura sac compression (left and middle). After 4 doses of neoadjuvant denosumab, the soft tissue mass within the spinal canal was reduced with decompression of dura sac (right). **d** The patient received T8-9 en bloc spondylectomy, and the resected specimens were shown. **e** The AP (right) and lateral (left) view of X-ray of surgical specimens were shown. **f** Hematoxylin and eosin (H&E) staining of the biopsy specimen, showing multinucleated giant cells and mononuclear stromal cells. **g** After 4 doses of neoadjuvant denosumab, the absence of multinucleated giant cells and new bone formation was observed. **h** Follow-up X-ray evaluation of thoracic spine was shown

575 ± 174 min, and the mean EBL was 2790 ± 1934 ml (Table 3).

One case with unilateral L3 nerve root was encased by the ossified soft tissue mass, and it was difficult to dissect the nerve root (Fig. 3). No obvious adhesion to dura mater or major vessels was encounter intraoperatively. Two cases showed minor adhesion to the segmental vessels which were still able to be ligated. In the case with the thoracic aorta encasement (180°), no obvious adhesion was found intraoperatively and the thoracic aorta was dissected safely away soft tissue component (Fig. 2).

The tumor margin was easily determined intraoperatively, and the stiff shell around the lesion is beneficial for resection (Figs. 1 and 2). There is no tumor collapse or breakage during surgery. No patients had intraoperative CSF leak, and one patient had postoperative CSF leak which was treated conservatively.

Clinical outcomes

No patients were lost to follow-up. One patient with preoperative Frankel A did not present improved neurological function 57 months after spondylectomy. One patient gained improved neurological function from Frankel D to E 3 months postoperatively. One patient with preoperative Frankel D did not obtain improved quadriceps femoris strength due to sacrifice of unilateral L3 nerve root. The other 7 patients had normal neurological function. No patient had a worsening of neurologic function after surgery.

No tumor recurrence was noticed within the mean follow-up of 24 ± 20 months. One patient with preoperative lung metastasis was treated with monthly denosumab, and her lung lesions were stable.

Discussion

Limitations

There were several limitations in this study. First, the sample size was relatively small, which may lead to observation bias. We are now enrolling more patients for this study in order to obtain more convincing conclusion. Second, some parameters were subjective and qualitative. To our knowledge, there were no consensual methods for quantifying tissue adhesion, fibrosis and ossification. Third, the follow-up was not long enough to detect secondary effects and the recurrence rate.

Radiological and histological response induced by short course of denosumab

A key feature after denosumab treatment is mineralization or ossification within the lesion and at the periphery of the lesion [14, 19]. In the present study, we used Hounsfield units (HU) to quantify the density of the lesion and found that 70% of the lesions (7/10) had a > 50% increase in density after treatment of denosumab.

MRI is sensitive to evaluate the soft tissue component of GCTB. The maximum diameter of soft tissue component, assessed on T2-weighted images, decreased by > 10% in 40% of the cases after short course of denosumab. T1 signal intensity did not change significantly after treatment, which was in accordance with previous studies [25]. However, decreased T2-weighted MR signal intensity was detected in 60% of the lesions. Our study indicated that T2-weighted MR signal intensity and Hounsfield units (HU) of the lesion were sensitive markers to assess treatment response in spinal GCTB.

Typical pathological features in denosumab treated GCT include a marked reduction or complete absence of multinucleated giant cells and formation of woven bone [19]. On histopathological examination, reactive or woven bone formation was seen in 80% cases and all the cases showed marked reduction or complete lack of multinucleated giant cells, despite of our short course of denosumab.

In summary, our short-course regimen can elicit radiological and histological response, which was variable among the cases. The finding of the present study is similar to previous study in sacrum and extremity GCTB. Liang et al. [26] reported that short course (≤ 3 doses) of denosumab could elicit radiological and histological responses in sacrum GCTB as conventional course did. Hindiskere et al. [18] also concluded that a short course (≤ 3 doses) of preoperative denosumab was associated with satisfying histological and radiological response in extremity GCTB. The reduced neoadjuvant doses have other advantages, including reduced

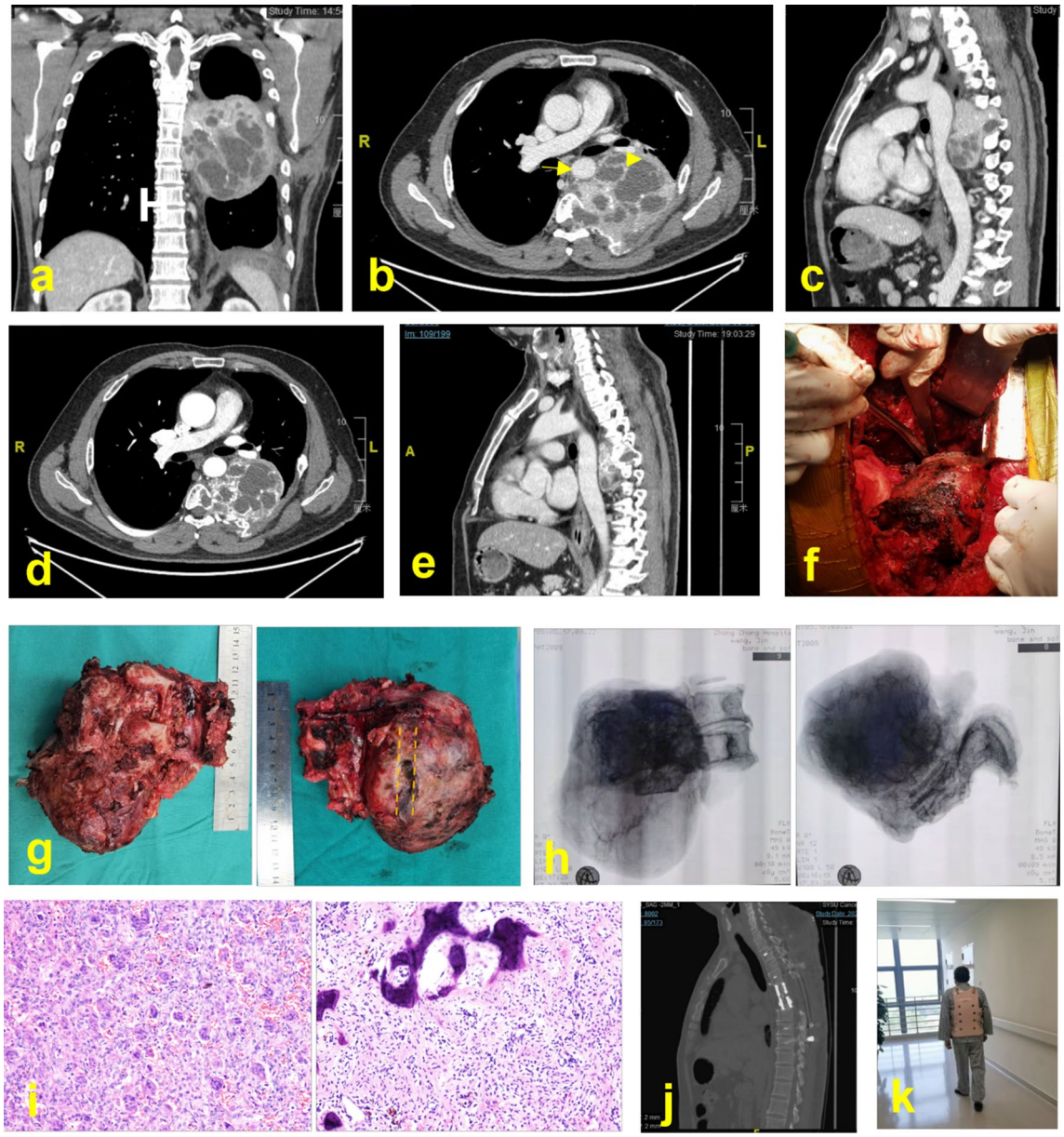

Fig. 2 Thoracic GCTB with thoracic aorta encasement, treated by en bloc spondylectomy after short course of neoadjuvant denosumab. **a**–**c** A 43-year-old male with biopsy confirmed GCTB (T5-6). Coronal (**a**), axial (**b**) and sagittal (**c**) CT showed bone destruction of T5-6 with huge soft tissue mass. The mass had an 180° encasement of thoracic aorta (arrow) and also abutted the inferior pulmonary artery (arrow head) (**d** and **e**). After 5 doses of neoadjuvant denosumab, the soft tissue mass within the spinal canal was reduced with decompression of dura sac (**d**). Moreover, encasement and compression of thoracic aorta were reduced (**e**). **f** This huge GCTB was resected via a combined anterior and posterior approaches. The picture showed intraoperative dissection of specimen the lung and thoracic aorta. **g** The surgical specimen showed thoracic aorta groove (dash line) which was formed by soft tissue mass encasement. **h** X-ray examination of the surgical specimen en bloc resection of T5-6 GCTB. **i** H&E staining of the biopsy specimen (left). Multinucleated giant cells were absent, and new bone formation were noticed after 5 doses of neoadjuvant denosumab (right). There were also abundant mononuclear stromal cells existing. **j** T5-6 GCTB was resected, and vertebral defect was reconstructed with expandable cage and pedicle screw–rod system. **k** The patient had normal neurological function after surgery

complications and economic costs as compared with prolonged therapy [14].

Clinical benefits of neoadjuvant denosumab treatment for spinal GCTB

The aims of neoadjuvant denosumab treatment for en bloc spondylectomy are to increase firmness of the tumor, reduce

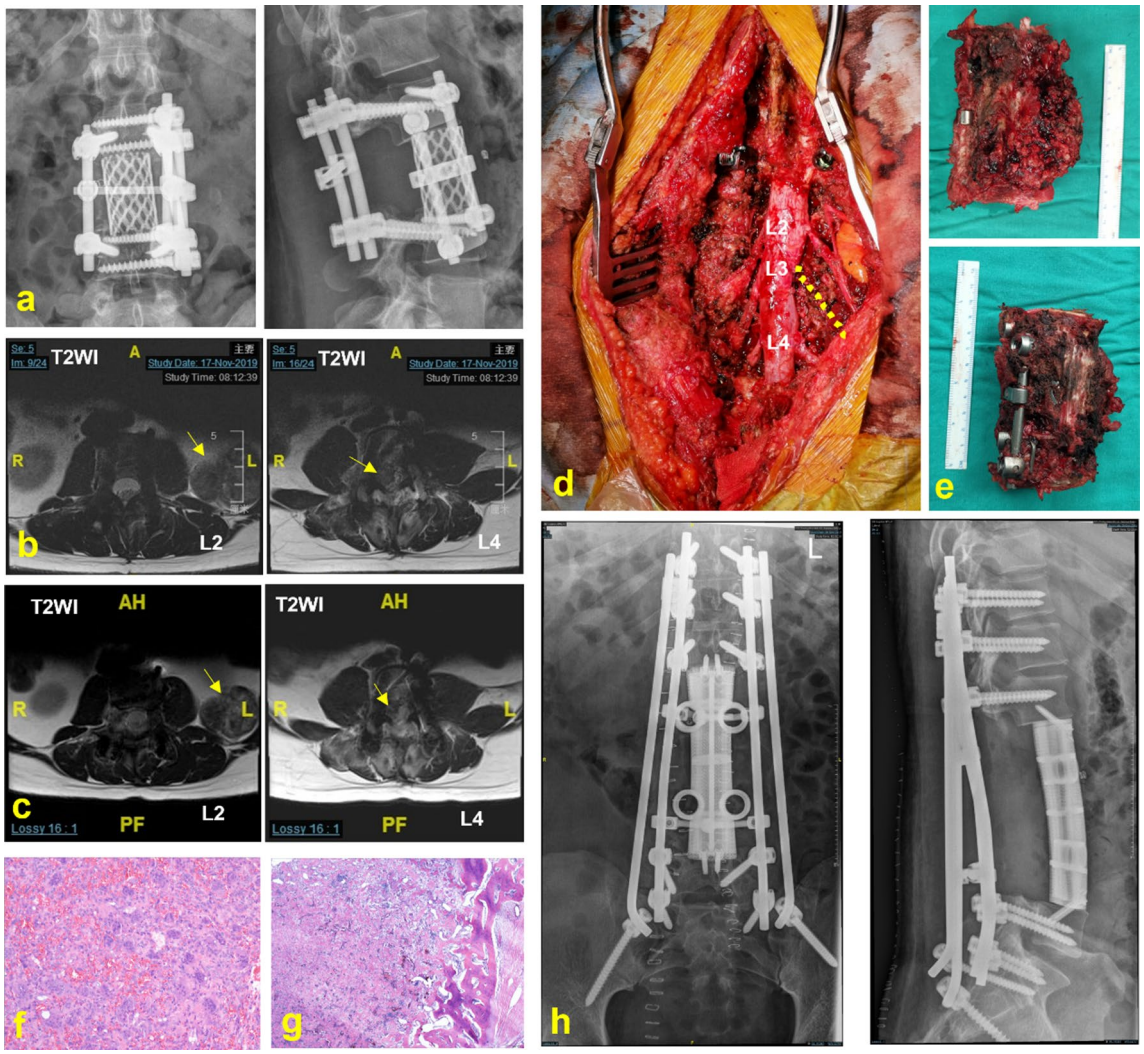

Fig. 3 Recurrent lumbar GCTB treated by en bloc spondylectomy after short course of neoadjuvant denosumab. **a** A 30-year-old man received L3 GCTB resection at local hospital, and he was referred to our institute for tumor recurrence 8 months after surgery. Lumbar X-ray did not reveal abnormity. **b** Soft tissue mass (arrow) near the psoas major and within the spinal canal was found by MRI. **c** The soft tissue mass (arrow) was reduced after 3 doses of neoadjuvant denosumab. **d** The recurrent tumor was resected via a combined anterior and posterior approaches. The picture showed intraoperative dissection of nerve roots and dura sac. The right side of L3 nerve root was encased by the ossified soft tissue mass, and it was difficult to dissect the nerve root, which was resected intraoperatively (dash line). **e** The en bloc surgical specimen was shown. **f** H&E staining of the biopsy specimen. **g** Multinucleated giant cells were absent, and new bone formation was noticed after 3 doses of neoadjuvant denosumab. **h** Vertebral defect was reconstructed with custom-made 3D printing artificial vertebrae and pedicle screw–rod system

Table 3 Operative data of patients with spinal GCTB treated with short course of neoadjuvant denosumab

Variables	
Duration from 1st dose to operation (day, mean ± SD)	60.6 ± 22.1
Duration of operation (min, mean ± SD)	575 ± 174
Blood loss (ml, mean ± SD)	2790 ± 1934
Adhesion/encasement of nerve root [*N* (%)]	1 (10)
Encasement of major vessels [*N* (%)]	1 (10)
Tumor collapse or breakage [*N* (%)]	0 (0)

soft tissue mass and decrease blood supply of tumor [17, 27, 28], which may lead to reduced blood loss and better management of surgical dissection.

Blood loss assessment is sometimes difficult to compare among different studies, as it is influenced by tumor location, tumor volume and tumor status (primary/recurrent). In this study, the mean blood lost for primary GCT without huge soft tissue mass was 2028 ml. Under similar tumor stage, Yokogawa et al. [29] reported mean blood lost was 2280 ml without denosumab. Also, Samartzis et al. [30] reported a similar stage GCT of L3 and the blood lost was 3400 ml

without denosumab. Paholpak et al. [31] reported average blood loss was 2833.33 ml, while Elder et al. reported average blood loss was 3663 ml [32]. Therefore, our preliminary data indicated that neoadjuvant treatment with denosumab may reduce blood loss, although more data are needed.

GCT is a lytic tumor which is soft and friable. Thus, spinal GCT has a high risk of collapse or breakage of the mass. By hardening the tumor and reducing soft tissue component with neoadjuvant denosumab, the dissection is becoming easier and the risk of tumor breakage during surgery is lowered. Indeed, no tumor collapse or breakage was observed in our study.

Optimal course of neoadjuvant denosumab for en bloc spondylectomy

Thus far, the optimal treatment duration of neoadjuvant denosumab is still not well defined. Yonezawa et al. found that prolonged denosumab may stimulate bridging callus formation between the affected and adjacent vertebra, making en bloc spondylectomy more difficult [21].

It is known that markers of bone resorption fall rapidly within 2 months of denosumab therapy and median time to the best tumor response was within 1–3 months [22, 23]. These studies pointed out that a short course of denosumab treatment is worthy of investigation in the setting of neoadjuvant therapy. However, there are scarce studies aiming to evaluate the short course of neoadjuvant denosumab treatment in GCTB. In sacrum GCTB, short course (≤ 3 doses) of neoadjuvant denosumab actually facilitated nerve-sparing surgery without unfavorable effects on local control and functional status [26]. Meanwhile, short course (≤ 3 doses) of neoadjuvant denosumab yields similar clinical scores and local control for extremity GCTB, as compared with longer duration of treatment [18].

In the present study, 40% of cases showed $> 10\%$ decrease in soft tissue mass after short-course neoadjuvant denosumab treatment. Fibrosis and ossification were observed in 80% of cases, which increase firmness of the tumor and induce marginal sclerosis. This help to avoid tumor collapse or breakage during surgery (Figs. 1, 2 and 3).

We also found minor tissue adhesion in the short-term protocol. In one case with 180° encasement of the thoracic aorta, we found minor adhesion during dissection of the thoracic aorta and the lung. It might be risky to dissect the thoracic aorta from the tumor if long-term denosumab was prescribed.

However, nerve root was found to be encased by ossified soft tissue mass in one case even the patient received only 3 doses of denosumab. This indicated that ultra-short course (< 3 doses) of neoadjuvant denosumab is worthy to be further investigated in the nerve-sparing surgery for lumbar spondylectomy. Liang et al. revealed that ≤ 3 course of neoadjuvant denosumab might actually facilitate nerve-sparing surgery in sacrum GCTB, as compared with conventional course [26]. Therefore, short course of neoadjuvant denosumab might be considered in lumbar and cervical GCTB when major never root or vertebral artery is preserved. Moreover, in case of huge soft tissue encasing the major vessels, neoadjuvant denosumab should be used cautiously and short course of denosumab is advisable by monitor the radiological response closely.

Conclusions

Short-term neoadjuvant denosumab for spinal giant cell tumor of bone (GCTB) could yield radiological and histological responses and might facilitate en bloc spondylectomy by hardening the tumor and reducing soft tissue component. Importantly, no obvious adhesion to major surrounding structures was observed, and optimal oncological and functional outcomes were achieved.

Declarations

Conflict of interest The authors declare no conflict of interest.

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