

Received: 2021.02.24

Accepted: 2021.04.08

Available online: 2021.04.27

Published: 2021.06.01

# Giant Cell Tumor of Bone of the First Rib Successfully Treated with Combined Preoperative Denosumab Therapy and Surgery via a Transmanubrial Approach

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

**Source of support:** This work was supported by in part by the National Cancer Centre Research and Development Fund (29-A-3) and the Practical Research for Innovative Cancer Control from the Japan Agency For Medical Research and Development, AMED (20ck0106614h0001)

**Patient:** Female, 27-year-old  
**Final Diagnosis:** Giant cell tumor of bone  
**Symptoms:** No symptom  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Oncology

**Objective:** Rare disease

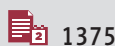
**Background:** Giant cell tumor of bone (GCTB) is a locally aggressive, intermediate tumor that rarely metastasizes. GCTB typically affects the ends of long bones and rarely involves the ribs. Curettage is typically the treatment of choice for GCTB in long bones. However, the optimal treatment of GCTB in ribs remains unclear. We report the case of a patient with asymptomatic GCTB of the first rib that was successfully treated with combined preoperative denosumab therapy and surgery via a transmanubrial approach without resection of the clavicle.

**Case Report:** A healthy 27-year-old woman presented with a bone tumor involving the left first rib that was incidentally discovered on routine chest X-ray. Histological examination of core-needle biopsy specimens of the lesion led to a pathological diagnosis of GCTB. After preoperative denosumab treatment for 6 months, en bloc resection via a transmanubrial approach was performed. There were no serious postoperative complications. The patient remained free of symptoms and had no recurrence 4.5 years after surgery.

**Conclusions:** Compared with other ribs, masses located in the first rib can be challenging to treat surgically because of the clavicle and neighboring neurovascular structures. This report is the first to describe GCTB located on the anterior aspect of the first rib that was successfully treated with combined preoperative denosumab therapy and surgery via a transmanubrial approach, with no recurrence or functional impairment of the shoulder girdle.

**Keywords:** Denosumab • Giant Cell Tumor of Bone • Giant Cell Tumors • Ribs

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/931796>



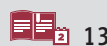
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## Background

Giant cell tumor of bone (GCTB) is an unusual neoplasm that accounts for about 4-5% of all primary bone tumors [1]. It is an invasive bone tumor characterized by highly aggressive behavior and frequent recurrence, and it typically involves the ends of long bones. The ribs are rarely affected; indeed, Gupta and Mittal [2] reviewed the English literature and reported that GCTB involving the ribs accounted for only 1.4% of instances of GCTB (26 of 1870 cases). To the best of our knowledge, there is only one case report of a patient with GCTB arising from the first rib [3].

Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor- $\kappa$ B ligand (RANKL). It inhibits activation and differentiation of osteoclast-like giant cells and consequent osteolytic damage mediated by RANKL. Recently, denosumab has been widely recognized as an effective treatment for unresectable GCTB [4]. In addition, preoperative denosumab therapy was beneficial for surgical downstaging in patients with resectable GCTB [4].

In the present article, we report a case of GCTB of the first rib that was successfully treated with combined preoperative denosumab therapy and surgery via a transmanubrial approach.

## Case Report

An asymptomatic 27-year-old woman with no medical history or history of trauma to the chest wall was referred to a previous hospital due to a bone tumor involving the left first rib. The lesion was incidentally discovered on routine chest X-ray in October 2015 (Figure 1). No abnormalities were detected on physical examination. Electrocardiography and spirometry were normal. All laboratory parameters, including blood cell count, biochemistry, and coagulation panels, were unremarkable. Computed tomography (CT) showed an expansive osteolytic lesion involving the anterior arc of the left first rib (Figure 2). Magnetic resonance imaging revealed that the lesion measured 5.2×4.8×4.5 cm in size and demonstrated a homogeneous intermediate signal intensity on T1-weighted images and a heterogeneous intermediate-to-high signal intensity on T2-weighted images (Figure 3A, 3B). CT-guided core-needle biopsy was performed. Histological examination revealed a proliferation of mononuclear oval or short spindle cells admixed with many osteoclast-like multinucleated giant cells, arranged in a haphazard fashion (Figure 4). The pathological diagnosis was GCTB.

Based on evidence reported in a phase 2 clinical study, denosumab was administered as a subcutaneous injection of 120 mg every 4 weeks for 6 months, with additional 120-mg single

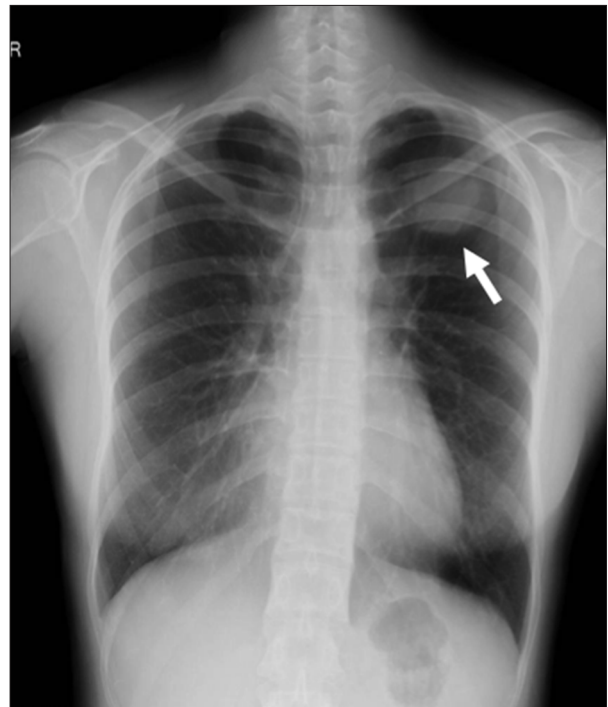
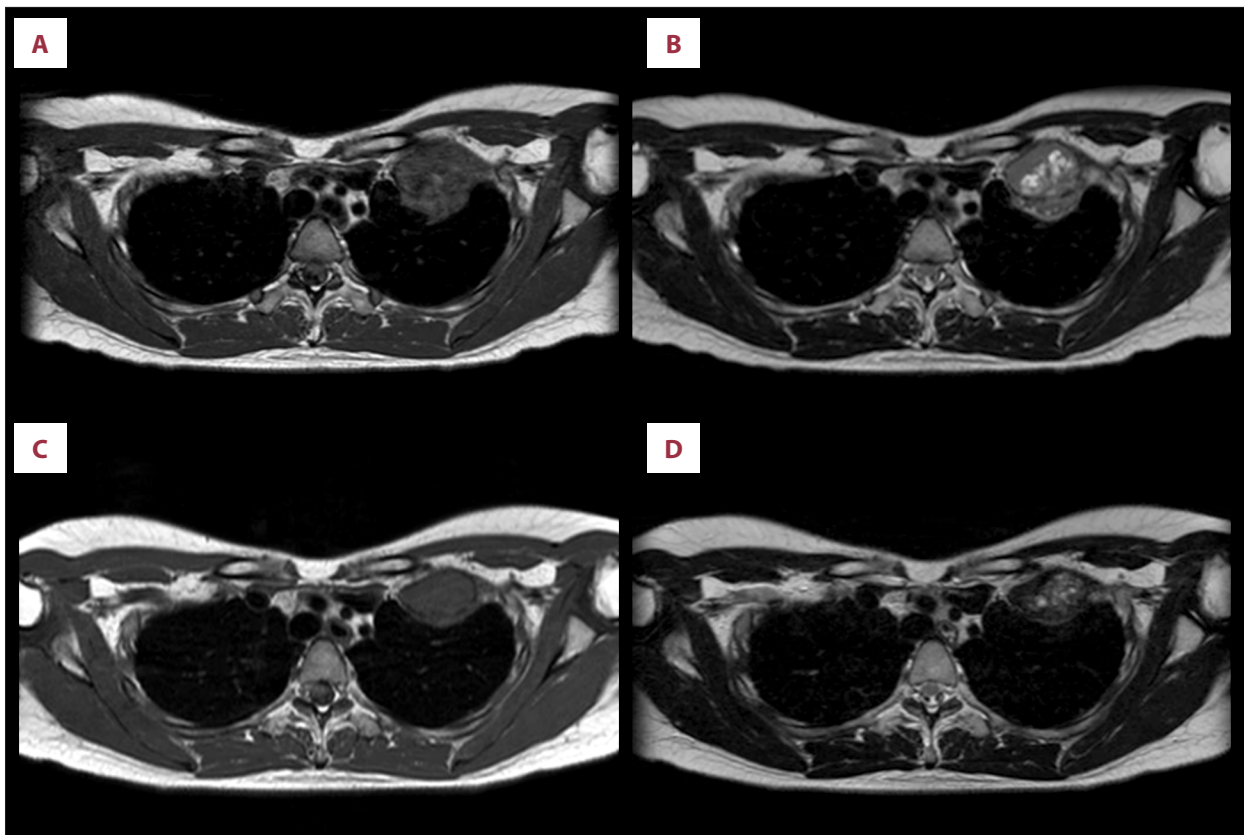


Figure 1. Chest X-ray examination shows a lesion on the left first rib (arrow).

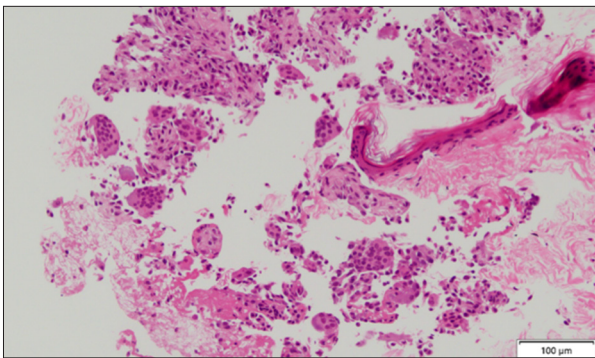


Figure 2. Chest computed tomography shows an osteolytic mass arising from the anterior arc of the first rib.

doses on days 8 and 15 of the first month of treatment, and initiation of the second cycle on day 29 or 4 weeks after day 15 [4]. Follow-up magnetic resonance imaging at 4 months after initiation of denosumab therapy showed that the mass had decreased in size. In addition, the high-intensity area in the center of the lesion had become smaller, and the intensity of the surrounding area had decreased on T2-weighted images (Figure 3C, 3D). Six months after the start of denosumab therapy, a chest CT scan showed tumor shrinkage and cortex consolidation of the border of the first rib (Figure 5).



**Figure 3.** (A) T1-weighted and (B) T2-weighted magnetic resonance images show an axial view prior to denosumab therapy. (C) T1-weighted and (D) T2-weighted magnetic resonance images at 4 months after denosumab therapy.



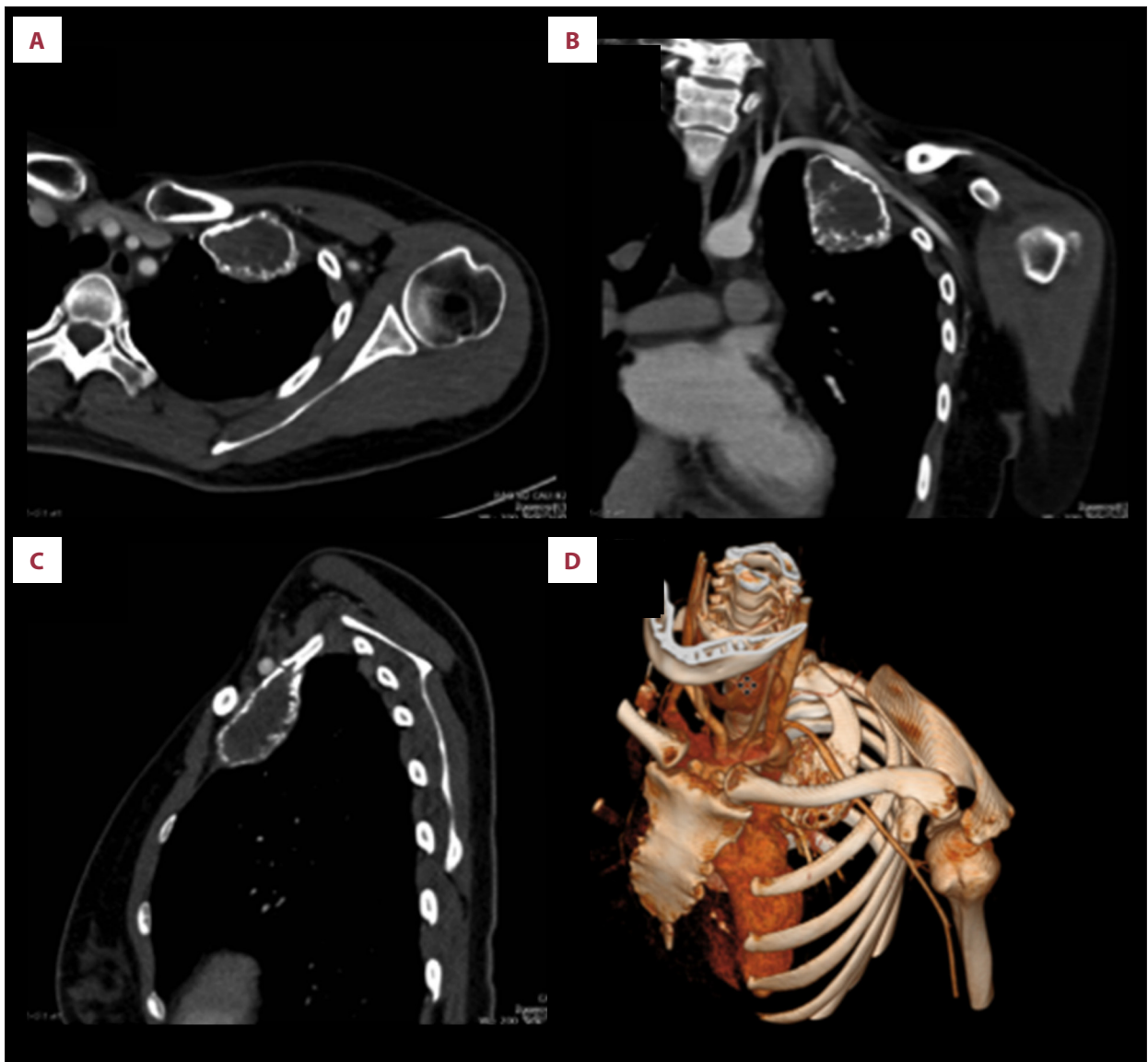
**Figure 4.** Microscopic images of the tumor specimen prior to denosumab therapy (hematoxylin and eosin staining). The tumor demonstrates diffuse proliferation of multinucleated, osteoclast-like giant cells and uniform ovoid- to spindle-shaped mononuclear stromal cells.

Seven months after the initiation of denosumab treatment, we performed surgery for the rib tumor. Briefly, the operation was performed under single-lung anesthesia. The patient was placed in the supine position. Using the transmanubrial approach, the left-upper part of the sternum and the cartilage of the first rib were both cut without dividing the left clavicular-sternum joint. The sternocleidomastoid muscle insertion was

detached from the manubrium sterni and clavicle (**Figure 6A**). Mild pleural adhesion was found in the apical area of the left lung without apparent tumor invasion. The first rib was resected at the first intercostal space, and the anterior and middle scalene muscle insertions were detached from the first rib. The first rib was then cut just posterior to the insertion of the middle scalene muscle. Finally, the tumor was successfully excised without damage to the subclavian vessels or brachial plexus. The transected manubrium sterni was refixed to the sternum with stainless steel wire. The detached sternocleidomastoid muscle was reattached to its original insertion site. The operation time was 5 h, 1 min. Blood loss was 270 mL.

The resected tumor is shown in **Figure 6B**. Microscopically, the resected specimen showed diffuse proliferation of short, spindle-shaped cells without nuclear atypia, and there was extensive osteoid formation and fibrosis throughout the entire specimen. Neither stromal cells nor giant cells were observed (**Figure 6C**). The pathological diagnosis was a posttherapeutic lesion after denosumab treatment for GCTB.

The postoperative clinical course was uneventful. Sternal union was achieved 6 months after surgery. The patient had been active athletically and was able to return to gym workouts. No



**Figure 5.** Computed tomography images 6 months after starting denosumab therapy. (A) Axial view. Significant tumor shrinkage and calcified sclerotic rim compared with pretreatment images (Figure 2). (B) Sagittal view. (C) Coronal view. (D) Three-dimensional reconstruction of computed tomography arteriography shows the subclavian artery passing between the tumor of the first rib and clavicle.

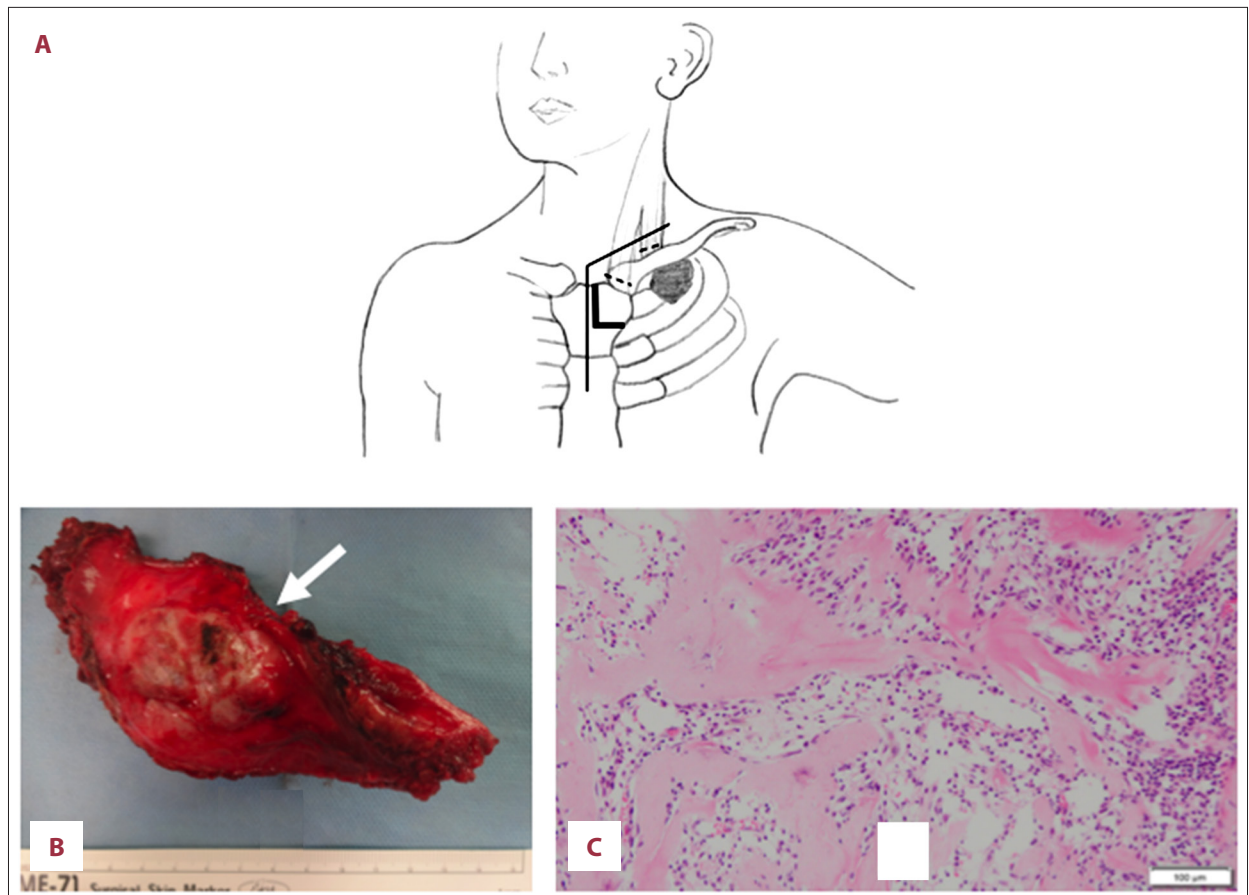
tumor recurrence was found on chest X-ray during 54 months of follow-up.

## Discussion

Surgical excision is the only curative treatment in patients with GCTB. Curettage and bone grafting with or without adjuvant therapy are the mainstays of treatment, although high recurrence rates (up to 50%) have been reported [5]. While GCTB of the ribs is rare, Sharma and Armstrong [6] reviewed the literature and found that en bloc resection rather than curettage was

an appropriate treatment because 10% of GCTB cases involving the ribs underwent malignant transformation [6]. Because of the specific anatomy involved, en bloc resection rather than intralesional curettage seems ideal for GCTB of the ribs.

Resection of the first rib is surgically challenging due to the clavicle and neighboring neurovascular structures. Removal of the clavicle might offer a good surgical view, but postoperative deformity and function impairment of the shoulder girdle were reported [7]. In addition, Demura et al [8] reported that aggressive GCTB arising from the thoracic spine caused adhesion to the lungs and pleural effusion. Accordingly, we had to



**Figure 6.** (A) Skin incision (thin solid line), L-shaped sternal division (thick solid line), and release of the sternal head and the clavicular head of the sternocleidomastoid muscle from its origin (dashed line) are illustrated. (B) Gross specimen and pathological findings. The tumor in the first rib was resected. The tumor (arrow) was covered by smooth pleura. (C) A microscopic view shows diffuse proliferation of short, spindle-shaped cells without nuclear atypia, as well as osteoid formation and extensive fibrosis throughout the entire specimen. No giant cells are observed (hematoxylin and eosin staining).

consider not only first rib resection, but also partial lung resection if necessary. To obtain good exposure of the thoracic outlet, we chose a modified version of Grunenwald's transmanubrial approach, in which the sternoclavicular joint is preserved and the incidence of functional and cosmetic complications can be minimized [9].

Recent studies reported that preoperative denosumab treatment induced marked regression of GCTB [4,10,11]. Therefore, preoperative denosumab therapy to reduce tumor size may be an ideal treatment option. The combination of preoperative denosumab therapy for 6 months and surgery via the transmanubrial approach resulted in an excellent clinical outcome in this case. Sternal union was achieved, and the patient resumed gym workouts 6 months after surgery and has remained free of recurrence for 4.5 years after surgery as of this writing.

The optimal duration of preoperative denosumab therapy for resectable GCTB remains unclear. Semionov and Kosiuk [11]

reported a case of GCTB of the eighth rib in which the tumor was resected after 3 doses of preoperative denosumab administration. A couple of case reports describing total en bloc spondylectomy after preoperative denosumab treatment have been published. de Carvalho Cavalcante et al [12] performed total en bloc spondylectomy of the fourth lumbar vertebra for GCTB after 6 months treatment with preoperative denosumab. Goldschlager et al [10] reported that the mean duration of preoperative denosumab treatment was 6 months in 5 cases of GCTB of the spine, and denosumab reduced the tumor size by 10-40%. In the present case, we consider that 6 months of preoperative denosumab administration was adequate because tumor shrinkage with marked peripheral osteosclerosis made resection easier.

We followed the procedure of the previous phase II trial described by Chawla et al [4], in which denosumab caused diverse side effects such as arthralgia (20%), headache (18%), nausea (17%), fatigue (16%), back pain (15%), extremity pain

(15%), hypocalcemia (5%), and osteonecrosis of jaw (1%) of any grade. Those events are preventable and manageable. Attention should be paid to malignant transformation of GCTB during denosumab therapy in patients without previous exposure to radiation therapy [13]. The relationship between malignant transformation of GCTB and denosumab should be investigated further, and longer follow-up of our patient is necessary.

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## Conclusions

Aggressive GCTB of the first rib can be challenging to treat surgically because of the clavicle and neighboring neurovascular structures. However, GCTB involving the anterior aspect of the first rib may be safely treated with combined preoperative denosumab therapy and surgery via a transmanubrial approach without recurrence or impairment of shoulder girdle function.

## Acknowledgments

We appreciate the help of Drs. Kosuke Makihara and Masanori Hisaoka, who diagnosed GCTB in the patient and obtained photographs of resected specimens and the histological structure.

## Conflicts of Interest

None.