AOSIS

# Denosumab in irresectable giant cell tumour of the cervical spine

CrossMark

**Authors:**
Ntumsi A. Tontu[1]
Sanesh Miseer[2]
Henriette Burger[1]

**Affiliations:**
[1]Division of Radiation Oncology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

[2]Division of Orthopaedic Surgery, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

**Corresponding author:**
Ntumsi Tontu,
antumsibaba1@yahoo.com

Giant cell tumours of bone (GCTB) are rare benign, locally aggressive bone tumours that are characterised by mononucleated mesenchymal stromal cells that overexpress receptor activator nuclear factor kappa B (RANK) ligand and multinucleated osteoclast-like giant cells that express RANK. Surgery is the primary management option for operable disease but may cause significant functional morbidity in cervical vertebral GCTB. Case series of denosumab use in irresectable GCTB have reported good long term local control and downgrading of surgical extent. Concerns exist about the increased risk of local recurrence when neoadjuvant denosumab is followed by intralesional surgery, and when treatment is discontinued in cases of advanced disease.

**Contribution:** We describe the management of a 21-year-old female with cervical vertebral GCTB with long-term adjuvant denosumab after partial resection who continues to show good clinical and radiologic control.

**Keywords:** giant cell tumour; cervical spine; irresectable; radiotherapy; denosumab.

## Introduction

Giant cell tumours of bone (GCTB) are exceedingly rare, locally aggressive, benign tumours that mostly affect the meta-epiphyseal region of long bones in young adults.[1] They account for 3% – 5% of primary bone tumours and have a strong tendency for local recurrence after primary resection. Benign metastases, mostly to the lungs, are rare, but have been reported, and are more likely to be associated with local recurrence. In rare cases, malignant transformation of a primary lesion can occur. This can be spontaneous but is often linked to prior radiotherapy treatment.[2] Common primary sites of involvement include the distal femur and proximal tibia.[3] Other sites include the long bones, pelvis and vertebrae, with the cervical spine being the least affected axial site.[4] Histologically, it is characterised by mononuclear stromal cells, thought to be the true neoplastic component, and osteoclast-like multinucleated giant cells. The receptor activation by nuclear factor kappa B (RANK) ligand seems to be critical in the pathogenesis of GCTB. Receptor activation by nuclear factor kappa B ligand is overexpressed by stromal cells within GCTB. When binding to the RANK receptor on osteoclast precursor cells, the RANK ligand expressed on the stromal cells stimulates recruitment of osteoclast precursor cells including the multinucleated giant cells that actively absorb host bone tissue, resulting in the characteristic osteolysis associated with GCTB.[5] As per the WHO classification of soft tissue and bone tumours (5th edition, 2020), GCTB is diagnosed based on the typical features found on radiology and histomorphology, with molecular identification of a *G34W* mutation being a desirable add on.[4]

Wide resection or intralesional curettage with or without a local adjuvant (bone cement, cryotherapy, arterial embolisation) are the two principal treatment options for operable GCTB. Wide en bloc resection is associated with lower rates of local recurrence compared to intralesional curettage, but may result in higher rates of functional morbidity, especially in central sites such as the spine.[6] As an example, the local recurrence rates in a retrospective cohort of 384 patients were 2% after wide resection, 49% after curettage alone, and between 15% and 27% after curettage with an adjuvant, depending on the adjuvant used.[6] Megavoltage radiation therapy (RT) at doses of 45 Gy – 60 Gy has been utilised as primary or adjuvant treatment in tumours not amenable to complete surgical resection, resulting in high rates of local control and overall survival.[7,8,9] The RT has, however, been historically associated with high reported rates of malignant transformation of up to 11% and is therefore reserved for primary or recurrent cases where surgical treatment options are not feasible and as adjuvant therapy for spinal GCTB.[8,10,11] Denosumab is a fully humanised systemic monoclonal antibody against the RANK ligand that has demonstrated tumour-controlling activity in case series and non-randomised phase II trials

enrolling patients with irresectable or recurrent GCTB. In these studies, the use of denosumab for a minimum of 6 months allowed for less morbid resection to be performed or resulted in long-term tumour control on its own. This has led to it being approved by the United States Food and Drug Administration for potentially resectable GCTB where upfront surgery would cause significant functional impairment or morbidity.[12,13,14] Through competitive binding to the RANK ligand expressed on stromal cells in bone, it inhibits osteoclast formation, resulting in decreased bone resorption and increased bone mass. Through this mechanism, denosumab is used in the management of osteoporosis and bone metastasis from solid tumours. In GCTB, this disruption of the RANK is believed to inhibit the formation of multinucleated giant cells. After an initial loading schedule, it is administered subcutaneously on a 4-weekly basis. Reported side effects include musculoskeletal pain, fatigue, hypocalcaemia and rarely, osteonecrosis of the jaw.[13,15] Based on data from two recent meta-analyses, concerns have been raised about the risk of increased local recurrence rates when neoadjuvant denosumab therapy is followed by less aggressive intralesional curettage instead of en bloc resection.[16,17] Concern about the risk of malignant transformation on long-term denosumab therapy has also been raised.[15]

## Case presentation

We present a 21-year-old female who complained of an 18-month history of worsening neck pain radiating to the head. She was initially treated for neck muscle spasm and depression by her general practitioner. The eventual onset of weakness in the upper and lower extremities triggered a referral to the tertiary hospital for review by an orthopaedic surgeon. She was found to have severe neck pain at presentation and had decreased strength of 4/5 in all her limbs. Faecal and urinary incontinence as well as decreased sensation in the Cervical spinal nerve 8 (C8) to Thoracic spinal nerve 4 (T4) dermatomes could be elicited. An initial X-ray of the cervical spine showed a lytic expansile destructive lesion involving the second and third cervical vertebrae with loss of normal disc space and a resultant kyphotic deformity at this level.

An urgent magnetic resonance imaging scan (MRI) of the spine showed a destructive second cervical vertebral body (C2) lesion (4.1 cm × 2.9 cm) extending into the odontoid peg as well as posterior elements (Figure 1a). Anterior subligamentous extension and anterior angulation of the upper cervical spine was also found. There was upper cervical cord compression with increased signal intensity at C1–C2, as well as encasement of both vertebral arteries by the lesion. The initial differential diagnosis included a metastatic bone lesion, lymphoma, tuberculosis (TB) of the spine or a vertebral chordoma.

The patient was immediately placed in cervical spine traction. A staging CT scan of the chest, abdomen and pelvis was performed in view of the possibility of metastatic carcinoma of unknown primary. This showed only markedly distended
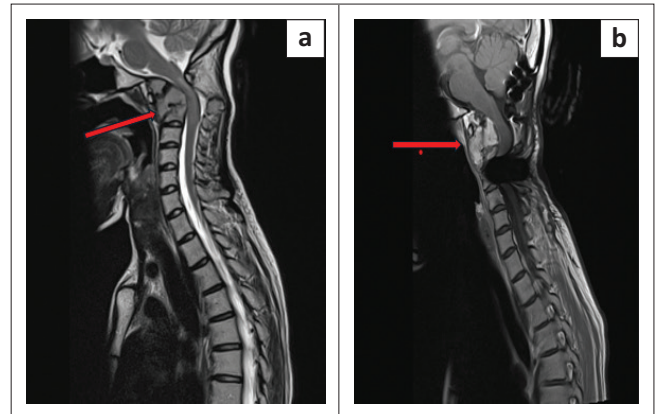


FIGURE 1: (a) Pre-operative sagittal magnetic resonance imaging (MRI) scan showing lesion in second cervical vertebra (C2) and associated spinal cord compression; (b) sagittal MRI scan at 22 months of denosumab therapy showing reduced tumour size with interval sclerosis and normal cord signal.

large bowel to the level of the rectum, most likely neurological in origin. An erect abdominal X-ray showed dilated bowel loops with no air-fluid levels, and a diagnosis of neurogenic ileus was made, which was managed conservatively. No other primary or metastatic cancerous lesions were seen on the CT scan. A repeat X-ray after 4 days showed no change in the degree of kyphosis, although the patient reported an improvement in motor function.

After 14 days of traction, the patient underwent a posterior surgical decompression, cranio-cervical fusion and partial resection with biopsy of the C2 vertebral lesion. An urgent MRI was requested on day 1 post-operatively because of an unexpected worsening of motor function in all extremities. It demonstrated remnants of the C2 tumour mass now causing compression of the spinal cord because of the correction of the kyphosis. The patient was immediately taken for revision surgery with clearance of the spinal cord and improvement in neurological function. At discharge, she mobilised unassisted with complete resolution of her bowel and bladder symptoms and required only tramadol and paracetamol for pain control.

The histomorphology of the tumour was consistent with giant cell tumour of bone with no sarcomatous transformation. No features of TB infection were found. Sections showed solid sheets of mononuclear cells that were round, ovoid and slightly spindled in regions, as well as regularly interspersed osteoclast-like multinucleated giant cells. Immunohistochemistry for the pathognomonic G34W mutation was not performed because of resource constraints and the radiology and histomorphology being diagnostic in this case.

The patient was referred to the oncology division 2 months after her initial surgery for consideration of adjuvant radiotherapy because of incomplete resection. On her first oncology visit, she had normal power in all her extremities, no faecal or urinary incontinence, and her systemic examination was unremarkable. She was using tramadol and paracetamol regularly for pain control. The potential benefits

and risks of adjuvant radiotherapy were discussed with the patient in detail and weighed up against the risk of local recurrence in this high-risk tumour location. This included the chance of reducing local recurrence with RT and the risk of RT-induced myelopathy. The small risk of malignant transformation of the GCTB with the use of RT was also discussed. At the time the oncology team and the patient felt that the risk benefit ratio for RT was too high. An alternative option was using denosumab post-operatively as continuous tumour control therapy. Denosumab is unfortunately not funded in the SA public health sector and was prohibitively expensive to buy out of pocket for this student. A motivation was written to hospital administration for special consideration to fund denosumab for this patient, which was accepted.

A pretreatment 18-Fluoro-deoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan was performed to establish a radiological baseline (Figure 2a). This showed moderate FDG uptake in a destructive lesion in the vertebral body, odontoid process, and posterior elements of C2 and C3, with a residual soft tissue component and spinal canal stenosis. Baseline dental health, renal function and serum calcium levels were assessed. The patient was administered subcutaneous (SC) denosumab at 120 mg on day 1, day 8 and day 15 for the first month as a loading dose, and then 120 mg SC every 4 weeks. Oral calcium and vitamin D supplementation was given to reduce the risk of hypocalcaemia.

Periodic FDG PET-CT and MRI scans at month 7, month 13, and month 22 (Figure 1b and Figure 2b) have shown continued reduction in the size of the C2 lesion, signs of continuing benign bone remodelling, and reduction in myelopathic cord signal over time. At the time of writing this report, the patient is on her 41st month of SC denosumab therapy. The patient tolerated denosumab well and only complained of occasional paraesthesia in the left arm. Serum calcium levels have remained normal. She is functioning independently and has resumed her tertiary studies. There is currently no plan to stop her denosumab therapy.
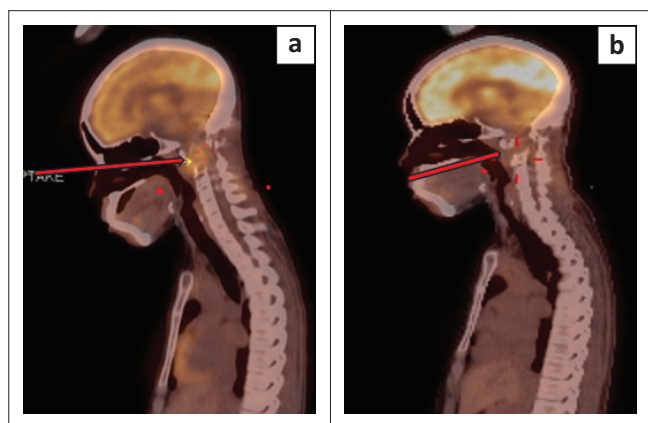


**FIGURE 2:** (a) Post-operative 18-Fluoro-deoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan prior to denosumab therapy showing moderate uptake in the second to third cervical (C2-C3) vertebra; (b) FDG PET-CT after 7 months of denosumab therapy showing decreased FDG avidity.

## Discussion

Giant cell tumours of bone are extremely rare and the cervical vertebrae are reported to be among the less common sites. The rarity of GCTB in this location, the fact that it has the highest incidence in 20-year olds – 40-year-olds,[3,4] and its initial presentation with neck pain make clinical suspicion for GCTB low. X-ray imaging showing lytic bone changes would increase suspicion. In the South African Adult Primary Care treatment guideline for neck pain in the absence of high-risk features (neurological fall-out, trauma, features of meningitis, escalating pain), an X-ray should be performed if neck pain persists for 6 weeks in an otherwise well person under the age of 50 years. Our patient had non-specific neck pain for 18 months before developing severe neurological deficits from spinal cord compression, after which she was referred for imaging.

The lowest rate of local recurrence in GCTB is achieved with wide surgical resection, but this is more feasible in long bones sites. In the spine, wide resection and the use of adjuvants after curettage can potentially damage important neurovascular structures and result in severe morbidity.[18] Alternative options to upfront surgery are embolisation, definitive radiotherapy or upfront denosumab.[7] Our patient was diagnosed late with significant neurological compromise and a threatened spinal cord, which necessitated urgent decompressive and stabilising surgery. Because of the location of the GCTB in C2 with extensive surrounding of the vertebral arteries, an en bloc resection was not feasible. This placed her at high risk of local recurrence.

Limited data are available on the use of adjuvant radiotherapy after incomplete resection of spinal GCTB with no definitive data on local recurrence risk reduction.[10] Although GCTB are radiosensitive tumours, high RT doses above 50 Gy are generally recommended.[7] As a result of the lesion encircling the cervical spinal cord, it would have been impossible to keep the dose to the cord below the recommended tolerance dose to prevent RT-induced myelopathy.[19] Although malignant transformation rates after RT up to 11% have been reported in older cohorts, modern series using megavoltage RT report rates of < 1%.[8,10,11,20] In our case, the risk of RT toxicity and the lack of strong evidence for tumour control led us to reject this option.

The administration of denosumab after surgery for GCTB remains investigational, with the only reports on this treatment approach being of the continuation of denosumab for about 6 months after neoadjuvant denosumab and surgery.[13,21] In our case, denosumab presented the only feasible adjuvant treatment option after incomplete surgical resection. It was made clear to the patient that such treatment would have to be life-long, as evidence for recurrence rates of 26% – 40% after cessation of long-term denosumab has been reported.[13,22] In the light of the fact that the patient is of child-bearing age, contraception is of vital importance, as denosumab cannot be given during pregnancy. The risk of malignant transformation because of denosumab was

considered low as the study that led to its FDA approval demonstrated a rate of true malignant transformation after 4 years of < 1%, with patients being on treatment for a median of 20 months.[13,23] In patients treated with surgery alone transformation rates of 4% – 8% have been reported.[8]

# Conclusion

This case study highlights the significant challenges involved in managing a young patient with an irresectable GCTB in the cervical spine, beginning with delays in establishing a diagnosis to selecting the optimal treatment approach. Despite obtaining good radiological and clinical improvement with postoperative denosumab therapy in this case, there remains uncertainty regarding the optimal duration of therapy and risk of long-term complications. Denosumab can be useful in the management of irresectable GCTB, but access is currently cost-prohibitive in low- and middle-income countries.

# Acknowledgements

## Competing interests

## Authors' contributions

The initial draft was written by N.A.T. and then sent to both S.M. and H.B. who were involved in the patient management from the beginning and who read the draft and made corrections and edits and also provided supervision of the work.

## Ethical considerations

Ethical clearance to conduct this study was obtained from the Stellenbosch University Health Research Ethics Committee (SU HREC) (reference no. C24/02/007) on 25 March 2024.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the particpant involved in the study.

## Funding information

## Data availability

Data sharing is not applicable to this article, as no new data were created or analysed in this study. The patient images used in this case study are available on the Tygerberg Hospital electronic imaging system and may be requested from the corresponding, author, N.A.T., upon reasonable request. The images were obtained after ethical clearance from the SU HREC and consent from the patient.

## Disclaimer

The views and opinions expressed in this case study are those of the authors and are the product of professional research. It does not necessarily reflect the official policy or position of any affiliated institution, funder, agency, or that of the publisher. The authors are responsible for this case study results, findings, and content.

# References

1. Baena-Ocampo LDC, Ramirez-Perez E, Linares-Gonzalez LM, Delgado-Chavez R. Epidemiology of bone tumors in Mexico City: Retrospective clinicopathologic study of 566 patients at a referral institution. Ann Diagn Pathol. 2009 Feb;13(1):16–21. https://doi.org/10.1016/j.anndiagpath.2008.07.005

2. Muheremu A, Niu X. Pulmonary metastasis of giant cell tumor of bones. World J Surg Oncol. 2014 Aug;12:261. https://doi.org/10.1186/1477-7819-12-261

3. Amelio JM, Rockberg J, Hernandez RK, et al. Population-based study of giant cell tumor of bone in Sweden (1983–2011). Cancer Epidemiol. 2016 Jun;42:82–89. https://doi.org/10.1016/j.canep.2016.03.014

4. IARC Publications. WHO classification of tumours: Soft tissue and bone tumours [homepage on the Internet]. 5th edn. 2020 [cited 2024 Jun 11]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Soft-Tissue-And-Bone-Tumours-2020

5. Morgan T, Atkins GJ, Trivett MK, et al. Molecular profiling of giant cell tumor of bone and the osteoclastic localization of ligand for receptor activator of nuclear factor kappaB. Am J Pathol. 2005 Jul;167(1):117–128. https://doi.org/10.1016/S0002-9440(10)62959-8

6. Becker WT, Dohle J, Bernd L, et al. Local recurrence of giant cell tumor of bone after intralesional treatment with and without adjuvant therapy. J Bone Joint Surg Am. 2008 May;90(5):1060–1067. https://doi.org/10.2106/JBJS.D.02771

7. Biermann JS, Hirbe A, Agulnik M. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Bone Cancer. Version 2.2024 — March 12, 2024 [cited 2024 Jun 11]. Available from: https://www.NCCN.org

8. Shi W, Indelicato DJ, Reith J, et al. Radiotherapy in the management of giant cell tumor of bone. Am J Clin Oncol. 2013 Oct;36(5):505–508. https://doi.org/10.1097/COC.0b013e3182568fb6

9. Caudell JJ, Ballo MT, Zagars GK, et al. Radiotherapy in the management of giant cell tumor of bone. Int J Radiat Oncol Biol Phys. 2003 Sep;57(1):158–165. https://doi.org/10.1016/S0360-3016(03)00416-4

10. Junming M, Cheng Y, Dong C, et al. Giant cell tumor of the cervical spine: A series of 22 cases and outcomes. Spine (Phila Pa 1976). 2008 Feb;33(3):280–288. https://doi.org/10.1097/BRS.0b013e318162454f

11. Leggon RE, Zlotecki R, Reith J, Scarborough MT. Giant cell tumor of the pelvis and sacrum: 17 Cases and analysis of the literature. Clin Orthop Relat Res. 2004 Jun;(423):196–207. https://doi.org/10.1097/01.blo.0000128643.38390.07

12. Dubory A, Missenard G, Domont J, Court C. Interest of denosumab for the treatment of giant-cells tumors and aneurysmal bone cysts of the spine. About nine cases. Spine (Phila Pa 1976). 2016 Jun;41(11):E654–E660. https://doi.org/10.1097/BRS.0000000000001350

13. Chawla S, Blay J-Y, Rutkowski P, et al. Denosumab in patients with giant-cell tumour of bone: A multicentre, open-label, phase 2 study. Lancet Oncol. 2019 Dec;20(12):1719–1729. https://doi.org/10.1016/S1470-2045(19)30663-1

14. Rutkowski P, Ferrari S, Grimer RJ, et al. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. Ann Surg Oncol. 2015 Sep;22(9):2860–2868. https://doi.org/10.1245/s10434-015-4634-9

15. Li H, Gao J, Gao Y, Lin N, Zheng M, Ye Z. Denosumab in giant cell tumor of bone: Current status and pitfalls. Front Oncol. 2020;10:580605. https://doi.org/10.3389/fonc.2020.580605

16. Tsukamoto S, Tanaka Y, Mavrogenis AF, Kido A, Kawaguchi M, Errani C. Is treatment with denosumab associated with local recurrence in patients with giant cell tumor of bone treated with curettage? A systematic review. Clin Orthop Relat Res. 2020 May;478(5):1076–1085. https://doi.org/10.1097/CORR.0000000000001074

17. Chen X, Li H, Zhu S, Wang Y, Qian W. Pre-operative denosumab is associated with higher risk of local recurrence in giant cell tumor of bone: A systematic review and meta-analysis. BMC Musculoskelet Disord. 2020 Apr;21(1):256. https://doi.org/10.1186/s12891-020-03294-2

18. Shimizu T, Murakami H, Demura S, et al. Total en bloc spondylectomy for primary tumors of the lumbar spine. Medicine (Baltimore). 2018 Sep;97(37):e12366. https://doi.org/10.1097/MD.0000000000012366

19. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative analyses of normal tissue effects in the clinic (QUANTEC): An introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010 Mar;76(3 Suppl):S3–S9. https://doi.org/10.1016/j.ijrobp.2009.09.040

20. Ruka W, Rutkowski P, Morysiński T, et al. The megavoltage radiation therapy in treatment of patients with advanced or difficult giant cell tumors of bone. Int J Radiat Oncol Biol Phys. 2010 Oct;78(2):494–498. https://doi.org/10.1016/j.ijrobp.2009.07.1704

21. Errani C, Tsukamoto S, Leone G, et al. Denosumab may increase the risk of local recurrence in patients with giant-cell tumor of bone treated with curettage. J Bone Joint Surg Am. 2018 Mar;100(6):496–504. https://doi.org/10.2106/JBJS.17.00057

22. Palmerini E, Chawla NS, Ferrari S, et al. Denosumab in advanced/unresectable giant-cell tumour of bone (GCTB): For how long? Eur J Cancer. 2017 May;76:118–124. https://doi.org/10.1016/j.ejca.2017.01.028

23. Palmerini E, Seeger LL, Gambarotti M, et al. Malignancy in giant cell tumor of bone: Analysis of an open-label phase 2 study of denosumab. BMC Cancer. 2021 Jan;21(1):89. https://doi.org/10.1186/s12885-020-07739-8