Cancer Association of South Africa (CANSA)

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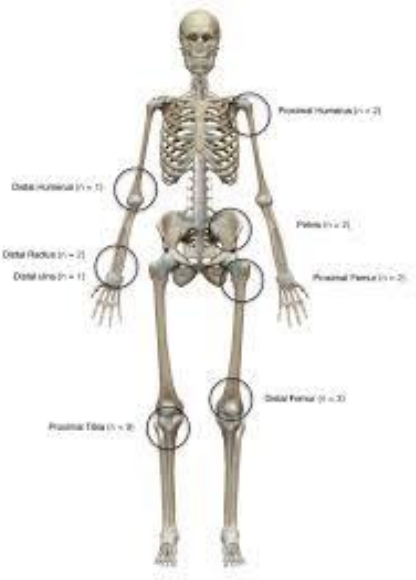
Fact Sheet
on
Giant Cell Tumour of Bone

Introduction

Giant Cell tumours (GCT) are benign tumours with potential for aggressive behaviour and capacity to metastasize. Although rarely lethal, benign bone tumours may be associated with a substantial disturbance of the local bony architecture that can be particularly troublesome in peri-articular locations. Its histogenesis remains unclear. It is characterized by a proliferation of mononuclear stromal cells and the presence of many multi-nucleated giant cells with homogenous distribution.

Rarely, Giant Cell Tumours of the Bone undergo true malignant transformation.



[Picture Credit: Giant Cell Tumour of Bone Picture]

Giant Cell Tumour of Bone

Giant Cell Tumour of Bone (GCTB) is a relatively rare, benign, but locally aggressive osteolytic skeletal neoplasm of young adults. Although regarded as a benign tumour, GCTB represents a continuum of neoplasia – it has the ability similar to that of cancerous tumours to infiltrate tissue, and metastasise. GCTB can be locally aggressive, and it has a propensity to recur locally after curettage alone. Furthermore, in approximately 2 to 3 percent of cases, distant metastases occur, most often to the lungs. However, pulmonary metastases do not carry the same connotation as metastases associated with malignant tumours, such as lung cancer or sarcoma. In most cases, clinical behaviour is benign, and metastatic disease does not lead to the death of the patient, hence the designation "benign pulmonary implants."

Giant Cell Tumour of Bone typically occurs as single lesions. Although any bone can be affected, the most common sites are:

- around the knee: distal femur and proximal tibia: 50-65%
- distal radius: 10-12%
- sacrum: 4-9%
- vertebral body: 7%
- thoracic spine most common, followed by cervical and lumbar spines

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Multiple locations: ≈1% (multiple lesions usually occur in association with Paget Disease)

Yamamoto, H., Ishihara, S., Toda, Y. & Oda, Y. 2020.
"Giant cell tumor of bone (GCTB) is a locally aggressive bone tumor that frequently shows local recurrence and occasionally shows malignant transformation to high-grade sarcoma. Histologically, conventional GCTB is composed mainly of three types of cells: mononuclear neoplastic cells with an osteoblastic precursor phenotype, mononuclear histiocytic cells, and osteoclast-like multinucleated giant cells. These cells interact with each other via the RANKL-RANK axis and other mechanisms for tumor formation. The vast majority of GCTBs were recently revealed to harbor H3F3A p.G34W mutation, and a minor subset have H3F3A p.G34L, p.G34M, p.G34R, or p.G34V mutation. H3.3 G34W mutant-specific immunohistochemistry is a highly sensitive and specific surrogate marker for H3F3A p.G34W mutation in GCTB and thus useful for differential diagnoses of histological mimics. H3.3 mutant-specific immunohistochemistry has also contributed to the understanding of the bone-forming ability of neoplastic cells of GCTB and the remarkable new bone formation after treatment with denosumab, an inhibitor of RANKL. In primary and secondary malignant GCTBs, the H3F3A gene allele can be preserved or lost with malignant transformation."

Incidence of Giant Cell Tumour of Bone in South Africa
The National Cancer Registry (2016) does not provide any information regarding Giant Cell Tumour of the Bone.

Signs and Symptoms of Giant Cell Tumour of Bone
Patients with Giant Cell Tumours usually describe a deep, persistent pain in the area of the tumour that is not related to an injury. The pain progressively worsens and may result in limited function. Sometimes there is swelling of the affected area, especially if the joint line has been affected.
Other symptoms may include:

- A visible bump
- Bone fracture
- Fluid build-up in the joint nearest the affected bone
- Limited movement in the nearest joint
- Swelling
- Pain at the nearest joint

The symptoms of a giant cell tumour may look like other health problems. Always talk with your healthcare provider for a diagnosis.

Causes of Giant Cell Tumour of Bone
The cause of giant cell tumours is unknown. The tumours occur spontaneously. They are not known to be caused by trauma, environmental factors, or diet. Giant cell tumours of bone are not inherited. In rare cases, the tumours may be associated with over activity of the parathyroid glands—a condition known as "hyperparathyroidism."

Complications of Giant Cell Tumour of Bone

Bone Cell Tumours are benign (meaning they are not cancerous) but are very aggressive, destroying healthy bone and joints. There are rare cases that the tumour spreads to the lungs. The lesions in the lungs are usually benign as well.

Because Giant Cell Tumours of the Bone destroy bone, there is risk of pathologic fractures in the area of the tumour.

Rarely, GCTB undergoes true malignant transformation.

Muheremu, A. & Niu, X. 2014.

"Giant cell tumor of bone (GCTB) accounts for 5% of primary skeletal tumors. Although it is considered to be a benign lesion, there are still incidences of pulmonary metastasis. Pulmonary metastasis of GCTB may be affected by tumor grading and localization as well as the age, gender and overall health status of the patient. Patients with local recurrence are more likely to develop pulmonary metastasis of GCTB. High expression of some genes, cytokines and chemokines may also be closely related to the metastatic potential and prognosis of GCTB. The treatment of the primary GCTB is key to the final outcome of the disease, as intralesional curettage has a significantly higher local recurrence and pulmonary metastasis rate than wide resection. However, even patients with pulmonary metastasis seem to have a good prognosis after timely and appropriate surgical resection. It is hoped that with the development of novel surgical methods and drugs, pulmonary metastasis of GCTB can be prevented and treated more effectively."

Alaqaili, S.I., Abduljabbar, A.M., Altaho, A.J., Khan, A.A. & Alherabi, J.A. 2018.

"Giant cell tumor of bone (GCTB) is a biologically benign and locally aggressive tumor that most often affects the epiphyseal and metaphyseal sites of long bones in the young adult population. Overexpression of receptor activator of nuclear factor kappa B ligand (RANKL) by cancerous mesenchymal stromal cells stimulates a signal transduction cascade that recruits and activates multinucleated osteoclast-like giant cells, resulting in pathologic bone resorption. Denosumab, an RANKL inhibitor that blocks the RANKL-mediated osteoclast activation, has been recently approved by the United States Food and Drug Administration (FDA) for the treatment of aggressive GCTB. Although uncommon, several studies reported drug-related malignant morphological transformation of benign GCTB following treatment with denosumab therapy. The aim of the article was to review the clinicopathological characteristics of all the reported cases of malignant sarcomatous transformation of GCTB after treatment with denosumab therapy in patients without any history of prior exposure to radiotherapy."

Diagnosis of Giant Cell Tumour of Bone

- Physical Examination.

The following imaging tests may be used to confirm the diagnosis:

- X-ray - Uses x-radiation to take images of dense tissues inside the body such as bones or tumours.
- CT Scan - The Computer Tomography (CT) scan takes a number of x-rays to make a 3D image of an affected area.
- MRI Scan - Magnetic Resonance Imaging (MRI) uses magnets to create an image of the tissues of the body.
- Bone scan – Use of radioactive chemicals called radionuclides which are injected, swallowed or breathed into the body, to take images of bones.

- Histopathology - Examination of a tissue sample by a pathologist under a microscope to identify disease.
- Whole body scan - Shows "hot" often with a central "cold" spot in the centre of lesion, called “Doughnut Sign”
- Needle biopsy - a procedure where a doctor places a small needle through the skin and into the lesion to withdraw a sample of the abnormal tissue. The tissue is analysed to confirm any findings.
- Blood test - Laboratory analysis of a blood sample.

Differential Diagnosis of Giant Cell Tumour of Bone

There is a relatively wide differential similar to that of a lytic bone lesion:

- Chondroblastoma
- Chondromyxoid fibroma
- Aneurysmal bone cyst
- Non-ossifying fibroma
- Giant Cell Reparative Granuloma “Brown Tumour”
- Enchondroma
- Haemophilic pseudotumour
- Chondrosarcoma
- Desmoplastic fibroma

Treatment of Giant Cell Tumour of Bone

The treatment will depend on a number of factors including:

- The size of the tumour
- Where it is in the body
- Whether it has spread to another part of the body
- General health and wellbeing of the patient

Treatment may include:

- Individualised surgical treatment:
- Extensive curettage resection where the tumour is curetted and the tumour cavity shaved with a high speed burr wherever possible. The cavity is then subjected to cryosurgery that involves the direct application of liquid nitrogen to eradicate microscopic tumour cells.
- Adjuvant treatment: Cryosurgery, phenol, hydrogen peroxide reduces the local recurrence rate.
- Irradiation can be used if surgery is contraindicated however there is a significant risk of malignant transformation
- Embolisation can make surgery safer for large lesions arising in the sacrum.
- Chemotherapy, XGEVA® (denosumab), an FDA-approved medication for adults and some teens who have recurrent or difficult-to-remove giant cell tumours of bone.
- Innovative treatments: Anti RANK-L antibody has shown promising results.

Errani, C., Tsukamoto, S., Ciani, G. & Donati, D.M. 2019.

Background: The ideal treatment for giant cell tumor of bone (GCTB) is still controversial. The purpose of this study was to evaluate whether curettage was successful in the treatment of GCTB. Intralesional curettage with adjuvant therapies, such as high-speed burring, polymethylmethacrylate, phenol, ethanol, and liquid

nitrogen, may be used to reduce the local recurrence rate. However, there is no consensus on the optimal use of curettage, along with fillers and adjuvants, to limit the recurrence rate.
Methods: We performed a systematic review of articles using the terms long bones, GCTB, and treatment. Case reports, reviews, opinion articles, or technique notes were excluded based on the abstract. Twenty-six articles included in this review were then studied to establish the index in suggesting the surgical treatment of GCTB.
Results: The patient's gender, their age, the Campanacci grade of their tumor, and the type of surgery they had were not significantly associated with the local recurrence rate. Local recurrences seemed to be associated with the site of the tumor, occurring more frequently in the proximal femur or distal radius. A pathological fracture was not a contraindication for intralesional curettage. Treatment with denosumab did not decrease the local recurrence rate in patients who had been treated with curettage.
Conclusion: The current literature seems to suggest that the ideal treatment for GCTB is to remove the tumor while preserving as much of the joint as possible. Local recurrent tumors can be treated with curettage to keep the re-recurrence rate within an acceptable limit. The choice for how to treat GCTB in the proximal femur or distal radius requires special attention.

Luengo-Alonso, G., Mellado-Romero, M., Shemesh, S., Ramos-Pascua, L. & Pretell-Mazzini, J. 2017.
BACKGROUND: Denosumab is a human monoclonal antibody (mAb) that specifically inhibits tumor-associated bone lysis through the RANKL pathway and has been used as neoadjuvant therapy for giant-cell tumor of bone (GCTB) in surgical as well as non-surgical cases. The purpose of this systematic review of the literature, therefore, is to investigate: (1) demographic characteristics of patients affected by GCTBs treated with denosumab and the clinical impact, as well as, possible complications associated with its use (2) oncological outcomes in terms of local recurrence rate (LRR) and development of lung metastasis, and (3) characteristics of its treatment effect in terms of clinical, radiological, and histological response.
METHODS: A systematic review of the literature was conducted using PubMed, EMBASE, and COCHRANE search including the following terms and Boolean operators: "Denosumab" AND "primary bone tumor", "denosumab" AND "giant cell tumor", "denosumab" AND "treatment", and finally, "denosumab" AND "giant cell tumor" AND "treatment" since 2000. After applying inclusion and exclusion criteria, a total of 19 articles were included. The quality of the included studies was assessed using STROBE for the assessment of observational studies.
RESULTS: A total of 1095 patients were included across all 19 studies. Across all the studies included, there were 615 females and 480 males. The mean patient age was 33.7 ± 8.3 years when starting the denosumab treatment. The pooled weighted local recurrence rate was 9% (95% CI 6-12%) and the pooled weighted metastases rate was 3% (95% CI 1-7%). The most common adverse event was fatigue and muscular pain. Radiologic response was estimated to occur in 66-100% of the patients. A significant reduction in pain under denosumab treatment was reported in seven studies and additional improvement in function and mobility was reported by several authors. Only two studies reported musculoskeletal tumor society (MSTS) scores which were better after denosumab treatment.
CONCLUSIONS: The use of denosumab as an adjuvant treatment of GCTB has shown a positive but variable histological response with consistent radiological changes and several types of adverse effects. There is a positive clinical response in terms of pain relief with decrease on the morbidity of surgical procedures to be performed. Finally, oncological outcomes are disparate with neither effect on metastatic disease nor local recurrence rates.

Jia, Q., Chen, G., Cao, J., Yang, X., Zhou, Z., Wei, H., Liu, T. & Xiao, J. 2019.
BACKGROUND CONTEXT: Giant cell tumors (GCTs) of the bone are benign but locally aggressive. Pediatric spine giant-cell tumors (PSGCTs) have been infrequently reported in the literature because of the rarity of the disease.

PURPOSE: The purpose of this study was to define the overall occurrence rate of PSGCTs among all spinal GCTs in our center and investigate the clinical features and prognostic factors of this rare disease.
STUDY DESIGN: A retrospective review.
PATIENT SAMPLE: Thirty-one PSGCT patients, screened from 226 patients with spine GCTs who received treatment in our center between 1998 to 2017.
OUTCOME MEASURES: The clinical symptoms, neurologic status, radiologic manifestations, treatment, outcome, and complications were recorded and analyzed.
METHODS: The postoperative recurrence-free survival (RFS) rate was estimated by the Kaplan-Meier method. Factors with p values ≤.1 were subjected to multivariate analysis for RFS by proportional hazard analysis, among which p values ≤.05 were considered statistically significant.
RESULTS: A total of 31 (31 of 226, 13.7%) PSGCTs patients (9 male and 22 female) were included in the study, with a mean age of 15.9 years and a mean follow-up period of 85.1 (median 84.0; range 12-221) months. The majority of patients (80.6 %) were 14-18 years of age. Recurrence was detected in 12 (38.7%) of the 31 patients. Univariate and multivariate analyses suggested that Jaffe grade II-III was an adverse prognostic factor for RFS, while total spondylectomy and bisphosphonate treatment were positive prognostic factors.
CONCLUSIONS: Total en bloc spondylectomy (TES) is associated with excellent prognosis for PSGCTs, and total piecemeal spondylectomy is a viable alternative if total en bloc spondylectomy is unfeasible. Long-term bisphosphonate administration could significantly reduce the recurrence risk of PSGCTs. Denosumab treatment is recommended, especially for advanced PSGCTs. Jaffe grade II-III is an adverse prognostic factor for recurrence.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Urakawa, H., Mizusawa, J., Tanaka, K., Eba, J., Hiraga, H., Kawai, A., Nishida, Y., Hosaka, M., Iwamoto, Y., Fukuda, H. & Ozaki, T. 2019.
"A randomized phase III trial was planned to commence in October 2017. Resectable giant cell tumor of bone (GCTB) without possible postoperative large bone defect has been treated by curettage with local adjuvant treatment, with the local recurrence rate found to be as high as 24.6-30.8%. The aim of this study is to confirm the superiority of preoperative denosumab for patients with GCTB without possible postoperative large bone defect. A total of 106 patients will be accrued from 34 Japanese institutions over 5 years. The primary endpoint is relapse-free survival (RFS). Secondary endpoints include overall survival, joint-preserved survival, local RFS, metastasis-free survival, adverse events, serious adverse events, surgical and

postoperative complications, and discontinuation of denosumab. This trial is conducted by the Bone and Soft Tissue TumorStudy Group in the Japan Clinical Oncology Group and has been registered in the UMIN Clinical Trials Registry as UMIN000029451 [http://www.umin.ac.jp/ctr/index.htm]."

Li, S., Chen, P. & Yang, Q. 2019.
BACKGROUND: Although denosumab has been approved as an antiresorptive agent for giant cell tumor of bone, its efficacy has not been proven.
OBJECTIVES: To compare the efficacy and safety of denosumab and zoledronic acid treatment in patients with surgically unsalvageable giant cell tumor of bone.
METHODS: A total of 250 patients with surgically unsalvageable giant cell tumor of bone were included in this randomized clinical trial. Patients received either subcutaneous denosumab (DB group; 120 mg per 4 weeks plus an additional 120 mg on days 8 and 15; $n = 125$) or intravenous zoledronic acid (ZA group; 4 mg per 4 weeks; $n = 125$) for six cycles. Disease status, clinical benefits, treatment-emergent adverse effects, overall survival, and cost of treatment were evaluated during the follow-up period. Statistical significance was determined using 95% confidence intervals.
RESULTS: Denosumab and zoledronic acid had similar tumor responses ($p = 0.18$) and clinical benefits ($p = 0.476$). Disease progression was observed in fewer patients in the DB group (1%) than ZA group (2%). Denosumab caused fatigue ($p = 0.0004$) and back pain ($p < 0.0001$), while zoledronic acid caused hypocalcemia ($p < 0.0001$), flu-like symptoms ($p = 0.021$), hypotension ($p = 0.021$), and hypokalemia ($p = 0.021$). Denosumab treatment was markedly more expensive than zoledronic acid treatment ($p < 0.0001$). The cost to manage treatment-emergent adverse effects was higher for the ZA group than the DB group ($p = 0.0425$). Overall survival was the same for both treatments ($p = 0.066$).
CONCLUSIONS: Denosumab is a safe but costly alternative to zoledronic acid for treatment of surgically unsalvageable giant cell tumor of bone.

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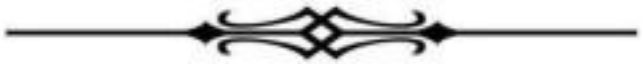

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