# Cancer Association of South Africa (CANSA)

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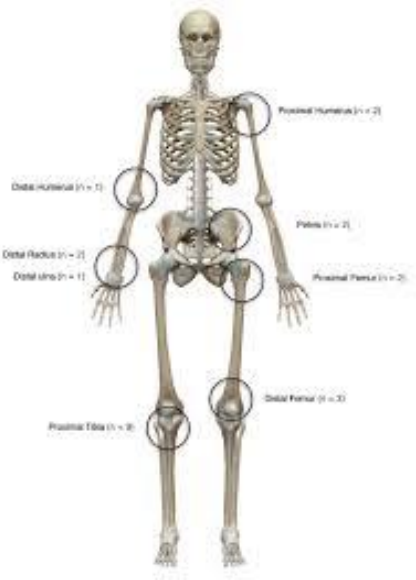
Fact Sheet
on
Giant Cell Tumour of Bone

**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

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

**Scotto di Carlo, F., Whyte, M.P. & Gianfrancesco, F.** 2020.
"Giant cell tumor (GCT) is a bone-destructive benign neoplasm characterized by distinctive multinucleated osteoclast-like giant cells with osteolytic properties distributed among neoplastic stromal cells. GCT is locally aggressive with progressive invasion of adjacent tissues and occasionally displays malignant characteristics including lung metastasis. GCT is characterized genetically by highly recurrent somatic mutations at the G34 position of the H3F3A gene, encoding the histone variant H3.3, in stromal cells. This leads to deregulated gene expression and increased proliferation of mutation-bearing cells. However, when GCT complicates Paget disease of bone (GCT/PDB) it behaves differently, showing a more malignant phenotype with 5-year survival less than 50%. GCT/PDB is caused by a germline mutation in the ZNF687 gene, which encodes a transcription factor involved in the repression of genes surrounding DNA double-strand breaks to promote repair by homologous recombination. Identification of these driver mutations led to novel diagnostic tools for distinguishing between these two tumors and other osteoclast-rich neoplasms. Herein, we review the clinical, histological, and molecular features of GCT in different contexts focusing also on pharmacological treatments."

**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."

**Tumour Grade and Tumour Stage**
Tumour grade and stage are terms used to describe the severity of a tumour, while tumour grade describes the appearance of cancerous cells in the tissue by examining them under a microscope.

Tumour stage encompasses:

- The location of the tumour.
- The size and/or extent of the original tumour.
- Whether cancer cells have spread to lymph nodes or anywhere else in the body.
- The number of tumours present.

Doctors use tumour grade, cancer stage, and a patient's age and general health to decide the course of treatment for the patient and determine prognosis. Prognosis describes all factors including the disease course, cure rate, chances of survival, and risk of recurrence of cancer.

<u>What are the cancer stages?</u>

Different systems of cancer staging are used to describe the types of cancer. Below is a common method in which stages are ranged from 0 to IV.

- Stage 0: The tumour is confined to its place of origin (in situ) and has not spread to nearby tissue.
- Stage I: The tumour is located only in the original organ, is small, and has not spread.
- Stage II: The size of the tumour is large but has not spread.
- Stage III: The tumour has become larger and may have spread to surrounding tissues and/or lymph nodes.
- Stage IV: The tumour has spread to other distant organs of the body, which is known as the metastasis stage.

TNM staging

Another common staging method used for cancer is the TNM system, which stands for tumour, node (which means spread of the tumour to lymph nodes), and metastasis. When a patient's cancer is staged using the TNM system, a number will be present along with the letter. This number signifies the extent of the disease in each category - tumour, node, and metastases.

Another system of cancer staging divides cancer into five stages, which include:

- In situ: Abnormal cells are present but have not spread to nearby tissue.
- Localized: Cancer is located only in the original organ and shows no sign of its spread.
- Regional: Cancer has spread to nearby lymph nodes, tissues, or organs.
- Distant: Cancer has spread to distant parts of the body.
- Unknown: The stage cannot be figured out due to a lack of enough information.

What are the cancer grades?

Cancer grades are based on examination of the suspected tissue sample under a microscope. This involves surgically removing a piece of the suspected cancerous tissue and sending it to the lab for analysis. The entire procedure is known as a biopsy.

A doctor who specializes in diagnostic tests (pathologist) examines the cells of the tissue and determines whether they are harmless (benign or noncancerous) or harmful (malignant or cancerous). They describe the microscopic appearance of the cells and assign a numerical "grade" to most cancers.
Generally, a lower grade indicates slow-growing cancer and a higher grade indicates fast-growing cancer.

The most commonly used grading system is as follows:

- Grade I: Cancer cells that look like normal cells but are not growing rapidly.
- Grade II: Cancer cells that don't look like normal cells with their growth being faster than normal cells.
- Grade III: Cancer cells that look abnormal and have the potential to grow rapidly or spread more aggressively.

Sometimes, the following system can be used:

- GX: Grade cannot be assessed (undetermined grade)
- G1: Well-differentiated (low grade)
- G2: Moderately differentiated (intermediate grade)
- G3: Poorly differentiated (high grade)

- G4: Undifferentiated (high grade)

**Incidence of Giant Cell Tumour of Bone in South Africa**
The National Cancer Registry (2017) 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.

**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.

**Howard, E.L., Gregory, J., Winn, N., Flanagan, A. & Cool, P.** 2020.
"Introduction The aim of this study was to evaluate radiological measurements to establish the origin of giant cell tumours of bone. Methods A multi-centre retrospective review was conducted of patients with histologically confirmed giant cell tumours of bone. Images were analysed to estimate the centre of the tumour. Measured from the joint line, the ratio between the distance of the centre of the tumour and the physeal scar was calculated. Results Ninety-five patients were included in the study. Two observers found the tumour to be arising from the metaphyseal area in 94% - 97% of the cases. There was good agreement between the measurements of observers (interclass correlation coefficient 0.71). Conclusion Giant cell tumours of bone appear to be arising from the metaphyseal region."

**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.

**van der Heijden, L., Dijkstra, S., van de Sande, M. & Gelderblom, H.** 2020.

**Purpose of review:** Giant cell tumour of bone (GCTB) is an intermediate, locally aggressive primary bone tumour. In addition to local therapy, new drugs became available for this disease. Denosumab, a receptor activator of nuclear factor κ-B-ligand inhibitor, was introduced as systemic targeted therapy for advanced or inoperable and metastatic GCTB. Also, the bisphosphonate zoledronic acid has activity in GCTB by directly targeting the neoplastic stromal cells.

**Recent findings:** In a small RCT, bisphosphonates were successful in controlling tumour growth and a higher apoptotic index of tumour cells was seen after zoledronic acid versus controls. Although bisphosphonate-loaded bone cement has not been studied to a large extent, it does not seem harmful and may constitute a logical local adjuvant. From the largest clinical trial to date, the risk-to-benefit ratio for denosumab in patients with advanced GCTB remains favourable, also in facilitating less morbid surgery. Concerns have arisen that recurrence rates would be higher than after conventional treatment, ranging from 20 to 100% in a systematic review, although this may be because of bias. H3F3A (G34W) driver mutations are helpful in the differentiation between GCTB and other giant cell-containing malignancies. H3.3-G34W proved sufficient to drive tumourigenesis. The cumulative incidence of malignancy in GCTB is estimated at 4%, of which primary malignancy 1.6% and secondary malignancy 2.4%, the latter mainly after radiation. To date, a potential causal relationship between denosumab and pulmonary metastases has not been confirmed; if they do not behave indolently, it would be advised to reassess diagnosis and consider malignancy.

**Summary:** Denosumab remains a highly effective treatment option for patients with advanced GCTB. A short duration of 2-4 months neoadjuvant denosumab is advised to facilitate less morbid surgery and prevent incomplete curettage by macroscopic tumour alterations. Reduced dose intensity is being studied to reduce

long term side-effects. Further research on bisphosphonates and other targets including H3.3-G34W remains warranted.

**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.

**Medical Disclaimer**

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**Tumour Grade and Tumour Stage**
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