Acta Ortopédica Mexicana 2026; 40(1): Jan.-Feb. 21-27

Original article

doi: 10.35366/122369

Clinicopathological features, prognostic factors, and survival outcomes in giant cell tumors of bone: a retrospective study at the Instituto Nacional de Cancerología, Mexico

Características clinicopatológicas, factores pronósticos y resultados de supervivencia en tumores de células gigantes del hueso: un estudio retrospectivo en el Instituto Nacional de Cancerología, México

Reyna-Pérez K,* González-Álvarez C,‡ Tahuahua-Flores O,* Rivero-Zambrano L,* González-Prieto RE,‡ Clara-Altamirano MA,‡ Alamilla-García GC,* García-Ortega DY‡

Instituto Nacional de Cancerología. Ciudad de México, México.

ABSTRACT. Introduction: giant cell tumor of bone (GCTB) is a locally aggressive bone neoplasm that predominantly affects young adults. It most frequently involves the distal femur and proximal tibia. Despite its benign classification, GCTB carries a significant risk of local recurrence and pulmonary metastasis. Surgical resection remains the cornerstone of treatment, often complemented by local adjuvants. Denosumab has emerged as a therapeutic option, although its impact on recurrence rates remains controversial. Evidence regarding early predictors of recurrence remains limited. **Material and methods:** this retrospective cohort study included 97 patients with confirmed GCTB treated at the INCan in Mexico City between 2010 and 2023. Inclusion required a minimum follow-up of six months. Clinical, demographic, and treatment-related variables were analyzed to identify prognostic factors for local and distant recurrence. Kaplan-Meier survival analysis and log-rank tests were used to assess recurrence-free and overall survival. **Results:** the median patient age was 30 years, with a median tumor size of 8.8 cm. The femur (28%) and tibia (22%) were the most commonly affected sites. Campanacci grade III was present in 77% of cases. Recurrence occurred in 22% of patients,

RESUMEN. Introducción: el tumor de células gigantes del hueso (TCGH) es una neoplasia ósea de comportamiento localmente agresivo que afecta predominantemente a adultos jóvenes. Se localiza con mayor frecuencia en el fémur distal y la tibia proximal. El TCGB conlleva un riesgo significativo de recurrencia local y de metástasis pulmonares. La resección quirúrgica continúa siendo la piedra angular del tratamiento, a menudo complementada con adyuvantes locales. El denosumab ha emergido como una opción terapéutica; sin embargo, su impacto en las tasas de recurrencia sigue siendo controvertido. La evidencia sobre predictores tempranos de recurrencia continúa siendo limitada. **Material y métodos:** este estudio de cohorte retrospectivo incluyó a 97 pacientes con diagnóstico de TCGH, tratados en el Instituto Nacional de Cancerología entre 2010 y 2023. Se incluyeron únicamente pacientes con un seguimiento mínimo de seis meses. Se recopilaron y analizaron datos clínicos, demográficos y relacionados con el tratamiento para identificar factores pronósticos de recurrencia local y metástasis a distancia. Se emplearon análisis de Kaplan-Meier para estimar la supervivencia libre de recurrencia y global, y se utilizaron pruebas log-rank para comparar subgrupos. **Resultados:** la mediana

Evidence level: Prognostic studies. Level II

* Medical Oncology Department, National Cancer Institute. Mexico City, Mexico.
‡ Surgical Oncology, Skin and Soft Tissue Tumors Department. National Cancer Institute. Mexico City, Mexico.

Correspondence:
Dorian Yarih García Ortega
E-mail: dgarciao@incan.edu.mx

Received: 04-09-2025. Accepted: 05-30-z2025.

How to cite: Reyna-Pérez K, González-Álvarez C, Tahuahua-Flores O, Rivero-Zambrano L, González-Prieto RE, Clara-Altamirano MA et al. Clinicopathological features, prognostic factors, and survival outcomes in giant cell tumors of bone: a retrospective study at the Instituto Nacional de Cancerología, Mexico. Acta Ortop Mex. 2026; 40(1): 21-27. https://dx.doi.org/10.35366/122369

with local relapse in 15% and pulmonary metastases in 8%. Tumors located in the lower extremities and those treated initially at outside institutions showed significantly higher recurrence rates. Denosumab use was not associated with recurrence. **Conclusions:** treatment at high-volume centers and early identification of high-risk features are critical for reducing recurrence in GCTB. Denosumab remains a valuable adjunct in selected cases within a multimodal approach.

Keywords: giant cell tumor of bone, local recurrence, prognostic factors, denosumab.

de edad fue de 30 años y el tamaño tumoral medio de 8.8 cm. Las localizaciones más frecuentes fueron el fémur (28%) y la tibia (22%). Setenta y siete por ciento presentó enfermedad Campanacci grado III. La recurrencia total fue de 22%, siendo local en 15% y pulmonar en 8%. Se encontró mayor recurrencia en tumores de extremidades inferiores y en pacientes tratados inicialmente en otros centros. El uso de denosumab no se asoció con mayor ni menor recurrencia. **Conclusiones:** el tratamiento en centros de alta especialización y la identificación temprana de características de alto riesgo son fundamentales para reducir la recurrencia en el TCGH. El denosumab sigue siendo un complemento terapéutico valioso en casos seleccionados, dentro de un enfoque multimodal.

Palabras clave: tumor de células gigantes del hueso, recurrencia local, factores pronósticos, denosumab.

Abbreviations:
GCTB = Giant cell tumor of bone.
INCan = Instituto Nacional de Cancerología.

Introduction

Giant cell tumor of bone (GCTB) is a locally aggressive but typically benign neoplasm that has garnered significant attention in oncology. Although considered to be benign tumors of bone, GCTB has a relatively high recurrence rate, and metastases occur in 1 to 9% of patients.[1]

The hallmark of GCTB is the presence of numerous, evenly distributed multinucleated giant cells.[2] These giant cells resemble osteoclasts and contain up to 50 nuclei. They are interspersed within a stroma of mononuclear and spindle-shaped cells. The mononuclear cells are considered the neoplastic component of GCTBs, driving the tumor's growth.[3]

GCTB represents 4-5% of primary malignant and 20% of benign bone tumors. It most commonly affects individuals aged 20-40, with a slight female predominance.[1] The distal femur and proximal tibia are the most frequent sites (50-70%), followed by the distal radius (10-15%), sacrum, spine (2-5% each), and other bones. The tumor's origin near the growth plate suggests a possible link to bone development.[4]

GCTBs are known for their aggressive nature and high post-treatment recurrence rates. Various factors contribute to the likelihood of recurrence, which can complicate management and treatment strategies. Understanding these risk factors is crucial for improving patient outcomes and tailoring treatment plans. Curettage vs resection: curettage, a common surgical method for GCTB, is associated with higher recurrence rates, approximately 18.4 to 32.4%, compared to *en bloc* resection, which has a significantly lower recurrence rate of 4.6 to 10.6%.[5] Tumors located in the proximal tibia and distal radius are more prone to recurrence. The proximal tibia has been identified as an independent risk factor for recurrence, regardless of the surgical method used.[5] Similarly, the distal radius is frequently associated with soft tissue recurrence,[6] and the proximal Femur also shows a higher recurrence rate, mainly when treated with curettage.[7] Younger patients under 30 years old are at a higher risk of recurrence; this may be due to the biological behavior of the tumor in younger individuals.[8] Soft tissue invasion and pathological fractures at presentation are associated with increased recurrence rates. It has been hypothesized that these factors complicate surgical management and may lead to incomplete tumor removal.[7] Higher mitotic counts and vascular invasion are significant predictors of recurrence.[8] Denosumab has been shown to influence recurrence rates. While it is used to reduce tumor size preoperatively, its impact on recurrence is complex and may depend on the surgical method employed.[5]

While these factors are significant, it is important to consider the variability in individual cases. Factors such as tumor size, Campanacci grade, and inflammatory markers have not shown consistent associations with recurrence.[9] Additionally, the potential for malignant transformation in recurrent cases highlights the importance of vigilant follow-up and management strategies.[3]

Material and methods

We performed a retrospective analysis of 97 cases of GCTB treated at the Instituto Nacional de Cancerología (INCan) in Mexico City, a leading institution in oncological care, between 2010 and 2023. The inclusion criteria were a confirmed histopathological diagnosis of GCTB, a minimum follow-up of six months, and the availability of complete medical records.

The analysis included epidemiological data, clinical assessments, radiographic and histopathological findings, surgical approaches, the application of local adjuvants, and the administration of denosumab. The study population comprised patients of all age groups with tumors located in

the appendicular or axial skeleton, as well as the head and neck regions. The cohort also included individuals who had previously undergone treatment at other healthcare institutions and those presenting with de novo metastatic disease.

Clinical and radiographic assessments were performed during follow-up evaluations using standardized protocols derived from international guidelines.

Statistical methods

Continuous variables were expressed as means with their respective ranges, while categorical variables were summarized as absolute frequencies and percentages.

Recurrence rates were evaluated using the chi-square test, and odds ratios were computed to examine associations between key demographic, clinical, and pathological risk factors for recurrence. Kaplan-Meier analysis was employed to estimate cumulative recurrence-free survival and overall survival, while statistical differences were assessed using log-rank tests.

All statistical analyses were conducted using SPSS software (version 29). A two-tailed approach was applied for all tests, and statistical significance was defined as a p-value < 0.05.

Results

This analysis included 97 Mexican GCTB patients treated at INCan from 2010 to 2023. The median follow-up duration for these patients was 55 months (IQR 21 to 91 months). The patients are located across the country's central and southern regions, reflecting a diverse socioeconomic background. Their distances to healthcare facilities vary significantly, with a mean radius of 238 kilometers, ranging from 2 to 2,590 kilometers *(Figure 1)*.

Table 1 summarizes the demographic and histopathological characteristics of the cohort. The group comprised 38 women (39%) and 59 men (61%), with a medium age at diagnosis of 30 years (range 23-39 years). Campanacci stages I and II represented 21% of the cases (n = 21), while Campanacci stage III accounted for 77% (n = 75). The medium tumor size was 8.8 cm (range 6.0-11.0).

Most tumors, accounting for 82% (n = 80), were in the appendicular skeleton. Within this group, the femur was the most frequently affected bone, representing 28% (n = 27) of the cases, followed by the tibia at 22% (n = 21), the radius at 13% (n = 13), and the humerus at 7% (n = 7). Tumors in the axial skeleton comprised 18% of the total cases (n = 17). Among the tumors in the axial skeleton, the most common sites were the sacrum at 5% (n = 5), dorsal spine at 4% (n = 4), and skull bones at 2% (n = 2) *(Figure 2)*. Additionally, 23% (n = 22) of the cases presented with a pathologic fracture, and 10% (n = 10) of patients had lung metastases at the initial staging.

Of 97 tumors, 72% (n = 70) were classified as primarily resectable. Surgical interventions were conducted on 83% (n = 81) of the patients, with the following distribution of treatment modalities: intralesional resection combined with

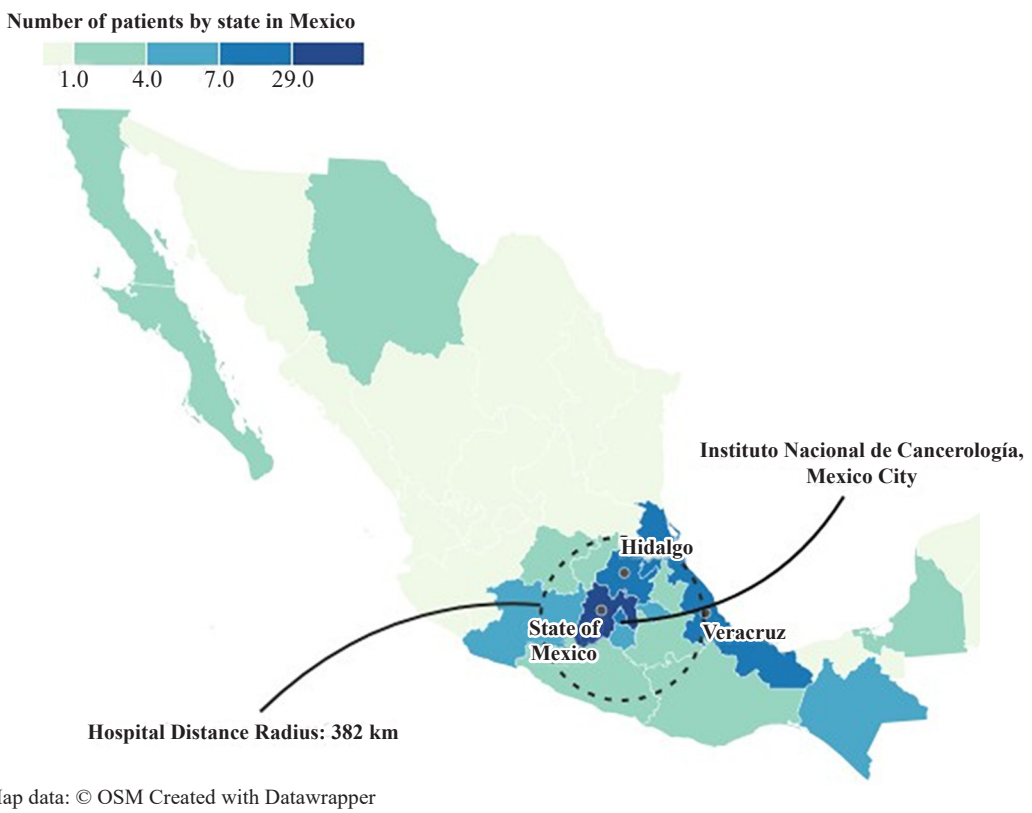

Figure 1:

Geographic landscape of Mexicans with giant cell tumor at the Instituto Nacional de Cancerología (N = 97).

Table 1: Baseline demographic and histopathological characteristics of patients diagnosed with giant cell tumor of bone and treatment data (N = 97).

Variables	n (%)
Age in years, median [range]	30 [23-39]
Gender	
Male	38 (39)
Female	59 (61)
BMI	25.7 [22.1-29.7]
Distance to INCan in km, median [range]	131 [37.5-277]
Tumour size in cm, median [range]	8.8 [6-11]
Skeletal distribution	
Axial	17 (18)
Appendicular	80 (82)
Primary tumour site	
Humerus and scapula	7 (7)
Wrist and hand	18 (18)
Sacrum and spine	10 (11)
Pelvis	6 (6)
Femur	27 (28)
Foot and ankle	24 (25)
Other sites	5 (5)
Campanacci grade	
I/II	20 (20)
III	75 (77)
Joint or soft tissue involvement	48 (47)
Pathological fracture	22 (23)
Secondary aneurysmal bone cyst	8 (8)
Type of surgery	
Curettage	26 (26)
Marginal/wide	49 (50)
Amputation	6 (6)
Adjuvant	22 (23)
Preoperative denosumab	18 (19)
Pulmonary metástasis	10 (10)

INCan = Instituto Nacional de Cancerología.

local adjuvant therapy for 26% (n = 26), and marginal or wide resection, with or without reconstruction, for 50% (n = 49); while 15% (n = 15) received medical management. Furthermore, one patient (1%) received radiotherapy, while 6% (n = 6) required amputation *(Figure 3)*. The remaining 27% (n = 26) were deemed unresectable due to various factors, including significant surgical morbidity, personal and familial decisions, poor clinical condition, preoperative cytoreduction, and the presence of pulmonary metastases.

The local recurrence rate among patients who underwent surgical intervention was 15%. As expected, recurrence rates were significantly higher following intralesional and marginal resections compared to wide resections, at 67, 14, and 0%, respectively. Local recurrence was more frequent in the axial skeleton (23%, n = 4) than in the appendicular skeleton (14%, n = 11). Stratification by individual tumor sites revealed recurrence rates of 31% in the radius (4 of 13 cases), 10% in the tibia (2 of 21), and 7% in the femur (2 of 27). No significant associations were found between clinicopathologic characteristics, surgical approach, and distant recurrence.

In the univariate analysis, factors such as age, sex, aneurysmal bone cyst component, tumor extension, neutrophil-to-lymphocyte ratio, prognostic nutritional index, overweight or obesity, neoadjuvant denosumab, and pathological fractures showed no significant correlation with recurrence rates. However, as a group, tumors in the lower extremities were significantly associated with local recurrence (p = 0.036). *Table 2* summarizes the univariate analyses and associated factors.

In this cohort, treatment at a high-volume center and local therapy were key determinants of recurrence risk. Patients managed at a high-volume center had a local recurrence rate of 11% (10 of 87) versus 50% (5 of 10) among those initially treated elsewhere (p = 0.001) *(Figure 4)*. Local adjuvant therapy was associated with lower local recurrence (p = 0.002), though the sample size was limited.

Finally, we analyzed Kaplan-Meier curves *(Figure 5)* and demonstrated that among the 81 tumors (83%) treated with primary intervention, the median recurrence-free survival was 139 months, with a 100% five-year overall survival rate. Additionally, in patients with de novo lung metastases, the overall survival analysis indicated a median survival of 127 months.

Discussion

GCTB is a rare but locally aggressive tumor primarily affecting young adults. Although it is classified as benign, it poses significant therapeutic challenges due to its potential for local recurrence, pathological fractures, and even distant metastases. Effective management relies on a multidisciplinary approach, with surgical resection as the cornerstone of treatment.[10,11] However, recurrence rates remain highly variable, influenced by factors such as tumor location, surgical technique, and adjuvant therapies.[12,13] This study evaluates the unique characteristics of a Mexican cohort, emphasizing clinicopathological features, geographic disparities, and surgical techniques as critical factors associated with local and distant recurrence.

Incidence rates vary from 1.03 to 1.33 cases per million annually, with recurrence rates reported between 10 and 75%.[14,15,16,17,18] Intralesional resections, while effective in preserving function, carry a higher risk of recurrence unless combined with adjuvant therapies such as phenol, cryotherapy, or cement augmentation.[10,17,19,20] Wang, et al. demonstrated that local recurrence increases the risk of pulmonary metastases, corroborated by our finding that 10% of patients present with lung metastases at diagnosis.[12,21,22]

Lesions in the axial skeleton present unique challenges, with higher recurrence rates and surgical complexities compared to appendicular locations.[15,23,24] In our cohort, axial lesions exhibited a 23% recurrence rate compared to 14% in appendicular tumors, consistent with reports by Balke et al. skull bone lesions showed a 50% recurrence rate, underscoring the difficulty of achieving clear margins in these locations.[15,16,25,26,27]

Geographic disparities emerged as a significant factor, with patients traveling up to 2,590 kilometers for treatment. Becker et al. found similar disparities in Brazil, highlighting worse outcomes among underserved populations.[4,17] Our findings suggest that such disparities likely delay diagnosis and limit access to timely intervention, contributing to more advanced disease stages at presentation. Tsukamoto et al. highlighted that outcomes improve significantly in high-volume centers due to standardized practices rather than surgeons' expertise. Our findings corroborate this trend, even with a limited cohort initially treated elsewhere.[3,28,29,30]

Denosumab is pivotal in managing GCTB, particularly as a cytoreductive agent and in the metastatic setting. Targeting the RANKL pathway effectively reduces tumor burden, enhancing the feasibility of surgical resection, especially in cases deemed unresectable or located in anatomically challenging regions. This benefit is particularly relevant given that 23% of our cohort presents with pathological fractures, where denosumab facilitates stabilization and preserves skeletal integrity. Additionally, denosumab demonstrates efficacy in controlling disease progression and minimizing complications from skeletal-related events in patients with pulmonary metastases, observed in 10% of our study population. However, its use introduces surgical challenges due to sclerotic bone formation, as confirmed by our findings, necessitating precise preoperative planning

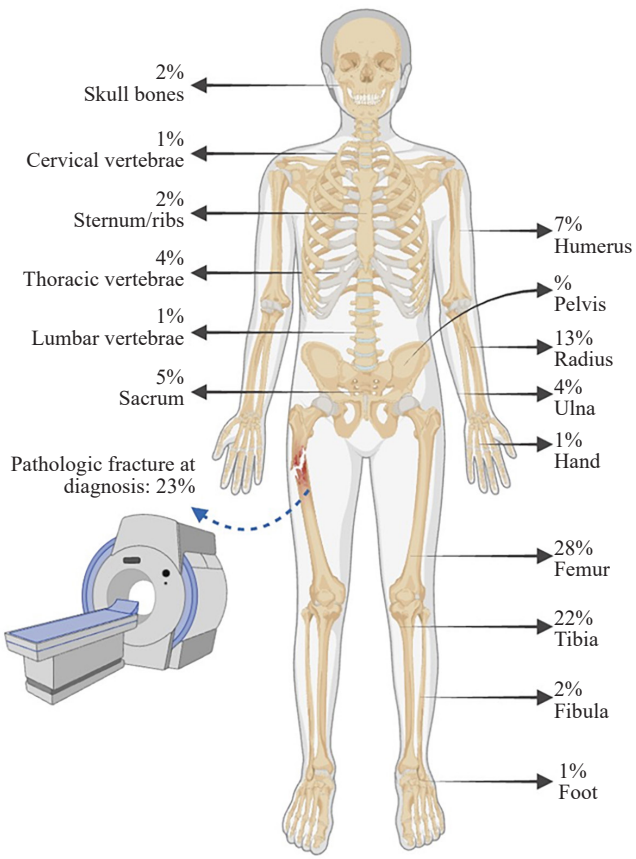

Figure 2: Location of tumors in the axial skeleton.

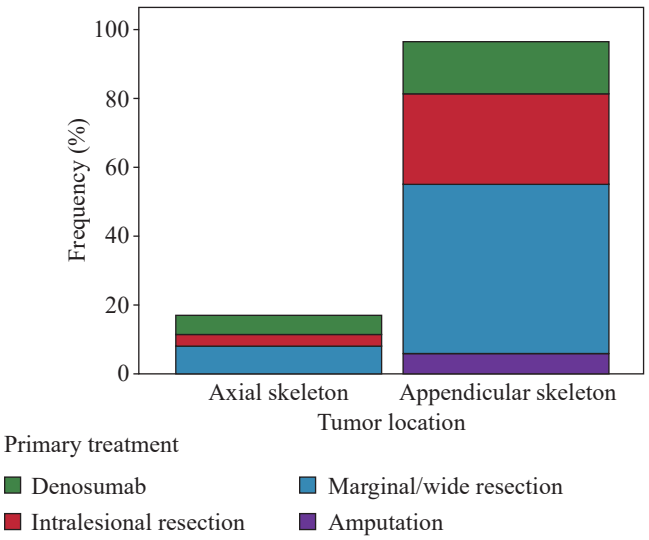

Figure 3: Treatments.

Table 2: Factors influencing the risk of local recurrence: results from univariate analyses.

Characteristics	Odds ratio	95% CI	p
Pathological fracture	1.9	0.465-7.816	0.347
Joint or ST involvement	1.5	0.590-3.972	0.376
Location (lower extremity)	3.2	1.041-10.030	0.036
Primary resectability	0.6	0.15-2.33	0.461
Local adjuvant therapy	0.257	0.105-0.629	0.002
Perioperative denosumab	0.63	0.13-3.09	0.571

95% CI = 95% Confidence Interval.

and experienced surgical teams. Despite these limitations, denosumab remains an indispensable component in the multimodal treatment of GCTB, optimizing both local control and systemic outcomes in carefully selected patients.[26,31,32,33,34,35,36,37,38,39,40]

Strengths and limitations

Strengths: this study utilizes a comprehensive dataset from a high-volume referral center in Mexico, enabling a detailed analysis of clinical and demographic factors influencing GCTB outcomes. Advanced statistical methods, including Kaplan-Meier survival analysis, add reliability to our findings. Moreover, including geographic factors provides a comprehensive perspective on healthcare disparities and their impact on outcomes-an area often overlooked in GCTB research.[41]

Limitations: the monocentric design limits generalizability to the broader Mexican population, potentially underrepresenting underserved areas and introducing selection bias. The retrospective nature is prone

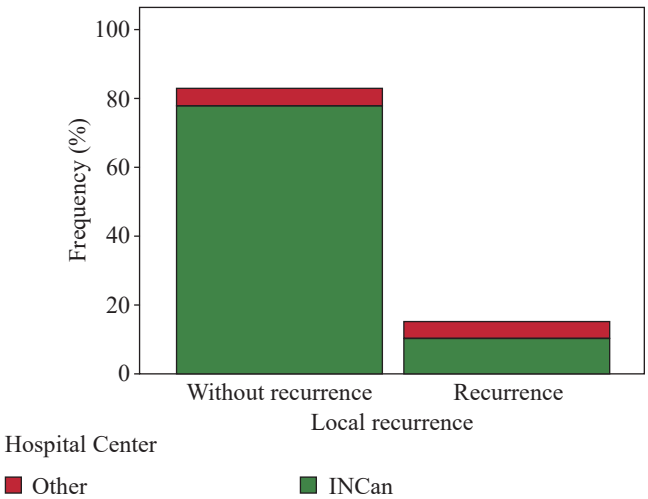

Figure 4: Recurrence rates.
INCan = Instituto Nacional de Cancerología.

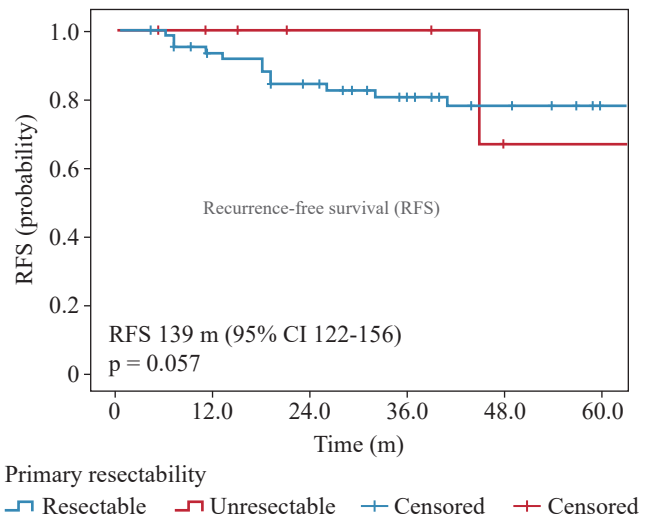

Figure 5: Recurrence-free survival.
95% CI = 95% Confidence Interval. RFS = recurrence-free survival.

to data collection and interpretation biases. The absence of a control group from non-specialized centers restricts direct outcome comparisons between high- and low-volume institutions. Additionally, variability in follow-up duration may affect long-term outcome assessment.

References

1. Sobti A, Agrawal P, Agarwala S, Agarwal M. Giant cell tumor of bone - an overview. *Arch Bone Jt Surg*. 2016; 4(1): 2-9.
2. Jha Y, Chaudhary K. Giant cell tumour of bone: a comprehensive review of pathogenesis, diagnosis, and treatment. *Cureus*. 2023; 15(10): e46945. Available in: https://www.cureus.com/articles/175240-giant-cell-tumour-of-bone-a-comprehensive-review-of-pathogenesis-diagnosis-and-treatment
3. Tsukamoto S, Mavrogenis AF, Tanzi P, Leone G, Akahane M, Tanaka Y, et al. Curettage as first surgery for bone giant cell tumor: adequate surgery is more important than oncology training or surgical management by high volume specialized teams. *Eur J Orthop Surg Traumatol*. 2020; 30(1): 3-9.
4. Khashan M, Haim A, Chechick O, Dekel S. Longstanding knee joint preserved functional outcome following medial femoral condyle resection. A case report. *Knee*. 2010; 17(4): 303-5.
5. Mahdal M, Tomás T, Apostolopoulos V, Adámková D, Múdry P, Staniczková ZI, et al. Proximal tibia tumour location and curettage are major risk factors of local recurrence in giant cell tumour of bone. *Cancers (Basel)*. 2023; 15(18): 4664.
6. Cui L, Sun Y, Jin T, Fan D, Liu W. Giant cell tumor of bone at distal radius suffered more soft tissue recurrence and ultrasonography is effective to detect the soft tissue recurrence. *Discov Oncol*. 2024; 15(1): 103.
7. AbdelKawi NM, Abed Y, University M, El-negery AA, Mohamed KSZ. Risk factors for local recurrence of giant cell tumor of bone of the extremities: a retrospective study. *Curr Orthop Pract*. 2022; 34: 16-21.
8. Konishi E, Outani H, Mano M, Nagata S, Shirai T, Naka N, et al. Giant cell tumor of bone - Analysis of 213 cases involving extra-craniofacial bones. *Pathol Int*. 2021; 71(8): 500-11.
9. Tsukamoto S, Mavrogenis AF, Alvarado RA, Traversari M, Akahane M, Honoki K, et al. Association between inflammatory markers and local recurrence in patients with giant cell tumor of bone: a preliminary result. *Curr Oncol*. 2023; 30(1): 1116-31.
10. Tsukamoto S, Mavrogenis AF, Masunaga T, Honoki K, Fujii H, Kido A, et al. Current concepts in the treatment of giant cell tumor of bone: an update. *Curr Oncol*. 2024; 31(4): 2112-32.
11. Abbasi AN, Qamar J, Habib A, Ali SME, Ahmed S, Khan MW. Unraveling the mystery: A comprehensive review of multidisciplinary strategies for managing giant cell tumor of the bone. *J Orthop Rep*. 2025; 4(1): 100384.
12. Wang J, Liu X, Yang Y, Yang R, Tang X, Yan T, et al. Pulmonary metastasis of giant cell tumour: a retrospective study of three hundred and ten cases. *Int Orthop*. 2021; 45(3): 769-78.
13. Becker RG, Galia CR, Pestilho JFCS, Antunes BP, Baptista AM, Guedes A. Giant cell tumor of bone: a multicenter epidemiological study in Brazil. *Acta Ortop Bras*. 2024; 32(1): e273066.
14. Errani C, Ruggieri P, Asenzio MA, Toscano A, Colangeli S, Rimondi E, et al. Giant cell tumor of the extremity: a review of 349 cases from a single institution. *Cancer Treat Rev*. 2010; 36(1): 1-7.
15. Balke M, Henrichs MP, Gosheger G, Ahrens H, Streitbuerger A, Koehler M, et al. Giant cell tumors of the axial skeleton. *Sarcoma*. 2012; 2012: 410973.
16. Balke M, Schremper L, Gebert C, Ahrens H, Streitbuerger A, Koehler G, et al. Giant cell tumor of bone: treatment and outcome of 214 cases. *J Cancer Res Clin Oncol*. 2008; 134(9): 969-78.
17. Van der Heijden L, Lipplaa A, van Langevelde K, Bovée JVMG, van de Sande MAJ, Gelderblom H. Updated concepts in treatment of giant cell tumor of bone. *Curr Opin Oncol*. 2022; 34(4): 371-8.
18. Basu MA, Chawla SP. Giant cell tumor of bone: an update. *Curr Oncol Rep*. 2021; 23(5): 51.
19. Montgomery C, Couch C, Emory CL, Nicholas R. Giant cell tumor of bone: review of current literature, evaluation, and treatment options. *J Knee Surg*. 2019; 32(4): 331-6.
20. Gouin F, Dumaine V; French sarcoma and bone tumor study groups GSF-GETO. Local recurrence after curettage treatment of giant cell tumors in peripheral bones: retrospective study by the GSF-GETO (French sarcoma and bone tumor study groups). *Orthop Traumatol Surg Res*. 2013; 99(6 Suppl): S313-8.
21. Ebeid WA, Badr IT, Mesregah MK, Hasan BZ. Risk factors and oncological outcomes of pulmonary metastasis in patients with giant cell tumor of bone. *J Clin Orthop Trauma*. 2021; 20: 101499.
22. Muheremu A, Niu X. Pulmonary metastasis of giant cell tumor of bones. *World J Surg Oncol*. 2014; 12: 261.
23. Kamath N, Agarwal J, Gulia A. Axial giant cell tumor-current standard of practice. *J Clin Orthop Trauma*. 2019; 10(6): 1027-32. doi: 10.1016/j.jcot.2019.09.025. Epub 2019 Oct 9. Erratum in: *J Clin Orthop Trauma*. 2020; 11(6): 1169-71.
24. Leggett AR, Berg AR, Hullinger H, Benevenia JB. Diagnosis and treatment of lumbar giant cell tumor of the spine: update on current management strategies. *Diagnostics (Basel)*. 2022; 12(4): 857.
25. Martin C, McCarthy EF. Giant cell tumor of the sacrum and spine: series of 23 cases and a review of the literature. *Iowa Orthop J*. 2010; 30: 69-75.

26. Sambri A, Medellin MR, Errani C, Campanacci L, Fujiwara T, Donati D, et al. Denosumab in giant cell tumour of bone in the pelvis and sacrum: Long-term therapy or bone resection? *J Orthop Sci*. 2020; 25(3): 513-9.
27. Puri A, Gupta SM, Gulia A, Shetty N, Laskar S. Giant cell tumors of the sacrum: is non-operative treatment effective? *Eur Spine J*. 2021; 30(10): 2881-6.
28. Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality: systematic review and meta-analysis. *CA Cancer J Clin*. 2009; 59(3): 192-211.
29. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med*. 1979; 301(25): 1364-9.
30. Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. *J Clin Oncol*. 2000; 18(11): 2327-40.
31. Branstetter DG, Nelson SD, Manivel JC, Blay JY, Chawla S, Thomas DM, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res*. 2012; 18(16): 4415-24.
32. Chawla S, Blay JY, Rutkowski P, Le Cesne A, Reichardt P, Gelderblom H, et al. Denosumab in patients with giant-cell tumour of bone: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2019; 20(12): 1719-29.
33. 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.
34. Palmerini E, Chawla NS, Ferrari S, Sudan M, Picci P, Marchesi E, et al. Denosumab in advanced/unresectable giant-cell tumour of bone (GCTB): For how long? *Eur J Cancer*. 2017; 76: 118-24.
35. Palmerini E, Staals EL, Jones LB, Donati DM, Longhi A, Randall RL. Role of (Neo)adjuvant denosumab for giant cell tumor of bone. *Curr Treat Options Oncol*. 2020; 21(8): 68.
36. Traub F, Singh J, Dickson BC, Leung S, Mohankumar R, Blackstein ME, et al. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. *Eur J Cancer*. 2016; 59: 1-12.
37. Ueda T, Morioka H, Nishida Y, Kakunaga S, Tsuchiya H, Matsumoto Y, et al. Objective tumor response to denosumab in patients with giant cell tumor of bone: a multicenter phase II trial. *Ann Oncol*. 2015; 26(10): 2149-54.
38. Van der Heijden L, Dijkstra PDS, Blay JY, Gelderblom H. Giant cell tumour of bone in the denosumab era. *Eur J Cancer*. 2017; 77: 75-83.
39. Agarwal MG, Gundavda MK, Gupta R, Reddy R. Does denosumab change the giant cell tumor treatment strategy? Lessons learned from early experience. *Clin Orthop Relat Res*. 2018; 476(9): 1773-82.
40. Trovarelli G, Rizzo A, Cerchiaro M, Pala E, Angelini A, Ruggieri P. The evaluation and management of lung metastases in patients with giant cell tumors of bone in the denosumab era. *Curr Oncol*. 2024; 31(4): 2158-71.
41. Ambroggi M, Biasini C, Del Giovane C, Fornari F, Cavanna L. Distance as a barrier to cancer diagnosis and treatment: review of the literature. *Oncologist*. 2015; 20(12): 1378-85.

Funding: this study was not funded and is of an academic nature.