



Benefício clínico e segurança do denosumabe no tumor de células gigantes do osso: revisão sistemática e meta-análise de braço único

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Resumo

O tumor de células gigantes do osso é uma neoplasia osteolítica localmente agressiva na qual o denosumabe se tornou uma opção sistêmica importante, porém ainda há incerteza quanto à durabilidade do controle e à segurança em esquemas do mundo real. Este estudo teve como objetivo sintetizar a efetividade e a segurança do tratamento baseado em denosumabe em pacientes com TCGO com maturidade esquelética. Realizou-se busca nas bases PubMed, EMBASE, Scopus e Cochrane Library estudos clínicos em texto completo e em língua inglesa que avaliaram denosumabe em pacientes com maturidade esquelética e tumor de células gigantes do osso até janeiro de 2026. Os desfechos primários foram benefício clínico e eventos adversos, e os desfechos secundários foram resposta por imagem, recidiva local e falha do tratamento. Uma meta-análise de braço único com modelo de efeitos aleatórios foi realizada, com estabilização de variância e ponderação pelo inverso da variância. A heterogeneidade foi quantificada pelo I^2 , e intervalos preditivos e análises leave-one-out foram utilizados para avaliar a robustez. As análises de subgrupo foram limitadas ao desenho do estudo. Foram analisados 22 estudos, incluindo 1.170 pacientes. A taxa combinada de benefício clínico foi de 79,94% (IC 95% 74,21–85,02; I^2 85,8%), e a taxa combinada de resposta por imagem foi de 72,72% (IC 95% 59,46–84,04; I^2 97,2%). A recidiva local ocorreu em 24,49% dos pacientes (IC 95% 14,30–36,54; I^2 96,5%) e a falha do tratamento em 10,36% (IC

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95% 6,74–14,69; I^2 57,0%). A taxa combinada de eventos adversos foi de 31,16% (IC 95% 6,76–63,08; I^2 98,5%). A análise de subgrupo por desenho do estudo não reduziu de forma consistente a heterogeneidade, os intervalos preditivos foram amplos para a maioria dos desfechos e a meta-regressão utilizando idade média e a proporção de pacientes do sexo feminino não identificou moderadores significativos das estimativas combinadas. Observou-se que o denosumabe esteve associado a benefício clínico significativo e resposta radiológica em pacientes com maturidade esquelética e TCGO, porém, a durabilidade do controle e as estimativas de segurança variaram amplamente entre os estudos, ressaltando a necessidade de desfechos padronizados e de evidência prospectiva comparativa.

Clinical benefit and safety of denosumab in giant cell tumor of bone: a systematic review and single-arm meta-analysis

Abstract

Giant cell tumor of bone is a locally aggressive osteolytic neoplasm in which denosumab has become an important systemic option, yet uncertainty remains regarding durability of control and safety across real-world regimens. This study aimed to synthesize the effectiveness and safety of denosumab-based treatment in skeletally mature patients with GCTB. A systematic search was conducted in PubMed, EMBASE, Scopus, and the Cochrane Library for full-text English-language clinical studies evaluating denosumab in skeletally mature patients with giant cell tumor of bone through January 2026. Primary outcomes were clinical benefit and adverse events, and secondary outcomes were imaging response, local recurrence, and treatment failure. Event proportions were pooled using a random-effects single-arm meta-analysis with variance stabilization and inverse-variance weighting. Heterogeneity was quantified with I^2 , and prediction intervals and leave-one-out analyses were used to assess robustness. Subgroup analyses were limited to study design. Twenty-two studies including 1,170 patients were analyzed. The pooled rate of clinical benefit was 79.94% (95% CI 74.21–85.02; I^2 85.8%), and the pooled imaging response rate was 72.72% (95% CI 59.46–84.04; I^2 97.2%). Local recurrence occurred in



24.49% of patients (95% CI 14.30–36.54; I^2 96.5%) and treatment failure in 10.36% (95% CI 6.74–14.69; I^2 57.0%). The pooled adverse event rate was 31.16% (95% CI 6.76–63.08; I^2 98.5%). Subgroup analysis by study design did not consistently reduce heterogeneity, prediction intervals were wide for most outcomes, and meta-regression using mean age and the proportion of female patients did not identify significant moderators of the pooled estimates. Denosumab was associated with meaningful clinical benefit and radiologic response in skeletally mature patients with GCTB, but durability of control and safety estimates varied widely across studies, underscoring the need for standardized outcomes and prospective comparative evidence.

Keywords: Giant cell tumor of bone; Denosumab; Systematic review; Single-arm meta-analysis.

1. Introduction

Giant cell tumor of bone (GCTB) is a primary bone neoplasm characterized by locally aggressive behavior and a strong predilection for the metaphyseal regions of long bones, particularly in young adults [1]. It accounts for approximately 4% to 10% of all primary bone tumors and up to 20% of benign bone tumors, with peak incidence between the second and fourth decades of life [2]. Clinically, GCTB commonly presents with pain, swelling, functional limitation, and pathological fractures, often leading to joint destruction and the need for complex surgical procedures [3]. Because it predominantly affects individuals during their most productive years [4], GCTB carries a substantial societal and economic burden, contributing to long-term disability, psychological distress, and reduced quality of life, thereby underscoring the importance of continued investigation into optimal treatment strategies.

Denosumab, a fully human monoclonal antibody against the receptor activator of nuclear factor kappa B ligand (RANKL), has emerged as a major therapeutic advance in the management of GCTB [5]. The neoplastic stromal cells in GCTB overexpress



RANKL, which drives the recruitment and activation of osteoclast-like giant cells responsible for extensive bone destruction [6]. By inhibiting the RANKL-RANK interaction, denosumab suppresses osteoclast activity, reduces tumor-associated osteolysis, and induces an osteogenic response characterized by new bone formation [5]. These effects can result in significant tumor downstaging, symptom control, and improved surgical feasibility, particularly in advanced or unresectable cases [6].

Despite its clinical efficacy, several uncertainties remain regarding the optimal use of denosumab in GCTB. Concerns have been raised about an increased risk of local recurrence after intralesional surgery, potentially due to the formation of a dense bone matrix that may harbor residual neoplastic cells [7]. Additionally, the lack of consensus on treatment duration, the possibility of rebound phenomena following drug discontinuation, and reports of malignant transformation during or after therapy continue to generate debate [6]. These unresolved issues highlight the need for further high-quality evidence to clarify the long-term safety and appropriate integration of denosumab into the treatment algorithm for GCTB.

This study aims to assess the effectiveness of different Denosumab-based treatment regimens in patients with GCTB, focusing on clinical benefit, imaging response, local recurrence, and adverse events, while secondarily examining the impact of age and sex on these outcomes.

2. **Methodology**

This is a systematic literature review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [8], to assess the efficacy and safety of denosumab for giant cell tumor of bone in skeletally mature patients. Eligible studies included adults aged 18 years or older with histologically confirmed disease who received denosumab for the treatment of giant cell tumor of bone, regardless of dosing regimen, duration of therapy, or treatment intent, and no comparator



was required for inclusion. The primary outcomes of interest were clinical benefit and adverse events, while secondary outcomes included imaging response, local recurrence, and disease progression or treatment failure.

This review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261288840. The review protocol, including eligibility criteria and outcome definitions, was established and submitted prior to initiating the database search.

2.1. Eligibility Criteria

Eligible studies were full-text clinical studies in English published up to January 2026 that reported outcomes of denosumab for giant cell tumor of bone in skeletally mature patients. Studies had to include adults aged 18 years or older with a histologically confirmed diagnosis of giant cell tumor of bone, with no restrictions regarding sex, ethnicity, geographic region, tumor location, or disease status at primary or recurrent presentation. Denosumab could be administered at any dose, loading regimen, dosing interval, or duration, and for any treatment intent, including neoadjuvant, adjuvant, or definitive or palliative use. Studies were eligible if outcome data for the prespecified efficacy or safety endpoints could be clearly identified and extracted for the prespecified population. A comparator was not required, and both randomized and nonrandomized designs were considered, including randomized controlled trials and prospective or retrospective cohort studies.

Studies were excluded if they were case-control studies, case reports, case series, or included fewer than 10 patients, as well as narrative reviews, systematic reviews and meta-analyses, editorials, conference abstracts, and letters to the editor. We also excluded in vitro, cadaveric, and purely biomechanical studies. Studies were additionally excluded when outcome data were not extractable or when the reporting of outcomes was insufficient to support the planned synthesis.



2.2. Search Strategy

The database search strategy was derived from the following combination of terms: (“Giant Cell Tumor of Bone”[MeSH] OR “Giant Cell Tumour of Bone” OR “Giant Cell Tumor” OR “Giant Cell Tumour” OR osteoclastoma) AND (“Denosumab”[MeSH] OR denosumab OR Xgeva OR Prolia OR “AMG 162”). Controlled vocabulary terms were obtained from the Medical Subject Headings (MeSH) database and supplemented with relevant free-text terms, including commonly used synonyms and drug trade names. Boolean operators (AND, OR) were applied to combine search terms across databases, in accordance with the prespecified eligibility criteria. The literature search was conducted in PubMed, Embase, Scopus, and Cochrane CENTRAL.

2.3. Selection of studies

Two independent reviewers (C.F.G. and M.T.P.), blinded to each other’s assessments, jointly screened the titles and abstracts of all retrieved articles to identify those meeting the predefined inclusion criteria. Potentially eligible studies were then read in full to confirm their inclusion in the review. In cases of disagreement, a senior reviewer (F.W.L.G.F.), who had access only to the disputed articles, made the final decision. The studies were selected using the Rayyan app [9].

2.4. Data summarization

Data extraction was performed independently and in duplicate (J.G.G. and R.J.G.F.) to ensure accuracy and reliability. Two reviewers extracted data from the included studies using a pre-designed data extraction form created in Microsoft Excel® (version 2205). The form captured comprehensive details on study characteristics, including population size, intervention specifics, methodological approaches, and the outcomes assessed. Any discrepancies between reviewers were resolved through discussion or consultation with a senior reviewer (F.W.L.G.F.) to achieve consensus.



2.5. Outcomes definitions

Outcomes were extracted as pragmatic, study-reported endpoints and coded as dichotomous data whenever feasible to ensure consistent synthesis across heterogeneous definitions. Clinical benefit was treated as an investigator-reported indicator of symptomatic improvement, most commonly pain reduction with or without gains in function or mobility, and was recorded as present or absent when sufficient information was available. Treatment failure was captured as a lack of durable disease control and was generally defined by progression during treatment or local recurrence after initial control, including after surgery or treatment discontinuation, with some studies applying objective imaging thresholds to classify progression. Imaging response was collected from radiologic response categories reported by each study and dichotomized as response versus no response, based mainly on CT or MRI assessments and, when available, on adapted response frameworks for GCTB. Local recurrence was recorded as a binary event during follow-up, reflecting any return of tumor at the index site identified on surveillance imaging and clinical assessment, with histopathologic confirmation when reported. Adverse events were abstracted as patient-level counts of any event during treatment or follow-up, with attention to serious events and events leading to interruption or discontinuation, prioritizing the number of patients affected rather than continuous laboratory changes.

2.6. Statistical analysis

All statistical analyses were performed in RStudio using the meta and metafor packages. We conducted a single-arm meta-analysis to pool event proportions across included studies. Proportions were calculated as the number of events divided by the total number of assessed patients for each outcome. Both primary and secondary outcomes were extracted at the study level as absolute event counts and sample size, allowing direct calculation of proportions. To stabilize variances, the Freeman-Tukey double arcsine



transformation was applied, and pooled estimates were obtained via inverse-variance weighting. Results were reported with 95% confidence intervals, and statistical significance was set at $p < 0.05$. Statistical heterogeneity was assessed using the Cochran Q test and the I^2 statistic, with p values below 0.10 and I^2 above 25% considered suggestive of substantial heterogeneity. Given the expected clinical and methodological heterogeneity, random-effects models were used for all analyses, with between-study variance estimated by the restricted maximum likelihood method (REML). When Tau^2 differed from zero, the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment was applied to improve the accuracy of confidence intervals. Prediction intervals were also calculated to estimate the range of true effects expected in future similar studies.

Subgroup analyses were performed only by study design, as other planned subgroup analyses could not be conducted due to limited reporting. Sensitivity analysis was performed using a leave-one-out approach by sequentially excluding one study at a time to assess the influence of individual studies in the pooled analysis. When sufficient data were available, meta-regression analyses were conducted using mean age and the proportion of female patients as moderators.

3. **Development and discussion**

A comprehensive literature search across multiple databases initially identified 1,665 records. After removal of duplicates, 772 articles were screened based on titles and abstracts. After applying the eligibility criteria, 33 studies were selected for full-text review, of which 22 ultimately met the inclusion criteria. The complete study selection process, including the reasons for exclusion at each stage, is detailed in 1.

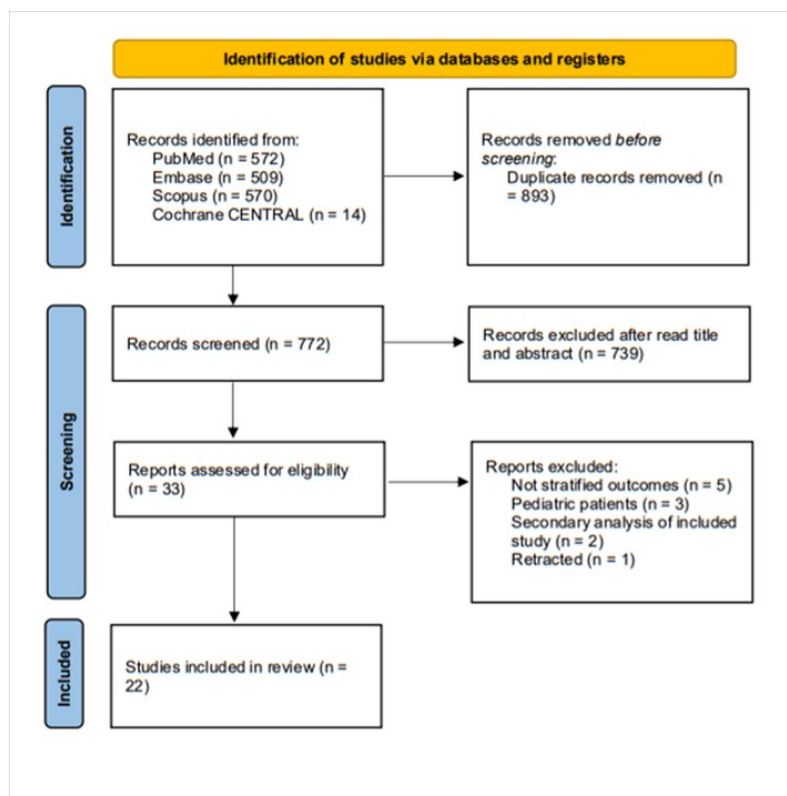


Figure 1: PRISMA flowchart
Fonte: Autores (2026).

3.1. Characteristics of the Studies

A total of 22 studies were included, encompassing 1,170 patients. Most studies were retrospective (17) [10–26], while the remaining comprised 2 randomized [27,28] and 3 non-randomized clinical trials [29–31]. Sex distribution was reported for 1,037 patients, of whom 554 (53.4%) were female, and 483 (46.6%) were male, whereas six studies involving 133 patients did not report sex-specific data. The weighted mean age was 33.4 years, based on 16 studies that reported age, with an overall age range of 17 to 76 years. Tumor location was documented for 934 patients, with appendicular involvement being more frequent (589 cases) than axial disease (345 cases).

Denosumab was administered predominantly at a dose of 120 mg subcutaneously in 17 of the 22 included studies, most commonly using a loading dose strategy followed



by monthly or every four-week maintenance dosing. While this general paradigm was consistent across studies, substantial heterogeneity existed in the timing of loading doses, initial dosing frequency, and overall treatment duration. Several studies used fixed short-course regimens ranging from 2 doses to 3 or more cycles, whereas others employed multi-month schedules with a predefined number of doses. A small number of studies used alternative non-monthly or intensive short-term protocols. Dosing details for denosumab were not reported in five studies. The median follow-up ranged from 12 to 99.84 months. Further details on the included studies are provided in 1.

Table 1: Baseline characteristics of included studies

Study	Country	Design	No. of patients	Male/Female	Age (years)†	Axial (N)	Appendicular (N)	Dosage regimen	Follow-up (months)‡
Ueda <i>et al.</i> 2015 [22]	Japan	Cohort	17	8/9	30 (18-66)	12	5	120 mg SC every 4 weeks with loading doses on days 8 and 15	13.1
Lee <i>et al.</i> 2018 [25]	China	Cohort	12	NR	38 (21-66)	NR	NR	120 mg SC every 4 weeks with loading doses on days 8 and 15	NR
Scoccianti <i>et al.</i> 2018 [20]	Italy	Cohort	12	5/7	30 (17-66)	2	10	120 mg SC for 3 weeks, then monthly for 3 months	39
Tsukamoto <i>et al.</i> 2019 [21]	Italy	Cohort	30	15/15	NR	NR	28	120 mg SC weekly for 1 month, then monthly for 6-9 months	42.4
Yang <i>et al.</i> 2018 [31]	China	NRCT	6	2/4	36.2 (21-63)	6	0	120 mg SC every 4 weeks, with additional doses on days 8 and 15 in month 1	12
Chawla <i>et al.</i> 2019 [29]	USA	NRCT	532	231/301	33 (25-45)	252	244	120 mg SC every 4 weeks with loading doses on days 8 and 15	58.1
Chinder <i>et al.</i> 2019 [12]	India	Cohort	42	29/13	27.4 ± 11.6*	6	36	120 mg SC every 4 weeks with booster doses on days 7 and 15 in month 1	32
Sambri <i>et al.</i> 2020 [19]	UK	Cohort	26	13/13	46 (20-76)	26	0	120 mg SC on days 1, 8, 15, 29, then monthly	65



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Study	Country	Design	No. of patients	Male/Female	Age (years) [†]	Axial (N)	Appendicular (N)	Dosage regimen	Follow-up (months) [‡]
Lim <i>et al.</i> 2020 [15]	China	Cohort	26	NR	NR	26	0	120 mg SC on days 1, 8, 15, 28, then every 4 weeks	47.7
Murphy <i>et al.</i> 2020 [17]	Australia	Cohort	21	11/10	32.8 (21.6-44)	1	20	120 mg SC on days 1, 8, and 15, then monthly for 3–6 months	NR
Konishi <i>et al.</i> 2021 [14]	Japan	Cohort	10	NR	NR	NR	NR	NR	NR
Sahito <i>et al.</i> 2022 [10]	Pakistan	Cohort	29	15/14	29.9 (17-47)	0	29	120 mg SC weekly for 4 weeks	12
Asano <i>et al.</i> 2022 [11]	Japan	Cohort	21	12/9	34 (28-46)	2	19	NR	24
Deventer <i>et al.</i> 2022 [13]	Germany	Cohort	33	NR	NR	NR	NR	120 mg SC every 4 weeks with doses on days 8 and 15 in cycle 1 for 3 cycles	NR
Urakawa <i>et al.</i> 2022 [28]	Japan	RCT	7	4/3	37 (29-56)	0	7	120 mg SC on days 1, 8, 15, 29 and 57	19.2
Yue <i>et al.</i> 2022 [27]	China	RCT	80	31/49	34.3 (28-52)	38	42	120 mg SC every 4 weeks with loading doses on days 8 and 15	48
Mahdal <i>et al.</i> 2023 [16]	Czech Republic	Cohort	20	NR	NR	0	20	NR	99.84
Rasheed <i>et al.</i> 2024 [30]	Pakistan	NRCT	23	16/7	34.6 ± 10.07*	0	23	120 mg SC on days 1, 8, 15, 29, 57, and 85	37
Rodrigues <i>et al.</i> 2025 [18]	Brazil	Cohort	32	NR	NR	0	32	NR	89.6
Singh <i>et al.</i> 2025 [26]	India	Cohort	17	11/6	31 (20-47)	0	17	120 mg SC on days 0 and 14	16
Xu <i>et al.</i> 2025 [23]	China	Cohort	88	47/41	33 (18-63)	NR	NR	NR	NR
Yang <i>et al.</i> 2025 [24]	China	Cohort	86	33/53	35.72 ± 5.94*	0	86	120 mg SC on days 1, 8, and 15, then monthly for a total of 5 doses	NR



Legend: N = Absolute number of patients included; NRCT = Nonrandomized Clinical Trial; RCT = Randomized Clinical Trial; USA = United States of America; NR = Not reported; mg = milligrams; SC = Subcutaneous; *Mean ± Standard Deviation; †Median (Range); ‡Median.

Fonte: Autores (2026).

3.2. Clinical Improvement

Clinical benefit was assessed in 771 patients using Denosumab. The meta-analysis yielded a pooled clinical improvement rate of 79.94% (95% CI, 71.29% to 87.49%; 2), with a prediction interval of 61.70% to 93.77%. Moderate heterogeneity was observed ($I^2 = 48.6\%$, $P = 0.0586$), and no significant differences were detected between study designs ($P = 0.83$). Leave-one-out analysis confirmed the robustness of the findings, with pooled estimates ranging from 77.84% when Sambri *et al.* [19] was excluded to 81.81% when Yang *et al.* [31] was omitted.

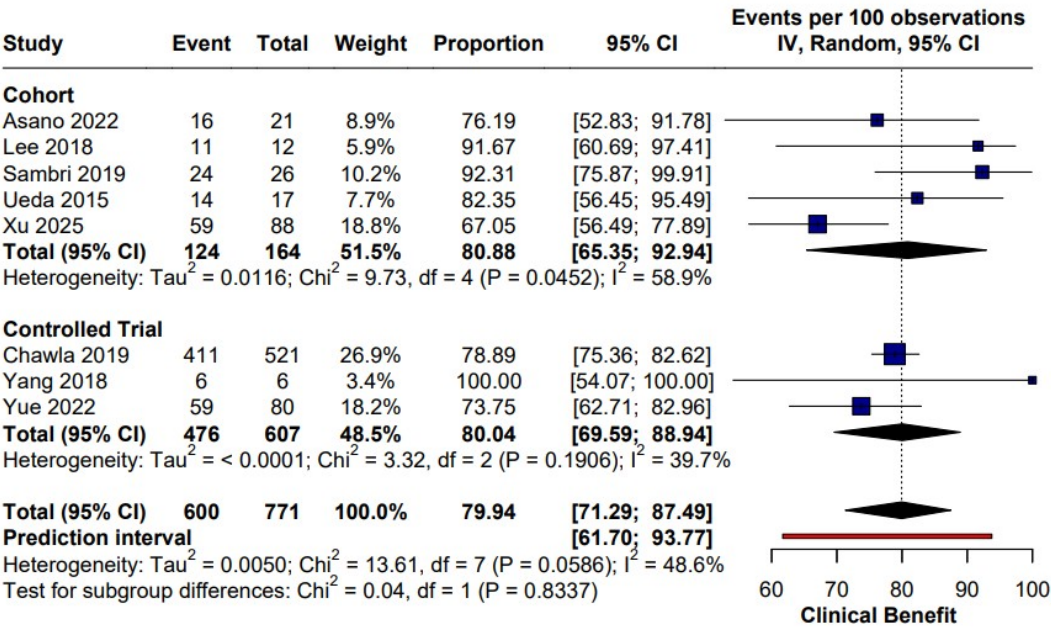


Figure 2: Forest plot for clinical benefit in patients with giant cell tumor of bone treated with denosumab

Fonte: Autores (2026).



3.3. Treatment Failure

The analysis of treatment failure included 636 patients using Denosumab. The pooled treatment failure rate was 10.36% (95% CI, 1.76% to 23.25%; 3), with a prediction interval extending from 0.00% to 43.12%. Substantial heterogeneity was identified ($I^2 = 71.5\%$, $P = 0.0018$). A significant subgroup difference was observed ($P = 0.0133$), with clinical trials demonstrating a higher failure rate (19.37%) compared with cohort studies (6.49%). A leave-one-out sensitivity analysis showed that the pooled estimate ranged from 7.76% after excluding Chawla *et al.* [29] to 13.88% after excluding Murphy *et al.* [17].

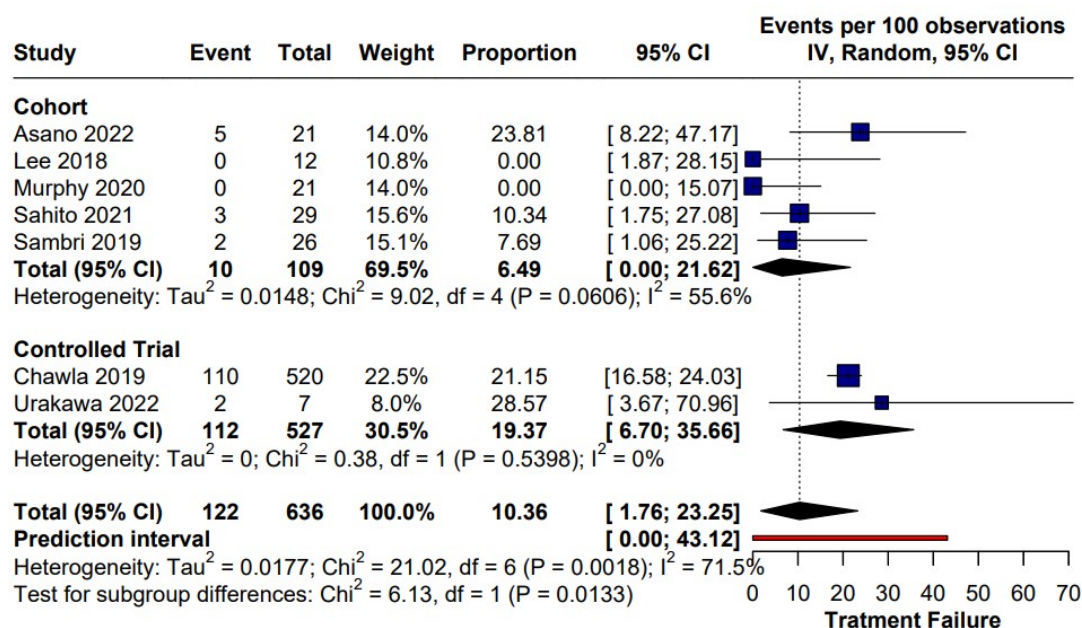


Figure 3: Forest plot for treatment failure in patients with giant cell tumor of bone treated with denosumab

Fonte: Autores (2026).

3.4. Imaging Response

Imaging response was evaluated in 765 patients. The pooled response rate with Denosumab was 72.72% (95% CI, 67.47% to 77.70%; 4), with a relatively narrow prediction interval of 68.50% to 76.77%. Heterogeneity was low to moderate and not



statistically significant ($I^2 = 35.0\%$, $P = 0.1608$). No significant differences were observed between subgroups ($P = 0.4187$). Leave-one-out analysis confirmed the stability of the results, with pooled estimates ranging from 72.24% to 75.57% across the studies excluded.

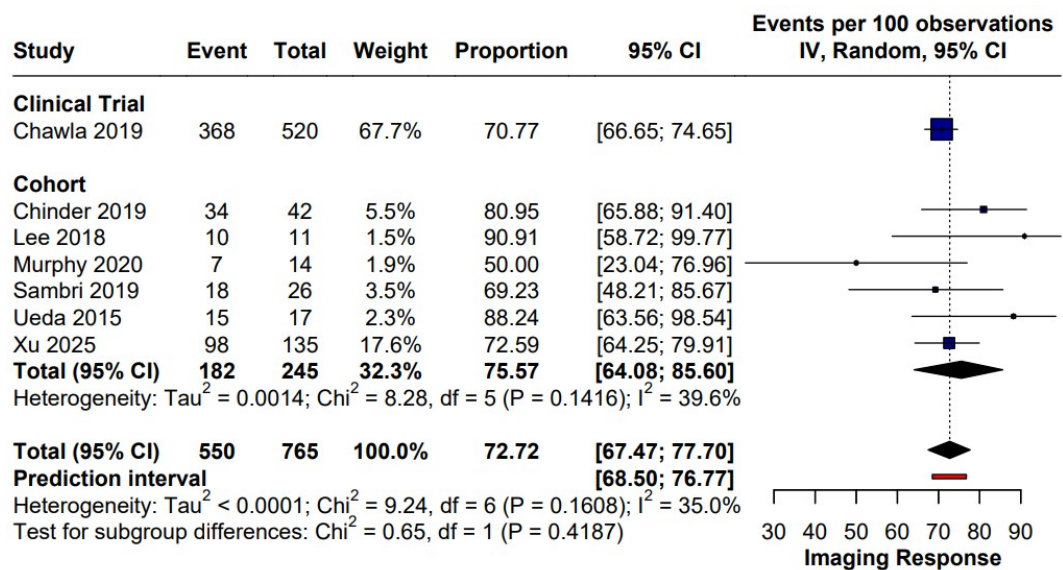


Figure 4: Forest plot for imaging response in patients with giant cell tumor of bone treated with denosumab

Fonte: Autores (2026).

3.5. Local Recurrence

A total of 674 patients in the Denosumab group were included in the local recurrence analysis. The pooled local recurrence rate was 24.49% (95% CI, 17.11% to 32.60%; 5), with a prediction interval of 2.30% to 57.11%. Significant heterogeneity was present ($I^2 = 72.8\%$, $P < 0.0001$), although no significant differences were identified between subgroups ($P = 0.7485$). Leave-one-out sensitivity analysis demonstrated relative stability of the pooled estimate, which ranged from 22.99% after excluding Tsukamoto *et al.* [21] to 25.98% after excluding Sahito *et al.* [10].

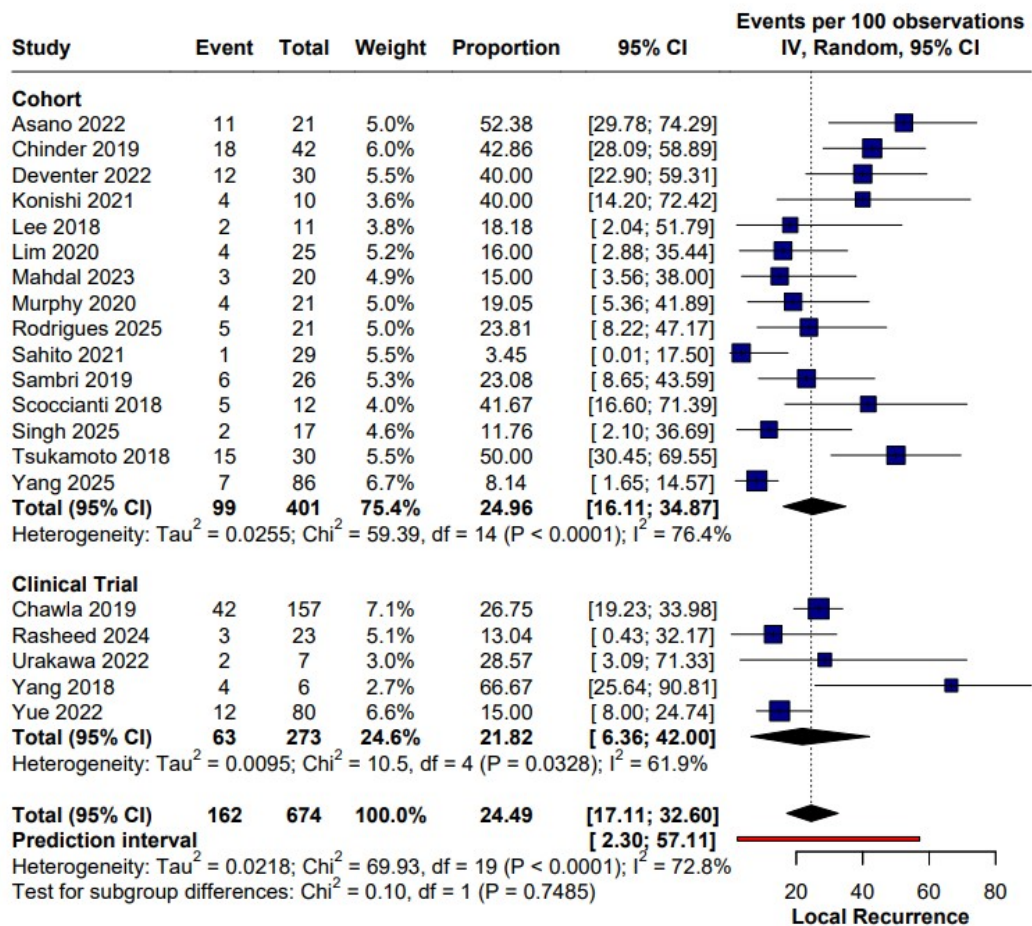


Figure 5: Forest plot for local recurrence in patients with giant cell tumor of bone treated with denosumab

Fonte: Autores (2026).

3.6. Adverse Events

A total of 742 patients across the included studies were analyzed to evaluate the incidence of adverse events in the Denosumab group. The pooled adverse event rate was 31.16% (95% CI, 1.63% to 72.67%; 6), with a wide prediction interval ranging from 0.00% to 100.00%. Substantial heterogeneity was observed ($I^2 = 98.5\%$, $P < 0.0001$). Subgroup analysis showed no statistically significant difference between clinical trials and cohort studies ($P = 0.20$). Leave-one-out sensitivity analysis demonstrated

considerable variability in the pooled estimate, which ranged from 22.17% after exclusion of Ueda *et al.* [22] to 36.65% after exclusion of Singh *et al.* [26], while heterogeneity remained consistently high (I^2 range, 93.1% to 98.6%).

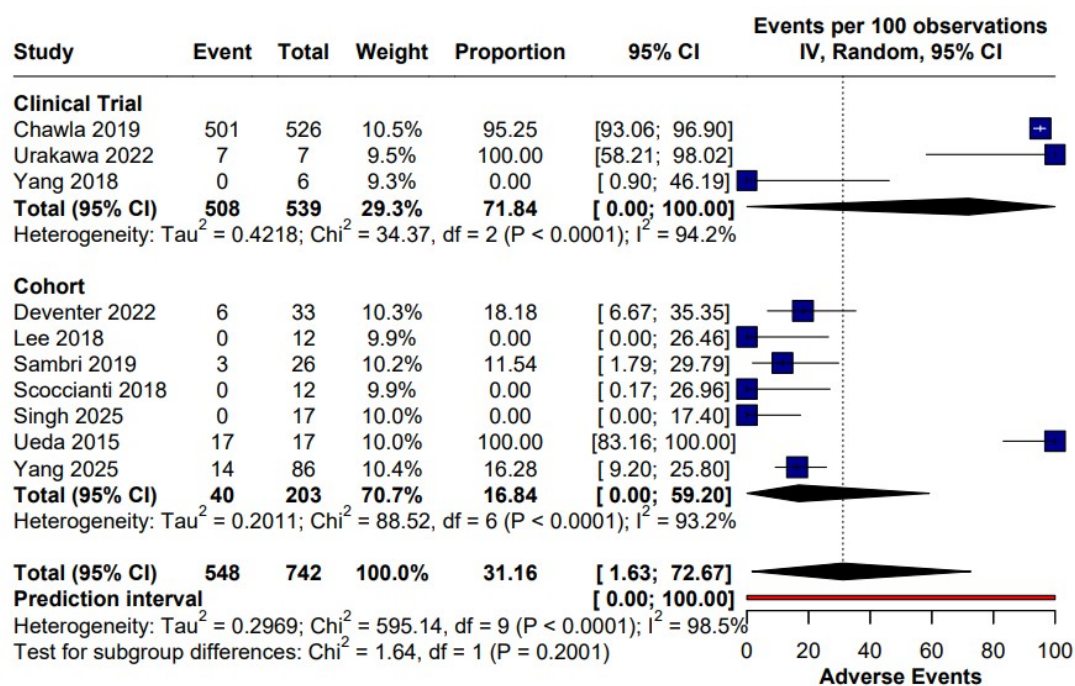


Figure 6: Forest plot for adverse events in patients with giant cell tumor of bone treated with denosumab

Fonte: Autores (2026).

3.7. Meta-regressions

Meta regression analyses were conducted to assess the potential moderating effects of age and sex on the observed clinical outcomes. Patient age was not significantly associated with adverse events ($p = 0.6138$), treatment failure ($p = 0.7824$), imaging response ($p = 0.5495$), or local recurrence ($p = 0.7824$). For clinical improvement, a non-significant trend was observed ($p = 0.0876$), indicating that age was unlikely to be a major determinant of clinical benefit in this cohort. Similarly, sex was not a significant predictor of any evaluated outcome, with no meaningful associations identified for adverse events ($p = 0.7822$), clinical improvement ($p = 0.4840$), treatment failure ($p = 0.9086$), imaging



response ($p = 0.4215$), or local recurrence ($p = 0.9874$). Overall, these findings suggest that the between-study variability in clinical outcomes is unlikely to be explained by differences in age or sex distributions and is more plausibly attributable to other clinical or methodological factors.

3.8. Risk of bias of the included studies

The risk of bias of included studies is summarized in 7.

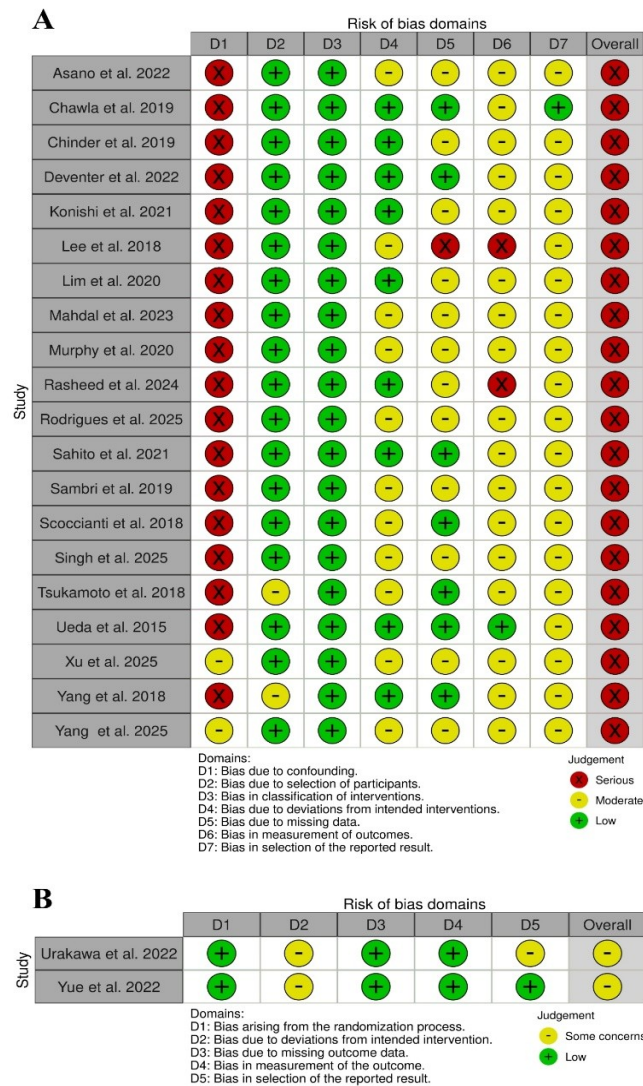


Figure 7: Risk of bias in observational studies (A) and randomized studies (B)

Fonte: Autores (2026).

3.8.1. Risk of bias in observational studies

In Domain 1 (confounding), the vast majority of non-randomized studies were judged to be at serious risk of bias due to confounding by indication, as denosumab was predominantly administered to surgically challenging, recurrent, or highly aggressive



tumors. Xu *et al.* [23] was rated as having a moderate risk of bias because the use of propensity score matching partially addressed baseline imbalances, and Yang *et al.* [24] was also classified as moderate risk after demonstrating no significant differences between groups for the most evaluated confounders. In Domain 2 (selection of participants), most studies were considered at low risk owing to the inclusion of consecutive cohorts and the use of clear diagnostic criteria, whereas Tsukamoto *et al.* [21] and Yang *et al.* [24] were judged to be at moderate risk because of potential time period bias related to the use of broad historical control groups. In Domain 3 (classification of interventions), all studies were assessed as low risk of bias since exposure to denosumab was clearly documented in medical records. In Domain 4 (deviations from intended interventions), most studies were rated as moderate risk due to heterogeneity in systemic treatment duration and variability in surgeon experience across institutions, whereas studies employing standardized protocols or fixed-dosing regimens were judged to be at low risk. In Domain 5 (missing data), several studies were classified as moderate risk due to exclusions based on incomplete medical records or insufficient follow-up, whereas Lee *et al.* [25] was rated as serious risk owing to substantial missing data and a limited follow-up duration, and the remaining studies were considered at low risk. In Domain 6 (measurement of outcomes), most studies were judged to be at moderate risk due to the absence of blinded outcome assessment, while Ueda *et al.* [22] was classified as low risk because outcomes were evaluated through independent central review, and Lee *et al.* [25] and Rasheed *et al.* [30] were rated as serious risk due to the high subjectivity of outcome assessment and irregular data collection intervals. Finally, in Domain 7 (selection of the reported result), nearly all studies were assessed as having a moderate risk of bias due to the lack of a pre-registered protocol, with Chawla *et al.* [29] being the only study rated as low risk because of the availability of a prospective public registry.



3.8.2. Risk of bias in randomized studies

In Domain 1 (randomization process), both randomized controlled trials were judged to be at low risk of bias because they reported adequate random sequence generation and allocation procedures. Urakawa *et al.* [28] used a minimization method with randomization stratified by institution and tumor status, while Yue *et al.* [27] employed simple randomization with allocation concealment via opaque envelopes. In Domain 2 (deviations from intended interventions), both studies raised some concerns because they were essentially open-label trials. In Yue *et al.* [27], the different routes of administration, subcutaneous denosumab and intravenous zoledronic acid, without a double dummy design, likely prevented effective blinding of participants and personnel. In Domain 3 (missing outcome data), both trials were assessed as low risk of bias due to high data completeness and the use of intention-to-treat analyses. In Domain 4 (measurement of outcomes), all studies were judged to be at low risk of bias, as outcome assessment was objective and unlikely to be influenced by the lack of blinding. Finally, in Domain 5 (selection of the reported result), Yue *et al.* [27] was rated as low risk of bias because the reported outcomes were consistent with the registered protocol, whereas Urakawa *et al.* [28] was judged to have some concerns owing to early termination of the trial due to poor accrual, which necessitated a departure from the planned inferential analyses and resulted in predominantly descriptive reporting of the findings.

3.9. Discussion

In the present systematic review and single-arm meta-analysis, denosumab was associated with high rates of clinical benefit and imaging response in skeletally mature patients with giant cell tumor of bone, supporting its role as an active systemic option across different clinical settings. These findings align with the established biological rationale of targeting the RANK/RANKL axis, which is central to osteoclast-mediated osteolysis in GCTB and underpins the clinical effects observed with RANKL blockade



[32,33]. Importantly, our pooled estimates are consistent with the landmark international phase 2 clinical program of denosumab in GCTB, which initially demonstrated meaningful clinical activity and later provided mature evidence of sustained disease control in a large prospective cohort [29,34]. Taken together, our results reinforce current practice recommendations that position denosumab as standard therapy for unresectable or advanced GCTB and as a useful option when surgery would carry major morbidity, while acknowledging that its integration with local treatment should be individualized [35].

Local recurrence and treatment failure in our pooled analysis highlight that early clinical and radiologic improvement with denosumab does not necessarily translate into durable local control, particularly when denosumab is integrated into surgical workflows. Several surgical cohorts have reported higher local recurrence rates among patients receiving neoadjuvant denosumab followed by intralesional curettage compared with curettage alone, raising concern that drug-induced bone formation may complicate complete removal of residual neoplastic stromal cells during intralesional procedures [7,12,36]. Mechanistically, histopathologic data indicate that stromal cells may remain viable despite marked depletion of giant cells and extensive sclerosis, providing a plausible explanation for recurrence after apparent response in curettage-based strategies [37]. In contrast, recurrence risk appears substantially lower after en bloc resection, where wider margins reduce the impact of microscopic residual disease and the influence of preoperative denosumab is less pronounced [21]. Beyond the surgical setting, durability of disease control also depends on treatment continuity in advanced or unresectable disease, as discontinuation has been associated with clinically relevant rates of progression within months in observational series [38]. Together, these findings reinforce that local control after denosumab is highly dependent on the subsequent surgical approach and treatment sequencing, with intralesional strategies warranting particular caution when recurrence risk is a primary concern [39].



Between-study heterogeneity was substantial for several endpoints in our analysis, and the wide prediction intervals indicate that the expected effect in a new clinical setting may differ materially from the pooled. This dispersion is clinically plausible because denosumab is applied within heterogeneous care pathways, ranging from short neoadjuvant courses intended for surgical downstaging to prolonged treatment in unresectable disease, with wide variation in duration, dose spacing, discontinuation practices, baseline disease severity, and local management strategies across cohorts [39,40]. Imaging response further illustrates this variability, as studies used different modalities and response frameworks, and size-based criteria may underestimate benefit in GCTB because denosumab commonly induces sclerosis and neocortex formation without early proportional shrinkage, whereas density-based and metabolic approaches can capture response more sensitively [41,42]. We explored potential sources of heterogeneity through subgroup analysis by study design and study-level meta-regression using mean age and the proportion of female patients, but these analyses did not meaningfully explain the observed variability, suggesting that residual heterogeneity is driven by factors that were inconsistently reported across studies.

Safety outcomes in our review should be interpreted with particular caution because adverse events were reported and ascertained very differently across studies. In the pooled analysis, the overall adverse event rate was 31.16% and heterogeneity was extreme (I^2 98.5%) with a very wide prediction interval, indicating that this summary estimate mainly reflects that events are commonly reported rather than providing a precise risk for any specific complication or clinical setting. This dispersion is clinically expected in GCTB because patients are often younger and exposure can be prolonged, so cumulative toxicities and surveillance practices meaningfully influence what is captured, and long-term prospective data have highlighted clinically relevant but relatively infrequent serious complications such as osteonecrosis of the jaw and atypical femoral fractures alongside more common nonspecific events [29,38]. Importantly, the spectrum



of reported events in GCTB aligns with broader bone-oncology experience with denosumab, and recent pharmacovigilance analyses also signal ONJ and hypocalcemia among the most prominent serious signals in real-world reporting [43,44]. From a risk–benefit standpoint, these data support structured mitigation strategies, including dental assessment before therapy and ongoing oral monitoring as well as routine laboratory surveillance and supplementation, which are consistently recommended in oncology guidelines and consensus statements [45,46].

First, the evidence base consisted largely of single-arm and observational cohorts, which limits causal inference and increases susceptibility to confounding by indication and center-specific treatment pathways. Secondly, this concern is supported by our risk-of-bias assessment, in which most nonrandomized studies were judged at serious risk of bias mainly due to confounding and variability in outcome ascertainment, while the randomized trials raised some concerns related to deviations from intended interventions. Thirdly, publication and reporting bias cannot be excluded. Formal assessments are challenging in single-arm meta-analyses of proportions, and funnel plots may be unreliable for this purpose, so we did not rely on these methods, but the possibility of selective publication remains [47]. Lastly, outcome definitions were highly heterogeneous across studies, and several endpoints were captured pragmatically and in a liberal manner to enable synthesis, which may have increased between-study variability and should be considered when interpreting the pooled estimates.

4. **Final considerations**

In summary, this systematic review and single-arm meta-analysis indicate that denosumab is associated with meaningful clinical benefit and favorable radiologic response in patients with GCTB, supporting its role as an active systemic option in settings where surgery is morbid, impractical, or used in combination with local treatment. However, local recurrence and treatment failure remain clinically relevant concerns, and the safety profile should be interpreted cautiously given heterogeneous



reporting and variable follow-up across studies. Overall, denosumab appears effective for disease control in many patients, but the certainty of evidence is limited by nonrandomized designs, inconsistent outcome definitions, and substantial heterogeneity, highlighting the need for standardized endpoints and well-designed prospective comparative studies to better define optimal sequencing, duration, and monitoring.

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