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Denosumab treatment for giant-cell tumor of bone: a systematic review of the literature

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Abstract

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.

Level of evidence IV.

Keywords Denosumab · Local recurrence · Metastasis · Systematic review · Fatigue

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Introduction

Giant-cell tumor of bone (GCTB) typically affects young adults during the second–fourth decades of age. Histologically, this tumor is composed of neoplastic ovoid mononuclear cells with high RANK ligand (RANKL) expression, RANK-positive mononuclear cells of myeloid linage, and a randomly distributed population of large RANK-expressing osteoclast-like giant cells [1, 2].

It is a benign tumor most of the times, and could be locally aggressive [3, 4], causing bone destruction, and

since it is commonly localized at the epiphyseal/metaphyseal region of long bones can cause significant morbidity with joint involvement. However, it can involve any bone including the pelvis and spine potentially resulting in significant morbidity. It is very rare that this disease metastasizes, but when it happens, pulmonary metastases are the most frequent [5].

Denosumab is a human monoclonal antibody (mAb) that specifically inhibits tumor-associated bone lysis by preventing RANKL-mediated formation and activation of multinucleated osteoclasts or giant cells from RANK-positive mononuclear preosteoclasts and macrophages [6–8]. This drug has been used in the treatment of GCTB showing marked reduction in tumor giant cells, and significant histologic evidence of treatment-induced differentiation of highly cellular proliferative tumor stromal cells into non-proliferative osteoid bone matrix, woven bone, and mature bone [8, 9].

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.

Materials and methods

This review was conducted in accordance to the PRISMA guidelines [10]. The PubMed, EMBASE, and COCHRANE search engines were used to identify all relevant publications since 2000, wherein tumor characteristics, treatment approach and/or response and/or oncological outcomes/complications of giant-cell tumors treated with denosumab, were described. Articles 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", were initially searched for (Fig. 1).

Articles were considered eligible if they met the following inclusion criteria (Table 1) [1]. The target population consisted of adults (age ≥ 18 years of age) with giant-cell tumor treated with denosumab [2]; tumor characteristics, treatment approach and/or response and/or oncological outcomes/complications were described adequately [3]; case series with minimum of five [4]; articles in English, Spanish or French. Expert opinions, publications on congress proceedings, review articles, editorials, letters to the

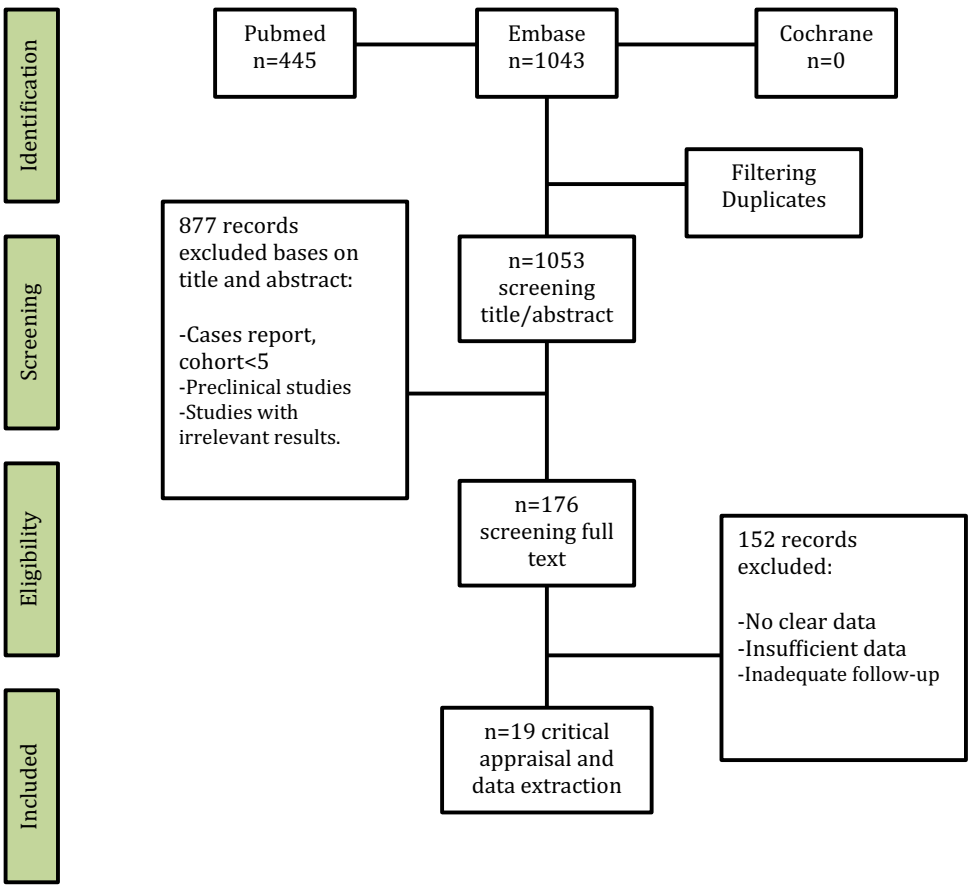

Fig. 1 Flowchart showing methodology followed by authors during systematic review of the literature

Table 1 PICO table and selection criteria

	Inclusion criteria	Exclusion criteria
Population	GCT of bone treated with denosumab	Other tumors treated with denosumab GCT without denosumab treatment
Intervention	Denosumab treatment	Surgical treatment with no denosumab
Outcomes	Primary endpoint: LR/metastatic rate Secondary endpoint: treatment time, type and rate of complications, treatment response	Cost-effectiveness
Study design	Randomized controlled trials, cohort studies, case–control studies and case series	Case report, simulation studies, animal studies, letters, editorials, notes, congress abstracts, conference papers and unpublished studies

GCT Giant-cell tumor, *LR* local recurrence

editor, autopsy studies, unpublished series, and articles with incomplete or irrelevant information were excluded.

All eligible studies were assessed for methodological quality by two independent reviewers (GLA, MMR). The study design, methodology, patient population parameters and outcomes for all studies included in the systematic review were extracted into a pre-specified grid. Data extraction was performed by a single individual (GLA) with independent verification by a second reviewer (MMR), with disagreements resolved by consensus or third and fourth reviewer (JPM, LRP) arbitration. In cases where the level of evidence was not specified by the authors, two independent reviewers (GLA, JPM) assigned levels of evidence to each eligible study using the Centre for Evidence-Based Medicine in Oxford guidelines for therapeutic studies.

Most of the citations were immediately excluded on the basis of information provided by the title or abstract. The complete manuscripts of the remaining papers were obtained and were carefully examined for eligibility criteria. Moreover, their references were carefully scrutinized for potentially additional eligible papers. The reviewers were not blinded to the names of authors, institutions, and journals.

Relevant data of the included studies were inserted into an electronic database [Microsoft® Excel for Windows® (Microsoft Corp, Redmond, WA)] for further analysis and included [1]: demographic data (age, gender, follow-up time) [2]; tumor location (upper extremity/lower extremity/axial skeleton) [3]; complications related to the use of denosumab and [4] oncological outcomes: local recurrence (LRR), and development of metastasis during its use; [5] clinical benefit in terms of pain relief, and surgical planning, [6] Radiological characteristics present with the use of denosumab and [7] histological response characteristics.

Quality appraisal

The quality of the included studies was assessed using STROBE for the assessment of observational studies [11]. We utilized 9 out of the 22 items of the STROBE checklist for the methodological assessment. Each item was scored as: well described (+), partly described (±), or poorly/not described (−). The final score was rounded off downward (e.g., an item that consisted of 1 well described [+] and 1 partly described [±] subitem was scored as partly described [±]) (Table 2). In cases of disagreement, consensus was sought between two investigators (GLA, MMR). Articles were included if 75% of items were well described (+). Two partly described items (±) counted as one well-described item (+). Quality assessments were conducted from the perspective of the populations and outcomes of interest to this review.

After calculating and weighting the STROBE, all 19 [6, 8, 9, 12–27] studies were found to be relevant and eligible for inclusion in the systematic review.

Outcomes

Demographic variables

Age, gender, tumor type (primary vs recurrent), tumor location (upper extremity/lower extremity/pelvis/spine), denosumab dosage, and length of the treatment.

Oncological outcomes

The oncological analysis was based on the presence of local recurrences (LR) and metastases. LR was defined as any recurrence of tumor following surgical treatment in patients treated with denosumab, as reported by the authors, regardless of the imaging modality used for surveillance. And metastasis was based on the presence of any distant lesion as reported by the author.

Complications

For each study included in the analysis, we retrieved the description of every complication specified in the text. We evaluated the following complications: fatigue/muscular

Table 2 Quality appraisal of articles included in the study using STROBE

Study	Item 5	Item 6	Item 7	Item 8	Item 12	Item 13	Item 14	Item 15	Item 16
Deveci et al	+	+	+	+	±	±	±	+	+
Rekhi et al	±	+	+	+	±	±	±	+	+
Dubory et al	+	±	±	±	±	±	+	+	+
Erdogan et al	+	+	+	+	±	±	±	+	+
Branstetter et al	+	+	+	+	+	±	±	+	+
Palmerini et al	+	+	+	+	+	±	±	+	+
Muller et al	+	+	+	+	±	±	±	+	+
Goldschlager et al	+	±	+	±	±	±	+	+	+
Traub et al	+	+	+	+	±	±	±	+	+
Borkowska et al	+	+	+	+	±	±	±	+	+
Roitman et al	+	±	+	+	±	±	±	+	+
Wojcik et al	+	+	+	+	±	±	±	+	+
Boye et al	+	+	+	+	±	±	±	+	+
Girolami et al	+	±	+	+	±	±	±	+	+
Thomas et al	+	+	+	+	±	±	±	+	+
Rutkowski et al	+	+	+	+	+	+	+	+	+
Chawla et al	+	+	+	+	+	±	±	+	+
Ueda et al	+	+	+	+	+	+	±	+	+
Martin-Broto et al	+	+	+	+	+	+	+	+	+

pain/arthralgia/extremity pain/back pain/headaches/nausea/infection/osteonecrosis of the jaw/peripheral neuropathy/skin rash/atypical femur fracture, malignant transformation/hypophosphatemia and hypocalcemia. Owing to the limited information available, we narratively reported the data regarding different complications.

Response to treatment variables

Histologic response, radiological changes, clinical benefits (pain, MSTS score), and surgical planning.

Statistical analysis

The heterogeneity among the selected studies was evaluated using the Cochran Q test with a p value set at 0.1 for significance. The I2 statistic is reported as well and represents the percentage of total variation across studies owing to heterogeneity.

We used a random-effects model (DerSimonian-Laird) that accounted for between-study heterogeneity owing to the inherent heterogeneity of case series to calculate the pooled weighted proportion. The pooled weighted proportions of local recurrence and metastases, with 95% CI for single-group studies, are reported.

Data analysis was performed with ProMeta software Version 2 (INTERNOVI di Scarpellini Daniele s.a.s., Cesena FO, Italy). All other statistical analyses were carried out using IBM spss version 24.0 (IBM SPSS, Armonk, NY, USA), and significance of pooled estimates was set at $p < 0.05$.

Results

All the studies included in our analysis were retrospective chart reviews that reported on local recurrence, metastases, complication rates, and characteristics on treatment response after denosumab therapy for GCT.

A total of 1095 patients were included across all 19 studies (Table 3). There were 615 females and 480 males. The mean age was 33.7 ± 8.3 years when starting the denosumab treatment. Of note, five studies reported median age only, and this ranged from 30 to 34 years [6, 13, 18, 20, 23].

There were two patients from two different studies, diagnosed with Aneurysmal bone cyst (ABC) or GCTB with secondary ABC co-existing in the same tumoral mass [25, 26].

Overall, there were 574 primary tumors and 521 recurrent tumors, which were treated with denosumab. Ten studies reported a mixed population of both primary and recurrent tumors [8, 9, 13, 16, 18, 20, 22, 23, 27], eight studies reported primary tumors alone [12, 14, 15, 17, 19, 21, 25, 26], and one study involved only recurrent tumors [6].

The anatomical location of the primary or recurrent GCTB was as follows: lower extremity 392 (35.8%), axial/pelvic 253 (23.1%), upper extremity 211 (19.2%), spine 108 (9.8%) and other 25 (2.2%).

The treatment duration with denosumab varied significantly between the different studies, and between subjects in

Table 3 Demographic characteristics of the included studies

Study	Year	No. of patients	Age (mean) range	Gender	Denosumab dose (mg s.c)	Monthly doses of Denosumab	Treatment time—mean (months)	Postoperative treatment (months)	Follow-up in months (mean)	Level of evidence
Deveci et al	2016	13	38.3	5M/8F	120	1	9.61	–	> 12	IV
Rekhi et al	2016	27	29.5	16M/11F	120	4	5.33	–	17.1	IV
Dubory et al	2016	9	35	4M/5F	120	1	6	6	19.3	IV
Erdogan et al	2016	10	35.6	4M/6F	120	3 first month	4.5	–	> 12	IV
Branstetter et al	2012	20	33	9M/11F	120	3 first month	3 to 7	–	> 12	IV
Palmerini et al	2017	54	35	21M/33F	120	4	54	–	> 60	II
Muller et al	2016	25	35	13M/12F	120	3	6	6	23	IV
Goldschlager et al	2015	5	38.2	0M/5F	120	3	9.6	–	12.8	III
Traub et al	2016	20	28	10M/10F	120	3	6	–	30	III
Borkowska et al	2016	35	32	14M/21F	120	3	7.4	–	> 12	IV
Roitman et al	2017	9	36	5M/4F	120	3	5.9	–	16.4	IV
Wojcik et al	2016	9	32	3M/6F	120	1	25.79	–	> 12	IV
Boye et al	2017	18	39	13M/5F	120	3	41	–	> 18	IV
Girolami et al	2015	15	31.4	6M/9F	120	3	3	6	> 12	IV
Thomas et al	2010	34	30	17M/17F	120	3	Non-stop	–	> 18	II
Rutkowski et al	2015	222	34	102M/120F	120	3	15.3	–	> 24	II
Chawla et al. (surgically unsalvageable)	2013	170	33	118M/164F	120	3 first month	> 6	6	13	II
Chawla et al. (severe morbidity)	2013	101	33	68M/102F	120	3 first month	> 6	6	9	II
Chawla et al. (previous study)	2013	11	34	6M/5F	120	3 first month	> 6	6	9	II
Ueda et al	2015	17	30	8M/9F	120	3	6	–	9	II
Martin-Broto et al	2014	170	33	68M/102F	120	3 during 6 months	Non-stop	–	> 36	II
Martin-Broto et al	2014	101	34	44M/57F	120	3 during 6 months	6 months	Non-stop	> 36	II

the same study, and ranged from 4 months [24] to 55 months [19]. Dosing was similar across all studies, and was 120 mg, given subcutaneously once a month.

Loading dose was not administered to all subjects in three studies [19, 24, 25], while the majority of studies provided a loading dose [6, 8–10, 12, 13, 15, 16, 18–21, 23–25]. Denosumab was given together with supplemental Calcium and Vitamin D in all patients excluding 138 patients from 9 studies [8, 9, 14, 16, 19, 24–27]. Denosumab was defined as the definitive treatment in 561 patients across 9 studies [6, 8, 12, 13, 15, 21–24].

Local recurrence

Local recurrence outcomes across 10 studies ranged from 3% [18] to 19% [9]. Overall, the pooled weighted local recurrence rate was 9% (95% CI 6–12%) (Fig. 2). When the local recurrence rates reported among the 10 studies were further assessed for publication bias using a funnel plot, no publication bias was uncovered, as the associated funnel plot appeared symmetric (Fig. 3).

Metastases

Metastases outcomes were reported across 12 studies, with only one study reporting a single case of metastasis [12] out of 197 cases included. The overall pooled weighted metastases rate was 3% (95% CI 1–7%) (Fig. 4). Assessment for publication bias using a funnel plot, showed that no publication bias was uncovered, as the associated funnel plot appeared symmetric (Fig. 5).

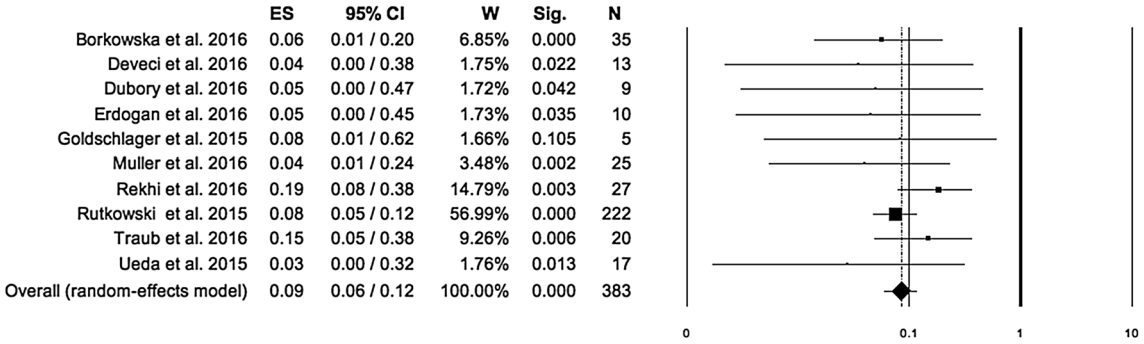

Fig. 2 Random-effect model for calculation of recurrence rates with the use of denosumab as adjuvant therapy

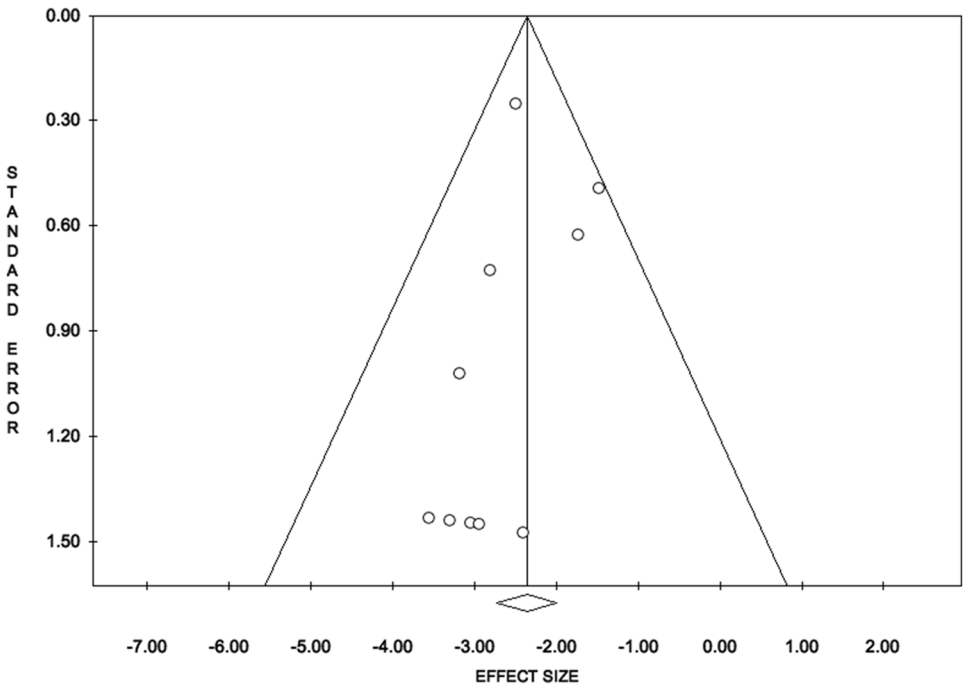

Fig. 3 Publication bias for calculation of local recurrence rates: the Cochran *Q* and I2, representing the percentage of total variation across studies owing to heterogeneity, suggested low heterogeneity in local recurrence rates across all studies ($Q = 6.92$, $I2 = 0.0$; $p = 0.645$)

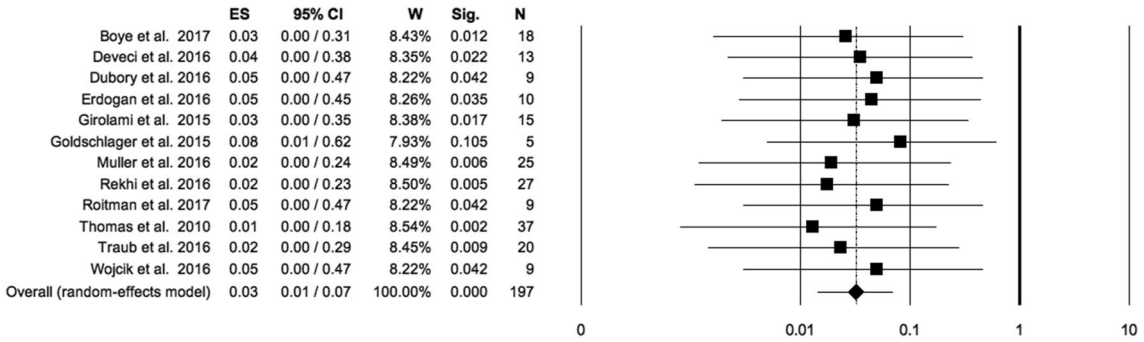

Fig. 4 Random-effect model for calculation of metastatic rates with the use of denosumab as adjuvant therapy

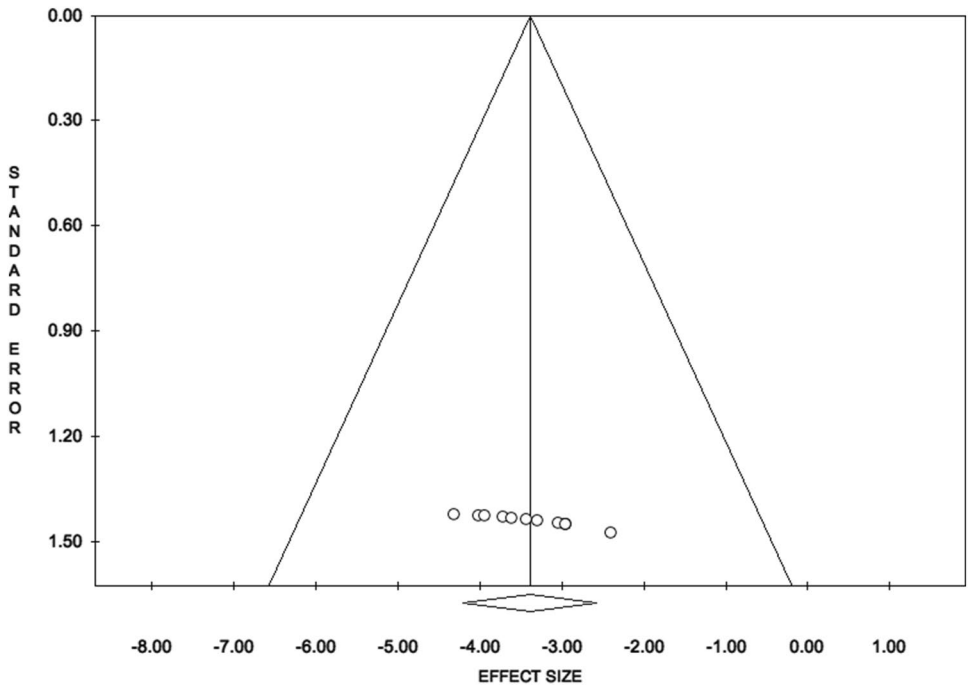

Fig. 5 Publication bias for calculation of metastatic rates: the Cochran *Q* and I2, representing the percentage of total variation across studies owing to heterogeneity, suggested low heterogeneity in metastases rates across all studies ($Q = 1.63$, I2 = 0.0; $p = 0.99$)

Adverse events and complications

Overall, there were 360 documented complications or treatment-related adverse events (AI) reported in 8 studies, whereas 11 studies did not report complications or AI [8, 9, 12–14, 16, 19, 23, 25–27]. The most common AI was fatigue/muscular pain/arthralgia/extremity pain/back pain, reported in 185 patients. Other AI included headaches ($n = 46$), nausea ($n = 40$), infection ($n = 17$), Osteonecrosis of the jaw ($n = 8$), peripheral neuropathy ($n = 6$), skin rash ($n = 5$), atypical femur fractures ($n = 2$), and malignant transformation ($n = 1$). Blood Electrolyte disorders were reported in 50 patients and included Hypophosphatemia ($n = 26$) and Hypocalcemia ($n = 24$). New primary malignancy was reported by Ueda et al. in a single patient who was diagnosed with a Glioblastoma [18] and was reported to be related to the treatment received. Borkowska et al. [21] observed tumor progression to osteosarcoma 3 months after initiation of therapy, and malignant GCTB after 7 months of therapy, respectively. Roitman et al. [16] described one case of malignant transformation to undifferentiated pleomorphic sarcoma.

Histologic response to denosumab

Most studies included in this review have addressed the histopathologic changes between pre-treated and post-treated GCTB [6, 8, 9, 12, 14, 17–19, 21, 23–27]. Most of these studies have shown either complete absence of osteoclast-like giant cells [12, 21, 25, 27], or marked regression of those cells [6, 8, 17, 19, 26]. Reduction has also been reported in the tumor stromal/spindle cell population [8, 9, 13, 17, 21, 23, 25, 26], with a marked reduction in RANKL-positive

stromal cells [8, 17, 26]. However, there is no specific cutoff value that is related to a decreased recurrence rate.

With regards to the tumor matrix, most studies describe the presence of either reactive/woven bone formation or abundant collagenous matrix [6, 8, 9, 14, 16, 19, 21, 26, 27]. Several authors describe the deposition of trabecular collagen matrix and osteoid, maturing mostly at the peripheral portions of the lesion [14, 16, 19, 27].

Cellular proliferation index was analyzed in four of the studies [8, 14, 19, 27]. Three of those studies showed a significant decrease in the Ki67 cellular proliferation index [14, 19, 27].

Finally, several studies describe an inflammatory cellular component consisting of mononuclear cells, predominantly lymphocytes and histiocytes, in the background to varying degrees [16, 19, 27].

Post-treatment radiologic changes

Several studies addressed the radiologic changes following treatment with denosumab [6, 10, 12–16, 18, 20, 22, 23]. The radiologic changes described include: reduction in the tumor size [12, 14, 17, 20, 25], arrest in bone lysis with central sclerosis and new bone formation [15, 17, 20, 24, 25], peripheral bone formation [14, 16, 20, 25] and soft tissue components' shrinkage [15] which could be observed in about 66–100% of the patients [6, 15–18]. Also, Traub et al. observed that pathological fractures identified at the start of the study demonstrated complete healing during the course of medical treatment [17]. Other imaging modalities have been used to assess response to treatment such as PET-CT. Three studies evaluated the tumor response with this modality [6, 15, 22], and showed a reduction in FDG uptake. Palmerini et al. reported a decrease in the median SUVmax from 15 (range 4.1–18.3) at baseline to 3 (range 1.4–4.9) after 2 years of treatment, in 4 of the patients [15]. Boye et al. reported a reduction in SUVmax seen in 16 of 17 patients (94%), with a mean reduction of 5.6 (range 1.4–9.7) [22]. Thomas et al. suggested that PET may be a sensitive and early biomarker for clinical response in GCT of bone [6].

Clinical benefit of denosumab treatment

A significant reduction in pain under denosumab treatment was reported in seven studies [6, 13, 15, 17, 18, 23, 24] with reported improvement in 50–80% of the cases at 6 months in surgical cases [15, 17, 24], and 28–42% in cases were surgery was not possible [13, 23]. Additional improvement in function and mobility was reported by several authors [6, 17, 18, 24].

Only two studies reported improvement in musculoskeletal tumor society (MSTS) scores: Traub et al. reported an improvement from mean of 86 to 92 at latest follow-up, that was not statistically significant ($p = 0.37$) [17]. Deveci et al. reported an MSTS score of 87. However, the pre-treatment score was not reported [24].

Surgical planning

Several studies reported an alteration in the planned treatment due to denosumab treatment [14, 17, 20, 22, 23].

Muller et al. [14] showed that in 16 (64%) of their cases, in whom a resection of the involved bone or joint was indicated, the plan was changed after denosumab treatment, and 10 of them ultimately underwent intralesional curettage. In the other 6, the indication for a resection remained, although it was less invasive and easier to perform. Denosumab has led to an ossification of the soft tissue mass, facilitating the en-bloc resection.

Traub et al. [17] presented a series of 20 patients in whom joint salvage was either not possible or questionable. Following preoperative denosumab treatment, no patient required en-bloc resection. All 20 patients underwent intralesional resection preserving the anatomy of the involved bone, and in 18 cases the joint and articular surface were spared. The cases which initially demonstrated expanded and thinned cortical bone at diagnosis, which could be easily perforated with minimal pressure, were found to have thicker and better-quality bone at surgical resection. Joint preservation was not possible in only 2 of 20 (10%) patients. Rutkowski et al. [20] demonstrated that 38% of their patients had a less morbid procedure than originally planned, and high-morbidity procedures were avoided in 80% of the cases. Boye et al. [22] showed that in their six patients who had surgery, it was considered in three patients (50%) to be less extensive due to preoperative treatment.

Discussion

GCTB is an aggressive benign bone tumor that usually occurs during the second–fourth decades of life [6], with a female preponderance with high recurrence rates and potential morbidity due to bone destruction and joint involvement due to its location. Bone resorption follows the tumor activation via direct osteoclast activated with RANKL so denosumab could be used as neoadjuvant therapy or as an alternative to surgery in some cases [6, 8, 12, 13, 15, 21–24]. Most authors recommend 120 mg sc; however, number of doses, and loading dose have not been standardized yet, and the time of treatment varies between 4 months [24] and 55 months [19], depending on the tumor size and its location; however, this therapy is not complication free and the most common side effects reported are fatigue, muscle pain, arthralgias, extremity pain, and back pain, with others such as: headache, hypophosphatemia, hypercalcemia, and jaw

osteonecrosis [13, 18]. These findings must to be discussed with the patient to establish treatment and follow-up regimen with blood analysis and supplementation with calcium. Malignant transformation has been reported and should be kept in mind but still needs further studies to establish this as a proven fact.

It is well known that surgical treatment of GCTB has a recurrence rate of 15–45% [28, 29] and could even decrease to 2–14% when intralesional surgery is done using high-speed burr and bone-cement [30, 31]. However, there is controversy on whether the use of denosumab has any impact on the recurrence rates of surgically treated patients. Jamshidi et al. [32] performed a systematic review of the literature, and found a 2% recurrence rate in patient treated with denosumab and intralesional curettage. In this study, there were several flaws in the methodology followed to perform the systematic review making this study unlikely to be reproduced with questionable results. On the other hand, Errani et al. [33] recently published a retrospective study in which 25 patients with GCTB underwent curettage and neoadjuvant therapy with denosumab with a median follow-up of 42.1 months. The local recurrence rate was 60% (15/25 patients). In that study, the patients included as comparative cohort in which denosumab was not used were collected from a 24-year period of time in which different surgeons used different techniques. The group treated with denosumab was older, had more tumors in the distal radius (which is associated with a higher recurrence rate), had more Campanacci stage-III tumors, and phenol was used less frequently. All these findings made the cohorts that were comparatively very heterogeneous which potentially could made multivariable analysis unable to correct the influence of confounding factors. Because, there were substantial differences in the cohorts and randomization was not applied, causation could not be evaluated. It has been reported that with the use of denosumab there is deposition of trabecular collagen matrix and osteoid that could be seen in imaging studies as formation of new bone and during surgery as septum of bone which potentially could make the curetting process harder and leave residual tumor-impacting recurrence rates. In our study, we found a pooled weighted local recurrence rate of 9% which is comparable to previously reported recurrence rates using extended intralesional curettage. In our opinion, recurrence rate depends on tumor biological behavior and surgical technique used during treatment, and there is not enough evidence to suggest that denosumab could affect local control.

Even though GCTB is considered mainly as a benign neoplasia it has the potential to present metastatic disease to the lungs in less than 5% of the cases [5]. Some authors have claimed that local recurrence is a significant risk factor for lung metastases in patients with GCTB [34–36]. Rosario et al. reported a 7.5% rate of lung metastasis in their patients with GCTB and reported that local recurrence was the only multivariate predictor for the development of lung metastasis [35]. Wang et al. reported a 6.5% rate of lung metastasis in their patients with GCTB; the number of local recurrences was also an important multivariate predictor for lung metastases in their study, in addition to malignancy and tumor size [36]. There are studies that reported an increased rate of lung metastases for patients with advanced Campanacci or depending on the anatomic location [33, 37]. In contrast with local recurrence in which denosumab has been associated with potential risk for increasing its rate, there has not been found a correlation with increasing metastatic rate to the lungs [38]. Tsukamoto et al. described a retrospective study with 30 patients in which denosumab was administered and treated with surgery and a median follow-up of 85.2 months denosumab was not found as an important predictor of lung metastases in either univariate or multivariate analysis of variables; being the only important predictors for lung metastases the type of surgery and local recurrences [38]. In our study we found a pooled weighted metastases rate of 3% which correlates with the previously reported outcome and reflects a neutral effect on the metastatic rate.

Overall, the literature on adjuvant use of denosumab in the treatment of GCTB is lacking in both quality and quantity. The vast majority of studies are level IV evidence. An inherent limitation of this systematic review is the risk of selection bias because all included studies were not randomized. Homogeneity of the study population included in the studies was questionable in terms of tumor characteristics and surgical treatment. There was no control for inconsistencies in inclusion and exclusion criteria used by the authors of the included studies, though we did adhere to strict criteria when selecting the studies to be reviewed. Publication bias must also be considered when interpreting the reported results due to the known effect of statistical insignificance of primary research negatively impacting the likelihood of publication [39].

The strengths of our systematic review are the inclusion of the analysis of oncological outcomes (local recurrence and metastatic rates) that are under debate using a comprehensive and critical analysis to interpret their results, and a pooled weighted statistical analysis of studies presenting those results with low heterogeneity in publication bias analysis; also, the description of updated literature on histologic response, radiological changes, and clinical benefits including surgical planning. All of this, we believe will provide treating physicians in special orthopedic surgeons with the tools needed to better understand the role of denosumab in the treatment of these tumors. While aware of the limitations in this study, it is our opinion that 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.

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Compliance with ethical standards

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