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Research Article

Preoperative Denosumab is Associated with a Higher Risk of Local Recurrence in Giant Cell Tumor of Bone: A Systematic Review

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Abstract

Objectives: Giant cell tumors are locally destructive tumors that can cause loss of a limb at a young age. It is characterized by its high recurrence rate despite radical surgical removal. Denosumab was the first approved drug for the treatment of giant cell tumors and successfully decreased its morbidities, however, controversial reports suggested that preoperative Denosumab was associated with a high recurrence rate.

Methods: Six databases were searched using specific search terms. We included studies that assessed the recurrence rate after the removal of giant cell tumors in patients who received preoperative Denosumab. The studies were assessed for the quality of evidence using the NIH quality assessment tool before being included for the review.

Results: Ten studies fulfilled our inclusion criteria and had passed the quality assessment to be included for the qualitative evidence synthesis. Based on these studies, there was a high recurrence rate associated with the preoperative administration of Denosumab. The recurrence rate was not associated with the site nor the type of surgery. Besides, the duration of administration may affect the recurrence rate.

Conclusion: Preoperative denosumab is associated with a high recurrence rate, however, more studies are needed to assess factors influencing the recurrence rate and whether dosage and duration affect this rate.

Keywords: *Giant Cell Tumors; Denosumab; Recurrence; Epiphyseal Tumors; Tumors; Bone*

Introduction

Giant cell tumors constitute 5% of all tumors of bone and are considered benign tumors with a high potential of metastasis [1]. Their name is derived from giant cells which are macrophage cells that acquire osteoclastic activity which leads to increased bone resorption

[2]. It had a worldwide incidence of one to six patients every ten million persons annually [1]. They are often described as locally destructive tumors and are prevalent in the third and fourth decades of life and mostly in female patients [1]. The origin of giant cell tumors is located in the epiphysis of the bone; usually in the long bone. However, some cases were reported to be located at the metaphysis of the bone [3].

The tumor is locally destructive and aggressive, and is accompanied by local tissue destruction and a high rate of recurrence [4,5]. Usually, the patient is asymptomatic and suffers from a pathological fracture in the adjacent areas. Other patients suffer from pain, limited motion, swelling and some patient have a visible mass [3]. Also, some patients reported muscular or nerve pain. If left untreated, the giant cell tumors can cause deformities and loss of the limb [2,3]. Another evident phenomenon in giant cell tumors of the bone is pulmonary metastasis which, was evident in one to six percent of cases. The prognosis of these metastatic lesions is usually good, and some cases can be left untreated [6].

The grading of giant cell tumors follows one of two systems; either the Enneking staging classification, based on radiological, histological, and clinical features [7] or Campanacci grading that depends on the radiographic presentation of the tumor [8].

Complete removal of the tumor is the ideal treatment since the tumor has a high recurrence rate specifically in the distal radius and proximal femur [5]. Surgical treatment with wide excision margin is associated with decreased limb functionality and postoperative complications including pathological fractures and infections in 2 to 25% of patients [9-11]. Another technique is intralesional curettage, which is used widely for less aggressive tumors. Nevertheless, both techniques were associated with a high recurrence rate ranging from 20% in cases with cementation and 56% in patients without cementation [4,10,12,13].

Another less-favorable option is radiotherapy, as it is usually associated with malignant transformation [14]. In addition to previous treatment, embolization and laser photoablation are usually used in selected patients and has shown to be effective in decreasing the tumor size and associated morbidities [15,16].

After understanding the pathogenesis of the giant cell tumors, Denosumab was used as an adjuvant and medical treatment for giant cell tumors. It is considered the first drug to be accepted by the FDA for the treatment of the giant cell tumors [17-19]. The pathophysiology of giant cell tumors depends on stromal cell expression of RANK receptors, which are activated by RANKL, that is responsible for osteoclastic activity and survival. Furthermore, the osteoclastic activity will release growth factors into microenvironment increasing bone resorption [20].

Denosumab is a monoclonal antibody that binds to these receptors in giant cells preventing its osteoclastic activity and formation of new osteoclasts, thus decreasing bone resorption [21]. It is indicated in cases with unresectable tumors and when surgical treatment results in severe morbidity. In other cases, it was used as a preoperative to decrease pain, tumor size, and promote localization of the tumor making it easy for resection or curettage [17-19,21,22]. Notwithstanding, some studies indicated that it increases the recurrence rate after surgical removal [23,24].

In this study, we aimed to summarize the results of these studies to stand on the real efficacy of Denosumab in giant cell tumors and whether it should be used preoperatively or not.

Methods

Database search

A comprehensive search approach was used to identify randomized controlled trials from six databases: PubMed, Google Scholar, SCOPUS, ISI web of science, clinicaltrials.gov, and Cochrane Collaboration. The search terms used were ("Giant Cell Tumor of Bone" OR

"Giant Cell Tumors" OR "Gene Cell Tissue" OR "gct" OR "giant cell tumor" OR "giant cell tumors") AND ("denosumab"). We restricted our search to human studies.

Inclusion and exclusion criteria for screening

Specific inclusion criteria were used to identify high quality and studies that fulfill the goals of this study. Inclusion criteria are i) Randomized controlled studies that assess the efficacy of Denosumab in giant cell tumors of the bone. ii) Case-control studies that compare the recurrence rate between Denosumab and any other treatment. We excluded case reports, case series, any descriptive studies without a control group, books, review articles, letters to the editor, editorial reports, and conference abstracts and duplicates were excluded.

Screening for studies

The retrieved studies from each database were screened based on inclusion and exclusion criteria. First, title/abstract screening was conducted by three independent reviewers. The included studies were then screened thoroughly to make sure it fulfilled the target of this review. Each study was reviewed thoroughly to extract and build a qualitative review.

Quality assessment of the included papers

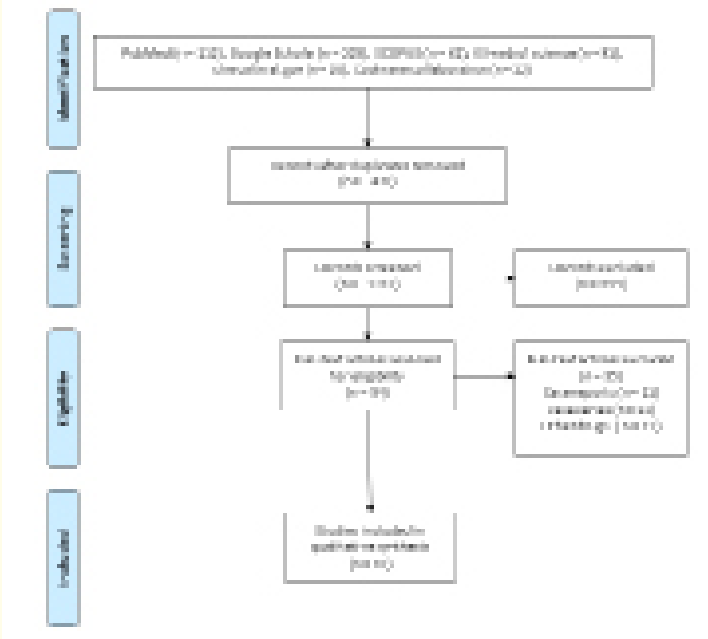
The quality of the included studies was evaluated by three reviewers using the NIH quality assessment tool that has 13 domains assessing the quality of evidence in different study designs including the cohort studies. Table 1 illustrates the 13 domains and possible answers. Two reviewers assessed the quality of each study and any disagreement was solved through discussion with the third reviewer.

Domains	Yes	No	Other (CD, NR, NA)
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Results

Search results

The search performed on six databases yielded 512 studies, of which, only ten studies fulfilled the inclusion criteria and were used for qualitative evidence synthesis (Figure 1).



Risk of bias

All studies had a good quality except for three studies due to low numbers of cases compared to control, and all studies did not report the loss to follow-up (Table 2).

ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Agarwal/2018 [25]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	NA	No
Chen/2020 [23]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	NA	No
Errani/2010 [30]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	NA	No
Medellin/2018 [26]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	NA	No
Scoccianti/2018 [24]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	NA	No
Tsukamoto/2019 [27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Urakawa/2018 [22]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	NA	No
Yang/2018 [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Zou/2019 [11]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	NA	No

1. Was the research question or objective in this paper clearly stated?														
2. Was the study population clearly specified and defined?														
3. Was the participation rate of eligible persons at least 50%?														
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?														
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6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?														
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?														
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?														
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12. Were the outcome assessors blinded to the exposure status of participants?														
13. Was loss to follow-up after baseline 20% or less?														
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?														

Table 2: *The NIH quality assessment results.*

Patient characteristics

The included studies had 168 patients treated with Denosumab, the studies assessed the efficacy of the Denosumab in giant cell tumors of bone. One of the outcomes assessed is the recurrence rate and postoperative outcome. All studies used histopathology for confirmation of the diagnosis in table 3. Three studies assessed the giant cell tumors in the trunk. Four studies assessed the efficacy of Denosumab in both trunk and extremities. Only four studies used curettage as a treatment for the giant cell tumors in table 3. For the grading system, all studies used Campannaci grade. Only four studies reported side effects related to the Denosumab [23,25-27]. The dose of Denosumab was similar in all studies and was administered subcutaneously.

Study	Study design	Country	Site	Number of cases	Number of controls	Follow-up (years)	Surgery
Agarwal/2018 [25]	Case control	India	Extremity and trunk	25	34	Up to two years	Curettage and resection
Chen/2020 [23]	Retrospective cohort studies	China	Trunk	20	10	Up to three years	Resection
Errani/2010 [30]	Retrospective cohort studies	Italy	Extremity and trunk	25	222	More than two years	Curettage
Liu/2016 [29]	Retrospective cohort studies	China	Extremities	2	4	Eight months	Curettage
Medellin/2018 [26]	Case control	UK	Extremity	7	100	One year	Curettage and resection
Scoccianti/2018 [24]	Prospective cohort studies	Italy	Extremity and trunk	12	9	Eight years	Curettage
Tsukamoto/2019 [27]	Case control	Japan	Extremity and trunk	25	317	Eleven years	Curettage and resection
Urakawa/2018 [22]	Retrospective cohort study	Japan	Extremity and trunk	40	158	Six years	Curettage
Yang/2018 [28]	Case control	China	Trunk	6	10	More than two years	Curettage and resection
Zou/2019 [11]	Case control	China	Trunk	8	50	27 years	Curettage and resection

Table 3: *Characteristics of the included studies.*

Effect of preoperative denosumab on local recurrence in giant cell tumors

Agarawal., *et al*. found that there was no increased risk of recurrence of giant cell tumors. However, they advised using it cautiously [25]. Medellin., *et al*. investigated the effect of Denosumab in giant cell tumors in extremities with fractures. Denosumab was beneficial in these patients with fractures as it was associated with the consolidation of the peripheral rim facilitating the curettage. They found that 25% of cases had local recurrence and found that Denosumab increased the risk of recurrence three times compared to cases with no treatment with curettage [26]. In a multi-center study performed by Urakawa et al. they revealed that preoperative Denosumab in

curettage procedures had increased risk of local recurrence. The recurrence rate was highly dependent on Campanacci grade; the higher recurrence rate was observed with higher grades. They found that embolization before the procedure increased the risk of recurrence. It was explained that this may be related to the indication for embolization before the tumor. Usually, embolization is indicated in the case of the large and vascular tumor to avoid the risk of bleeding. Another risk factor was the site of the tumor, there was no difference in risk of local recurrence whether the tumor in extremities or the trunk. Moreover, they also found that the dose and duration of administration significantly affected the risk of recurrence. The higher the dose and duration, the lower the risk of local recurrence was. In addition to the previous results, Tsukamoto et al. found that Denosumab did not increase the risk of metastasis, in particular, lung metastasis [27]. Many other studies concluded that the increased risk of lung metastasis in patients treated with Denosumab was associated with a high recurrence rate. Tsukamoto., *et al*. refuted this claim as they also suggested that Denosumab was not significant predictor in univariate risk analysis and other factors including grade and age were significant predictors [27].

Yang., *et al*. investigated the efficacy of Denosumab in a more concentrated study; population of giant cell tumors in sacral bone. They found that the Denosumab increased the risk of local recurrence because it increased the bone sclerosis and bony separation, which will result in increasing the difficulty of the curettage. There was specific difficulty during the separation of the tumor from the sacral nerve [28]. However, the risk will decrease with a more careful study of tumor extent, and proper selection of the surgery timing during the treatment. The benefits of Denosumab treatment were decreased pain and improved function after tumor removal. It also decreased intraoperative blood loss, but it did not affect the intraoperative time [28]. They found that the new osseous matrix hides the tumor cells and made it hard for the surgeons to mark the boundaries of the tumors. They recommended that the surgeons should remove the tumor based on the initial presentation not after the Denosumab treatment as the old boundaries are more accurate. They also found a higher recurrence rate in sacral giant cell tumors due to the difficulty of extensive curettage unlike extremities [28]. A similar study found that preoperative Denosumab significantly enhanced motor, sensory, bladder incontinence, constipation, and bowel dysfunction in patients with giant cell tumors in the sacral region. Also, treated cases had more pain relief and fewer complications. Moreover, the incidence of recurrence was very low in this study [19].

In contrast to the previous studies, Scoccianti., *et al*. found that there was no difference between groups treated with Denosumab and those who did not. They found that Denosumab treatment was associated with peripheral rims saving the patients from radical procedures. Peripheral rim facilitated the curettage and preserved the limb or joint to the patient, that is why, it was recommended in younger patients [24].

Zou et al. investigated the management of giant cell tumors in the distal radius including the administration of pre-operative Denosumab. They found that it was not associated with a higher risk of local recurrence. Notwithstanding, it was associated with dramatic tumor suppression, pain reduction, and easier curettage.

Another study with limited evidence is a study of Liu et al. which was performed on six patients and they did not find a significant increase of local recurrence in patients receiving preoperative Denosumab [29]. The study had a small sample size and its results should be interrupted cautiously.

Type of surgical intervention and recurrence of giant cell tumors

Medellin., *et al*. found that the high risk of recurrence was more evident in the cases treated with curettage. They also found that patients with fractured Campanacci stage III tumors, total resection had a better outcome even after Denosumab [26]. Other studies found a similar risk of recurrence in any type of surgery.

Factors affecting the efficacy of denosumab

Based on Urakawa., *et al*. findings, they found that the cost of the treatment in Japan significantly affected the prescription and commitment to a larger dose and longer duration of the drug. They found that the risk of recurrence increased with smaller doses and shorter duration. Unfortunately, other studies did not investigate other factors.

For the dosage, all studies administered Denosumab subcutaneously once a month in a dosage of 120 mg per injection, but duration differed between the studies. Unfortunately, the duration of administration was not assessed as one of the factors affecting the risk of recurrence in giant cell tumors patients.

Recurrence-free survival

Based on our review of the included population, there was a very high risk of recurrence. Thus, Denosumab has a very low recurrence-free survival.

Side effects of denosumab

One of the observed complications in the treated groups was a malignant transformation in the recurrent tumor [19,25]. Medellin., *et al*. had observed a longer preoperative time is needed before deciding to perform surgery [26]. Tsukamoto., *et al*. reported jaw-related side effects mainly periodontal abscess. Other studies did not report any side effects related to Denosumab [27].

Two studies performed teeth check, renal function, and serum calcium level before the administration of Denosumab [24,25]. Four studies administered vitamin-D and calcium before the Denosumab administration to avoid any side effects [24,25,27,30].

Conclusion

Based on studies included in this review, preoperative Denosumab was associated with a high recurrence rate of giant cell tumors. However, we believe that a more careful assessment of other factors like duration, the dosage of administration, and careful surgical removal of the whole tumors may change the recurrence rate as it was reported in these studies that Denosumab successfully reduced tumor size, pain, vascularity, and associated morbidities.

Recommendation for Future Work

The duration of administration of Denosumab should be assessed as one of the factors affecting the recurrence rate. Also, one of the included studies suggested that the tumor should be removed using the old boundaries before Denosumab administration as this part of the tumors contain hidden tumor cells that contribute to the recurrence rate. We believe that this is an important suggestion that should be investigated thoroughly.

Conflict of Interest

None.

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