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Review Article

Effects of Neoadjuvant Denosumab on Radiological and Histological Responses in Patients Undergoing En Bloc Resection for Giant Cell Tumor of Bone: A Systematic Review

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ABSTRACT

Background: Giant cell tumor of bone (GCTB) is a rare primary bone tumor. The standard treatment is en bloc resection, which can be challenging due to tumor size or location. Denosumab, a monoclonal antibody, has emerged as a promising neoadjuvant therapy for GCTB, potentially facilitating surgical resection. However, its optimal use remains unclear, with debate surrounding its impact on local recurrence. This systematic review aims to synthesize evidence on the histological and radiological changes induced by neoadjuvant denosumab and its impact on surgical outcomes.
Methods: This review followed PRISMA guidelines. The medical term "denosumab", "neoadjuvant", "GCTB", "radiological", and "histological" were used in PubMed (423 articles) and Google Scholar (18,100 articles), totaling 18,523 articles to discover studies of the effect of neoadjuvant denosumab on radiological and histological response up to July 2023. Six remaining studies were reviewed and screened for inclusion criteria based on their relevance to the study subject and clinical outcomes.
Results: Based on six studies in this review, five showed histological response by decreasing the multinucleated giant cells and osteoclasts after neoadjuvant DT. Six studies showed increased significant bone reconstitution as a radiological response in the GCTB locale, replaced the extending tumor into soft tissue by abundant bone production with peripheral shell, and increased ease of en bloc resection.
Conclusions: Neoadjuvant denosumab therapy shows promise in managing giant cell tumors of bone (GCTB) by reducing osteoclasts, shrinking tumor volume, and promoting cortical bone formation, thus facilitating en bloc resection. However, further research is needed to confirm these findings.

Keywords: Cancer; Denosumab; Giant cell tumor of bone; Human and medicine

INTRODUCTION

Giant cell tumor of bone (GCTB) is a rare, locally aggressive primary bone tumor that typically affects the epiphysis of long bones in young adults. Although considered benign, GCTB can exhibit aggressive behavior, including local recurrence and, in rare cases, metastasis.[1] The current standard treatment for GCTB is en bloc resection, with the goal of achieving complete tumor removal to minimize the risk of local recurrence. However, en bloc resection can be challenging, particularly in cases where the tumor is large or involves critical anatomical structures.[2]

In recent years, denosumab, a monoclonal antibody that inhibits osteoclast activity, has emerged as a promising neoadjuvant therapy for GCTB. Several studies have demonstrated that

neoadjuvant denosumab can induce significant tumor necrosis and bone formation, potentially facilitating surgical resection and improving patient outcomes.[2] However, the optimal use of denosumab in the context of GCTB treatment remains to be fully elucidated.

While denosumab's use in cases of advanced, unresectable disease is well known, its use in cases of surgically treatable disease is still up for debate.[3] Giant cell tumor of the bone progression has been proven significantly inhibited by denosumab.[4] Recent research has raised questions about using denosumab in conjunction with surgery to treat GCTB since it may increase the chance of local recurrence after surgery.[5] However, denosumab can also facilitate complete en bloc tumor removal and lower the risk of surgical complications by causing an extraosseous tumor to shrink.[6]

Despite the potential benefits of denosumab, details on the histological and radiological changes induced by neoadjuvant denosumab treatment (DT) for GCTB remain unknown. This systematic review aims to address this gap in the literature by synthesizing the available evidence on the histological and radiological changes induced by neoadjuvant denosumab and their impact on surgical outcomes.

METHODS

Data Collection

This systematic review adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for literature searching. PubMed and Google Scholar databases were consulted to identify relevant studies published up to July 2023. The search strategy employed a combination of medical terms including "denosumab," "GCTB" (Giant Cell Tumor of Bone), "radiological," and "histological" to capture studies investigating the impact of neoadjuvant denosumab therapy on radiological and histological responses in GCTB. The search was limited to original studies and case reports that specifically reported on both radiological and histological outcomes following denosumab treatment. Two independent reviewers meticulously screened the identified articles, excluding review articles and clinical studies that were deemed irrelevant to the research question. This initial screening process resulted in a selection of six studies that were further evaluated for inclusion based on their relevance to the study objective and the presence of pertinent clinical outcomes (Figure 1).

Screening Process

The initial search using the defined keywords yielded a substantial number of articles from both databases, with Google Scholar providing 18,100 items and PubMed providing 423, totaling 18,523 articles. The initial screening involved a thorough review of titles and abstracts, which effectively narrowed down the pool to 350 potentially relevant papers. Subsequently, a full-text review was conducted by the researcher to assess the eligibility of these articles. A significant number of articles (340) were excluded during this stage due to their lack of adherence to the predefined inclusion criteria. The remaining 10 articles underwent a rigorous evaluation, leading to the exclusion of 4 more studies that did not meet the necessary prerequisites. Finally, 6 studies were deemed suitable for inclusion in the final analysis based on their reported outcomes and direct relevance to the research topic.

Inclusion and Exclusion Criteria

This literature review specifically focused on studies evaluating the efficacy of denosumab in the treatment of GCTB. Notably, no randomized controlled trials were identified during the search. To provide a comprehensive overview of the available evidence, the review encompassed various study designs, including case reports, case series investigations, and non-ran-

domized, uncontrolled studies, all assessing the radiological and histological responses to denosumab treatment in GCTB patients.

To be included in the analysis, studies had to fulfill the following criteria: (a) Report on the treatment outcomes of denosumab, specifically focusing on histological and radiological responses that facilitated en bloc resection, (b) Clearly specify the location of the tumor, (c) Detail the surgical en bloc resection procedure performed, (d) Document any side effects associated with denosumab treatment, (e) Indicate the duration of denosumab treatment, and (f) Provide information on the duration of follow-up after treatment.

Studies were excluded from the review if they met any of the following criteria: (a) Involved non-human subjects, (b) Were review articles, meta-analyses, or clinical studies irrelevant to the primary research question, (c) Did not explicitly mention the use of denosumab for treating GCTB, (d) Focused on other diseases

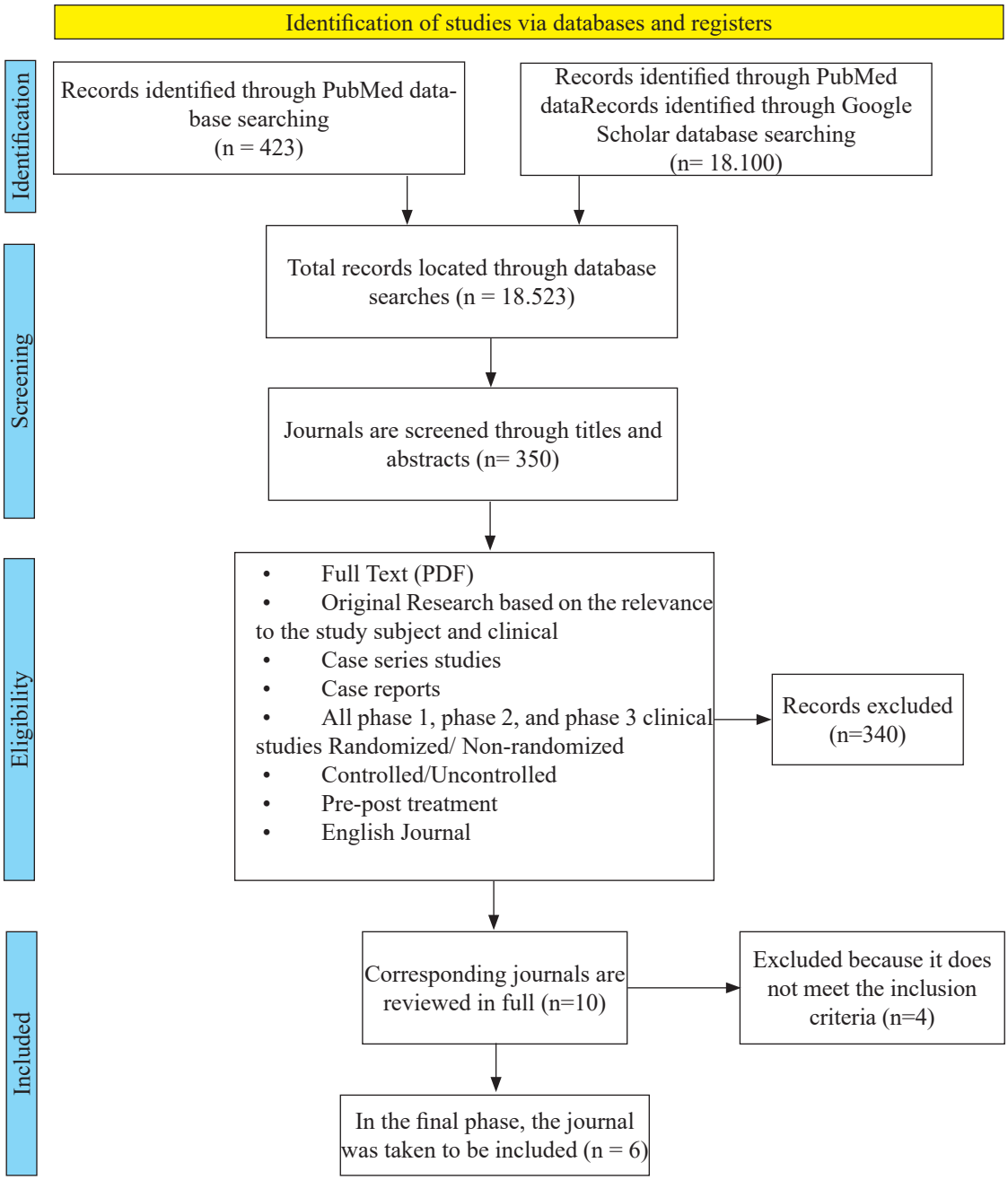

Figure 1. PRISMA Flowchart

or interventions, and (e) Were published in unknown or unreliable databases.

Data Extraction and Synthesis

Two researchers independently extracted data from the included studies to ensure accuracy and minimize bias. The extracted data encompassed key trial characteristics and relevant outcomes, including histological and radiological responses, tumor characteristics, surgical details, and any reported adverse events. The analysis of the extracted data revealed consistent findings across the included studies. Five studies demonstrated a significant decrease in multinucleated giant cells and osteoclasts following neoadjuvant denosumab therapy, indicating a positive histological response. Furthermore, five studies reported substantial bone regeneration around the giant cell tumor, new ossification, the replacement of tumor extension into soft tissue with prolific bone production and a peripheral shell, and overall improved feasibility of en bloc excision. These findings collectively highlight the potential benefits of denosumab in the neoadjuvant setting for GCTB.

RESULTS

Based on the six studies included in this review, five showed a histological response to neoadjuvant denosumab therapy, as evidenced by a decrease in multinucleated giant cells and osteoclasts. All six studies demonstrated significant bone reconstitution around the giant cell tumor (GCTB) site, including new ossification, replacement of tumor extension into soft tissue by abundant bone production with a peripheral shell, and increased ease of en bloc resection. These findings can be seen in Table 1.

Across the six studies, key findings consistently demonstrated positive responses to neoadjuvant denosumab therapy. For instance, a study by Tang et al. showed a decrease in multinucleated giant cells in 60% of patients, a return of cortical integrity in five patients, and new ossification in nine cases. Din, Umer and Park, revealed a complete absence of osteoclast-like giant cells in 13 cases. Similarly, a study by Yonezawa et al. showed a noticeable decrease in large cells across all four patients. Tepper et al. and Apostolopoulos and Mahdal both reported successful tumor resection with histological evidence of reduced giant cells and osteoclasts following denosumab treatment. Bukata et al. observed significant bone reconstitution and tumor reduction in spinal GCTB. These findings indicate that neoadjuvant denosumab therapy can induce positive histological and radiological responses in GCTB, facilitating en bloc resection and potentially improving patient outcomes.

DISCUSSION

Six studies were relevant to this study. Five of the six studies included demonstrated a histological response, showing a reduction in osteoclasts and multinucleated giant cells following neoadjuvant denosumab therapy. GCTB are often composed of RANK-positive circular mononuclear cells, "reactive" rich multinucleated large cells, and "neoplastic" densely cellular spindled cells, along with RANKL-positive tumor cells with stromal characteristics, a scant osteoid matrix, and woven bone. Overexpression of RANKL by stromal cells not only aids in the formation of multinucleated giant cells that resemble osteoclasts but also encourages the recruitment of monocyte precursors. Denosumab exhibits greater specificity and affinity to RANKL compared to RANK. Overexpression of RANKL by stromal cells not only aids in the formation of multinucleated giant cells that resemble osteoclasts but also encourages the recruitment of monocyte precursors. Denosumab exhibits greater specificity and affinity to RANKL compared to RANK.[15,16] In response to the significant role of the RANK/RANKL pathway in GCTB pathogenesis, denosumab was de-

Table 1. Study of the effect of neoadjuvant denosumab toward its outcome

No	Study	Intervention (Comparison N/A)	Subject	Follow-up	Clinical Outcome			Adverse Events/ Recurrence
					Histological response	Radiological response	En Bloc Resection	
1.	Tang et al., 2023[7] (Retrospective study)	Neoadjuvant DT before surgery 3-5 doses (120 mg) SC (D1, D8, D15, D28 and monthly)	Spinal GCTB n=10	3-4 months	Six patients (60%) had a decrease in multinucleated large cells, while four cases showed none at all.	Five patients saw the cortical integrity return, while nine cases showed fresh ossification. In 4 cases, there was a soft tissue mass reduction of more than 10%.	enable en bloc spondylectomy by hardening the tumor and reducing adherence to nerve roots, major arteries, and segmental vessels..	No tumor collapsed or broke during surgery, and no patient's neurologic function deteriorated as a result. During the average follow-up of 24 ± 20 months, no tumor recurrence was noted. After receiving monthly denosumab treatment, one patient with preoperative lung metastases had stable lung lesions.
2.	Din at al., 2020[8] (Pre-post Study)	Neoadjuvant DT before surgery 3-5 doses (120 mg) SC every 2 weeks	Tibia/Femur/Radius GCTB n=19	3-4 months	In 13 cases, OCLGCs were completely absent. The remaining 6 instances all had persistent giant cells, which could have been rare or as much as 25% of the tumor. In each of the 19 cases, a fibro-osseous component combined with a periphery of reactive bone.	The extensive bone development with peripheral shell has taken the position of the tumor that extended into soft tissue.	The radiological response facilitates easy surgery that allows for full excision of the tumor with no residual disease.	At the time of the latest recent follow-up, every patient who was still alive was free of recurrence and/or metastasis.

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3.	Yonezawa et al., 2019[9] (Case Series)	Neoadjuvant DT before surgery (120 mg) SC 1-10 cycles	Spinal GCTB n=4	66 months	All patients had a noticeable decrease of large cells. There were a few multinucleated giant cells found in patient 2, but none were found in patients 1, 3, or 4. Patients 2, 3, and 4 displayed a highly cellular tumor with localized bone development in the stroma's back ground. In patient 1, the tumor had less cells and was gradually dominated by newly produced woven bone at the excised vertebra's peripheral lesion. Stromal cells that were RANKL-positive were seen in all cases.	After DT, the amount of osteolytic tumors and the height of the vertebral bodies decreased in all patients. 18.8% was the average percentage of osteolytic tumor volume reduction.		There were no postoperative drug-related adverse effects in patients 1, 3, or 4. Patient 2 on the other hand, began to have hypocalcemic tetany a day after the surgery. None of the patients acquired DT following surgery. At the final check-up, all patients were doing everyday tasks properly and there was no sign of a local recurrence or distant metastases.
4.	Tepper et al., 2022[10] (Case Report)	Neoadjuvant DT before surgery (120 mg) SC/ 1 week (3 weeks) followed 1/ month (2 months)	Proximal fibula GCTB n=1	6 months	On an H3.3 G34W immunostaining, fibrotic appearance and a lack of large cells and osteoclasts were noticed.	After finishing denosumab, computed tomography pictures of the left lower extremity show considerable bone reconstruction in the location of the giant cell tumor of the bone.	In the present case, neoadjuvant denosumab was administered before en bloc resection to solidify the tumor and make excision easier.	In the present case, neoadjuvant denosumab was administered before en bloc resection to solidify the tumor and make excision easier. At the 6-month checkup, there was no sign of recurrence.

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5.	Apostolopoulos and Mahdal, 2023[11] (Case report)	Neoadjuvant DT before surgery (120 mg) SC/ 4 weeks (3 months) 2 loading doses in the first month	Proximal ulna GCTB n= 1	24 months	The resection was successful, as evidenced by the final histology report, which revealed that the bone that was removed had completely lost all of its osteoclasts.	The CT scan and X-rays after the neoadjuvant therapy indicated a calcified rim enclosing the soft tissue component	The use of denosumab improved tumor grading, enabling a secure full excision.	The radiography scans showed no indications of aseptic loosening or a local recurrence of the tumor three years after surgery.
6.	Bukata et al., 2021[12] (Open lable study, Phase 2)	Neoadjuvant DT before surgery (120 mg) SC/ 4 weeks (3 months) 2 loading doses in the first month (Median DT Dose 11.5 (9.0–17.0) months	Cohort 1,2,3 (n=132) Cohort 2 Spinal or Sacrum GCTB N=24 Only n= 10 underwent surgery	60 months		On spinal GCTB, the cortex is rebuilt around the entire lesion and internal mineralization is present. The canal on the sacrum has no more tumors. The axial sacral canal has rebuilt. The bulk of the anterior soft tissues is less. The promontory has started to calcify.	10 patients from cohort 2 received surgery. One patient out of ten (10%) who underwent total surgical resection experienced a disease recurrence.	After on-study surgery, one patient in ten (10%) experienced recurrence, while 86% of patients, on average, had no progression or recurrence after two years.

Abbreviation: DT, Denosumab Therapy; SC, Subcutaneous (injection); D1, Days one; GCTB, Giant Cell Tumor of Bone; OCLGCs,Osteoclast-Like Giant Cells

veloped as a fully human monoclonal antibody against RANKL. According to the US Food and Drug Administration (FDA) and the European Medicines Agency, denosumab is the only drug approved as neoadjuvant therapy for unresectable advanced GCTB or when surgical resection is anticipated to result in severe morbidity.[15]

Histological analyses revealed varying degrees of response to neoadjuvant denosumab therapy. Tang et al. reported that 60% of patients exhibited a complete absence of multinucleated giant cells, while 80% showed mononuclear stromal cells and new bone growth.[7]

According to histological analysis, Tang et al. reported that compared to the other four cases, six patients (or 60%) had no multinucleated giant cells, but multinucleated giant cells were present in the other four cases. Mononuclear stromal cells, however, were seen in eight cases (or 80% of the patients). New bone growth was seen in 8 cases (80%) of the time.[7] Din et al. observed a complete absence of osteoclast-like giant cells (OCLGCs) in 68% of cases, with the remaining cases showing remnant giant cells comprising up to 25% of the tumor. All 19 cases in their study presented with a fibro-osseous component that merged with a peripheral shell of reactive bone.[8] Yonezawa et al. demonstrated a depletion of giant cells in all four patients, with a few multinucleated giant cells observed in one patient. In this study, patients 2, 3, and 4 displayed a highly cellular tumor with localized bone development within a highly cellular stroma. In contrast, patient 1 exhibited a less cellular tumor progressively dominated by newly produced woven bone at the peripheral lesion of the resected vertebra.[9] Tepper et al. showed that following neoadjuvant DT, the resected specimen had a fibrotic appearance, and immunostaining revealed no giant cells or osteoclasts.[10] Apostolopoulos and Mahdal demonstrated that neoadjuvant DT prior to en bloc resection resulted in adequate resection, with the final histology report indicating a complete absence of osteoclasts in the resected bone.[11]

All six studies in this review demonstrated radiological responses to neoadjuvant denosumab therapy, characterized by significant bone reconstitution in the area of the GCTB, induced new ossification, and replacement of tumor extension into soft tissue by abundant bone production with a peripheral shell. Tang et al. reported that after neoadjuvant DT, new ossification was observed in nine cases, and five cases showed a reappearance of cortical integrity. The values of Hounsfield units (HU) of the soft tissue component increased by more than 50% in seven cases, and shrinkage of the soft tissue mass by more than 10% was observed in four cases.[7] Similarly, Din et al. reported that post-denosumab therapy X-rays showed extensive bone development with a peripheral shell that replaced the tumor that had extended into soft tissue.[8] Yonezawa et al. observed a decrease in vertebral body height and the amount of osteolytic tumor in all patients following DT. They noted that if the damaged vertebrae are largely composed of osteolytic lesions, the tumor shrinkage effect of DT may increase mechanical stress on the delicate cortical rim, potentially causing the abrupt collapse of the affected vertebral body. However, they suggested that sufficient anterior cortical bone might prevent acute vertebral collapse following DT.[9] In the study by Tepper et al., computed tomography images of the left fibula showed significant bone reconstitution in the area of the GCTB following a regimen of 120 mg subcutaneous neoadjuvant DT administered once monthly for two months and once weekly for three weeks.[10] Apostolopoulos and Mahdal showed that after three months of neoadjuvant DT, CT scans and X-rays revealed a calcified ring enclosing the soft tissue component. The dosage regimen consisted of a 120 mg Xgeva subcutaneous injection every four weeks, along with two loading doses in the first month of treatment.[11] Bukata et al. reported reconstitution of the cortex around the entire lesion with internal mineralization in a patient with spinal GCTB after neoadjuvant DT.

In a patient with sacral GCTB, the canal was tumor-free after neoadjuvant DT, and the axial sacral canal had reconstituted. Additionally, the anterior soft tissue mass was smaller, and the promontory was partially calcified.[12]

The aims of neoadjuvant denosumab therapy for en bloc resection are to increase tumor firmness, reduce soft tissue mass, and decrease tumor blood supply, which may lead to reduced blood loss and better management of surgical dissection.[16] Five out of six studies in this review demonstrated that neoadjuvant DT facilitates en bloc resection.

Tang et al. reported that neoadjuvant DT facilitates en bloc spondylectomy by hardening the tumor and reducing adhesion to segmental vessels, major vessels, and nerve roots.[7] Tepper et al. reported that neoadjuvant DT enabled easier surgical resection and less morbid procedures.[10] Yayan et al. showed that en bloc resection after neoadjuvant DT allowed complete tumor removal, leaving no residual tumor cells. Neoadjuvant DT is becoming more commonly recognized as a neoadjuvant treatment in the spine, where en bloc resection is the preferred treatment when acceptable morbidity is expected.[17] Din et al. showed that abundant bone production with a peripheral shell replaced the tumor extending into soft tissue after neoadjuvant DT, making surgery easier and resulting in complete tumor removal with negative margins.[8] Similarly, Tepper et al. reported that neoadjuvant DT facilitates en bloc resection and permits acceptable functional outcomes in select cases by promoting cortical bone formation and mitigating GCTB symptoms.[10] Denosumab therapy, as revealed by Apostolopoulos and Mahdal, improved tumor grading and permitted secure total resection.[11] Bukata et al. reported that all 10 patients achieved complete surgical resection after neoadjuvant DT, after which one patient (10%) experienced disease recurrence.[12]

Neoadjuvant denosumab can promote en bloc resection and intralesional curettage by developing a calcified rim around the tumor and its soft tissue component. However, many studies have shown that the most common adverse event in long-term follow-up is local recurrence, especially with curettage procedures following neoadjuvant denosumab compared to en bloc resection or curettage without neoadjuvant therapy. In five of the six studies reviewed, there was no sign of recurrence at the time of the last follow-up. Tang et al. showed no tumor recurrence within a mean follow-up of 24 ± 20 months.[7] Din et al. reported that all remaining patients in their study were free of recurrence and metastasis at the last follow-up.[8] Yonezawa et al. reported that three out of four patients experienced no postoperative drug-related adverse effects; however, one patient experienced hypocalcemic tetany the day after the procedure. None of the patients received postoperative DT. At the final checkup, all patients were performing daily tasks regularly, and there was no sign of local recurrence or distant metastases.[9]

After 6 months of follow-up, Tepper et al. reported that the patient was ambulating without assistance and had no radiological signs of recurrence. The patient had no issues with daily living tasks at 18 months after surgery and reported no pain, radicular symptoms, or functional restrictions.[10] Apostolopoulos and Mahdal reported a Musculoskeletal Tumor Society functional score of 27 at the most recent checkup, 3 years after surgery, with the patient achieving complete elbow extension, 120 degrees of elbow flexion, and 75 degrees of supination and pronation. Radiography findings revealed no indications of aseptic loosening or local recurrence of the tumor. The patient regained almost complete use of all extremities, although heavy lifting and participation in sports involving the arms were prohibited.[11] Bukata et al. reported that back pain (49%) and fatigue (31%) were the two most frequently reported treatment-emergent adverse events (TEAEs). Serious TEAEs occurred in 36% of patients and were related to the treatment

in 11.4% of those cases.[12] In earlier investigations, Campanacci et al. reported that curettage was used after denosumab in 74% of patients, and resection was used in 26%. Patients who underwent intralesional curettage had a greater local recurrence rate than those who underwent en bloc resection (55.1% vs 0%, p = 0.001).[18] The fact that no signs of local recurrence were discovered at the 1-year follow-up following gross total excision and postoperative DT is pertinent to earlier investigations. The length of preoperative care ranged from 3 to 24 months. The en bloc resections were followed by no local recurrence.[19]

This review has identified several important avenues for future research on the use of denosumab in treating GCTB. A key priority is the need for randomized controlled trials to provide more robust evidence for the efficacy and safety of denosumab compared to other treatment options. This would involve randomly assigning patients to receive either denosumab or a control intervention, allowing for a clearer assessment of treatment effects. In addition, longer follow-up periods are crucial to evaluate the long-term effects of denosumab, particularly the risk of recurrence. Future research should incorporate extended follow-up durations to assess the lasting impact of denosumab on local recurrence rates, distant metastasis, and functional outcomes. It is also essential to address limitations identified in the current literature, such as potential bias and inadequate reporting, by implementing standardized reporting guidelines and ensuring complete data collection. Larger sample sizes and multicenter collaborative studies would increase the statistical power and generalizability of future research. Finally, further investigation into optimal denosumab dosing regimens and treatment durations for different GCTB subtypes and patient populations is warranted to personalize treatment approaches. By addressing these gaps, future research can contribute to a more comprehensive understanding of denosumab's role in managing GCTB and ultimately improve patient outcomes.

CONCLUSIONS

Neoadjuvant denosumab therapy demonstrates promising potential in the management of giant cell tumors of bone (GCTB). This review of available studies indicates that denosumab effectively reduces osteoclasts and multinucleated giant cells, shrinks tumor volume, and promotes cortical bone formation. These effects collectively contribute to facilitating en bloc resection by hardening the tumor and minimizing adhesion to surrounding structures. While these findings are encouraging, further research, particularly randomized controlled trials with longer follow-up periods, are needed to definitively establish the efficacy and safety of neoadjuvant denosumab in the treatment of GCTB and optimize treatment strategies for diverse patient populations..

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