Functional Outcomes of Limb Salvage Surgery in Patients with Giant Cell Tumor of Bone of the Lower Extremities: A Cross-sectional Comparative Study

Daniela Kristina D. Carolino, MD and Abigail R. Tud, MD-MBA

Philippine Orthopedic Center Musculoskeletal Tumor Service

ABSTRACT

Background and Objectives. Giant cell tumor of bone (GCTB) is a benign aggressive tumor primarily treated with surgery. Neoadjuvant treatment with denosumab or zoledronic acid is a common adjunct given to down-stage tumors and facilitate limb sparing surgery. This study sought to determine the characteristics, outcomes, and occurrence of complications following resection (RS) or extended curettage (EC) for GCTB of the lower extremities. Correlation of neoadjuvant therapy with the occurrence of complications was also investigated.

Methods. This is an analytical cross-sectional study of 30 patients diagnosed with GCTB of the lower extremity treated between 2015 to 2022 in a single tertiary hospital. Functional outcomes were determined using the 1993 version of the Musculoskeletal Tumor Society (MSTS) score. Mean follow-up for all patients was 2.6 years (SD 1.8). Twenty-two patients (73%) underwent resection, while eight (27%) patients underwent extended curettage. Of the 30 patients, 26 (87%) patients received neoadjuvant therapy, with 21 (81%) given denosumab and five (19%) given zoledronic acid.

Results. Functional outcomes were excellent for 23 patients (77%), with no significant difference between RS and EC groups. Nine complications occurred in the RS group, including dehiscence (n=3), superficial infection (n=2), implant failure (n=1), nonunion (n=1), palsy (n=1), and implant irritation (n=1). Five complications occurred in the EC group, four of which were noted to be recurrences, with one case of deep infection. Recurrence was noted to be significantly higher (p=0.0004) in the EC group. Separate correlation analysis showed no significant difference in incidence of complications but found that duration of surgery was significantly longer (p=0.0001), and intraoperative blood loss was significantly higher (p=0.0072) in the RS group. No significant difference (p=0.78) was noted in complication rate between patients given denosumab versus zoledronic acid.

Conclusions. Functional outcomes of EC and RS appear to be comparable, including the incidence of complications. However, recurrence was noted to be significantly higher in EC. There appears to be no clear advantage between denosumab or zoledronic acid for GCTB. As a neoadjuvant medication and/or to control tumor progression, zoledronic acid may be the more economic option especially for patients in developing countries.

Keywords: denosumab, extended curettage, giant cell tumor of bone, zoledronic acid

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Corresponding author: Daniela Kristina D. Carolino, MD
Philippine Orthopedic Center
Maria Clara St., Santa Mesa Heights,
Quezon City 1114, Philippines
Email: dkdcarolino@gmail.com
ORCiD: https://orcid.org/0000-0002-2452-0719

INTRODUCTION

Giant cell tumor of bone (GCTB) is a benign but locally aggressive neoplasm comprising approximately 5-6% of all primary bone tumors.[1-5] The natural history of GCT is progressive bone destruction leading to joint deformity with a tendency for local recurrence.[1,2,5,6]

While there is no widely held consensus regarding ideal treatment, surgical intervention remains to be the standard of care.[2,4-6] Surgical techniques range from intralesional curettage to wide excision, augmented with cement and implant fixation, depending on the amount of bone resected, integrity of the articular surface, and the preference of the surgeon.[2]

Regardless of technique, the goals of limb-salvage are eradication of the tumor, preservation of limb function, and prevention of local recurrence as well as distant metastasis. Some studies have shown a correlation between the rate of local recurrence with completeness of tumor removal.[2,3,5,6] Wide resection has been reported to have local recurrence rates approaching 0%, but with higher incidence of surgical complications and subsequent functional impairment.[2,3,6] While resulting in less morbidity and functional impairment, extended curettage alone has a tendency towards residual microscopic disease, with reported local recurrence rates as high as 60%.[2,3,7] This has led to the use of adjuvants such as liquid nitrogen, phenol, and hydrogen peroxide to extend margins and reduce average recurrence rates to 6%.[2,4]

Determining the outcomes of patients with GCTB occurring in the lower extremity is clinically relevant as these impact weight-bearing and function. Socio-economic factors for patients in developing countries also emphasize the need to select more economic options with comparable results to current standards.

MATERIALS AND METHODS

Study Design and Procedure

This is an analytical cross-sectional comparative study investigating patients who underwent limb-salvage surgery of the lower extremity for GCTB from January 2015 to February 2022 at a single tertiary hospital. Time frame of inclusion was determined in accordance to the available patient records. Limb salvage surgery in this study is defined as resection (RS) or extended curettage (EC) of the lesion with a Campanacci grading of 2 or 3.

Purposive data gathering was done by scanning the hospital census using the keywords "giant cell tumor", "resection", and "curettage". Patients were then filtered according to the inclusion and exclusion criteria. Those who satisfied the criteria (57 patients) were included in the study population. Hospital records of these patients were retrieved, and details regarding personal information, history and physical examination, preoperative management, operative procedure, and postoperative course were collated using a data collection tool. No missing data were encountered upon data collection. Each of the patients were contacted and advised a scheduled follow-up. Among 57 patients, 13 came for physical consult, 17 opted for a virtual consult, and 27 did not respond or refused to participate in the study. Consent was obtained from the 30 participants after full disclosure of study details.

Functional outcomes were evaluated using the 1993 version of the Musculoskeletal Tumor Society (MSTS) score, a validated questionnaire for patients with tumors affecting the extremities.[8] This scoring tool measures outcomes in seven categories, including motion, pain, stability, deformity, strength, activity, and emotional acceptance, specified to the anatomic location of interest (i.e., hip, knee, or ankle).[8] Each parameter is scored 0-5 and combined for a possible total score of 35.

The occurrence of any complication was noted during the interview and based on the patient's records. A complication is defined as the development of any event for which the patient required a specific intervention such as wound complications, infection, tumor recurrence, implant failure/loosening, fracture, and stiffness of the joint.[4]

Approval was first obtained from the Institutional Review Board and Ethics Committee of our institution prior to the commencement of this study.

Eligibility Criteria

Inclusion criteria for the patients to be recruited were as follows:

1. More than 18 years old during time of limb-salvage surgery
2. Diagnosed with GCTB of the lower extremity via imaging (radiographs, CT scan, MRI)
3. Classified with GCTB Campanacci grade 2 or 3 who underwent limb-salvage surgery done by orthopedic oncologists at a single orthopedic specialty center
4. Has a histopathology result confirming the diagnosis of GCTB
5. With active follow-up of up to at least six months post-operatively

Exclusion criteria were as follows:

1. Those with open wounds, skin lesions directly overlying the surgical area, and/or active infections (either local or systemic)
2. With pre-surgical conditions or comorbidities other than GCTB rendering the patient unable to ambulate or do range of motion of the lower extremities
3. With incomplete medical data from either hospital or clinic records

OBJECTIVES

The general objective of this study was to determine the outcomes of limb-salvage surgery in patients diagnosed with

GCTB of the lower extremities. The specific objectives were to obtain the following:

1. Demographic and surgical profile of the selected participants.
2. Functional outcomes among participants using the Musculoskeletal Tumor Rating Scale (MSTS) score. This will be determined according to the surgical techniques. Each parameter is scored 0-5 and combined for a possible total score of 35. A score of 23 or greater is considered an excellent result; a score of 15-22 is considered a good result; a score of 8-14 is considered a fair result; and lastly, a score of less than 8 is considered a poor result, in terms of functionality.[9]
3. Presence of complications among the participants. This will be analyzed in accordance to the Campanacci grade of the patients and to the use of neoadjuvant therapy.

Sample Size Estimation

Sample size was calculated based on the estimation of the population proportion for functional score (MSTS). Assuming that the proportion of post-limb salvage surgery in patients with primary bone tumors with good to excellent results is 90%,[9] with a maximum allowable error of 7.5%, and a reliability of 80%, the sample size required is 27.

Statistical Analysis

Statistical analyses were performed using Stata15.1. Cross-tabulation of frequencies for characteristics was done between the treatment group for each of the baseline characteristics. Wilcoxon Rank Sum Test was used for the comparison of scores in the categories and other parameters which were quantitative. Chi-square test of independence was applied for testing correlations. Significance level is set at 0.05 for both comparisons and testing correlations.

RESULTS

Thirty patients histologically confirmed to have GCTB of the lower extremities who underwent limb salvage surgery in a single institution from January 2015 to February 2022 were assessed. Mean follow-up of patients was 2.6 years (SD 1.8), with comparable follow-up time between the RS and EC groups. Twenty-two patients underwent tumor resection (73%), while eight patients underwent curettage (27%). Table 1 illustrates demographic and surgical characteristics of the study population. Mean age of patients was 33.6 years (SD 11.8), with mean age noted to be comparable between the two groups. Majority of respondents were females (66.67%, n=20), with most of the tumor involving the distal femur (47%, n=14), followed by the proximal tibia (40%, n=12).

Table 1. Demographic and Surgical Characteristics of the Population (N=30)

Demographic and Surgical Characteristics of Respondents (N=30)	Specifications	Treatment Group		Total (%)
		Curettage	Resection	
Sex	Female	5	15	20 (67%)
	Male	3	7	10 (33%)
Bone Involved	Distal femur	2	12	14 (47%)
	Proximal tibia	5	7	12 (40%)
	Distal tibia	0	1	1 (3%)
	Proximal fibula	0	2	2 (7%)
	Talus	1	0	1 (3%)
Neoadjuvant treatment	With	6	20	26 (87%)
	Denosumab	5	16	21 (81%)
	Zoledronic Acid	1	4	5 (19%)
	Without	2	2	4 (13%)
Campanacci stage	2	2	2	4 (13%)
	3	6	20	26 (87%)
MSTS (General)	Excellent	7	16	23 (77%)
	Good	1	5	6 (20%)
	Fair	0	1	1 (3%)
Complications	With complications	5	9	14 (47%)
	Dehiscence	0	3	3 (21%)
	Implant failure	0	1	1 (7%)
	Nonunion	0	1	1 (7%)
	Palsy	0	1	1 (7%)
	Wound infection	0	2	2 (15%)
	Recurrence	4	0	4 (29%)
	Peri-implant infection	1	0	1 (7%)
	Implant irritation	0	1	1 (7%)
	Without complications	3	13	16 (53%)

Table 2. Correlation Analysis among the Characteristics of the Population in Terms of Surgical Procedure Done

Characteristics	*p*-value	Difference	Higher Median
Sex	0.7703	Not significant	
Age	0.2219	Not significant	
Days of hospital stay	0.0814	Not significant	
Campanacci grade	0.2651	Not significant	
Duration of follow-up	0.3973	Not significant	
Duration of operation time	0.0001	Significant	Resection
Intraoperative blood loss	0.0072	Significant	Resection
Duration of follow-up	0.3973	Not significant	
MSTS (score)	0.0525	Not significant	
Complications	0.2945	Not significant	
Recurrence	0.0004	Significant	Curettage
Time between 1st dose of neoadjuvant treatment to surgery	0.1551	Not significant	

**Significant correlation at p-value <0.05*

Twenty-six were classified as Campanacci 2 lesions (87%). Most underwent neoadjuvant therapy, with denosumab (81%, n=21), versus zoledronic acid (19%, n=5).

On most recent follow-up, functional outcomes were noted to be excellent in 23 patients (77%), good in six (20%), and fair in one (3%). The median MSTS for patients managed with curettage was 24 (IQR 4). Those managed by resection had a median MSTS score of 24 (IQR 5), whereas those managed by curettage had a median MSTS score of 30 (IQR 9.5).

Nine complications (64%) occurred in the resection group, which included three cases of dehiscence, two cases of wound infections, and one case each of implant failure, nonunion, palsy, and implant irritation. Five complications (36%) were recorded in the extended curettage group, which included four cases of recurrence and one case of peri-implant infection.

Table 2 demonstrates the correlation analysis among various characteristics for those who underwent curettage versus resection. There was no significant difference between the two treatment groups in terms of age and sex, days of hospital stay, Campanacci grade, duration of follow-up, MSTS score, incidence of complications, and time between 1st dose of neoadjuvant therapy to surgery. However, p-value was less than 0.05 for both duration of operation time (p=0.0001) and intraoperative blood loss (p=0.0072), indicating that the medians of the treatment groups were significantly different, with the higher median belonging to the resection group.

Separate correlation analysis was done for incidence of complications according to Campanacci grade, whether neoadjuvant treatment was given or not given, and the use of either denosumab or zoledronic acid among those who received neoadjuvant treatment. No significant relationship was seen between Campanacci grade and development of complications (p=0.223) (Table 3) as well as the use of neoadjuvant treatment and development of complications (p=0.886) (Table 4). No significant correlation was noted (p=0.780) in the development of complications among patients who received either denosumab or zoledronic acid (Table 5).

DISCUSSION

GCTB accounts for 5% of all primary bone tumors, with several authors reporting a slight predilection among

Table 3. Correlation Analysis between Campanacci Grade and Occurrence of Complications

Campanacci Grade	Complication		*p*-value
	With	Without	
2	3	1	0.223
3	11	15	

**Significant correlation at p-value <0.05*

Table 4. Correlation Analysis between Neoadjuvant Treatment Given (General) and Occurrence of Complications

Neoadjuvant treatment (general)	Complication		*p*-value
	With	Without	
Given	12	14	0.886
Not given	2	2	

**Significant correlation at p-value <0.05*

Table 5. Correlation Analysis between Neoadjuvant Treatment Given (Specific) and Occurrence of Complications

Neoadjuvant treatment (specific)	Complication		*p*-value
	With	Without	
Denosumab	9	12	0.780
Zoledronic acid	3	2	
None	2	2	

**Significant correlation at p-value <0.05*

females.[1-6] This is similar to our population, with majority being females (67%). Multiple studies have likewise shown that GCTB may occur in any age group but peaks during the 3rd decade, with 80% of cases occurring between 20-50 years of age.[3,5,6] This is comparable to our population, with a mean age of 33.6 years. Long bones were the most common location (75-90%), with most cases (50-65%) occurring adjacent to the knee.[2,5,6] This was consistent with our population, with the distal femur (47%), and the proximal tibia (40%) as the most affected sites.

On radiographs, GCTB is seen as a lytic lesion, often geographic in appearance, and located in the epiphysis of the affected bone. In the presence of a more aggressive lesion, this may extend to the subchondral bone and into the articular surface, with cortical thinning, expansile remodeling, and cortical bone destruction.[1,3,6] The Campanacci grading was created to classify GCTB based on radiographic appearance and has been proposed to guide treatment.[3,5] Type 1 lesions are well-defined with an intact cortex. Type 2 is considered active, relatively well-defined, and typically larger than type 1 lesions, with an intact cortex. Type 3 is an aggressive lesion with indistinct borders. Intralesional curettage is recommended for grade 1 and 2 lesions, while resection and reconstruction are advised for grade 3 lesions.[5] No universally accepted treatment guidelines exist at present however, as GCTB tumor grade lacks reliable prognostic significance in terms of complications and recurrence.[5,9-12] This is consistent with the results of our study, which showed no significant correlation (p-value 0.223) between Campanacci grade and the occurrence of complications (Table 3).

Surgery is the standard treatment for GCTB, and depending on the extent of articular involvement, the tumor can be removed either by resection or curettage.[2,3,5,6] Therapeutic goals of surgery include removal of the tumor, maximizing function, and preventing occurrence of complications.[9-12] Two main treatment options are recommended: curettage with the use of adjuvants, with or without the use of bone grafts, cementation, and instrumentation; or wide excision and reconstruction.[9,13] Curettage alone provides less morbidity and functional impairment but is associated with local recurrence rates as high as 65%.[3,5,10,14] However, multiple studies have shown that extended curettage with the use of a mechanical burr combined with chemical adjuvants such as phenol, ethanol, or hydrogen peroxide, and cryo-adjuvants such as liquid nitrogen, may decrease recurrence to as low as 6%.[3-6,12] Wide resection is recommended for extensive bone destruction, when the joint cannot be preserved, and if the tumor is located in an expendable location (i.e., fibular head). This procedure is associated with decreased risk of local recurrence compared to intralesional curettage, but with greater surgical morbidity, increased complications, and substantial risk for revision surgery.[3,5,15-17] Options for reconstruction particularly in developing countries are often influenced by economic capacity.[13]

There are contradicting studies in terms of functional outcomes for limb salvage surgery in GCTB. A retrospective cohort by Jamshidi et al. among patients with GCTB of the knee showed that function was significantly better in the extended curettage group versus the resection group.[14] This was attributed to preservation of the native joint, thus preserving motion.[9,13,17,18] A study by Kamal et al. in 2016 on 82 patients treated with either tumor endoprosthesis or arthrodesis reported similar results showing that wide resection and extended curettage were comparable in terms of functional outcomes using the MSTS score.[19] Among our patients, wide resection was performed in 22 patients. Reconstructions consisted of Van Nes rotationplasty (n=5), D' Aubigne pedicled patella procedure (n=2), and arthrodesis (n=13). Two patients underwent fibular head resection. The variety of reconstruction techniques, some of which were joint-preserving, may account for comparable outcomes between extended curettage and wide resection groups.

Recurrence in particular was the most common complication (29%) in this study. Multiple studies report that recurrence is influenced by surgical method, with patients undergoing curettage more likely to develop recurrence.[3,5,9,11,14] This is similar to our findings, which may be due to microscopic residual tumor (p-value 0.0004) (Table 2). Authors surmise that aside from administering adjuvants to extend margins, other measures to decrease recurrence include the creation of a window large enough to remove all gross tumor under direct vision, and using sterile oral mirrors to facilitate visualization of the entire tumor cavity.[9]

Resection in this study was more commonly associated with wound complications such as dehiscence (21%) and infection (14%), which is likely due to extensive surgical dissection. Similarly, He et al. found high risk of infection following resection of periarticular GCTBs, as well as other long-term complications such as mechanical and structural complications requiring reoperation and revision.[9]

Duration of operation time (p-value 0.0001) and intraoperative blood loss (p-value 0.0072) were significantly greater for resection compared to extended curettage (Table 2). This may be explained by wide resection being more complex, requiring larger and more meticulous exposure, as well as more time to perform reconstruction. Interestingly, despite this, no significant difference in terms of hospital stay was noted (p-value 0.0814) between the two groups. This may be attributed to the fact that patients post-curettage were advised to undergo aggressive physical therapy while admitted, opting to stay longer to save on expenses associated with outpatient physical therapy. Most patients who underwent resection were initially placed on immobilization, and kept admitted longer for pain control, intravenous antibiotics, and monitoring.

Both denosumab and zoledronic acid have been widely used as adjuncts to surgery for GCTB. Denosumab prevents activation of RANK receptors on osteoclasts, thereby inhibiting resorption of bone. Zoledronic acid has

been found to induce osteoclast as well as neoplastic GCT stromal cell apoptosis. The tumoristatic nature of denosumab has been posited by experimental studies to cause a higher rate of disease recurrence, since live tumor cells may still be contained within bony niches in newly formed bone, which may not be adequately cleared out during curettage. This may eventually cause late reactivation of stromal cells in the sclerotic rim, causing recurrence.[20] In contrast, the tumoricidal nature of zoledronic acid causes stromal cell apoptosis, which decreases the load of live tumor cells within pockets of bone, decreasing the chance of eventual recurrence.[21] Studies report varying recurrence rates for neoadjuvant therapy with denosumab, ranging from 2% to 60%.[22-24] A prospective study by Puri et al. found a recurrence rate of 29% among patients given denosumab preoperatively and claimed that local disease control rates are not likely to be increased by neoadjuvant denosumab.[25] Another study by Kundu et al. reported a recurrence rate of 5.5% among patients given neoadjuvant zoledronic acid versus 21% for those treated with curettage alone.[26]

Concerns regarding malignant transformation of GCTB during denosumab treatment have also been raised, with more cases being reported in the past few years.[27,28] A study by Li et al. in 2020 reported 18 known cases of malignant transformation of GCTB during treatment with denosumab.[27] However, given the rarity of these cases, a definite causal relationship between denosumab and malignancy has yet to be established.[27,28]

Despite their widespread use in the treatment of GCTB, studies comparing clinical outcomes of denosumab versus zoledronic acid remain scarce. The previously cited study by Kanwat et al. in 2021 found no significant difference in terms of radiological outcomes, facilitation of surgery, MSTS scores, and complication rates between patients given denosumab and patients given zoledronic acid. Zoledronic acid therapy however, was found to cost significantly less (p-value 0.001) than treatment with denosumab, which is of relevance to the Philippine setting. Those in the zoledronic acid group were also noted to have a lower recurrence rate compared to those in the denosumab group (10.52% versus 25%, respectively), although this was not statistically significant.[24] These findings are echoed in a randomized clinical trial by Li et al, which concluded that denosumab and zoledronic acid did not significantly differ in terms of clinical benefits, but the total cost of denosumab therapy was estimated to be 3 times higher.[29] Those reports are consistent with our findings, which showed no significant difference (p-value 0.78) in complication rate including local recurrence, between the two groups (Table 5).

At present, the local cost of zoledronic acid (Zometa®, Novartis, USA) 4 mg/5 ml vial is estimated to be 5,000 PhP (110 USD). Intravenous infusion of zoledronic acid is given every 3-4 weeks, with a projected cost of 15,000 PhP (330 USD) for three months of treatment. On the other hand, denosumab (Xgeva®, Amgen, USA) 120 mg pre-filled syringe cost is estimated to be 28,000 PhP (535 USD). Subcutaneous administration of denosumab is given on days 1, 8, 15, and 28 as loading doses in the first month, followed by once every four weeks. This has an estimated cost of 168,000 PhP (3,210 USD) for three months of treatment. This study also did not find a clear advantage in giving neoadjuvant denosumab over zoledronic acid for GCTB, with zoledronic acid being a less costly, but similarly effective, alternative to denosumab, especially when treating patients with limited resources.

CONCLUSION

In patients with GCTB of the lower extremity, extended curettage appears to be comparable to resection in terms of functional outcomes and complications, despite having longer surgical time and more intraoperative blood loss. Recurrence, however, was noted to be significantly higher among patients who underwent extended curettage. This reiterates the need for full disclosure of all possible risks and benefits for available surgical options. While larger prospective studies are needed to further compare the long-term clinical outcomes of denosumab and zoledronic acid as adjuncts to surgery for GCTB, the short-term findings of this retrospective study suggest that zoledronic acid may be a more cost effective alternative especially for patients in developing countries.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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