JOURNAL OF SCIENTIFIC RESEARCH IN ALLIED SCIENCES
ISSN NO. 2455-5800
DOI No. 10.26838/JUSRES.2021.7.1.501
Contents available at www.jusres.com

GIANT CELL TUMOR MANAGEMENT: A STUDY IN A TERTIARY CARE HOSPITAL.

Dr. Md. Matiul Islam*[1], Dr. Md. Hassan Jamil Hedyatullah[2], Dr. Obaidul Haque[3]
1. Assistant Professor, Dept. of Orthopaedic & Traumatology, Rajshahi Medical College & Hospital, Rajshahi, Bangladesh.
2. Assistant Professor, Dept. of Orthopaedic & Traumatology, Rajshahi Medical College & Hospital, Rajshahi, Bangladesh.
3. Assistant Professor, Dept. of Orthopaedic & Traumatology, Rajshahi Medical College & Hospital, Rajshahi, Bangladesh

ARTICLE INFO **ABSTRACT** **ORIGINAL RESEARCH ARTICLE**

Article History
Received: Jan 2021
Accepted: March 2021
Keywords:
Management and outcomes, Giant cell tumors, GCT, Curettage, Resection.

Corresponding Author
***Dr. Md. Matiul Islam**

Background: Giant cell tumors (GCT) of bone are locally destructive benign entities that occur predominantly in long bones of post-pubertal adolescents and young adults. Most of such cases are treated by aggressive curettage or resection. Occasionally, Giant cell tumors of bone may undergo malignant transformation to undifferentiated sarcomas. We have very limited research-oriented information regarding the GCT management. **Aim of the study:** The aim of this study was to evaluate the management and outcomes of giant cell tumors (GCT) by aggressive curettage or resection procedure. **Methods:** This was a prospective observational study which was in the conducted in the Dept. of Orthopaedic & Traumatology, Rajshahiii Medical College & Hospital, Rajshahi, Bangladesh during the period from January 2020 to December2020. In total 26 patients with biopsy proven GCTs were enrolled as the study population. All patients were given one pre-operative and two post-operative doses of zoledronic acid. Extended curettage was done three weeks after the pre-operative dose of zoledronate. The functional status of the patients was assessed MSTS score. All data were processed, analyzed and disseminated by MS Office and SPSS version as per need. **Result:** In this study needed time to full weight bearing was found up to 12 weeks, up to 16 weeks and up to 20 weeks for 7.69%, 34.62% and 57.69% patients respectively. On the other hand, as complications rejection reaction, EHL weakness, osteoarthritis and joint stiffness was found among 23.08%, 19.23%, 11.54% and 7.69% patients respectively. According to the Musculoskeletal Tumour Society (MSTS) scoring system as final outcome 'Excellent', 'Good', 'Moderate', 'Fair' and 'Poor' results were found among 38.46%, 26.92%, 15.38%, 11.54% and 7.69% patients respectively. **Conclusion:** To decrease the recurrence of GCT surgeons use several methods. We think, by not adding cancellous bone graft to the cavity after curettage, with local adjuvant hydrogen peroxide and systemic zoledronic acid to supplement the curettage with power burrs, would decrease the recurrence rates in GCT. Considering short time recovery, low blood loss and minimum complication surgeons can choose curettage and zoledronic acid with structural support by fibula cortical struts in treating GCT.

INTRODUCTION

Giant cell tumor (GCT) is a primary bone tumor with potential invasion, local recurrence and low probability of distant metastasis[1]. Although the mortality rate associated with the disease is low, the tumor is locally aggressive and has a high tendency to recur[2]. With the advancement in treatment options, the recurrence rate associated with GCT has fallen from an excess of 40% to less than 20% with extended curettage and use of adjuvants[3]. The cavity left behind following the curettage is commonly filled with a bone graft or bone cement. Studies in literature[4] had reported higher recurrence rates when iliac crest bone graft was used to fill the cavity. Bone cement is an inert material and does not get incorporated or remodeled along the lines of stress. Studies have shown that GCTB (Giant cell tumor of bone) accounts for 5–7% of all primary bone tumors and 20% of all benign bone tumors [5]. GCTB tends to occur in people aged 20–40 years, accounting for 60–75% of all patients[6], and GCTB occurs in the meta-epiphyseal area of the limbs and in the around knee joint at around 50–65% of the whole body, especially in the distal femur and proximal tibia. GCTBs grow in an expansive manner and easily penetrate the cortex of the bone or even cause pathological fracture. Although they rarely expand into the articular cavity, they invade the subchondral bone, which seriously affects knee joint function[7]. These factors lead to an embarrassing situation during treatment as the knee joint is the main load-bearing joint of the lower limbs and has high functional requirements. The therapeutic purpose of GCTB around the knee joint is to reduce its recurrence rate and maximize the recovery of joint function, while reconstructing the integrity of bone structure and articular surface, as well as obtaining normal biomechanics and preventing the occurrence of long-term osteoarthritis[8].

There is still controversy about the surgical treatment options of GCTB in the around knee joints. How to achieve a balance between completely removal of tumors to reduce recurrence as well as preservation of knee joint function as much as possible was the linchpin for clinicians to balance. The surgical treatment of GCTB around knee joint mainly includes curettage and bone grafting[7], extended curettage (EC) and cement filling[1], segmental resection (SR) and artificial prosthesis reconstruction[9]. Although these methods have achieved certain results in the treatment of GCTB, some problems occur, such as local recurrence[10], secondary osteoarthritis[11], cartilage surface collapse[12], artificial prosthesis loosening and infection[9], which require deep focus and improvement.

METHODOLOGY & MATERIALS

This was a prospective observational study which was conducted in conducted in the Dept. of Orthopaedic & Traumatology, Rajshahiii Medical College & Hospital, Rajshahi, Bangladesh during the period from January 2020 to December2020. In total 26 patients with biopsy proven GCTs were enrolled as the study population. All patients were given one pre-operative and two post-operative doses of zoledronic acid. Extended curettage was done three weeks after the pre-operative dose of zoledronate. Fibular struts were used to support the cavity from collapse. Patients were followed-up for post-operative local recurrence. This study was approved by the ethical committee of the mentioned hospital. Proper written consents were taken from all the participants before starting data collection. A pre-designed questionnaire was used in patent data collection. The case of primary as well as recurrent GCT were all included. MRI was done to confirm the intramedullary extent of the tumor and possible soft tissue extension. CT chest was done to rule out pulmonary metastasis. All the patients were available for a final follow- up. All the cases in our study were treated in the same manner. A creatinine clearance of 60ml per minute was taken as the minimum value for the administration of 4mg of zoledronic acid as per FDA standards. Zoledronic acid was administered in 100ml normal saline over 15 minutes after adequate fluid preloading. The surgery was performed under tourniquet control. The cavity was well visualized, and a curettage of the lesion was done. Power burrs were used to enhance surgical clearance. The

cavity was thoroughly irrigated at the end of the procedure to wash away the tumor cells. The cavity was then treated with 3% hydrogen peroxide for three minutes. A total of three hydrogen peroxide washes were given. The dimensions of the cavity were measured to calculate the length of fibula needed to be rejected. Proximal tibia cavities were generally supported by two struts, one mediolateral and one super inferior strut. Distal femur cavities were given an additional anteroposterior strut when the tumor involved a large portion of the posterior femoral condyle. The measured length of the fibula was resected using a posterolateral approach. The ipsilateral fibula was harvested in lesions involving the distal femur while the contralateral fibula was used in proximal tibia lesions. This protocol was followed to prevent further compromise in the stability of the leg when a fibular defect was made on the same side as the tibial cavity. The fibula was harvested sparing the proximal and distal 8cm. The resected piece of fibula was split into multiple struts. The mediolateral strut was placed first. The super inferior strut was positioned over the above strut and hitched against the cortex proximally or distally. Patients were given above-knee casts in the immediate post-operative period. Three doses of antibiotics were given. Suture removal was done on the 12th post-operative day. The patients were kept non-weight bearing with above-knee casts. The first follow-up visit was at three weeks' post- surgery, during which the second dose of zoledronic acid was given. The final dose of zoledronic acid was given after another six weeks. Routine radiographs were taken at six weeks, twelve weeks, three months, six months, one year; and at six-month- intervals thereafter. MRI was taken two years' post-operative to detect recurrences. The decision to discontinue plaster immobilization and commence knee mobilization and weight-bearing was individualized for every patient depending on the consolidation of the graft. Functional outcome was evaluated using the Musculoskeletal Tumour Society (MSTS) scoring system.[13] For the lower extremity, this comprises categories of pain, function, emotional acceptance, supports, walking, and gait. For the upper extremity, the latter 3 categories are hand positioning, dexterity, and lifting ability. Excellent was defined as 75% to 100%, good as 70% to 74%, moderate as 60% to 69%, fair as 50% to 59%, and poor as s <50%. Local recurrence was confirmed by radiography and magnetic resonance imaging. All data were processed, analyzed and disseminated by MS Office and SPSS version as per need.

RESULTS

In this study among total 26 participants 58% (n=15) were male whereas 42% (n=11) were female. So male participants were dominating in number and the male-female ratio was 1.36:1. In analyzing the ages of the participants, we observed, 38.46%, 30.77%, 19.23%, 7.69% and 3.85% participants were from 18-30 (Highest), 31-40, 41-50, 51-60 and >60 years' age groups respectively. In this study cases of primary GCT were 84.62% whereas cases of recurrent GCT were 15.38%. In analyzing the location of GCT among total participants, we found proximal tibia, distal femur and patella were associated among 53.85%, 38.46% and 7.69% patients respectively. Right side was involved among 61.54% and left side was involved among 38.46% participants. Immobilization period among participants were up to 4 weeks, up to 8 weeks and up to 12 weeks to 11.54%, 61.54% and 26.92% participants respectively. In this study, needed time to full weight bearing was found up to 12 weeks, up to 16 weeks and up to 20 weeks for 7.69%, 34.62% and 57.69% patients respectively. On the other hand, as complications rejection reaction, EHL weakness, osteoarthritis and joint stiffness was found among 23.08%, 19.23%, 11.54% and 7.69% patients respectively. According to the Musculoskeletal Tumour Society (MSTS) scoring system as outcome 'Excellent', 'Good', 'Moderate', 'Fair' and 'Poor' results were found among 38.46%, 26.92%, 15.38%, 11.54% and 7.69% patients respectively.

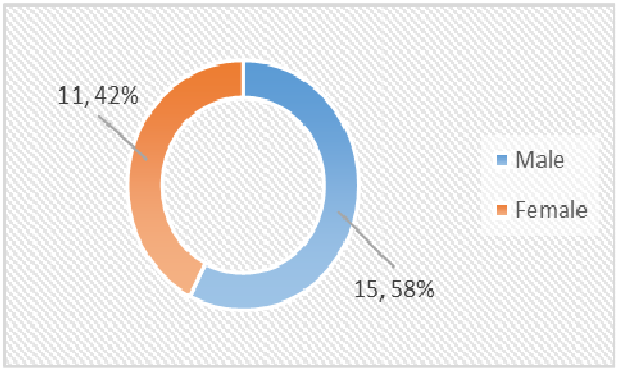

Figure I: Gender distribution of the participants (n=26)

Table I: Age distribution of participants (n=26)

Age (Yrs.)	n	%
18-30	10	38.46
31-40	8	30.77
41-50	5	19.23
51-60	2	7.69
>60	1	3.85

Table II: Clinical status of participants (n=26)

Characteristics	n	%
Type of surgery		
Primary GCT	22	84.62
Recurrent GCT	4	15.38
Location of GCT		
Proximal tibia	14	53.85
Distal femur	10	38.46
Patella	2	7.69
Side involvement		
Right	16	61.54
Left	10	38.46

Table III: Period of immobilization of participants (n=26)

Period	n	%
Up to 4 weeks	3	11.54
Up to 8 weeks	16	61.54
Up to 12 weeks	7	26.92
Total	26	100

Table IV: Time to full weight bearing for participants (n=26)

Period	n	%
Up to 12 weeks	2	7.69
Up to 16 weeks	9	34.62
Up to 20 weeks	15	57.69
Total	26	100

Table V: Complications among participants (n=26)

Complications	n	%
Rejection reaction	6	23.08
EHL weakness	5	19.23
Osteoarthritis	3	11.54
Joint stiffness	2	7.69

NB: EHL means extensor hallucis longus

Table VI: Outcomes among participants (n=26)

Outcomes	n	%
Excellent	10	38.46
Good	7	26.92
Moderate	4	15.38
Fair	3	11.54
Poor	2	7.69

DISCUSSION

The aim of this study was to evaluate the management and outcomes of giant cell tumors (GCT) by aggressive curettage or resection procedure. In our study among total 26 participants 58% (n=15) were male whereas 42% (n=11) were female. So male participants were dominating in number and the male-female ratio was 1.36:1. In analyzing the ages of the participants, we observed, 38.46%, 30.77%, 19.23%, 7.69% and 3.85% participants were from 18-30 (Highest), 31-40, 41-50, 51-60 and >60 years' age groups respectively. In this study cases of primary GCT were 84.62% whereas cases of recurrent GCT were 15.38%. The recurrent tumors were all operated primarily at other centers. The use of adjuvant therapy was not documented in both cases. A radical surgery like wide resection offered no significant additional disease control over extended curettage in the management of recurrent GCT. Steyern et al[14] did not find any significant difference in recurrence rate while managing primary and recurrent tumors with extended curettage. The presence of a pathological fracture was not a contraindication for inclusion in our study. Two patients in our series presented with a pathological fracture: one involving the distal femur and the other involving the proximal tibia. Intra-operatively, the tumor was found to be well contained within a pseudo capsule, and an intra-lesional curettage was done with resection of the pseudo capsule. Deheshi et al[15] compared recurrence-free survival and functional outcome after curettage in patients with and without pathologic fracture, with the outcomes being comparable. Intra-lesional curettage has emerged as the preferred mode of treatment in GCT, considering the benign nature of the disease and the longer life expectancy of the affected individuals compared to other bone tumors. Systemic adjuvants have supplemented the curettage technique by controlling the micro-metastasis. Two commonly used agents included zoledronic acid and denosumab. Zoledronic acid, a third-generation bisphosphonate, acted by promoting the apoptosis of stromal cells, the main neoplastic component in GCT[9]. Several studies had reported low recurrence rates while using zoledronic acid[16]. In our series of all cases of GCT followed-up for a minimum period of 6 months, there were no recurrences as confirmed using MRI scans. The number and duration of zoledronic acid administered varied in the reported studies. We administered three doses of zoledronic acid at an interval of six weeks for each. The first dose was given pre-operatively and two more doses were given after surgery to supplement our extended curettage with hydrogen peroxide. The time interval between administration of the pre-operative dose of zoledronic acid and surgery was 21 days. Nishisho et al[17] advocated a three weeks waiting period between zoledronic acid and surgery based on in vivo and in vitro studies.

In total 8 patients experienced a mild fever within 48 hours of administering zoledronic acid. This is the only notable reaction to the administration of zoledronate. The rise in temperature was benign and settled with antipyretics. The resected specimens were sent for histopathological investigation. The percentage of necrosis of the giant cells in the resected specimens was documented. Pre-operative administration of zoledronic acid had produced more than 50% necrosis in the resected specimens compared to the biopsy tissue. This was consistent with the observations of Cheng et al who had a stromal cell necrosis of 54% and giant cell necrosis of 74% while using zoledronic acid[18]. With the advent of denosumab, promising results had been shown in the management of inoperable or metastatic GCT. However, its superiority over zoledronic acid in conventional limb GCT had not been established[19]. High costs and long duration of treatment before surgery made it less cost-effective. Denosumab promoted new bone formation at the periphery of the tumor, which made the differentiation between normal and pathological tissue difficult during curettage. Neoplastic cells might be left behind the newly formed bone[19]. Denosumab had been associated with a higher incidence of grade 3-4 adverse reactions like osteonecrosis of jaw, hypocalcaemia, anemia and arthralgia[20]. In our study, EHL weakness had found among 19.13% participants. Verma et al[21] reported EHL weakness in 43 out of 85 cases of fibular resection (50%).

Singhade et al[22] had 10 cases (38%) of EHL weakness following fibular resection. Consistent with the observations of other authors, the weakness was partial and completely recovered within six months in both cases. The distal eight cm of the fibula was preserved to ensure ankle stability. In this study, the average time was taken 18 weeks (Range was12 - 24 weeks). All the patients were able to resume their pre-surgery work function. Consolidation of the graft was achieved in all the cases. The knee was stable and the alignment achieved intra- operatively was maintained until the final follow-up. The wafer-thin subchondral bone supported only with fibula struts did not collapse, and there was no radiographic evidence of arthritis at the final follow-up. In our study, according to the Musculoskeletal Tumour Society (MSTS) scoring system as outcome 'Excellent', 'Good', 'Moderate', 'Fair' and 'Poor' results were found among 38.46%, 26.92%, 15.38%, 11.54% and 7.69% patients respectively. The mean MSTS score of our series was 92% which is comparable to the results obtained by other surgeons using other modes of treatment. Saibaba et al[23] had an MSTS score of 92% in their series of 36 patients managed with curettage and reconstruction using the sandwich technique. Gao et al[24] had a mean MSTS score of 94.7% in 31 patients managed with curettage and cementation.

Limitations of the study:

This was a single centered study with a small sized sample. So, the findings of this study may not reflect the exact scenario of the whole country.

CONCLUSION AND RECOMMENDATIONS

To decrease the recurrence of GCT surgeons use several methods. We think, by not adding cancellous bone graft to the cavity after curettage, with local adjuvant hydrogen peroxide and systemic zoledronic acid to supplement the curettage with power burrs, would decrease the recurrence rates in GCT. Considering short time recovery, low blood loss and minimum complication surgeons can choose curettage and zoledronic acid with structural support by fibula cortical struts in treating GCT. For getting more reliable information we would like to recommend for conducting more studies in several places with larger sized samples.

Funding: No funding sources

Conflict of interest: None declared

REFERENCES

1. Van der Heijden L, van de Sande MA, Heineken AC, Fiocco M, Nelissen RG, Dijkstra PD. Mid-term outcome after curettage with polymethylmethacrylate for giant cell tumor around the knee: higher risk of radiographic osteoarthritis? J Bone Joint Surg Am. (2013) 95: e159. doi: 10.2106/JBJS.M.00066.

2. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. J Bone Joint Surg Am. 1987; 69(1): 106-14.
3. Turcotte RE. Giant cell tumor of bone. Orthop Clin North Am. 2006; 37: 35-51. doi: 10.1016/j.ocl.2005.08.005.
4. Gouin F, Dumaine V, French Sarcoma Group. Local recurrence after curettage treatment of giant cell tumors in peripheral bones: retrospective study by the GSF-GETO (French Sarcoma and Bone Tumor Study Group). Orthop Traumatol Surg Res. 2013; 99(6 Suppl): S313-318. doi: 10.1016/j.otsr.2013.07.006.
5. Unni KK, Inwards CY. Dahlin's Bone Tumors: General Aspects and Data on 10,165 Cases. Rochester, MN: Lippincott Williams & Wilkins (2010).
6. Niu X, Zhang Q, Hao L, Ding Y, Li Y, Xu H, et al. Giant cell tumor of the extremity: retrospective analysis of 621 Chinese patients from one institution. J Bone Joint Surg Am. (2012) 94:461–7. doi: 10.2106/JBJS.J.01922
7. Ayerza MA, Aponte-Tinao LA, Farfalli GL, Restrepo CA, Muscolo DL. Joint preservation after extensive curettage of knee giant cell tumors. Clin Orthop Relat Res. (2009) 467:2845–51. doi: 10.1007/s11999-009-0913-8
8. Medellin MR, Fujiwara T, Tillman RM, Jeys LM, Gregory J, Stevenson JD, et al. Prognostic factors for local recurrence in extremity-located giant cell tumors of bone with pathological fracture. Bone Joint J. (2018) 100-B:1626– 32. doi: 10.1302/0301-620X.100B12.BJJ-2018-0189.R2.
9. Myers GJ, Abudu AT, Carter SR, Tillman RM, Grimer RJ. Endoprosthetic replacement of the distal femur for bone tumors: long-term results. J Bone Joint Surg Br. (2007) 89:521–6. doi: 10.1302/0301-620X.89B4. 18631
10. Becker WT, Dohle J, Bernd L, Braun A, Cserhati M, Enderle A, et al. Local recurrence of giant cell tumor of bone after intralesional treatment with and without adjuvant therapy. J Bone Joint Surg Am. (2008) 90:1060– 7. doi: 10.2106/JBJS.D.02771.
11. Benevenia J, Rivero SM, Moore J, Ippolito JA, Siegerman DA, Beebe KS, et al. Supplemental bone grafting in giant cell tumor of the extremity reduces nononcologic complications. Clin Orthop Relat Res. (2017) 475:776–83. doi: 10.1007/s11999-016- 4755-x.
12. Szalay K, Antal I, Kiss J, Szendroi M. Comparison of the degenerative changes in weight-bearing joints following cementing or grafting techniques in giant cell tumor patients: medium-term results. Int Orthop. (2006) 30:505– 9. doi: 10.1007/s00264-006-0190-z.
13. Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. Clin Orthop Relat Res 1993; 286:241–6.
14. Steyern FV, Bauer HC, Trovik C, Kivioja A, Bergh P, Jorgensen PH. Treatment of local recurrences of GCT in long bones after curettage and cementing. A scandinavian sarcoma group study. J Bone Joint Surg Br. 2006; 88: 1656-8. doi: 10.1302/0301-620X.88B4.17407.
15. Deheshi BM, Jaffer SN, Griffin AM, Ferguson PC, Bell RS, Wunder JS. Joint salvage for pathologic fracture of giant cell tumor of the lower extremity. Clin Orthop Relat Res. 2007; 459: 96-104. doi: 10.1097/BLO.0b013e31805d85e4.
16. Tse LF, Wong KC, Kumta SM, Huang L, Chow TC, Griffith JF. Bisphosphonates reduce local recurrence in extremity giant cell tumor of bone: a case-control study. Bone. 2007; 42: 68-73. doi: 10.1016/j.bone.2007.08.038.
17. Nishisho T, Hanaoka N, Miyagi R, Sakai T, Toki S, Takahashi M, et al. Local administration of zoledronic acid for giant cell tumor of bone. Orthopedics. 2015; 38(1): e25-30. doi: 10.3928/01477447-20150105-56.

18. Cheng YY, Huang L, Lee KM, Xu JK, Zheng MH, Kumta SM. Bisphosphonates induce apoptosis of stromal tumor cells in giant cell tumor of Bone. Calcif Tissue Int. 2004; 75: 71-7. doi: 10.1007/s00223-004-0120-2.
19. Gaston CL, Grimer RJ, Parry M, Stacchiotti S, Dei Tos AP, Gelderblom H, et al. Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. Clin Sarcoma Res. 2016; 6(1): 15. doi: 10.1186/s13569-016-0056-0.
20. Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, et al. Safety and efficacy of Denosumab for adults and skeletally mature adolescents with giant cell tumor of bone: interim analysis of open-label parallel-group, phase 2 study. Lancet Oncol. 2013; 14(9): 901-8. doi: 10.1016/S1470-2045(13)70277-8.
21. Verma AK, Kushwaha NS, Saini A, Waliullah S, Navadaya MK, Kumar D. Retrospective analysis of donor site morbidity following partial fibular resection. Int J Contemp Med Res. 2016; 3: 1571-4.
22. Shingade VU, Jagtap SM, Ranade AB. Weakness of extensor hallucis longus after removal of non-vascularised fibula as an autograft. J Bone Joint Surg Br. 2004; 86(3): 384-7. doi: 10.1302/0301-620x.86b3.14748.
23. Saibaba B, Chouhan DK, Kumar V, Dhillon MS, Rajoli SR. Curettage and reconstruction by the sandwich technique for giant cell tumors around the knee. J Orthop Surg. 2014; 22: 351-5. doi: 10.1177/230949901402200317.
24. Gao ZH, Yin JQ, Xie XB, Zou CY, Huang G, Wang J, et al. Local control of giant cell tumors of the long bone after aggressive curettage with and without bone cement. BMC Musculoskeletal Disord. 2014; 15: 330. doi: 10.1186/1471-2474-15-330.