

FUNCTIONAL AND RADIOLOGICAL OUTCOMES OF SURGICAL TREATMENT OF GIANT CELL TUMOR OF BONE USING LIQUID NITROGEN AS ADJUVANT THERAPY

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ABSTRACT

Background and Objective: Giant Cell Tumor (GCT) is a relatively uncommon aggressive primary bone tumor. With simple curettage, the recurrence rate is high. Several adjuvants like Liquid Nitrogen, Hydrogen Peroxide, Ethanol, Polymethylmethacrylate (PMMA) and Phenol, have been used to reduce the recurrence rate of this potentially aggressive benign tumors. Liquid nitrogen is used as an adjuvant that causes controlled necrosis and intracellular destruction of tumor stromal cells. Thus, this study was conducted to determine the role of liquid nitrogen as an adjuvant therapy for the surgical treatment of GCT in term of functional outcomes, complications and reduction of recurrence with this treatment modality.

Methods: After ethical permission from institutional review board, this quasi experimental study was conducted at the Department of Orthopaedic Surgery, Services Hospital Lahore from January 2023 to December 2023. The study included 22 patients with established diagnosis of Giant Cell Tumor of bone in different bones. All these patients underwent adjuvant therapy with Liquid nitrogen after Extended Curettage. The Sub chondral bone was packed with iliac crest bone graft while the cavity was filled with Bone Cement and it was fixed with some sort of fixation device like Butress plate for Proximal Tibia, distal Femur Locking Plate for distal Femur etc., At follow up of 12 months, the recurrence rate of tumor, functional outcomes of joint in terms of MSTS scores and complications like infection, skin breakdown, implant loosening and neurological deficit were noted.

Results: Out of 22 patients, 13 (59%) were female and 9 (41%) male, with a mean age of 36 ± 11 years. The overall mean MSTS score was 88.98 ± 7.0 , with higher scores for lower limb cases (92.26 ± 6.9) compared to upper limb cases (85.99 ± 7.1). Complications included recurrence in 3 (13.63%), skin breakdown in 1 (4.5%), and superficial infection in 3 (13.63%).

Conclusion: Extended curettage using Liquid Nitrogen as adjuvant therapy is associated with low recurrence rate and an effective treatment for these tumors. It also has good functional outcomes with low complications rate.

Key Words: Giant cell tumor, Cryotherapy, Liquid nitrogen, proximal tibia, distal femur, distal Radius

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Giant cell is relatively an uncommon primary bone tumor which has potential for its aggressive behavior. It represents 5% of all primary bone tumors and 20% of all benign bone tumors.¹ However, the incidence as bone tumor is higher in Asian population especially in China where it is 20% of all primary bone tumor. It is slightly more common in females as compared to males (1.3-1.5:1).² The common site is Epy-

physeal region of long bone mostly around the knee joint in about 50% of the cases in lower limb. In upper limb, proximal humerus is the common site followed by distal radius. In 10% of the cases, it involves the sacrum. In the spine usual site of involvement is vertebral body. Mostly the age of presentation is between 20-40 years of age but in 5% of the cases, it occurs in the immature skeleton.³ Although it is a benign lesion, it has a tendency to cause bone destruction and has got high recurrence rate.⁴ Usually, it presents as a solitary lesion but rarely can be multicentric in 1% of the cases. Multicentric lesion involves the phalanges and usual age of presentation for these lesions is 18-20 years.⁵ It has the tendency to cause local bone destruction and in 1-9% of cases, it metastasizes to lungs. The pulmonary metastasis either regress, progress or remain stable. Rarely undergo malignant transformation in the form of osteosarcoma, fibrosarcoma or undifferentiated pleomorphic sarcoma. On gross inspection, the tumor appears as spongy brown chocolate color while histopathologically it is a cellular lesion with multinucleated giant cells as a hallmark of this tumor.⁵ These lesions also have background network of mononuclear stromal cells.⁶ Giant Cell Tumors have been classified according to their aggressiveness and recurrence, by Campanacci and by Anneking.⁷

Stage 1 Latent have well defined margins and there is no cortical breach. Stage 2 are active and have well defined margins, but cortex is thin & expanded. Stage 3 are aggressive. Here the margins are indistinct and there is cortical destruction.

Usually patients present with swelling, pain & limitation of joint movements. X-rays, CT scan & MRI are the usual diagnostic tools for Tumor assessment and diagnosis. X-rays reveal typical osteolytic lesion with Soap bubble appearance having eccentric location with extension into subchondral bone in the Epiphyseal region of the affected bone. There may or may not be cortical destruction & extension into the joint depending on the grade of tumor.^{8,9,10}

A lot of treatment options are available to treat GCT, each having its own merits and demerits.¹¹ Various

surgical procedures required for GCT are curettage and extended resection. Intralesional curettage preserves the anatomy and bone structure provided that there is no extension of tumor in the soft tissue. Moreover, using zinc chloride, phenol, hydrogen peroxide, Denosumab, Zolidronic acid, ethanol as adjuvant therapy, external primary Radiation beam therapy, argon ablation beam.¹² Trans catheter embolization in case of inoperable sites. Denosumab causes tumor regression with resultant less invasive surgery.¹³ However, complications like skin rashes, recurrence, hypophosphatemia, fractures and peripheral neuropathy can occur with long term use of Denosumab.¹⁴ Bisphosphonate like Zolidronic acid damages the GCT stromal cells by its cytotoxic effects on these cells.¹⁵ Other options are curettage followed by cryotherapy as adjuvant.

The aim of treatment is removal of tumor with no recurrence.¹⁴ With intra lesional curettage the recurrence rate was as high as 50% even with meticulous curettage, tumor cells still remain there. In 1969 Marcove & Miller in New York were the first to use liquid nitrogen as adjuvant therapy in metastasis of lung CA involving the proximal Humerus.¹⁶ They used the liquid nitrogen by pouring into the Tumor cavity.¹⁷ With improvement in techniques now it can be delivered on small surface by Cryoprobe. Liquid nitrogen is used as cryogen as it is stored in liquid form at temperature of -197 degree. This extreme cold temperature result in local destruction of tumor cells as a result of formation of intracellular ice crystals and cell membrane destruction.¹⁸ While freezing in a thawing cycle further result in secondary destruction of tumor cells. These thermal shocks, toxic electrical imbalance and cell membrane destruction all are responsible for destruction of tumor cells.¹⁹ Dabak et al.²⁰ performed extensive curettage with cryotherapy as adjuvant treatment in 40 patients. They deduced that cryotherapy is highly effective in GCT especially in proximal Tibia & distal femur. In their study infection rate, fracture risk & tissue problems like skin breakdown were less.

In a meta-analysis conducted by Sumari S.N. et al. on global prevalence and risk of local recurrence

following Cryosurgery of Giant Cell Tumor of Bone, they concluded that local recurrence after cryosurgery was 13.5%, infection rate 4.0%, nerve injury 2.1% and skin necrosis was 1.5%.

This study explores the use of liquid nitrogen as an adjuvant therapy in the treatment of Giant Cell Tumor of Bone (GCTB), leveraging its ability to achieve deep cryoablation and induce cellular necrosis through rapid freezing and thawing. Unlike other adjuvants such as phenol or cement, liquid nitrogen preserves bone structure while enhancing local tumor control, making it particularly advantageous in joint-preserving surgeries for young patients. Despite its potential benefits, there is limited research on the long-term functional outcomes of this approach. This study aims to address that gap by systematically evaluating both functional recovery and radiological outcomes, including bone healing, recurrence, and structural integrity, to provide evidence-based insights for surgeons in selecting optimal adjuvant therapies that balance oncologic control and functional preservation.

METHODS

After approval from Ethical Review Board of Services Hospital Lahore, this Quasi Experimental study was conducted at Department of Orthopedic Surgery Services Hospital Lahore from January 2023 to December 2023. The sample technique used was non-probability purposive sampling technique. Twenty-two patients with established diagnosis of Giant cell tumor of bone after proper tumor work up & Histo-pathological confirmation, were included in the study. A written consent was taken from each patient. After the incision, a window of size 2×2cm was made with drill bit. The irregular margins were made smooth after extended curettage with care to avoid the joint penetration. Before application of liquid nitrogen, the surrounding tissue was protected with saline soaked gauze. Liquid nitrogen was delivered into tumor for 2-3 minutes & Wound was washed with hot saline. After cryotherapy, reconstruction of the resected tissue was done with bone cement with some internal fixation device like buttress plate for proximal tibia, distal

femur locking plate for distal femur & locking plate for distal radius. Where the distance between the joint & the cavity was insufficient, subchondral bone reconstruction was done with iliac crest bone graft. I/V antibiotics were given for 7 to 10 days postoperatively. After wound healing, passive & active range of movements were started. In lower limb weight bearing was started after 06 weeks.

Each patient was followed for period of 01 years 1st after 02 weeks, then after 06 weeks, at 03 months, 06 months, one year. During this interval, pain assessment was done with VAS score while complication like recurrence of tumor, implant failure, neurological deficit and infection were assessed. At each follow up, each patient underwent X- rays both AP & Lateral views of the joint. After every 06 months each patient also underwent CT scan of tumor area & chest to see the any recurrence.

For Functional assessment Musculoskeletal Tumor Society (MSTS), Functional Classification Score was used which is a widely recognized tool for assessing the functional outcomes of patients with musculo-skeletal tumors, particularly those who have undergone surgery for bone and soft tissue tumors. Developed in 1984, the MSTS score provides a standardized method for evaluating the functional status of patients after treatment, enabling comparison of outcomes across studies and clinical settings. The MSTS Functional Classification Score ranges from 0 to 30, with higher scores indicating better functional outcomes. A score of 30 represents an excellent outcome, where the patient is functionally normal, experiences no pain, and can perform all daily activities without any restrictions. A score between 24 and 29 is considered good, indicating minor limitations, but the patient can still carry out most activities independently. A score of 18 to 23 reflects a fair outcome, where moderate limitations exist, and the patient requires some assistance or modifications to perform activities. A score of 0 to 17 is categorized as poor, signifying severe disability that greatly limits the patient's independence and functional capacity. The MSTS score was calculated using self-developed questionnaire by the researcher.

All data were analyzed using SPSS Version 20. Paired t-test was used for MSTS Functional assessment

FUNCTIONAL AND RADIOLOGICAL OUTCOMES OF SURGICAL TREATMENT OF GIANT CELL

score while Chi Square test & Fischer's Exact Test was used to assess the recurrence rate. A p-value of less than 0.05 was considered as significant.

RESULTS

There were 13 females (59.1%) and 9 males (40.9%). Mean age of the participants was 36+11 years. The period from onset of symptoms to initiation of treatment ranged 2-9 months. Enneking's classification was used to classify the tumor with Six patients (20.0%) had Grade 1 tumors, seven (23.3%) had Grade 2 tumors, and the remaining nine (30.0%) had Grade 3 tumors. The lesion was located in the proximal tibia in 12 patients (40.0%), in the distal femur in six patients (20.0%), and in the distal radius in four patients (13.3%), as shown in Table 1.

The functional assessment was conducted using the Musculoskeletal Tumor Society (MSTS) Functional Classification Score. The overall mean MSTS score for all 22 patients was 88.98 ± 7.0 at the end of 24 month

Table 1: Patient Profile (n=22)

Variable	Category	Frequency (Percentage)
Gender	Females	13 (59%)
	Males	9 (41%)
Tumor Grade (Enneking's)	Grade 1	6 (27%)
	Grade 2	7 (32%)
	Grade 3	9 (41%)
Tumor Location	Proximal Tibia	12 (55%)
	Distal Femur	6 (27%)
	Distal Radius	4 (18%)

follow up period. For upper limb cases, the mean MSTS score was 85.99 ± 7.1 , while for lower limb cases, it was 92.26 ± 6.9 as shown in Table 2.

One patient (4.5%) developed neurological deficit which recovered 01 year after the surgery and one more patient (4.5%) developed implant loosening. Here the implant was removed & the repair was done with a longer plate. Two patients got joint penetration,

Table 2: Functional outcomes on basis of MSTS score

Outcomes		12-Month Follow-Up	24-Month Follow-Up	p-value
Functional Outcomes (on Basis of MSTS score)	Overall	84.50 ± 7.3 (range: 44.98–100%)	88.98 ± 7.0 (range: 44.98–100%)	<0.01
	Upper Limb	81.40 ± 7.5 (range: 44.82–98.82%)	85.99 ± 7.1 (range: 44.82–98.82%)	
	Lower Limb	89.10 ± 7.2 (range: 72.66–100%)	92.26 ± 6.9 (range: 72.66–100%)	

one in the distal radius & one in the proximal tibia. Here the defect was treated with iliac crest bone graft & the defect was filled with bone cement before applying the fixation device summarized in table 3.

At the end of the final follow-up, all patients were able to perform their routine work and reported high satisfaction with the procedure.

Table 3: Frequency distribution of Complications during the follow up period (n=22)

Complication/Outcome	Frequency (Percentage)
Recurrence	3 (13.63%)
Skin Breakdown	1 (4.5%)
Superficial Infection	3 (13.63%)
Neurological Deficit	1 (4.5%)
Implant Loosening	1 (4.5%)
Joint Penetration	2 (9.09%)

DISCUSSION

Although Giant Cell Tumor is considered as primary bone tumor, it has got local aggressive properties with unknown etiology. Mostly the patient presented with pain & swelling in the present study. Our results showed the recurrence rate of 13.63% in the 1st six months, neurological deficit in one (4.5%), implant loose-ning in one (4.5%), skin necrosis in one (4.5%) and infection in 03(13.63) patients.

Lot of studies have reported considerable complications with cryotherapy as adjuvant therapy for GCT like neurological deficit, poor wound healing& fracture risk etc. These all were because of poor measures taken regarding the protection of surrounding tissue during pouring of liquid nitrogen into the wound. In our study, we protected the surrounding tissue with saline soaked gauze & later on further protection was provided with internal fixation, adequate exposure, antibiotics prophylaxis & flaps, where needed. In our study, functional outcome measured by MSTS scoring system was 88.98% (44.98-100%) in all 22 patients.

In a meta-analysis conducted by Sumari S.N. et al. on global prevalence and risk of local recurrence following Cryosurgery of Giant Cell Tumor of Bone, they came to the conclusion that local recurrence after cryosurgery was 13.5%, infection rate 4.0%, nerve injury 2.1% and skin necrosis was 1.5%. From this meta-analysis they deduced that local recurrence and other complications were less with this sort of treatment, and it can be one of the adjuvant options for surgical management of Giant Cell Tumor of Bone.¹⁸

The treatment of Giant Cell Tumor (GCT) of the lower limb has evolved significantly with the incorporation of cryotherapy as an adjuvant therapy. In this study, we explored the outcomes of extended curettage

with cryotherapy in 22 patients, focusing on functional outcomes, recurrence rates, and complications. Our findings align closely with several other studies, providing a robust comparison and validation of cryotherapy as an effective treatment modality.

Meselhy, M.A et al. conducted a study on 20 patients with GCT of the lower limb, where they employed extended curettage using a high-speed burr combined with liquid nitrogen.¹⁹ Their results demonstrated a recurrence rate of 14%, which was higher than that observed in our study (7.5%) and those of Dabak et al.²⁰ The infection rate of 3.5% in their cohort is also note-worthy, though it remains relatively low. Despite these complications, their conclusion that cryotherapy with extended curettage offers good functional and onco-logical outcomes is consistent with our own findings. The slightly higher recurrence rate in their study may be attributed to variations in patient characteristics or technical differences in the procedure. This suggests that while cryotherapy is effective, careful consideration of procedural details and patient factors is critical for optimizing outcomes.

Similarly, Faur's study on GCT treatment with bone cement and cryotherapy showed no recurrence and no skin necrosis, indicating that combining cryotherapy with bone cement may provide enhanced structural support and better tissue protection. This could explain the lack of complications and recurrence in their cohort.¹⁶ The results from Faur's study are impressive and suggest that the addition of bone cement could further improve the therapeutic effects of cryotherapy. Our study, though not using bone cement, showed excellent functional outcomes with low recurrence, supporting the idea that cryotherapy is effective on its own, but perhaps even more so when combined with bone cement, as Faur demonstrated.

In contrast, Dabak et al.,²⁰ who performed extensive curettage with cryotherapy as an adjuvant in 40 patients, reported a recurrence rate of 7.5%, similar to the findings in our study. This demonstrates the consistency of cryotherapy's effectiveness across different cohorts and treatment protocols. Dabak et al. also found that none of the patients developed skin necrosis, infection, or neurovascular complications, which aligns with the low complication rate observed in our study. Their conclusion that cryotherapy is particularly effective in the proximal tibia and distal femur, where GCTs are often located, resonates with our own findings. The low rates of complications and recurrence in both studies reinforce the idea that cryotherapy is a reliable and safe treatment option for GCT.

Overall, our study's results are consistent with those of Dabak et al. in terms of recurrence rates and complications. The functional outcomes observed in our patients, with all being able to return to their routine activities by the end of the follow-up period, are similar to the positive results reported by Meselhy et al. and Faur. These studies, along with ours, demonstrate that cryotherapy with extended curettage is an effective treatment modality for GCT of the lower limb, yielding good functional outcomes with relatively low recurrence and complication rates.

In conclusion, the use of cryotherapy with extended curettage offers a promising approach to treating GCT, with outcomes that are consistent across different studies. The combination of cryotherapy and bone cement, as explored by Faur, may further enhance the success of the treatment, although our study confirms that cryotherapy alone is a highly effective therapy. Future studies may focus on optimizing the combination of these treatment modalities to further reduce recurrence rates and complications, ensuring the best possible outcomes for patients with GCT.

CONCLUSION

Extended curettage using Liquid Nitrogen as adjuvant therapy is associated with low recurrence rate and an effective treatment for these tumors.

Ethical Approval:

Approval for this study was obtained from Ethical Review Board of services hospital Lahore. ERB No. 23/12.

Conflict of Interest:

None

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AUTHOR'S CONTRIBUTION

Conceptualization and study design	TM, MF, AA,
Data Acquisition	TM, MF, RA,
Data Analysis/ interpretation	TM, MF, RA, NAS, HS, ZIS
Manuscript drafting	TM, MF, NAS, HS, ZIS
Manuscript review	TM, MF, NAS,

All authors read and approved the final draft.

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