PROSPECTIVE STUDY ON MANAGEMENT OF RECURRENT GIANT CELL TUMOURS AND AGGRESSIVE GIANT CELL TUMOURS WITH PATHOLOGICAL FRACTURE

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ABSTRACT

BACKGROUND

Giant cell tumour is a primary bone tumour. It is benign but locally aggressive neoplasm with a tendency for local recurrence. The aim of treatment is to remove the tumour completely and to preserve the joint. Local recurrence is a well-documented problem. Treatment of recurrent lesions is the same as for primary lesions. This study is aimed at analysing the treatment of the recurrent GCT and aggressive GCT with pathological fracture by adequate curettage using adjuvant like H₂O₂, liquid nitrogen followed by filling the curetted cavity with bone grafts, bone substitutes and bone cement, thereby preventing the recurrence and to provide structural stability in aggressive GCT with pathological fracture.

MATERIALS AND METHODS

This is a prospective study of management of 32 cases of Giant Cell Tumour during 2003 to 2007 in Government Kilpauk Medical College, Chennai. Out of the 32 cases, 17 cases were Aggressive GCT with pathological fracture and 15 cases were Recurrent GCT.

RESULTS

For recurrent GCT, removal of previously applied bone cement, extended curettage with adjuvant Hydrogen Peroxide and reconstruction with bone cement/bone graft/amputation were the treatment methods employed.

For Aggressive GCT with pathological fracture, extended curettage with adjuvant H₂O₂/liquid nitrogen and reconstruction with fibular strut graft/cancellous bone graft, bone substitute and bone cement were the treatment methods employed.

CONCLUSION

GCT is a locally aggressive benign tumour occurring in young individuals with a normal life expectancy. If inadequately or inappropriately treated, it results in considerable morbidity and recurrence. Careful attention to soft tissue protection while using cryosurgery significantly decreased the previously published reports of high rates of infection and wound healing problem. Hydrogen peroxide is an ideal adjuvant, which gives a comparable rate of recurrence and least local or systemic complications. Free fibular strut graft along with PMMA incorporates in the bone early and the joints can be salvaged with useful function. En bloc resection must also be followed by adjuvant to prevent recurrence due to local tissue contamination.

KEYWORDS

GCT, Recurrent GCT, Aggressive GCT with Pathological Fracture, En Bloc Resection, Adjuvant.

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BACKGROUND

Giant cell tumour is a primary bone tumour. It is benign, but locally aggressive neoplasm with a tendency for local recurrence.

The optimum treatment of giant cell tumour of bone is a matter of controversy. With the advent of variety of adjuvant and reconstruction techniques, the recurrence rate has decreased remarkably. But there are no absolute clinical, radiological or histological parameters that accurately predict the tendency of any single lesion to recur or metastasise.¹

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Most patients incurring a giant cell tumour of bone are young and active with normal life expectancy. Giant cell tumours occur slightly more often in females than in males. The aim of treatment is to remove the tumour completely and to preserve the joint. These aims have not changed, but the methods of treatment have changed with time.

As might be expected, when feasible, curettage with preservation of the joint is to be preferred over an en bloc resection, which is associated with a higher rate of complications and less satisfactory functional results.

Local recurrence is a well-documented problem. It is more common after simple curettage; 25% of the recurrences were within six months and 97% within two years.²

Predominant symptoms are pain and swelling of variable severity. Patients may present with decreased joint range of motion or pathological fracture.³

On physical examination, a tender hard mass is typically found. The skin over the swelling may be warm. There may be joint effusion and disuse muscle atrophy. Egg shell crackling may be present, but it should not be elicited.

Giant cell tumours of the spine (2% to 5%) typically involves only one vertebra and have a predilection for vertebral body, kyphosis secondary to body collapse may be evident on initial presentation; extension of the tumour into the epidural space may produce radicular symptoms and paraplegia.³

Giant cell tumours of sacrum (10%) are eccentric and attain large size, but rarely produce bowel or bladder dysfunction.³ In pelvis, ilium is the most common site affected.⁴ GCT in children is almost always metaphyseal.

Giant cell tumour is typically monostotic with predilection for the ends of long bones. The most common sites of involvement are the distal femur, proximal tibia and the distal radius. A rare polyostotic form of giant cell tumour does exist.

Investigation and Diagnosis

Jaffe first emphasised and Evarts reaffirmed the triple approach by the surgeon, pathologist and radiologist.

1. Plain Radiograph.
2. Radionuclide Scintigraphy.
3. Angiography.
4. Computed Tomography.
5. Magnetic Resonance Imaging.
6. FNAC.
7. Open Biopsy.

Methods of Treatment

Treatment of recurrent lesions is the same as for primary lesions.

The available methods of treatment -

1. **Intralesional Excision**
 - a. Curettage only.
 - b. Curettage with bone grafting.
 - c. Curettage with bone cementing.
 - d. Extended curettage.
2. **En Bloc Resection**
 - a. En bloc resection only.
 - b. En bloc resection with reconstruction.
 - c. En bloc resection and custom arthroplasty.
 - d. En bloc resection and arthrodesis.
3. **Amputation**
4. **Radiotherapy**

This study is aimed at analysing the treatment of the recurrent GCT and aggressive GCT with pathological fracture by adequate curettage using adjuvant like H₂O₂, liquid nitrogen followed by filling the curetted cavity with bone grafts, bone substitutes and bone cement, thereby preventing the recurrence and to provide structural stability in aggressive GCT with Pathological fracture.

MATERIALS AND METHODS

This is a prospective study of management of 32 cases of Giant Cell Tumour during 2003 to 2007 in Government Kilpauk Medical College, Chennai. Out of the 20 cases, 17 cases were Aggressive GCT with pathological fracture and 15 cases were Recurrent GCT. In the cases of Aggressive GCT with Pathological fracture, the bone was structurally unstable and had to be mechanically stabilised. Mere cortical breach does not qualify for this criterion.

Recurrent GCT - 15 Cases

Distal Femur	5
Proximal Tibia	5
Proximal Fibula	1
Distal Radius	3
Metacarpal Bone	1

Table 1. Site

Sex	No. of Cases
Male	9
Female	6

Table 2. Sex

10 - 20	20 - 30	30 - 40
1	11	3

Table 3. Age Incidence

Staging Enneking System

Stage 2

Treatment Methods

- Removal of previously applied bone cement, extended curettage and refilling with bone cement - 5 cases.
- Extended curettage and filling up with bone cement - 6 cases.
- Curettage and bone grafting - 2 cases.
- Amputation of the involved limb with adjuvant usage - 1 case.
- Further Resection and Adjuvant used - 1 case.
- Tourniquet used in all cases. Blood transfusion was not used in any of these cases.

Aggressive GCT with Pathological Fracture - 17 cases

Distal Femur	11
Proximal Tibia	6

Table 4. Site

Sex	No. of Cases
Male	7
Female	10

Table 5. Sex

10 - 20	20 - 30	40 - 50
5	10	2

Table 6. Age Incidence

Staging Enneking System

Stage 3

Treatment Methods

Extended curettage with adjuvants H₂O₂/liquid nitrogen and reconstruction with Fibular Strut graft, cancellous bone graft/bone substitute/bone cement.

Surgical Technique

Intra-lesional excision with extended curettage, adjuvant hydrogen peroxide and reconstruction with bone graft/bone substitute/bone cement.

Patient in supine position under regional or general anaesthesia, tourniquet (without exsanguination) was used during the procedure to decrease local bleeding and prevent

blood from acting as a heat sink and being a barrier for the cryotherapy. Electrocautery was used on all soft tissue dissection, because it potentially extends the margin of tumour kill. Violation of the joint cavity avoided to prevent the possibility of contamination of the joint cavity with tumour cells and potential injury to the cartilage after direct exposure of liquid nitrogen.

Out of 17 cases with pathological fracture, eleven were in distal femur and six in proximal tibia, after exposure a large elliptical cortical window with its axis parallel to the long axis of the bone was made to reduce the stress raising effect on the side of maximum involvement and breach. Adequate window was made and the cavity was curettaged thoroughly. Hydrogen peroxide was used as an adjuvant in 14 cases and liquid nitrogen in three cases.

Before introduction of liquid nitrogen, bone perforations were identified and sealed. The surrounding skin, soft tissues and neurovascular structures were protected. Large skin flaps were retracted to protect them from any possible spillage of the liquid nitrogen.

The direct pour (open) technique as described by Marcove et al was used. Liquid nitrogen was poured through a stainless steel funnel into the tumour cavity and care was taken to fill the entire cavity. The surrounding soft tissues were irrigated with saline solution to decrease the possibility of thermal injury. Two freeze and thaw cycles were administered. In each cycle, liquid nitrogen was left in the cavity until it had evaporated completely. Spontaneous thaw was allowed to occur for 3 - 5 minutes. After evaporation, the cavity was irrigated with saline. Reconstruction was performed with polymethyl methacrylate.

In patients where hydrogen peroxide was used as adjuvant, undiluted hydrogen peroxide was used 3 times with a holding time of 3 minutes each time. When subchondral bone is thinned or absent, cancellous bone harvested from iliac crest mixed along with bone substitutes (G-bone) were packed to a thickness of 3 - 5 mm. Then fibular strut graft was placed across the fracture site longitudinally. If there was an intercondylar fracture of distal femur, the strut was placed transversely and the cavity filled with bone cement.

In 15 cases of recurrent GCT that we managed, five occurred in proximal tibia following curettage and bone cementing without any adjuvant, five occurred in distal femur following curettage and bone grafting without any adjuvant, one in proximal fibula following En bloc resection, another in metacarpal bone following En bloc resection and reconstruction with fibular graft and three in distal radius following curettage and bone grafting.

For proximal tibial recurrence the cement was removed and extended curettage was done using hydrogen peroxide and fixed again with bone cement. For distal femur recurrence, extended curettage with adjuvant H₂O₂ was done and cavity filled with bone cement. Proximal fibula where resection was done previously, further segment of bone was resected and hydrogen peroxide was used to prevent recurrence.

In the case of second metacarpal bone recurrence, second ray amputation was done and hydrogen peroxide was used. Recurrence in distal radius was managed with extended curettage using hydrogen peroxide and bone grafting.

Fresh instruments, an additional layer of surgical drapes and new surgeon gloves were used to complete surgery after the tumour resection and adjuvant treatment. Wound closed with suction drain in situ.

Post-Operative Management and Follow-Up

Routine antibiotics were administered for 5 - 7 days, the drain was removed after 48 hrs. and wound was examined.

For the patients with pathological fracture, the limb was protected in a removable brace for six weeks with intermittent gentle passive mobilisation done under strict supervision. After six weeks the brace was removed, full mobilisation was started and gradual weight bearing allowed only after radiological evidence of union which was between 10 - 12 weeks.

For the patients with recurrent GCT, the wound was examined on the third day after surgery. If the skin was intact, passive and active motion of the adjacent joint was begun. Weight bearing allowed with support after 72 hrs.

Roentgenogram of the tumour site and the chest at 3 months interval for 1 year, at 6 months interval for the following 2 years and annually thereafter was taken to detect local recurrence and pulmonary metastases.

Scoring System

The outcome was graded according to the scoring system of William F. Enneking.⁵

RESULTS

Observations

15 cases of Recurrent GCT and 17 cases of Aggressive GCT with pathological fracture were studied.

Out of 15 recurrent lesions, in five patients Proximal Tibia, in five patients Distal Femur, in three patients Distal Radius, in one patient Proximal Fibula and in one patient Metacarpal Bone were affected.

Out of 17 Aggressive GCT with pathological fracture in 11 patients Distal Femur and in six patients Proximal Tibia were affected.

For recurrent GCT removal of previously applied bone cement, extended curettage with adjuvant Hydrogen Peroxide and reconstruction with bone cement/bone graft/amputation were the treatment methods employed.

For Aggressive GCT with pathological fracture, extended curettage with adjuvant H₂O₂/liquid nitrogen and reconstruction with fibular strut graft/cancellous bone graft, bone substitute and bone cement were the treatment methods employed.

The results were assessed with the scoring system proposed by Enneking.

Factor	No. of Patients	Maximum Attainable Score	Total Score	Rating Percentage
Pain	28	85	82	96
Function	28	85	51	60
Emotional Acceptance	28	85	68	80
Support	28	85	70	82
Walking Ability	28	85	75	88
Gait	28	85	70	82
Average				81.3

Table 7. Scoring after Surgery in Lower Extremity

Factor	No. of Patients	Maximum Attainable Score	Total Score	Rating Percentage
Pain	4	15	15	100
Function	4	15	14	93
Emotional Acceptance	4	15	14	93
Hand Positioning	4	15	14	93
Manual Dexterity	4	15	14	93
Lifting Ability	4	15	13	86
Average				93

Table 8. Scoring after Surgery in Upper Extremity

The average follow-up was 2 years.

Two patients had superficial wound infection, which healed well with antibiotics.

There were no neurovascular complications, malignant change, recurrence, pathological fracture and metastasis.

Radiologically, there was no lysis at cement bone interface.

The average rating percentage for patients after surgery in lower extremity was 81.3. The average rating percentage for patients after surgery in upper extremity was 93.

Recurrent GCT

Fig 1: Initial Presentation

Fig 2: After 2 months of initial procedure, curettage & bone cement

Fig 3: Substitute Procedure – Cement Removal, Extended Curettage & Bone Cement

Aggressive GCT with Pathological Fracture

Fig 4: Pre-op Clinical

Fig 5: Pre-op X-ray

Fig 6: Lesion After Exposure

Fig 7: Cavity Before Curettage

Fig 8: Using H₂O₂ as Adjuvant

Fig 9: Curetted Material

Fig 10: Placing Fibular Strut Graft

Fig 11: With Bone Cement

Fig 12: Immediate Post-Op

Fig 13: One-Month Follow-Up

DISCUSSION

Local recurrence is a well-documented problem. Recurrence can be in the bone or in the soft tissue. Rate of local recurrence depends on the site (distal radius greater than proximal tibia or distal femur) and adequacy of treatment.⁶ Higher rates of recurrence have been noted in tumours of the distal end of radius, tumours with pathological fracture and Stage-III tumours according to the classification of Campanacci.⁷

Goldenberg stated that 25 percent of the recurrences were within 6 months and 97 percent within two years.⁸

The factors that would have led to recurrence were inadequate curettage and lack of extended curettage with adjuvants.

Local recurrence has been as frequent as 50% after simple curettage and 7% after excision with curettage, 0% after wide or radical resection. A report of a large series stated that 25% of the recurrences were within 6 months and 97% within 2 years.

In this study, we treated 17 cases of Aggressive GCT with pathological fracture and 15 cases of Recurrent GCT with pathological fracture.

Simple curettage or curettage with bone grafting resulted in recurrence varying from 30% to 80%.⁹ Various adjuvants such as electrocautery, phenol, liquid nitrogen and hydrogen peroxide have reduced the recurrence rate to 10%.¹⁰

Hydrogen peroxide is preferred over other adjuvants, because it is less toxic to surrounding tissues, has the same efficacy in terms of preventing recurrence¹⁰ and in vitro studies have demonstrated that in lesser concentration it produces cell lysis and death.¹¹

Patients presenting with pathological fracture and loss of cortical bone support of less than 50% of the cross sectional area of the bone, extended curettage with PMMA reconstruction as treatment is suggested.¹² Sung et al described a procedure of excision and curettage in such cases where the main bulk of tumour is excised, retaining the articular cartilage covered by a thin shell of bone and then the remaining cavity curetted. In their 12 cases, they have not had any recurrence.⁹

Other forms of treatment like massive allograft construction have increased chances of infection, fracture and recurrence. In patients with GCT occurring in third decade, having otherwise normal lifespan if constrained endoprosthesis is used; they will develop early loosening and loss of bone stalk. They will require a very complicated salvage procedure within a very short span of time.

We report 17 cases of aggressive GCT with pathological fracture with more than 50% of cortical bone involvement treated by partial excision and reconstruction with fibular strut graft and bone cement. All had good functional range of motion with an average flexion of up to 100° and full weight bearing on an average of 4.5 months following surgery.

Adjuvants - Their Mechanisms of Action and Complication

1. Liquid Nitrogen - Cryosurgery^{13,14,15}

Extreme cold is used to produce tissue necrosis.

Temperatures between - 21° and - 60° are needed to obtain cellular necrosis, temperatures below -60° exert no further lethality.

The following Mechanism Underlie Cellular Injury at Subzero Temperatures-

1. Thermal shock.
2. Dehydration and toxic effects of electrolyte changes.
3. Formation of intracellular ice crystals and membrane disruption - most important mechanism.
4. Denaturation of cellular proteins.
5. Microvascular failure - most likely cause of late complications.

Function involved in the Spread of Freezing and Subsequent Necroses are¹⁵

1. Density and vascularity of bone.
2. Presence or absence of tourniquet.
3. Size and temperature of the heat sink.
4. Duration of freeze.
5. The presence of cryoprotective molecules.

Limiting Factors of Cryosurgery are¹⁵

1. Size usually 5 inches is the maximum diameter capable of being adequately frozen and therefore necrotised.
2. When a tumour spilled into a joint, an en bloc resection would be preferable.

Marcove et al described a direct pour technique, in which liquid nitrogen is poured directly into a curetted tumour cavity instead of being introduced through the closed system.¹⁶ This method has the advantage of increasing the contact of the coolant with the irregular walls of curetted cavities.

Rapid Freeze and Slow Thaw Cycle is Recommended¹⁴

Rapid freeze causes intracellular ice crystals to form, whereas slow freeze causes cellular dehydration. Conversely, a slow thaw will cause intracellular crystallisation and membrane disruption, whereas a rapid thaw will not. This is explained by the physics of crystallisation. If there is slow warming, the numerous intracellular crystals will recrystallise into a few large crystals that will damage the cell membrane upon fast warming; the intracellular crystals will melt before they can damage the cell.

Repeated freeze thaw cycles will also increase the extent of necrosis. This is due to increased conductivity of cold after the first freeze.

Marcove et al stated that three freeze and thaw cycles produce tumour cell death up to 2 cms from the cavity margin.

Advantages

1. The rate of local recurrence is around 4 percent.
2. Preservation of adjacent joint.
3. Avoidance of the need for extensive reconstruction by prosthetic replacement, allograft or arthrodesis.

Disadvantages

1. Wound problems - 5 to 10%.
2. Late pathological fracture - 11 to 28%.
3. Transient neurapraxia.

2. PHENOL^{3,17,18}

Phenol solution eliminates the remaining cells by non-specific coagulation necrosis and DNA damage.

The reported concentration of phenol solution used for this purpose varies from 5% to 75%.

Curetted cavity should be filled with pure liquid phenol for 30 to 45 seconds. After removal of the phenol, the cavity is rinsed with 75 to 85% alcohol; the alcohol residue is then removed by vigorous saline lavage.

Advantage

1. Reduced penetration of phenol causes one to one and a half millimetres of bone injury and reduced rate of fracture.
2. High rate of cure and preservation of adjacent joint.

Disadvantages

Phenol is toxic to the nervous system, the heart, the kidneys and the liver and is readily absorbed through skin, mucosa and open wounds.¹⁸

The use of concentrations higher than 5 percent is hazardous and the lethal dose in 1 gm.¹⁸

3. Hydrogen Peroxide^{10,11}

H₂O₂ causes cell death by inhibiting lactate production in tumour cells.

Cell death occurs at concentration of 30 mm H₂O₂, which is substantially lower than the 3% (880 mm) H₂O₂ commonly used clinically.

In a follow up series of 38 patients treated with curettage, H₂O₂ adjuvant and bone cementing, the recurrence rate was 8%. There have been no reported negative clinical effects of exposure to H₂O₂.

Polymethyl Methacrylate acts as filler and provides immediate stability to the bone, but it does not act as an

adjuvant in reducing the rate of recurrence.¹⁰ Recurrence occurred following reconstruction with bone cement without using adjuvant. We removed the bone cement and the cavity was curettaged following by bone cementing.

En bloc resection resulted in similar or more recurrence rate than curettage, probably because of higher radiological grade or local tissue contamination. We had 4 cases of recurrent GCT out of 13 cases of En bloc resection, which were done without using adjuvant. They were managed with a proximal resection and hydrogen peroxide was used as an adjuvant. Three cases of distal radius where curettage and bone grafting resulted in recurrence. We did an extended curettage using hydrogen peroxide and bone grafting.

CONCLUSION

GCT is a locally aggressive benign tumour occurring in young individuals with a normal life expectancy. If inadequately or inappropriately treated, it results in considerable morbidity and recurrence.

Careful attention to soft tissue protection while using cryosurgery significantly decreased the previously published reports of high rates of infection and wound healing problem.

Hydrogen peroxide is an ideal adjuvant, which gives a comparable rate of recurrence and least local or systemic complications. Free fibular strut graft along with PMMA incorporates in the bone early and the joints can be salvaged with useful function. En bloc resection must also be followed by adjuvant to prevent recurrence due to local tissue contamination.

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