A DISSERTATION ON

"FUNCTIONAL OUTCOME AND TIME TAKEN FOR CONSOLIDATION IN GIANT CELL TUMOR AFTER FIBULAR STRUT GRAFTING BASED ON INTRATUMOR CAVITY VOLUME – A RETROSPECTIVE AND PROSPECTIVE STUDY"

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M.S. BRANCH II (ORTHOPAEDIC SURGERY)

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CERTIFICATE

This is to certify that this dissertation titled **"FUNCTIONAL OUTCOME AND TIME TAKEN FOR CONSOLIDATION IN GIANT CELL TUMOR AFTER FIBULAR STRUT GRAFTING BASED ON INTRATUMOR CAVITY VOLUME – A RETROSPECTIVE AND PROSPECTIVE STUDY"** is a bonafide record of work done by **DR.GOVINDARAJU M,** during the period of his post graduate study from May 2017 to April 2020 under guidance and supervision in the **INSTITUTE OF ORTHOPAEDICS AND TRAUMATOLOGY,** Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-600003, in partial fulfilment of the requirement for **M.S.ORTHOPAEDIC SURGERY** degree Examination of The Tamil Nadu Dr. M.G.R. Medical University to be held in April 2020.

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DECLARATION

I, **Dr.GOVINDARAJU M**, declare that the dissertation entitled **"FUNCTIONAL OUTCOME AND TIME TAKEN FOR CONSOLIDATION IN GIANT CELL TUMOR AFTER FIBULAR STRUT GRAFTING BASED ON INTRATUMOR CAVITY VOLUME – A RETROSPECTIVE AND PROSPECTIVE STUDY"** submitted by me for the degree of M.S ORTHO is the record work carried out by me during the period of April 2017 to September 2019 under the guidance of **Prof.V.SINGARAVADIVELU, M.S.Ortho.,D.Ortho.Ph.D,** Professor of Orthopaedics, Institute of Orthopaedics and traumatology,Madras Medical College, Chennai. This dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfilment of the University regulations for the award of degree of M.S.ORTHOPAEDICS (BRANCH-II) examination to be held in April 2019.

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CONTENTS

INTRODUCTION

Giant cell tumor is one of the commonly encountered bone tumor in the field of orthopaedics. Giant cell tumor represents around 4-5% of all primary bone tumors. Giant cell tumor tends to be more predominant in the Asian population, with the incidence being 20 % of all primary bone tumors. But there is no striking racial variation.

Giant cell tumor commonly affects the age group of 20 to 40 years, typically after epiphyseal closure. Although 10-15% occur in the second decade. Giant cell tumor is seldom seen in skeletally immature individuals and seen very rarely in children below 10 years. The incidence is found to be more common in females. The most common site of involvement is distal femur ,followed by proximal tibia, distal radius and proximal humerus .

Around 5% affect the flat bones, especially those of the pelvis. The sacrum is the commonest site in the axial skeleton while other vertebral bodies are less often involved. Fewer than 5% cases affects the tubular bones of the hands and feet. Multicentric giant cell tumors are very rare and tend to involve the small bones of the distal extremities. Rarely , tumors with the morphology of Giant cell tumor arise primarily with in soft tissue.

Patients with Giant cell tumor typically presents with pain ,swelling and often limitation of joint movement. The clinical presentation is usually delayed because of its slow growing nature. The severity of pain increases as the bone lesion expands.

Frequently, the patients are asymptomatic until a trivial trauma causes pain on the affected side .As the affected bone is osteoporotic these patients are easily susceptible to fracture with trivial trauma.5 -10% of such cases tend to sustain pathological fractures which is a common finding.

The most common site of metastasis is the lungs. The incidence of distant metastasis is low with this tumour. Less than 5% incidence of pulmonary metastasis has been reported. Therefore Giant cell tumour has a low mortality rate. It is frequently termed as a locally aggressive disease even though the distant metastasis is low. This is because of the local bone destroying nature of the tumor with a propensity for erosion through the cortical bone into the surrounding soft tissues.

Giant cell tumor involves the epiphysis region in proximity to the joint. In such case, surgical clearance of the tumour becomes difficult in an attempt to preserve subchondral bone.

The most common and dreaded complication following surgical resection is recurrence. The recurrence rates have been varying depending on the type of clearance and adjuvant agents used as described in literature.

Few years before the initial treatment of Giant cell tumor was amputation followed by radiotherapy. Once it was found to be a benign lesion the treatment principle changed to curettage of the lesion. Initial literatures reported high recurrence rates of more than 50%. A preference for wide resection then came into the treatment options. However wide resection associated with higher rates of surgical

complications and leads to functional impairment, generally necessitating reconstruction changed the emphasis back into improved methods of curettage. Extended curettage reduce the recurrence rate with use of power burrs and new surgical techniques. Use of local adjuvants like Liquid nitrogen, phenol and hydrogen peroxide decrease the recurrence rate which was proven on in vitro studies. Micro metastasis of the tumor is controlled by use of systemic adjuvants like Zoledronic acid and Denosumab.

Improvement in local control rate of the tumor is noted, with the use of modern techniques . A meticulous clearance of the tumor forms is very important in any surgical technique which cannot be replaced by use of adjuvants used by local and systemic routes.

AIMS & OBJECTIVES

- The aim of the study is to analyse consolidation time in relation to the intra tumor cavity volume in Giant cell tumor after treated with curettage & fibular strut grafting and zoledronic acid adjuvant.

- Functional outcome of the patients with giant cell tumor after treated with curettage & fibular strut grafting and zoledronic acid adjuvant.

REVIEW OF LITEARTURE

Cooper in 1818 first described Giant cell tumors (GCT) of the bone. Nelaton showed their local aggressiveness, and Virchow revealed their malignant potential.

McGrath PJ et al[1] in 1972 study shows that giant cell tumors are commonly affect third and fourth decades of life in more than half of the cases.

GCTs are benign tumors with potential for aggressive behaviour and capacity to metastasize.

Eckardt JJ et al[2] study shows the Incidence of Giant cell tumor is 5% of all primary bone tumors.

Although considered to be benign tumors of bone, GCT has a relatively high recurrence rate. Metastases occur in 1% to 9% of patients with GCT and some earlier studies have correlated the incidence of metastases with aggressive growth and local recurrence.

The management protocol for Giant cell tumor is not constant. It is continuously changing in the field of Orthopaedic oncology. The various treatment modalities aim to control the high recurrence rate inherent of the tumor while maximizing joint function.

Radiotherapy and amputation are the earliest treatment methods in literature a followed by simple curettage of the lesion with bone grafting. However, high recurrence rates are noted following these procedures.

DAHLIN et al [3] in 1970 study shows that the recurrence rate was as high as 60% in patients treated with curettage and bone grafting. Based on their observation

they recommends a more aggressive removal of the tumor to decrease the recurrence rate.

Other studies with high recurrence rates were observed. GOLDENBERG et al[4] study shows a recurrence rate of 55 %, while McCARTH PJ [1] in 1972 reported with a recurrence of 45 % in his study group.

Giant cell tumour mostly affects the patients in their third and fourth decades of the life and earlier studies favours the radical management which includes wide resection and arthrodesis which affects the quality of life of these patients. Although wide resection was associated with low recurrence rates, the functional activity of the native joint was severely compromised. .

Considering the benign nature of the tumor and the young population group affected , a conservative line of management was proposed.

MARCOVE in 1978 study reports only with 5% of recurrence rate by using liquid nitrogen as a adjuvant to curettage but has increased incidence of pathological fracture. [5]

Similar results produced by ROCK et al in 1984 used Phenol as a adjuvant, with fewer complications. [6]

The recurrence rate dramatically decreased to 10 % by treating with curettage and cauterization and filling the defect with methyl ,methacrylate by Prof De CAMARGO in 1990.[7]

Towards the end of the millennium, a large gathering happened in Rizzoli Institute, Bologna for the effective management of giant cell tumour. For that, 750 operated cases were analysed and finally concluded recurrence rate is drastically reduced with the use of two or more adjuvant local and systemic adjuvants. [8]

The adjuvants which are used to manage the recurrence of giant cell tumour includes both local adjuvant and systemic adjuvants. The local adjuvant destroys the tumour cells left behind the curettage while the systemic adjuvants control micro metastasis.

The major complication of giant cell tumour is the pathological fracture of the affected bone. The Traditional teachings suggested wide resection of the affected bone while recent studies suggests that the mere presence of fracture does not needs drastic resection.

FRASSICA et al , 1993 in their biomechanical studies concluded that 98% mechanical strength to bone defects can be attained with the use of bone cement. [9]

CHENG et al in 2004 used 6 doses of Pamidronate at weekly intervals prior to curettage of Giant cell tumor in 12 patients. At 4 years follow up the recurrence rate was 8.3%. [10]

LACKMAN et al in 2005 Conducted study on 63 GCT cases and found that when cement was used, there is only 6% recurrence rate. Additionally, they observed Excellent Musculo Skeletal Tumour Society scores in over 90 % of the patients. [11]

KRIEG et al study in 2007 showed equally good results with only slightly longer time of union in their study on 30 cases where non vascularised fibula was used to bridge the bone defect. [12]

In this study population, fibular graft was used as a single, double or triple strut which were stabilised with screws, plate or just wedged in the bone. With a mean time to consolidation of 6 months, they observed good functional activity postoperatively in all the patients.

Several points were put forth to contradict the common belief that there is no biological activity for non vascularised fibula and it undergoes eventual desorption with time.

Growth of the fibula can be determined by hypertrophy index over a period of time . It was found that stabilisation does not influence hypertrophy and 70% of the fibula showed hypertrophy. There was increased mobility of unsupported fibulas which showed faster growth rate.

In 2 cases, there was fracture of fibular graft that eventually healed with formation of callus when immobilisation was done with Plaster of Paris.

They observed that the donor site fibula have been completely regenerated at about 4 years after surgery.

BALKE et.al [13] in 2008 studied the efficacy of Bisphosphonates in 25 cases of aggressive recurrent, primary and metastatic Giant cell tumours which includes the

study group of persistently recurrent tumours, tumours with distant metastasis and inoperable tumours. No further recurrence of the tumor was noted in some patients. The Patients who are treated non operatively showed symptomatic improvement with no further increase in size of the tumor .In the later study, tumour tissue was taken from patients and incubated in vitro in bone tissue culture and found that lacunar resorption was inhibited when bisphosphonates was added to the sample.

TSE et al[14] in 2008 studied on Giant cell tumour . He divided 44 cases into two groups. One group was treated with Zoledronic acid in addition to curettage while for the other group curettage alone was done. The first group showed the recurrence rate of 5% , while the second group showed the recurrence rate of 30%. For the first group, 2 doses of Zoledronic acid was given prior to surgery and bone mineral density was evaluated at the time of initiation of treatment and at the time of surgery using Dual Emission X- Ray Absorptiometer (DEXA). Zoledronic acid were given prior to surgery. An increased mineralisation of the lesion was observed at the time of surgery.[14]

ARPORNCHAYANON et al [15] study in 2008 reported on case of Giant cell tumor of the sacrum with severe radiating pain and neurological deficit. The case was treated with 7 doses of Zoledronic acid on either side of surgery. At 2 years follow up, the patient had no pain or neurological deficit with no signs of recurrence.

Kivioja et al study in 2008 found a recurrence rate of 22% in cases treated with curettage and bone cement. The recurrence rate was increased to 47% when bone grafting was used to fill the defect which is formed after curettage. [16]

JAMSHIDI et al in his study of 42 giant cell tumour cases that were treated with curettage and cement packing reported 17% recurrence rate in 2008. [17]

PERRSONN [18] study in 2009 published the similar results with recurrence rate of 12% at a minimum follow up for 2 years and it is consistently reproduced by other surgeons.

KAFCHITSAS et al studied two groups of patients to find the recurrence rates of the disease. One group had a recurrence rate of 53% who are treated with curettage and bone graft. And another group showed 23% in recurrence rated who are treated with curettage and cementation in 2010.[19]

KAFCHITSAS et al in his study concluded that in cases where bone cement was used, recurrence can be detected early by observation of the lucent zone surrounding bone cement. 21 patients who are treated with bone cement after curettage were observed by him. He picked up 4 cases from progressively enlarging lucent zone in 2010 .[19]

TORIGOE et al in 2011 retrospectively studied 35 patients of giant cell tumor presented with pathological fracture. This study reviewed 35 patients Giant cell tumor complicating pathological fracture study reveals the recurrence rate of 29% which is

slightly higher than the overall recurrence rate of 21%. In this study curettage was done in 6 patients and one patient was treated with wide resection .[20]

HEIJDER et al in 2012 studied a population of 63 patients with pathological fracture from a total of 420 patients of giant cell tumor and reported that the recurrence rate is not much significant when curettage alone was performed. They also recommends wide resection only when there is a soft tissue involvement seen on MRI. [21]

As adjunct to curettage of giant cell tumour, anti osteoporotic agents like Denosumab and Bisphosponates were added following their successful use in osteoporotic conditions like Multiple myeloma and bone secondaries.

Promotion of stromal cell apoptosis is done by Bisphosphonates which are the chief neoplastic component promoting proliferation of osteoclasts. Denosumab interferes with RANK-RANK ligand interaction in the pathway at latter stages.

YU et al in 2013 studied on patients by administering oral alendronate daily for the first two years, who are already operated with curettage and found no recurrences at 2 years follow up. [22]

YU et al in his group of patients who are treated with curettage and bone cement, started knee joint mobilisation from the 3 rd postoperative day and toe touch weight bearing was started after 2 weeks in 2013.[22]

Although the use of bone cement has got number of advantages ,there are certain disadvantages of bone cement which are as follows :

It is an inert material and neither can it be incorporated with the host bone nor can remodel along the line of stress.

There is risk of injury to the articular cartilage due to the thermicidal action of bone owing to the location of such tumours at the epiphysis.

Hence, there is a concern about the usage of bone cement filling on the long run.

The use of vascularised fibular grafts is very much complicated,but for over 100 years, it has been used for filling the bony defects after tumor excision. Than vascularised fibular grafts , the use of non vascularised fibular struts is more favourable for supporting the cavity.

GOUIN et.al in 2013 studied for French Sarcoma and Bone Tumour. The study group analysed over 200 cases of Giant cell tumour.[23] They analysed various matching factors in the recurrent group and concluded with several possible factors for recurrence. The use of a high speed burr for curettage at the time of surgery was considered the main factor for preventing recurrence –a fact consistent with several other studies .Use of an auto graft to fill the cavity which is formed after curettage was ascribed an Odd's ratio of 3.9 for further recurrence. Another conclusion in their study was, the patients who are not treated with Bisphosponates as an adjuvant to curettage was associated with an increased risk of recurrence.

In 2014 Meta analysis of 6 studies performed by KAISER et al comprising more than 500 cases of giant cell tumour where use of systemic adjuvants had only 7% and the use of curettage alone shows a recurrence rate of 50%. The cases which are not responding to surgical excision with no further increase in size of the swelling shows stabilisation of the disease. [24]

Patients who are treated with i.v. bisphosphonates , the study recommends prior monitoring of renal parameters and oral alendronate had mild gastrointestinal complaints. 10% of patients discontinued denosumab with 84% patients having adverse side effects.

GOUIN et al in 2014 performed curettage of Giant cell tumor in 20 patients with no local adjuvant. Instead of that ,the patients for whom the curettage done was supplemented with five doses of post operative Zoledronic acid. This study shows 15% recurrence rate at 5 years follow up. [25]

GAO et al study in 2014 used bone graft to fill the cavity formed after curettage and found threefold increase in recurrence rates (36%vs 13%) .[26]

Yeng et al postulated that when the giant cell tumour irrigated with Zolendronic acid post curettage show decreased recurrence rate of the tumor.

The ideal choice for filling the cavity which is left behind by curettage has been greatly debated upon . Two method of choice was commonly employed - autogenous iliac crest grafting and cement filling . multiple studies are in the

literature for effective management, may have supremacy over the other but none was the universal accepted.

Bone graft packing has traditionally been thought to increase the recurrence rate in Giant cell tumour and several studies proved the same result.

Cement packing which has number of advantages over others was recently favoured by surgeons.

The surrounding tumour cells that are left behind the curettage are killed by the herbicidal action of the bone cement . Multiple studies in the literature shows that the filling the defect with bony cement leads to low recurrence rate. There is an advantage of weight bearing and earlier initiation of knee range of motion.

There was no literature found for assessing the volume of Giant cell tumor. Kyoto-Ho Shin, MD et al study in 2005 using ellipsoid formula in radiography and CT to measure the tumor volume in osteosarcoma . [27]

Jyoti Bajpai et al in 2010 study about Role of MRI in about 31 osteosarcoma patients, for its evaluation and prediction of its response to chemotherapy .In their study ellipsoid method of volume calculation was used. [28]

Panjabi et al study in 1985 demonstrated that continuity of the cortex was the best predictor while callus area was the least important predictor to determine healing of the fracture in an experimental study .[29]

Murray et al study of 18 patients of distal radius GCT treated with Fibular graft shows consolidation time of 4-5 months in 1986. [30]

M. San Julian Aranguren et al in 1995 concluded that after en block resection of tumors , the mean time of consolidation for metaphyseal and diaphyseal osteotomies was 6.5 and 16 months respectively , in their study about Consolidation of bone when massive bone allografts were used in limb-preserving operations for bone tumours .[31]

Alkalay et al in 1996 has been advised that first stage includes curettage, open reduction, autologous bone grafting, and temporary bone–cement filling. Following bone union, after mean average 5 months the second operation includes recurettage, cryosurgery, and cementing with stable internal fixation. In this series, four patients had intra-articular fracture and all treated by a single surgery by extended curettage bone grafting, minimum internal fixation and spanning external fixation, and all outcomes were successful. [32]

Aithal et al study of 30 patients of distal radius GCT treated with Fibular graft shows consolidation time of 5.2 months in 2003. [33]

Corrales et al review of 77 clinical studies in 2008, found that the most commonly used clinical criteria to define the fracture consolidation of long bones are as follows: Absence of pain or tenderness with bearing of weight, Absence of pain or tenderness at the site of fracture during examination.[34]

George et al study of 17 patients in 2008 with benign lesions of the proximal femur with non-vascularised, autologous fibular strut grafts, without osteosynthesis .All achieved partial or complete consolidation of the lesion within 12 months. Partial consolidation was defined as more than 50% radio-opacity of the defect and full consolidation as 100% radio-opacity. [35]

Jamshidi et al in 2008 study of fifteen patients treated with Osteoarticular allograft reconstruction of the distal radius after giant cell tumor resection. Primary fusion of the graft was achieved in 14 patients. The average time of union was 3.5 months (range: 2.5-6 months), found 3 cases of recurrence. One patient developed non-union and 9 patients had instability of the distal radioulnar joint. Degenerative changes were found in all of the patients .[36]

Bassiony et al AA study of ten patients in 2009 with a mean age of 33.4 years, with either Campanacci grade II or III histologically proven giant cell tumours of lower end radius were treated with wide excision and reconstruction with ipsilateral non-vascularised proximal fibular autograft. Host graft junction was fixed with dynamic compression plate (DCP) in all cases. Wrist ligament reconstruction and fixation of the head of the fibula with carpal bones and distal end of the ulna using K-wires and primary cancellous iliac crest grafting at graft host junction was done in all cases. The follow-up ranged from 30 to 60 months (mean, 46.8). The average union time was 7 months (range, 4 to 12). Non-union occurred in 1 case. Graft resorption occurred in another case. Localised soft tissue recurrence occurred in another case after 3 years and was treated by excision. There was no case of graft fracture,

metastasis, death, local recurrence or significant donor site morbidity. A total of 3 secondary procedures were required .[37]

Asavamongkolkul et al in 2009 study of 7 patients of distal radius GCT treated with Fibular graft shows consolidation time of 5 months with fewer complication.

Chadha et al study of 9 patients of distal radius GCT treated with Fibular graft shows consolidation time of 6 months with good functional outcome and fewer complication .[38]

Bone consolidation process which is a simple biological phenomenon occurs in stages as follows: Hematoma, Inflammation, Angiogenesis, Formation of cartilage (with subsequent calcification, removal of cartilage, and then formation of bone), and finally bone remodelling. Complete healing of the fracture takes several months, and occurs only after the completion of all these stages .[39]

From a clinical standpoint, consolidation of the fracture can be considered at the end of the repair phase. The criteria for this definition is subdivided into clinical examination data (e.g., bearing of weight without local pain and lack of mobility at the site of fracture) and patient-related factors (such as quality of life). [40]

Saini et al study of Twelve patients treated with En bloc excision and autogenous fibular reconstruction for aggressive giant cell tumor of distal radius shows Average time for union at fibuloradial junction was 33 weeks (14-69 weeks) but non union in two of our patients which was treated with bone grafting. Nevertheless, they eventually achieved union in both these cases in 2011. [41]

Hungria JOS et al found that plain radiography remains the most common radiological method for assessing healing of fractures. Some suggest that the presence of at least three consolidated cortices which when observed in two radiographic views (anteroposterior [AP] and lateral [L] can be considered as a criterion to determine fracture consolidation. [42]

Duan et al study shows 15 patients with giant cell tumors of the distal radius who were treated with en bloc excision and osteoarticular allograft reconstruction with LCPs .All of the junctions between the allogeneic radius and and the autogeneic radius exhibited callus after 2–3 months of operation and bone union on X-ray at 9 months (range 6–12 months). No patient had allograft bone fracture, non-union, or metastases found acceptable results after 5.2 years in 15 patients treated with radial allograft. They did not find non-union or allograft fracture. [43]

Chung et al treated 12 patients with GCT stage 2 based on the Enneking classification. Union had occurred after nearly 16 weeks in all patients with moderately satisfactory grip strength, range of motion and functional outcomes. However, skin grafting was required in 5 patients. [44]

Flouzat-Lachaniette et al treated 13 patients with distal radius GCT with limited arthrodesis after en bloc resection and reconstruction with nonvascularized fibular auto graft shows result of union with the average of 5- 6 months in 2017. [45]

Tuteja Sanesh et al study in 2016 shows a case of Recurrent GCT of Distal Femur Treated with Resection Arthrodesis with Non-Vascularised bilateral Fibular

Graft and a Custom - Made Interlock Nail . In follow up X-rays revealed consolidation of the graft and union at the graft-host junction and Hypertrophy of the fibular graft 2 years post surgery. [46]

Adel R. Ahmed ET AL[47] study in 2017 shows the results of 30 patients are continuously free of disease and there is no local recurrence.Extended curettage, bone grafting, and spanning external fixation for the treatment of juxta-articular giant cell tumor of the bone around the knee. All the patients showed union starting from 2 months after surgery with full consolidation 6 months after surgery. The fixator was removed at 4–12 months after surgery. Radiologically, 29 (97%) patients had complete incorporation of the graft and one (3%) patient had partial incorporation.

Farshad Safdari et al study of 5 patients in 2017 with primary Giant Cell Tumor and 2 patients with recurrent giant cell tumor of Distal Radius treated with En Bloc Resection and Partial Wrist Arthrodesis using Non-Vascularised Fibular Autograft . After 8.3 ± 0.5 months, complete union was achieved.

In this study a case of recurrent GCT initially treated with cementing treated with fibular graft autogenous corticocancellous ipsilateral patellar bone graft for arthrodesis . Follow up radiograph 5 years after surgery showed solid union and arthrodesis of the knee, but with persistent low-grade infection. [48]

Krieg et al in his study in 31 patients for whom a non-vascularised fibular graft was used after tumor resection of primary musculoskeletal tumors, in a median follow-up period of 5.6 years (3 to 26.7 years). Primary union was achieved in 89% (41 of 46) of the grafts in a median period of 24 weeks. They also found that fibular

grafts that were longer than 12 cm and those without fixation of plate or nail had a higher rate of hypertrophy due to the increased mechanical stress at the junctions .[12]

INCIDENCE AND LOCALIZATION

Giant cell tumor of the bone accounts for 5 % of primary bone malignancies, with the incidence rising up to 20 % in the Asian population.[49,50] The neoplasm is most common in the age group of 20 to 40. [51] Nearly 70 % of the cases fall within this age group. The occurrence of Giant cell tumor is uncommon in patients less than 20 years of age and in skeletally immature individuals. Similarly the occurrence of Giant cell tumor is unusual in individuals older than 55 years of age.

Giant cell tumor has been reported to be more common in the female population. The average ratio of involvement of females to males has been estimated to be around 1.25 : 1. [52]

The tumor has a predilection to occur around the knee joint. The distal end of the femur is the most commonly affected site followed closely by the proximal tibia and the distal radius. [53] Involvement of the axial skeleton is rare. If involvement does occur, the sacrum is affected most commonly. The occurrence of Giant cell tumor in flat bones and ribs is exceedingly rare.

Giant cell tumor occurs in the epiphyseal region close to the joint. Inspite of its location, the articular involvement is not common. The swelling is eccentrically located and tends to expand the cortex surrounding it, growing outward. The cortex may be eroded leading to contamination of the surrounding soft tissue with tumor cells.

PATHOGENESIS OF GIANT CELL TUMOR

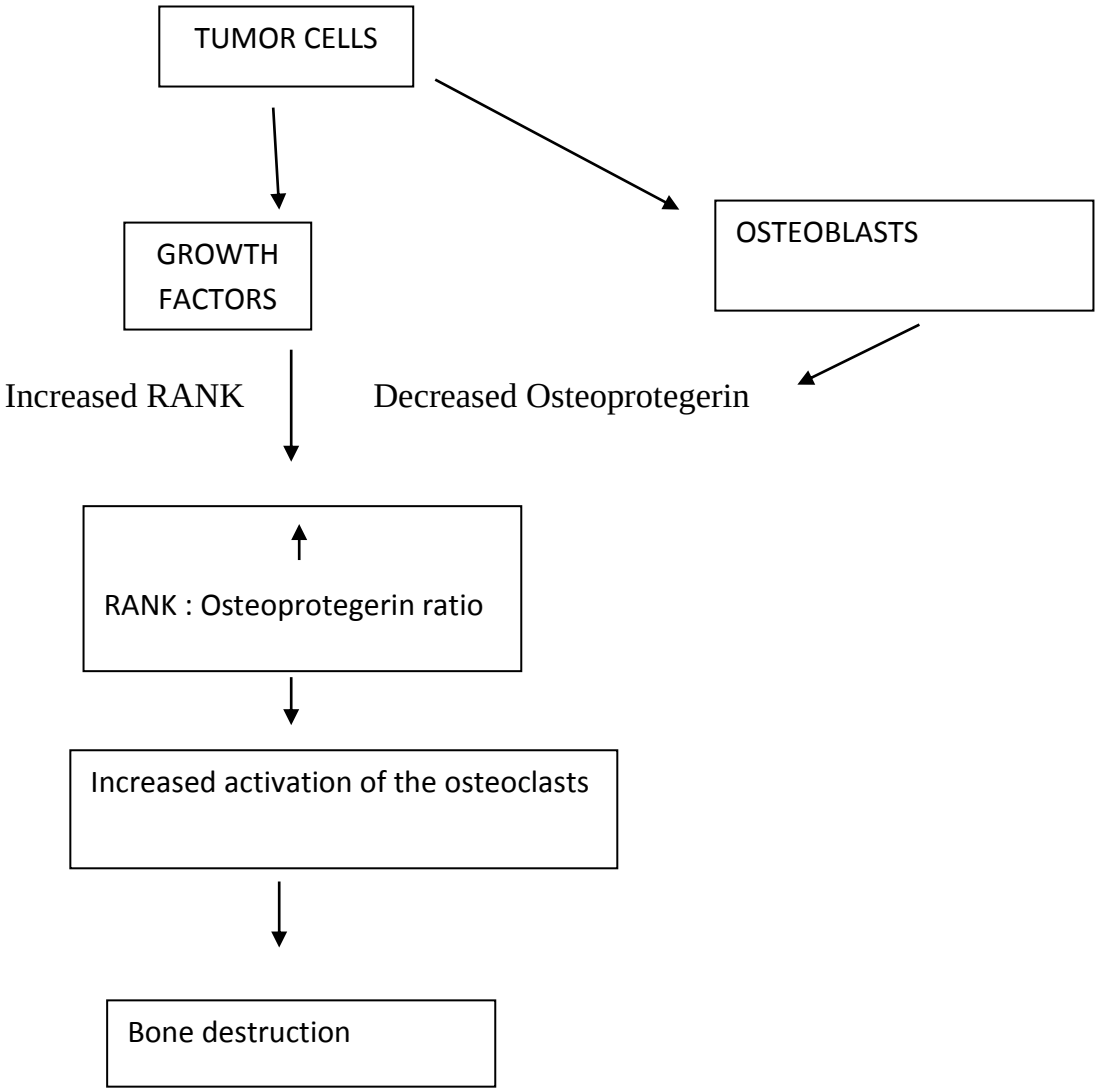
Of the three cellular elements constituting Giant cell tumor - only the stromal cells are malignant. The other two groups of cells are a reactive response to the stromal cells.

The ***RANK ligand –RANK – Osteoprotegerin pathway*** has been implicated in the pathogenesis of the disease. This signalling cascade is essential for bone remodelling.[54] Inappropriate and excess activation of the pathway leads on to tumor formation.

The RANK ligand binds to the RANK expressed on the surface of the osteoclast precursors. This in turn activates a group of molecules called TRAFs – Tumor Necrosis Factor Receptor Associated Factors which set into motion a sequence of events culminating in activation of NF-kB (Nuclear Factor Kappa – B). NF – Kb promotes the expression of genes required for osteoclast maturation.[55]

Osteoprotegerin is a molecule which down regulates the above pathway. It can bind to RANK and hence indirectly reduces the interaction of RANK – RANK ligand. The balance between the two molecules is tightly regulated under physiological conditions to meet the demands of the body. The ratio of RANK ligand to Osteoprotegerin increase during the activation and differentiation of osteoclasts and decreases during the differentiation of precursor osteoblast cells into mature osteoblasts.[56]

Over expression of RANK ligand by the stromal cells is the key factor in the pathogenesis of Giant cell tumor. This over expression drives the differentiation of monocytes into multinucleated Giant cells. The giant cells in turn promote the bone resorption at the tumor site and are responsible for the locally aggressive nature of the disease. A number of factors are secreted by the tumor cells which down regulate the expression of Osteoprotegerin. The RANK: Osteoprotegerin ratio is significantly decreased.



CLINICAL FEATURES

The patients typically complain of pain – initially related to activity and only in advanced cases being evident at rest. Frequently a history of trauma is given prior to the onset of symptoms. The pain is associated with a slow growing mass in the same site. The severity of the pain may be suddenly aggravated by a pathological fracture.[57]

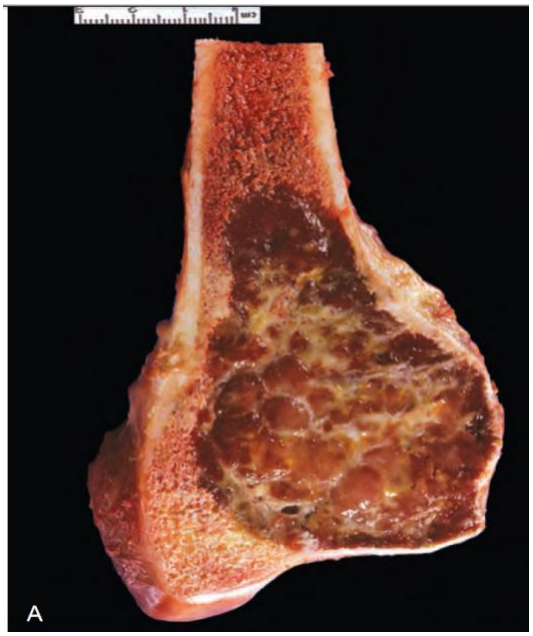
On physical examination a tender hard swelling can be palpated. The skin over the swelling may be warm. Egg shell crackling can be observed. There is disuse atrophy of the muscle and a decreased joint range of motion.

Giant cell tumor of the spine has a predilection to affect the vertebral body. The body may collapse leading on to a kyphotic deformity. The extension of the tumor into the surrounding epidural space can lead on to radicular pain and neurological deficit.[58]

GROSS APPEARANCE

The resected bone specimen of Giant cell tumor when bisected reveals a reddish brown growth interspersed with yellowish areas. The tumor is localized to one side of the bone and extends distally to the level of the articular cartilage. The articular cartilage is resistant to invasion by the tumor. The portion of the growth extending proximally tends to be more centrally located. The overlying cortex is frequently involved in the disease process and the native contour of the bone itself may be lost. The more benign lesions tend to be surrounded by a thin rim of periosteal new bone.[59]

It is common to find areas of haemorrhage and necrosis scattered within the tumor. The tumor may be multiloculated containing fluid filled cysts. The tumor is soft and friable on palpation. The cortical continuity may be compromised and pathological fractures are frequent complication. The tumor is well demarcated from the surrounding uninvolved region of bone.[60]



HISTOLOGY

On microscopic examination, three types of cells are seen in the Giant cell tumor that are distributed in a background of well vascularised stroma. The following are the cellular components seen in giant cell tumor :

1. Spindle shaped mononuclear stromal cells

2. Multinucleate giant cells

3. Mononuclear cells.[61]

SPINDLE SHAPED MONONUCLEAR STROMAL CELLS : These cells are the main neoplastic component of Giant cell tumor . RANK ligand (Receptor Activator for Nuclear Factor – kappa ligand) is released by these cells which promotes proliferation of osteoclasts that results in resorption of bone.[62]

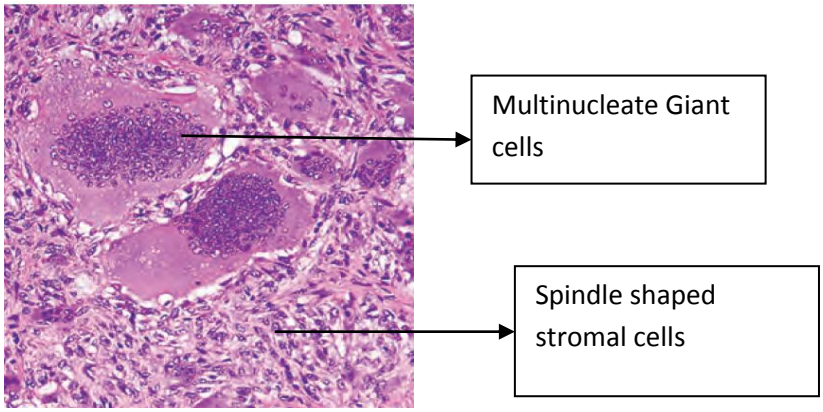
MONONUCLEAR CELLS : The precursor lesions of the multinucleate giant cells are represented by these cells. Giant cell is formed as a result of fusion of these cells in large number.[63]

GIANT CELLS : The hallmark feature of Giant cell tumor are these giant cells. However, they can occur in many other conditions . Those conditions are hence called as Giant cell variants. Upto 100 nuclei are packed centrally in these multinucleate giant cells.

Giant cells have well defined nucleus with a fine chromatin pattern and well defined nucleolus and densely eosinophilic cytoplasm with a ragged outline.[64] The stromal cells have similar nuclei like that of Giant Cells. This feature differentiates Giant cell tumor from other Giant cell variants.

The following are the histological variations of Giant cell tumor. The stromal cells can be pleomorphic appearing either as plump spindle shape cells or as elongated fibroblast like cells. Sometimes the tumor entirely can be masked by massive fibrohistiocytic reaction that resembles a benign fibrohistiocytoma. Sometimes, there can be co-existence of aneurysmal bone cyst. Giant cell tumor can itself lead to secondary aneurysmal bone cyst.[65]

There may be high mitotic rate but atypical mitosis does not occur. The tumor cells can cause vascular invasion. There may be areas of haemorrhage and necrosis. The nature of the tumor cannot be predicted by any of the features like mitosis, vascular invasion or necrosis.



HISTOLOGICAL GRADING SYSTEM OF JAFFE[66]

GRADE I – COMPLETELY BENIGN

Moderately vascular stroma containing spindle and ovoid cells.

Giant cells may be abundant in number.

Mitosis is absent or very minimal.

GRADE II – BORDERLINE

Compact cellular stroma with numerous mononuclear cells.

Evidence of atypia and mitotic activity.

GRADE III – FRANKLY SARCOMATOUS

Pleomorphic stromal cells.

Giant cells are very few in number.

High degree of cellular atypia and mitotic activity.

The drawbacks of this Jaffe's grading system are that neither the prognosis nor the aggressiveness of the tumor can be predicted .

RADIOGRAPHIC FINDINGS

On plain X – ray, giant cell tumor shows a well defined lytic lesion over the epiphysis which can extend into the metaphysis or even portions of the subchondral bone. The location of the tumor is eccentric and grows outward. There is frequent thinning of the overlying cortex and there is loss of bone contour. In long standing disease, erosion of the cortex may be observed. There are many trabeculations within the tumor making it appear multiloculated to be termed as radiographic *Soap Bubble appearance*.[67]

Bony or cartilaginous matrix is absent. There is no periosteal new bone formation. If so, it can be associated with pathological fracture. In a few cases, the tumor may be surrounded by a thin rim of sclerosis.

The intramedullary and extra osseous extent of the tumor can be identified by MRI.[68] On T1 weighted images, the lesion appears dark and on T2 weighted images, it gives a bright signal. When there is associated aneurysmal bone cyst, fluid – fluid levels can be identified by the MRI.[69]

There is only limited role for CT scan that can show subtle cortical erosions.[70] CT chest can be taken to rule out lung metastasis.

RADIOLOGICAL CLASSIFICATION – CAMPANACCI GRADING[71]

GRADE 1

Well defined margins.

The tumor is surrounded by a thin rim of mature bone.

The cortex is not involved or shows minimal involvement.

The bone is not deformed.

GRADE II

Well defined margins but surrounding rim is absent.

The cortex is moderately expanded but still intact.

GRADE III

Fuzzy margins.

Breach in the cortex.

Tumor extension into the surrounding soft tissue.

ENNEKING'S STAGING[72]

Enneking's staging of Giant cell tumors is based on clinical, pathological and radiological evaluation.

LATENT STAGE

10 to 15 % of the cases; often asymptomatic – discovered incidentally.

Histologically benign.

Surrounded by a rim of sclerotic bone on X Ray and inactive on bone scan.

ACTIVE STAGE

70 % of the cases; Symptomatic - often present with a pathological fracture.

Histologically benign.

Can present with an expanded cortex on X Rays but there is no breach.

Active on bone scan.

AGGRESSIVE STAGE

10 to 15 % of the cases; Symptomatic - rapidly growing tumor.

X Ray shows a breach in the cortex with surrounding soft tissue extension.

Activity on bone scan extends beyond the zone visible on X Rays. Intense vascularity on angiogram but histologically benign.

COMPLICATIONS

25 % of Giant cell tumors have aggressive behaviour.[73] The features of aggressive behaviour of the tumor are destruction of the local bone, cortex deformation and surrounding soft tissue invasion.[74] Histological examination and radiographs cannot pick up aggressive ones.

Curettage is the most commonly employed method of treatment. There is high recurrence rate of 25 to 35 % when simple curettage of the cavity is done.[75] Recurrence most commonly occurs in the first three years after surgery.[76] The recurrent tumor resembles the primary tumor. Recurrence can be reduced by wide local excision and allograft or prosthesis reconstruction. But the disadvantage is reduced joint function. There may be implantation of the tumor in the soft tissue region at the time of surgical removal that can result in recurrence.

Giant cell tumors are locally aggressive. In the past, Giant cell tumor was thought to undergo malignant transformation. This was the reason for giving radiation as part of treatment in the past.[77] It is no longer routinely used and there is decline of sarcomatous transformation of these lesions. De novo malignant transformation of Giant cell tumor is rare.

3 % of Giant cell tumors can metastasize to the lungs. It presents as lung nodule for which surgical excision is curative.[78] But pulmonary metastasis can lead to death in a small proportion of patients.[79]

DIFFERENTIAL DIAGNOSIS[80]

Several other conditions can mimic giant cell tumor on radiological or histological examination. They are as follows :

Giant cell reparative granuloma

It is a benign entity in which there is osseous reaction to many unknown conditions. Area of haemorrhage or trauma to a region of bone is the precursor for both the diseases. Giant cell reparative granulomas presents as solitary lesions involving the mandible or maxilla. But in Giant cell tumor, the craniofacial skeleton is involved de novo unless arising from a pre-existing Paget's disease. Reactive granulomas are characterized by the presence of an uniform giant cell arrangement that distinguishes them from giant cell tumor. There may be areas of bone production and stroma collagenisation.

Brown's Tumor :

It represents a subset of Giant cell granuloma. It occurs in response to a known inciting event – hyperparathyroidism. Clinically the patient will have an elevated parathyroid hormone levels, high calcium levels and low phosphorous levels, all of which are markers of hyperparathyroidism. Brown's tumor is characterized by multiple lytic lesions.

Non ossifying fibroma :

Radiograph shows lytic lesions. Non ossifying fibroma is characterized by tumor location in the metaphysis and an open epiphysis.

CARTILAGINOUS TUMORS:

Chondroblastoma and ***Chondromyxoid Fibroma*** also have multiple giant cells. But in Chondroblastoma, epiphysis is involved. Other distinguishing features are the presence of cartilaginous matrix and the absence of plump, spindle shaped mononuclear cells in cartilaginous tumors.

OSTEOSARCOMA AND MALIGNANT FIBROHISTIOCYTOMA :

Numerous giant cells are also present in these tumors on microscopic examination. But, these malignant tumors have other features such as nuclear atypia and atypical mitosis favouring their aggressive behaviour.

ANEURYSMAL BONE CYST :

These tumours show many similarities with giant cell tumor. A well recognised complication of Giant cell tumor is the formation of aneurysmal bone cyst. 10 % of secondary aneurysmal bone cysts is attributed to Giant cell tumors. It is characterized by solid areas of stroma with numerous giant cells. Careful examination and radiographic interpretation is needed to diagnose the primary condition.

MATERIALS AND METHODOLOGY

STUDY CENTRE:

Institute of Orthopaedics and Traumatology,

Rajiv Gandhi Government General Hospital, Chennai.

DURATION OF STUDY:

36 months.

TYPE OF STUDY:

Retrospective and Prospective study.

SAMPLE SIZE:

15 patients.

INCLUSION CRITERIA:

Patients with tissue diagnosis of giant cell tumor.

Solitary lesions.

Localised lesions.

All primary Giant cell tumors.

Recurrent Giant cell tumors.

Giant cell tumors with pathological fractures.

EXCLUSION CRITERIA:

Multicentric lesions.

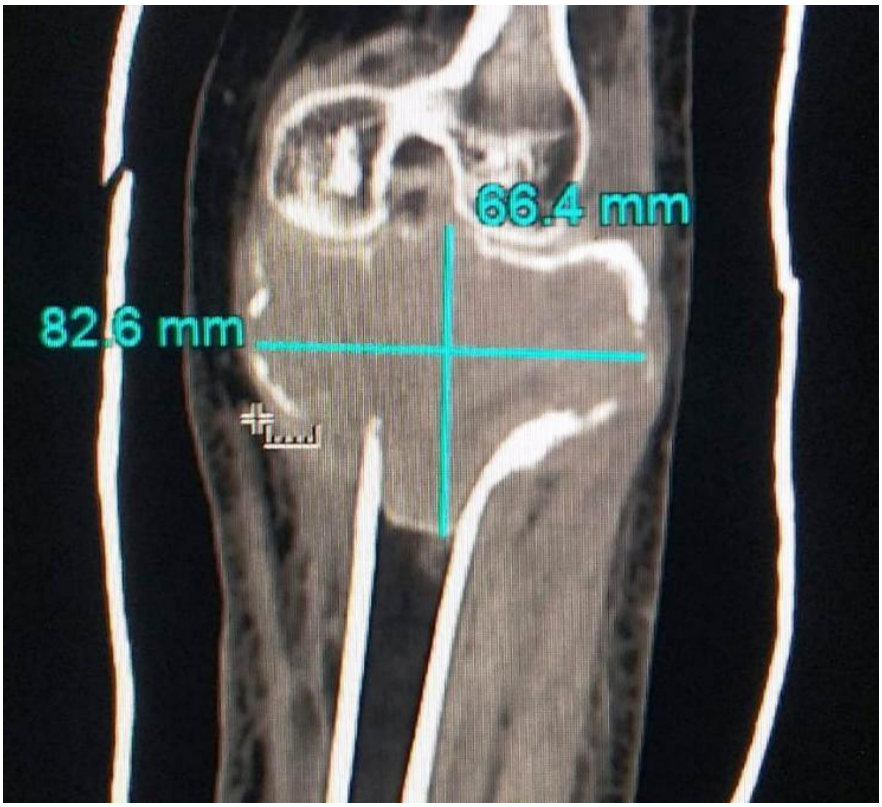
Patients with metastasis.

Fungating growth.

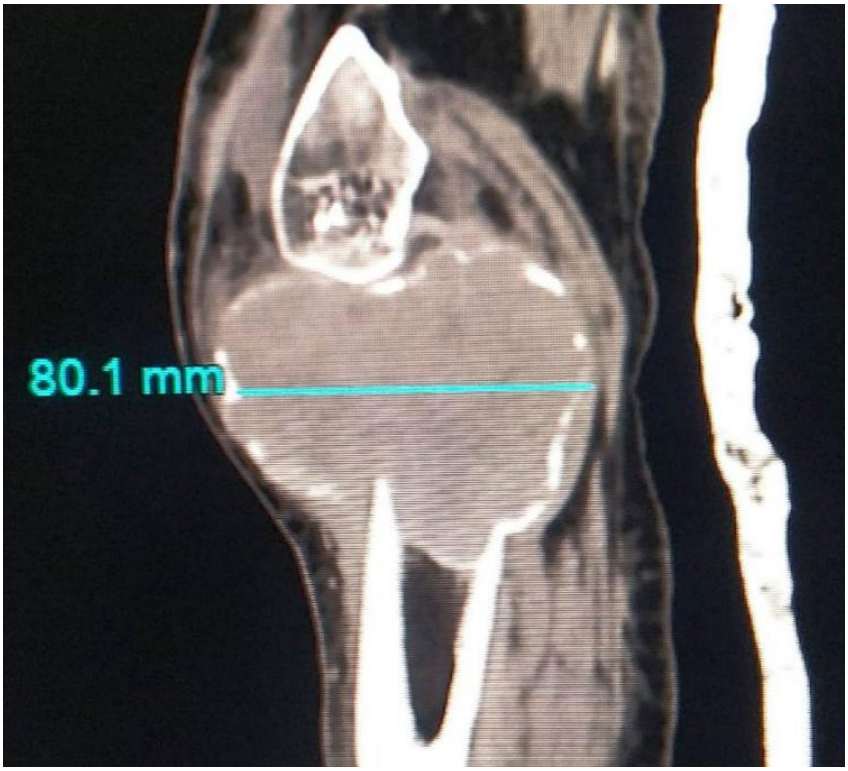
Patients with reduced creatinine clearance.

MEASUREMENT OF TUMOR VOLUME [27]

Tumour volume was measured on CT. The outermost boundaries of tumour density visible on three planes of the lesion site were marked, and the greatest dimensions for width (in anteroposterior (AP) view), depth (in lateral view), and length (in AP and lateral view) were measured. Tumor volume was calculated using the formula of an ellipsoid mass volume = [(0.5) X height X width X depth].



Measurement of width and length in anteroposterior view of CT.



Measurement of depth in lateral view of CT.

MANAGEMENT PROTOCOL

Core needle biopsy / fine needle aspiration cytology was done for patients with features suggestive of giant cell tumor such as epiphyseal, eccentric, expansile lytic lesion. Blood investigation such as serum calcium and phosphorus were taken along with the routine blood investigations. Intramedullary spread of the tumor and possible soft tissue invasion was confirmed by MRI. Lung metastasis was ruled out by doing CT chest. The tumor volume was measured using CT or MRI scan by ellipsoid method of volume calculation formula.

Informed written consent was obtained from all the patients regarding the course of the treatment. As stated by Cockrauft and Gault in *Nephron,1976.* Creatinine clearance was calculated using the Cockcroft Gault formula . As per FDA standards a minimum of 60 ml per minute creatinine clearance was taken for administration of 4 mg of Zoledronic acid. After adequate prehydration, Zoledronic acid was administered over 15 minutes in 100 ml of normal saline. After each dose of zoledronic acid creatinine clearance was calculated.

Following the administration of first dose of zoledronic acid surgery was done after 3 weeks. Under strict aseptic precautions, appropriate anaesthesia under tourniquet control, the surgery was performed. Thorough curettage of the lesion was done. Adequate surgical clearance was obtained using power burrs. Tumor remnants in the cavity was thoroughly washed. A total of three hydrogen peroxide washes were given with minimum of three minutes for each wash.

The length of fibula needed to be resected was calculated by measuring dimensions of the cavity intra operatively. Proximal tibia cavities were generally supported by two struts – one mediolateral and one superoinferior strut. An additional anteroposterior strut was given in addition when the support provided by the above two struts was inadequate in distal femur.

Measured length of fibula was resected using a posterolateral approach. Distal femur lesions were filled with fibular strut grafts taken from same side and the proximal tibia lesions were filled with fibular strut grafts taken from opposite side. The proximal 5cm of fibula was spared to protect the common peroneal nerve. The distal 5cm was spared to avoid ankle instability.

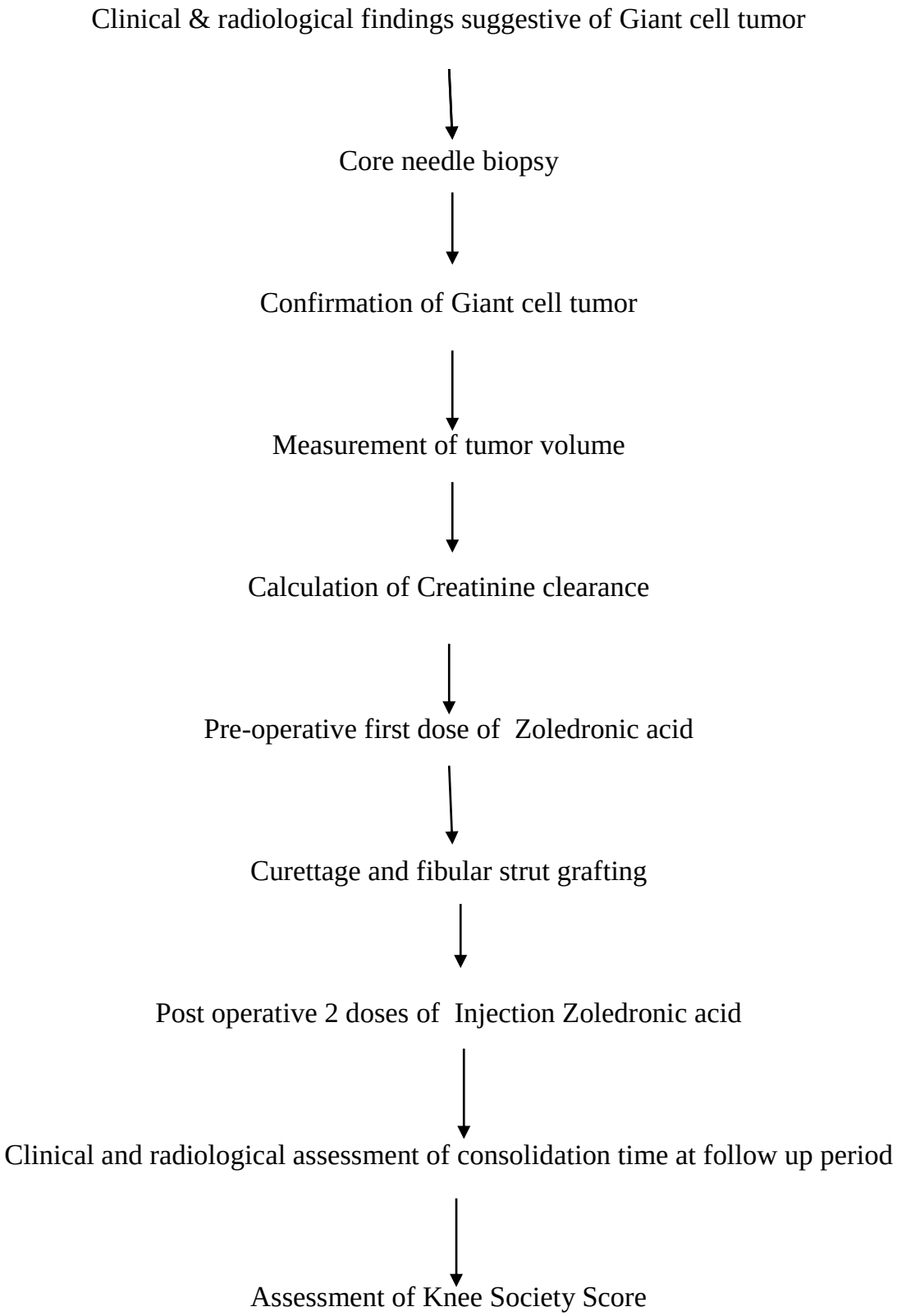
The superoinferior strut was placed over the mediolateral strut which was positioned initially. The another free end of the superoinferior strut was hitched against the host cortex. The cavity was well supported by the fibular graft construct.

In the immediate post operative period, patients were immobilized and supported by above knee slab. Antibiotics were started and given for the first three days to prevent postoperative infections. After ensuring adequate wound healing, suture removal was done on the 12^{th} post operative day. The patients were protected with above knee casts and were kept in strict non weight bearing.

The second dose of Zoledronic acid was given after three weeks post surgery. 6 weeks following second dose of Zoledronic acid ,the final dose of Zoledronic acid was administered.

Routine radiographs were taken at 6 weeks, 12 weeks, 4 months, 5 months, 6 months, 1 year and at 6 months intervals thereafter. The appearance of callus formation at graft host interface was noted. Filling of opacification in the cavity was noted. Incorporation of graft into the host bone was studied to assess the time taken for consolidation of the fibular graft. After appearance of callus formation and signs of union of the graft with the host, plaster immobilisation was discontinued and partial weight bearing was initiated. After complete consolidation of the graft which is assessed clinically and radiologically, full weight bearing was started.

Knee Society Score was used to assess the functional outcome of the patients every 6 months postoperatively.


Clinical & radiological findings suggestive of Giant cell tumor
Core needle biopsy
Confirmation of Giant cell tumor
Measurement of tumor volume
Calculation of Creatinine clearance
Pre-operative first dose of Zoledronic acid
Curettage and fibular strut grafting
Post operative 2 doses of Injection Zoledronic acid
Clinical and radiological assessment of consolidation time at follow up period
Assessment of Knee Society Score

NEER CLASSIFICATION

The quality of bone healing according to radiologic healing status was assesed in follow up X-rays using modified Neer's classification.

Score	Classification	Description
I	Healed	Cyst filled with new bone, with or without small radiolucent area(s) <1 cm in size.
II	Healed with defects	Radiolucent area(s)<50% of diameter of the bone with enough cortical thickness to prevent fracture.
III	Persistent cyst	Radiolucent area >50% of the diameter of the bone and with a thin cortical rim; no increase of the size of the cyst.
IV	Recurrent cyst	Cyst reappeared in a previously obliterated area or a radiolucent area has increased in size.

RESULTS

A total of 11 patients with Giant cell tumor admitted in Rajiv Gandhi Government General Hospital were included in the study. All the patients had a biopsy proven Giant cell tumor.

The average age group of the study population was 30 years (18 – 39).

Males and females were equally distributed in the study group – Males 5; Females 6 (Sex Ratio – 0.8 :1).

8 patients had a primary Giant cell tumor (80%) while two patients had a recurrent Giant cell tumor (20%). 1 patient had a giant cell tumour with pathological fracture.

Distal femur (50%) and Proximal tibia (50%) were equally involved in our study.

The primary tumors were staged radiologically with the Campanacci grading. There were no cases of Grade I tumors. The greatest propotion of the tumors were Grade II (63%) while Grade III tumors accounted for 37 % of the tumors.

1 case (10 %) had a pathological fracture through the affected region. MRI did not reveal any soft tissue extension through the defect.

CT scan of the chest was made mandatory for all the patients to look for metastasis at the time of diagnosis. Lung metastasis was not detected in any patient.

Measurement of tumor cavity volume was done using CT scan pre operatively.

The average tumor volume was 92 cm^3. 63% were having tumor volume less than 92 cm^3. 27% of cases had tumor volume more than 92 cm^3.

The mean time interval between Zoledronic acid administration and surgery was 20 days (10 – 26 days).

Ipsilateral fibula was harvested in 45 % of the patients while the contralateral fibula was used in 55 % of the cases.

Patients were immobilised post operatively in an above knee cast. The average period of immobilisation was 10 weeks (4 – 16 weeks). The patients were started on toe touch weight bearing at the time of plaster removal.

The average time taken to start full weight bearing was 18 weeks (12 – 22 weeks). The average time taken for consolidation is 18 weeks. 64% of cases showed consolidation in 10-15 weeks. 18% of cases showed consolidation in 15-20 weeks. 18% of cases showed consolidation in more than 20 weeks.

All patients were available for the final follow up. The longest follow up was 2 1/2 years while the shortest follow up was for 6 months.

No patient sustained a pathological fracture of the femur
following the procedure.

No recurrence was seen in any of the patients. There were no motor or sensory symptoms of common peroneal nerve palsy on the side of fibular resection.

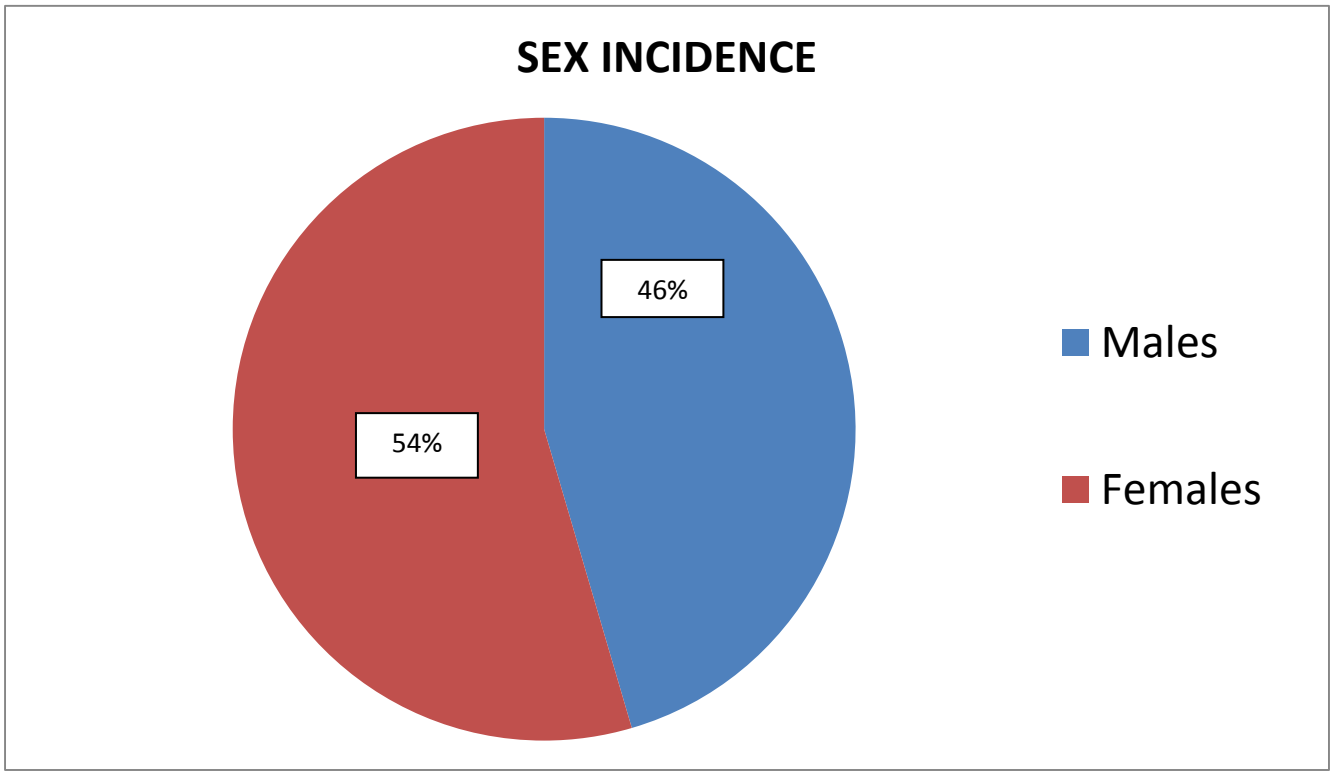
6 patients regained a knee flexion of more than 90 degree (55 %). 4 patients had a knee flexion between 60 and 90 degrees (36%). Only one patient had a knee flexion of less than 60 degrees (9%).

The Knee Society Score was calculated at 6 months interval. 6 patients had an excellent outcome at the final follow up (54%). 3 patients (27 %) had a good outcome. 2 patients (19%) had a fair outcome.

One patient had a post operative infection with Acinetobacter. The infection did not subside with i.v. antibiotics. A wound wash was performed and antibiotic beads were placed. The beads were removed after 6 weeks. The infection subsided post operatively.

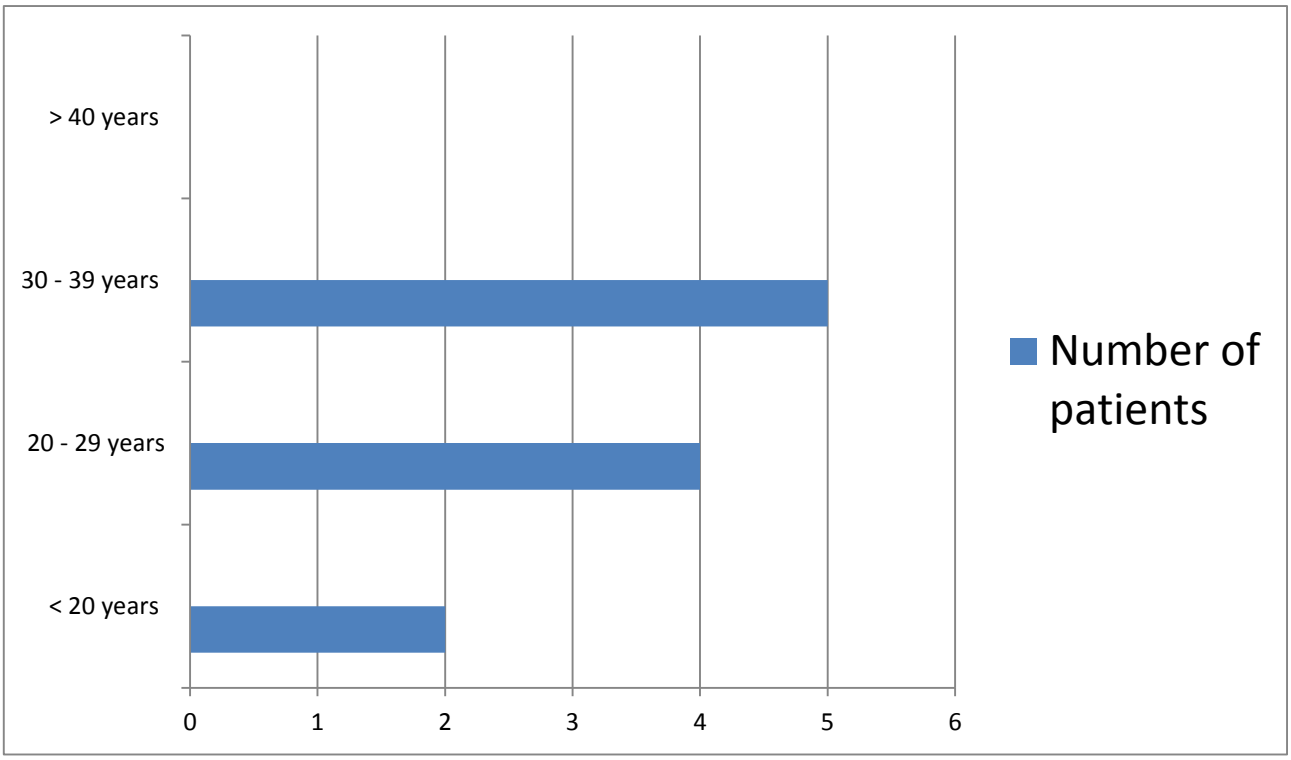
SEX INCIDENCE

In our study, males and females were equally affected. (0.8:1 ratio)



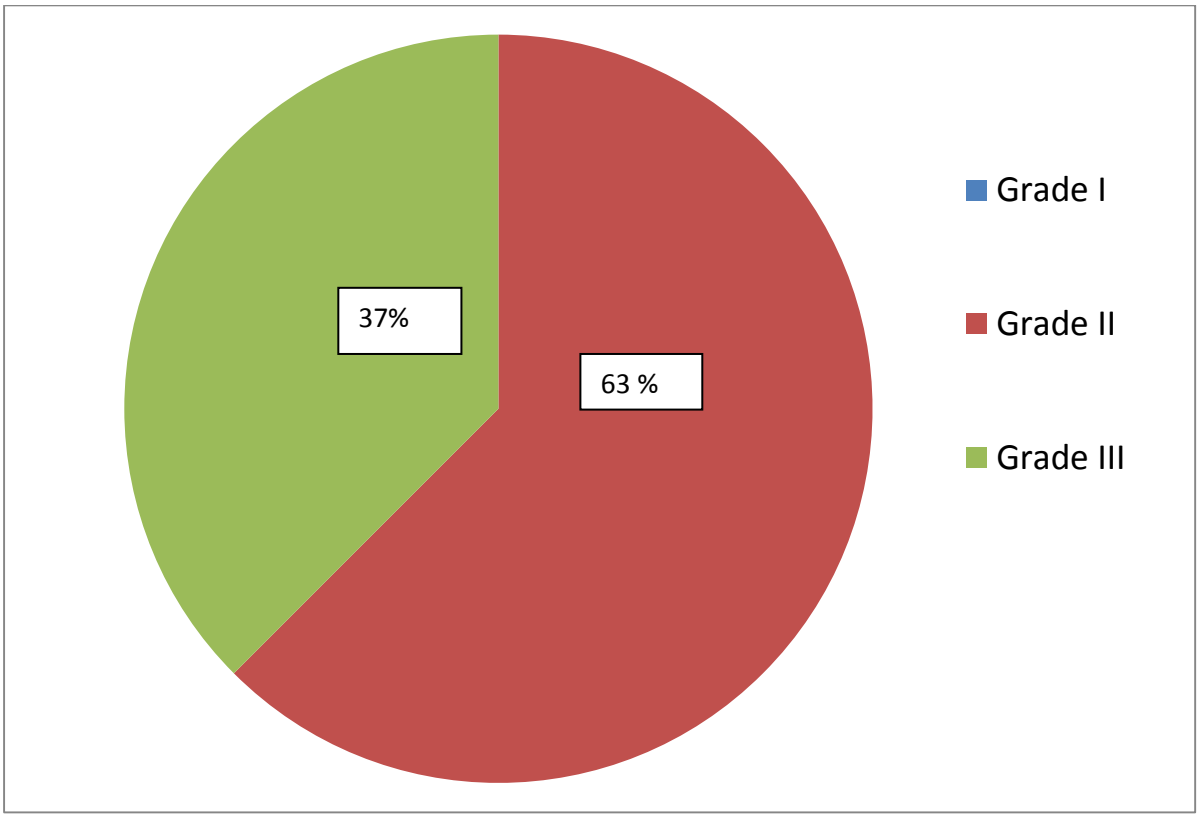
AGE INCIDENCE

The average age of the study group was 29. The minimum age was 18 and maximum 39.



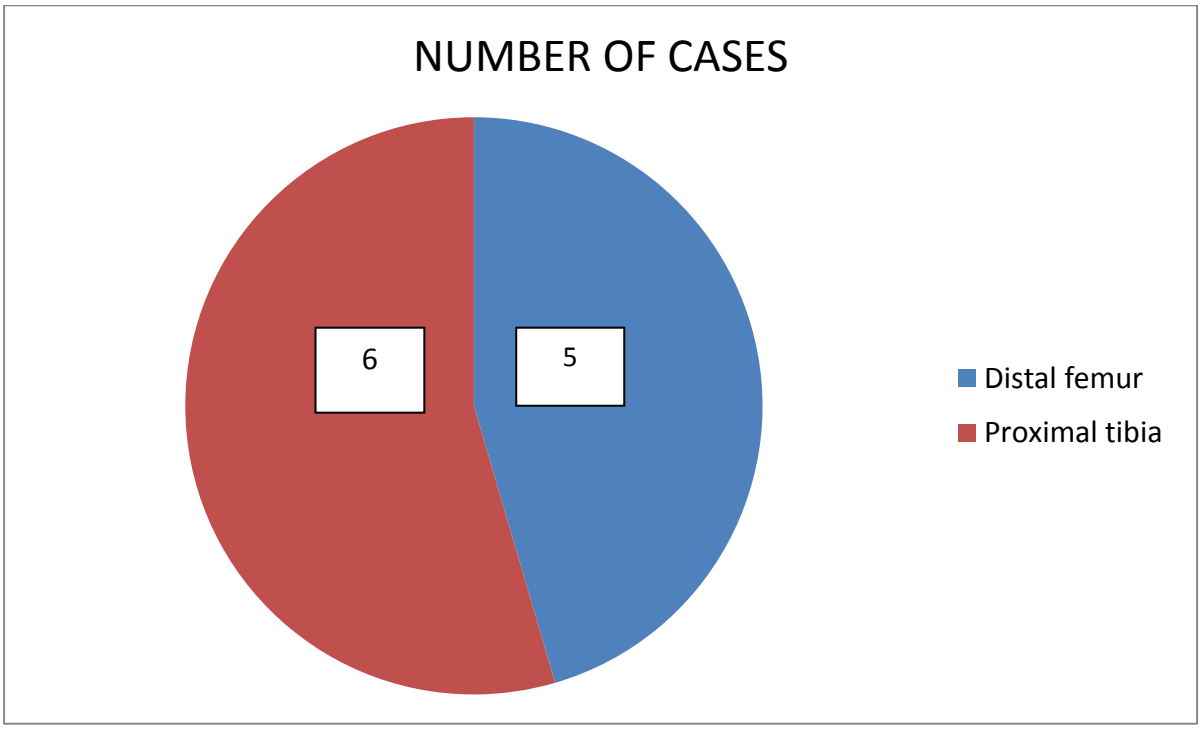
CAMPANACCI GRADING

56 % of the study group had a Grade II tumor while the remaining 30 % of primary cases had a Grade III tumor. No Grade I tumors were diagnosed in our study.



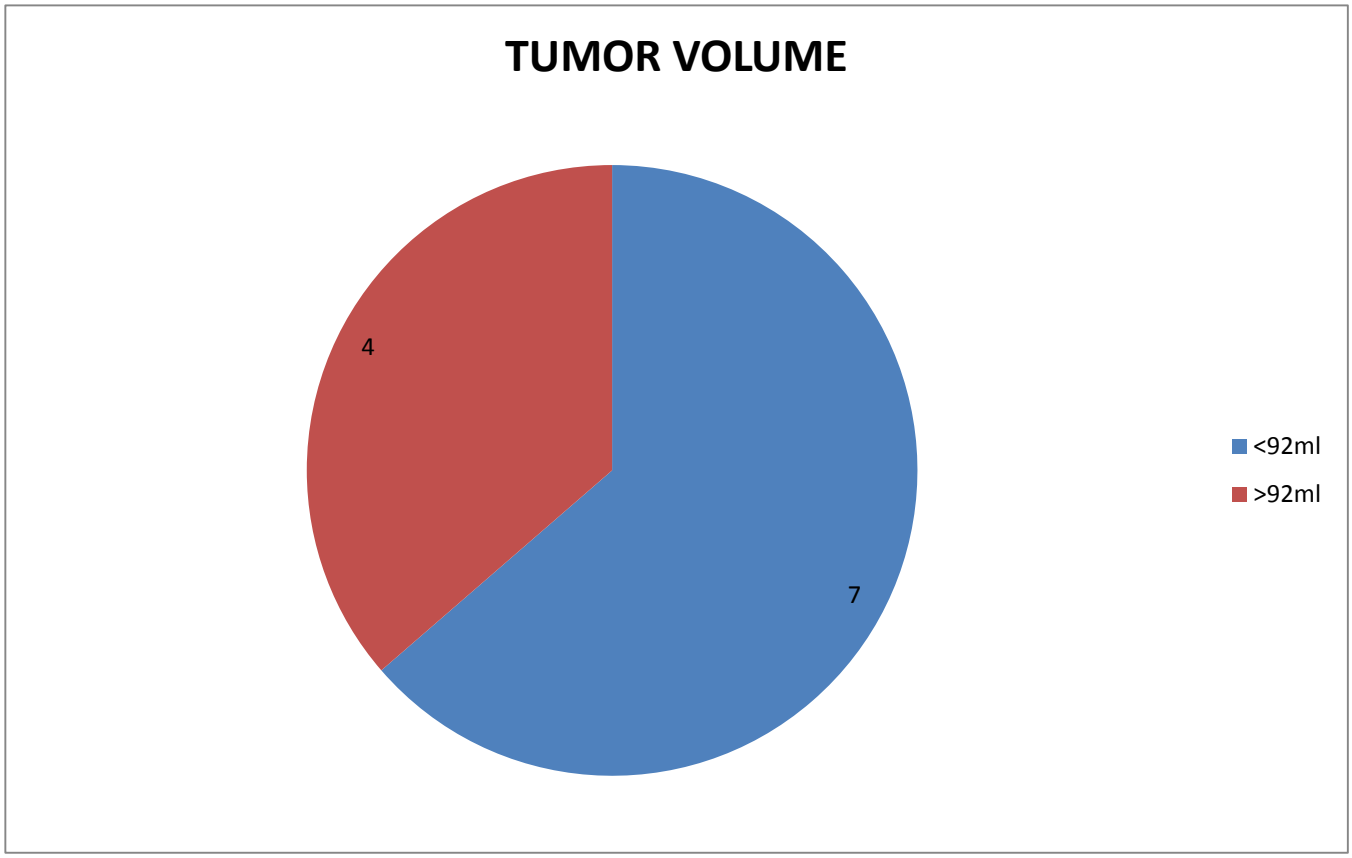
SITE OF INVOLVEMENT

Distal femur 5 cases and Proximal tibia 6 cases were affected in the study group .



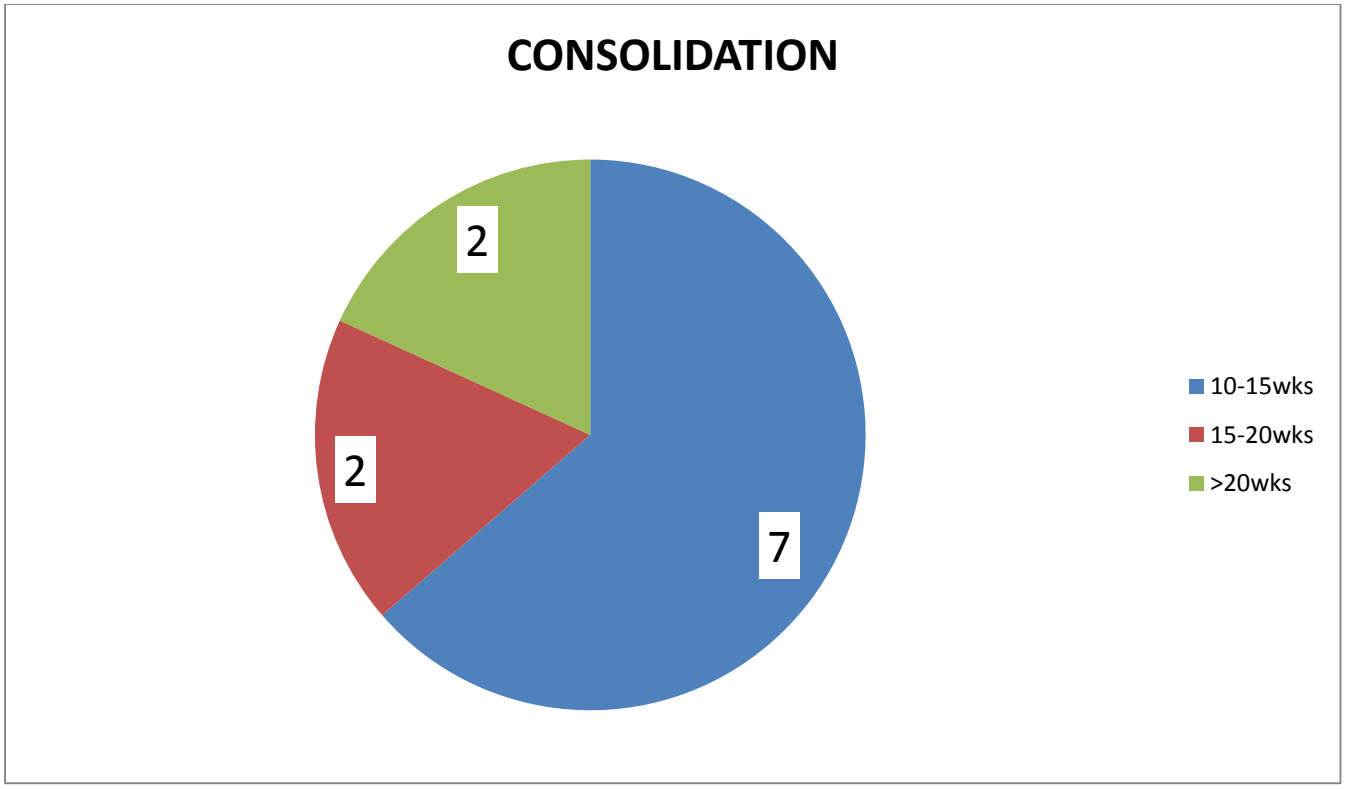
TUMOR VOLUME

The average tumor volume was 92 cm^3. 63% were having tumor volume less than 92 cm^3. 27% of cases had tumor volume more than 92 cm^3.



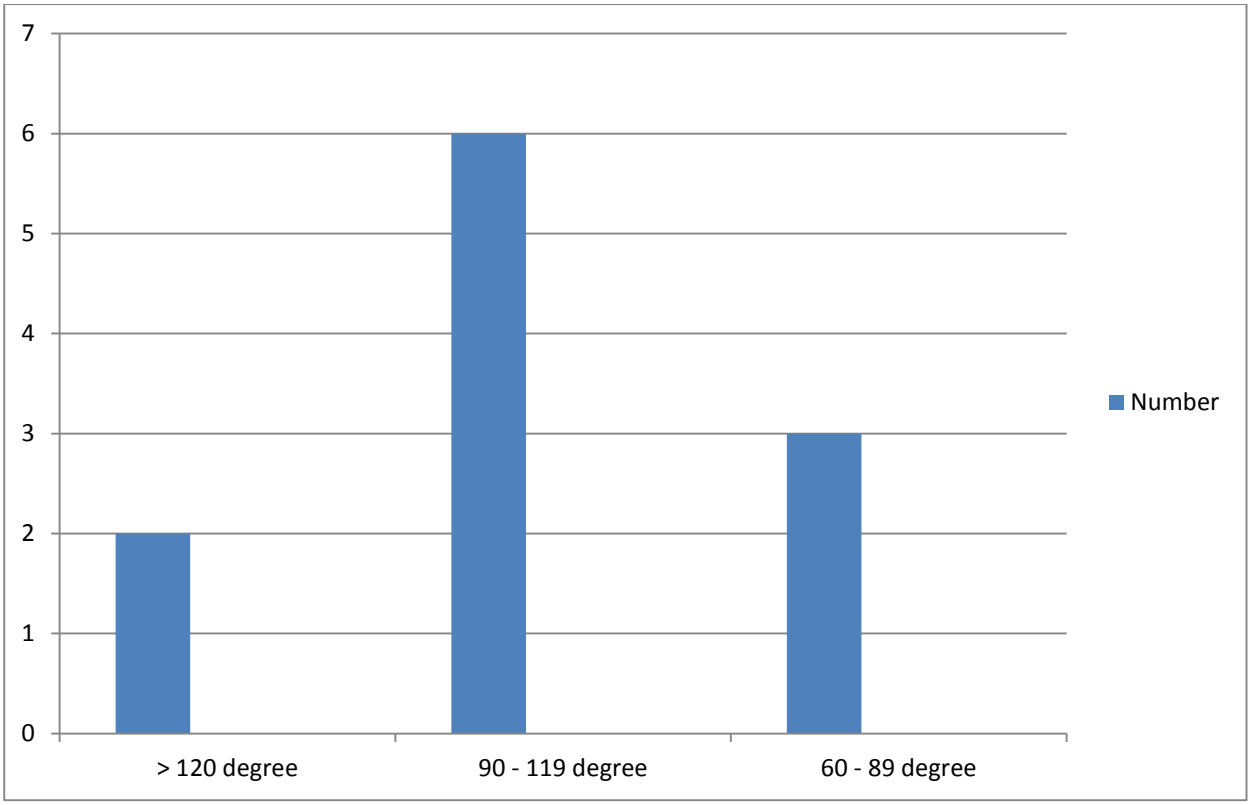
TIME TAKEN FOR CONSOLIDATION

The average time taken for consolidation is 18 weeks. 64% of cases showed consolidation in 10-15 weeks. 18% of cases showed consolidation in 15-20 weeks. 18% of cases showed consolidation in more than 20 weeks.



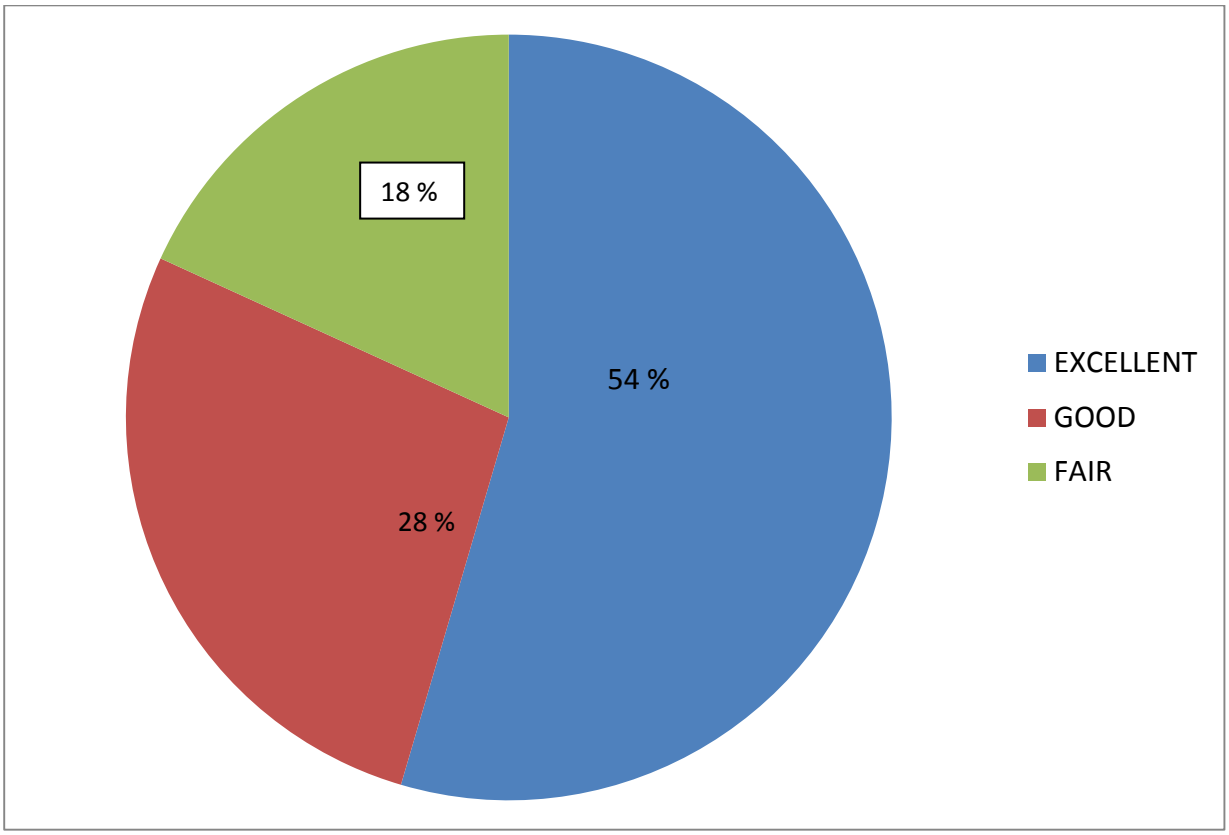
KNEE FLEXION

The average knee flexion was 94 degree. 55% had knee flexion 90 to 120 degree, 27 % had knee flexion between 60 and 90 degree and 2 patients had knee flexion more than 120 degree (18%).



KNEE SOCIETY SCORE

54 % of the study group had excellent outcome; 28 % had a good outcome while the outcome was fair in 18 %.



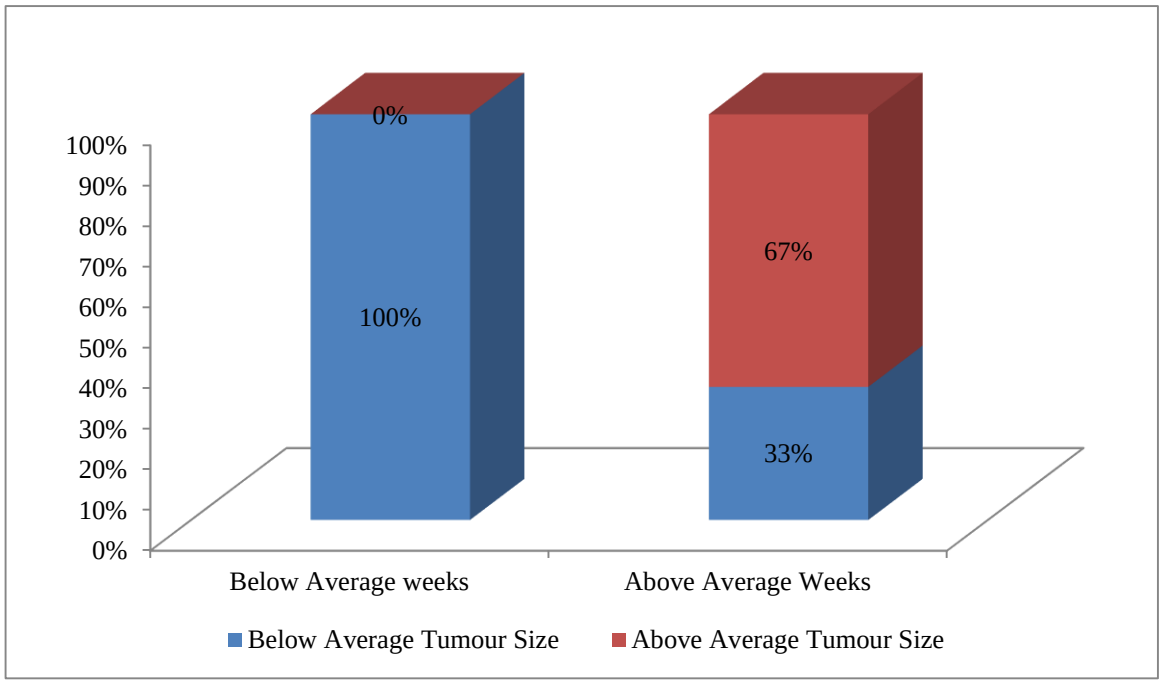
STATISTICAL ANALYSIS

The Cross tabulation shows the association between tumor size and period of consolidation.

TUMOR VOLUME X CONSOLIDATION IN WEEKS					
			CONSOLIDATION IN WEEKS		Total
			<18 Average	>18 Average	
TUMOR VOLUME	<92 Cm^3	Count	5	2	7
		%	100.0%	33.3%	63.6%
	>92 Cm^3	Count	0	4	4
		%	0.0%	66.7%	36.4%
Total		Count	5	6	11
		%	100.0%	100.0%	100.0%

Pearson Chi-Square=5.238* P=0.022

From the above table, all 5(100%) patients whose tumor size is less than 92cm^3 consolidated within 18 weeks. 6 patients were taken more than 18 weeks, among the 6 patients 4(67%) were consolidated more than 92 cm^3. Remaining 2(33%) were less than 92cm^3. The chi square values were significant when p is <0.05, which shows that period of consolidation was based on size of the tumor.



SENSITIVITY	100.00%
SPECIFICITY	66.67%
POSTIVE PREDICTIVE VALUE	71.43%
NEGATIVE PREDICTIVE VALUE	100.00%

71% of the tumor with size 92 cm^3 had consolidation period of 18 weeks.

DISCUSSION

A total of 11 cases of Giant cell tumor admitted in Rajiv Gandhi Government General Hospital were included in our study. All the patients were available for final follow up. 3 patients were referred from other centres with a biopsy report of Giant cell tumor.

CT scan of the chest was taken in all the patients to rule out pulmonary metastasis. No patients had any pulmonary metastasis or skip lesions. 3% incidence of lung metastasis has been reported in Giant cell tumors with a mortality rate of 15 %. Errani et al. reported a pulmonary metastasis ratio of 4 % in his study of 349 giant cell tumor cases.[81] Kremen et al. had a 2% pulmonary metastasis rate.[82]

The average age of the study population was 30 years. 90 % of the patients fell within the common age group cited in literature between 20 and 40 years.[83] Two patients presented at 18 years of age.

6 out of 11 patients were female in our study group. Female predominance was found in our study group. Lin et al. reported a sex ratio of 1.14:1 in favour of females[84]. Similar female predominance of 1.22:1 was reported by Klenke et al.[85]

Incidence in proximal tibia was comparatively more than in distal femur. This again, is in contrast to literature which favours distal femur as the most common region involved. In a multicentre Scandinavian study performed by Kivioja et al. encompassing 294 cases of giant cell tumor, distal femur and proximal tibia were involved in the ratio of 1.5 : 1.[86]

The tumors were graded according to the staging system described by Campanacci.[87] In our study we had 6 cases of Grade II tumor and 3 cases of Grade III tumor. There were no cases of Grade I tumor.

Tumor volume was measured preoperatively from CT or MRI using ellipsoid formula , volume = [0.6 x height x width x depth] , as used by Kyoo-Ho Shin et al in his study, as a predictor of chemotherapeutic response in osteosarcoma.[27]

The average time for appearance of callus in radiograph was 10 weeks. In total of 11 patients, callus appeared in less than 10 weeks in 8 patients whereas appearance of callus was more than 10 weeks with the maximum duration of 16 weeks in 3 patients.

In our study, average period of time to start partial weight bearing is 10 weeks after appearance of callus in radiographs. In total of 11 patients, 8 patients started partial weight bearing before 10 weeks and 3 patients started partial weight bearing more than 10 weeks with maximum period of 16 weeks.

The average period of time to start full weight bearing after complete incorporation of the fibular graft into the host bone with no pain and discomfort is 18 weeks. In total of 11 patients, 8 patients started full weight bearing before 18 weeks and 3 patients started full weight bearing more than 18 weeks with maximum period of 24 weeks.

George et al study of 17 patients with benign lesions of the proximal femur with non vascularised, autologous fibular strut grafts without osteosynthesis in which

patients started unprotected full weight bearing by 16 weeks correlates with our study. [35]

The average tumor volume in our study was 92 cm3 among which 7 cases have tumor volume less than 92cm^3 in which 5 cases consolidated less than the average consolidation period of 18 weeks and 2 cases were consolidated in more than 18 weeks. Total cases with tumor volume of more than 92cm^3 consolidated in more than 18 weeks was 4 and none of the cases were consolidated in less than 18 weeks. Positive predictive value of this study is 71% for the average tumour volume taken for the average consolidation time. There is no literature correlating tumor volume with its consolidation time of graft, prognosis and functional outcomes in GCT.

Wide resection greatly reduces the recurrence rate but the native joint function is severely compromised on the long run. Several options exist regarding the mode of reconstruction following the resection of the tumor. A resection arthrodesis provides a stable joint but the patient dissatisfaction rate is high.

Custom made prosthesis is an attractive option as it allows for early knee mobilisation and weight bearing. However, these prosthesis are more suited for malignant tumors with a low life expectancy. Several factors have been attributed to affect the long term survival of custom made prosthesis.

In a retrospective study of 1001 Custom prosthesis used for reconstruction of bone tumors by Unwin et al[88], aseptic loosening was considered as the principle mode of failure of the implants. Natarajan et al [89] experienced periprosthetic fractures in 12

out of 205 patients of Giant cell tumor who were treated by resection and reconstruction with Indian prosthesis. Eralp et al [90] had an infection rate of 5.5 % within two years of implantation.

Biau et al estimated an average survival time of 130 months for femoral component and 117 months for the tibial component in a study of 91 patients with tumor resection reconstructed with cemented custom prosthesis.[91] Mittermayer et al had a 10 year prosthesis survival in only 70 % of the patients with an uncemented prosthesis.[92] Despite several advancements in modern designs, Custom made prosthesis is not an ideal option in Giant cell tumor.

Intralesional curettage remains the preferred mode of treatment in Giant cell tumor, considering the benign nature of the disease and the longer life expectancy of the affected individuals compared to other bone tumors. Achieving a balance between disease eradication and joint preservation underlies the success of the surgery. A meticulous clearance of the tumor while avoiding spillage reduces the recurrence rates. Various agents have been added to the curettage process to minimise recurrence.

Johnson introduced Hydrogen peroxide as a cheap and safe adjuvant in 1977. Gortzak et al based on in vitro studies, suggested 3 % Hydrogen peroxide is a safe and effective agent with few complications to the living tissue on account of the short half span and low concentration used.[93]

Systemic adjuvants have supplemented the curettage technique by controlling the micro metastasis. Two commonly used agents include Zoledronic acid and Denosumab.

Zoledronic acid, a third generation Bisphosphonate acts by promoting the apoptosis of stromal cells – the main neoplastic component in Giant cell tumor. The efficacy of Zoledronic acid in destroying the tumor cells has been documented in invivo and invitro studies.

Tse et al had a recurrence rate of 5 % when Zoledronic acid was used an adjuvant compared to 30 % in the group treated without Zoledronic acid.[14] Balke et al reported on 25 cases of aggressive, multiple recurrent tumors stabilised with Zoledronic acid.[13] GOUIN et al performed curettage of Giant cell tumor in 20 patients using no local adjuvant.[25] The curettage was supplemented with five doses of post operative Zoledronic acid. At 5 years follow up, the recurrence rate was 15 %.

No recurrence was noted in our study at 2 years follow up. Similar results were observed by Yu et al.[22] and Balke et al.[13] while Gouin et al had a 10 % local recurrence rate at the end of two years.[25]

Iliac crest bone graft was not used in any patient due to the high recurrence rates reported in literature when the cavity was filled with bone graft. Gouin et al described an Odd's ratio of 3.9 for recurrence of the tumor when the cavity was filled with bone graft.[23] Gao et al. had a threefold increase in recurrence rate when bone graft was used compared to bone cement.[26] Kivioja et al found a recurrence rate of

22% in cases treated with curettage and bone cement which increased to 47% when bone grafting was used to fill the defect.[16]

Although bone cement allows for early rehabilitation, it is a biologically inert material and does not remodel along the lines of stress. Another possible complication while using bone cement is the risk of articular cartilage damage on account of variation in modulus of elasticity between bone cement and articular cartilage and the heat generated during cementation. Sandwich technique was introduced to overcome this potential problem by packing a layer of iliac crest bone graft between the subchondral bone and bone cement. Saibaba et al used the sandwich technique to fill the cavity in 36 patients and had a MSTS score of 27 at 5 year follow up.[94] However this technique introduces bone graft into the cavity which can possibly enhance the risk of recurrence.

The cavity was supported with autogenous non vascularised fibular graft taken from the same side of the lesion in 34% of the cases and from the contralateral side in 66 % of the cases. Hypertrophy and incorporation of the fibular graft were noted in all the cases. Krieg et al.[12] used non vascularised fibular grafts to bridge 30 cases of tumor cavity post resection. They concluded that non vascularised fibular grafts also show biological activity, evident by their hypertrophy and fracture healing potential through the formation of callus.

The presence of a pathological fracture was not a contraindication for inclusion in our study group. One patient with Giant cell tumor of the proximal tibia presented

with a pathological fracture. MRI imaging did not reveal any soft tissue contamination by the tumor cells. The patient was consequently treated by curettage.

Heijden et al.[21] retrospectively evaluated 422 operated Giant cell tumor patients, including 48 patients who presented with a pathological fracture. They noted a recurrence rate of 30 % for cases with Giant cell tumor and pathological fracture treated by curettage and adjuvant therapy. Soft tissue extension was the main reason cited for increased recurrence in the event of a pathological fracture managed by curettage.

The average time taken to commence knee mobilisation was 10.2 weeks. The patients were advised to do isometric quadriceps strengthening exercises during this period. The patients were then started on physiotherapy emphasizing on quadriceps strengthening and knee flexion. The prolonged period of knee immobilisation did not affect the post operative knee range significantly to deter normal activities. Five patients were able to achieve a knee flexion beyond 90 degree with two patients crossing 120 degree. Only one patient had a poor knee flexion of 45 degree. None of the patients developed knee flexion contracture or extensor lag.

The average time taken for the patients to fully weight bear without support was 18 weeks(12 – 24 weeks). All the patients were able to resume their pre surgery work function. Consolidation of the graft was achieved in all the cases.

Clinical and radioligical parameters of consolidation were observed in our study by serial follow ups. Corrales et al.[34] in a review of 77 clinical studies used

clinical criteria to define the consolidation , found that the three most commonly used criteria were absence of pain or tenderness with weight bearing, absence of pain or tenderness at the site during the examination. For the radiological evaluation, plain radiography remains the most common method to assess healing.

Some authors suggest as a criterion to determine consolidation the presence of at least three consolidated cortices observed in two radiographic views (anteroposterior [AP] and lateral [L]).[42]In our study we assessed the consolidation both clinically and radiographically. Luis A.Corrals assessed consolidation in his study clinically by absence of pain on weight bearing and radiologically by presence of bridging callus at graft host interface.[34]

R.George et al in his study on the treatment of benign lesions of the proximal femur with non-vascularised autologous fibular strut grafts showed consolidation at 16weeks in case of aggressive GCT.[35]

In our study complete opacification of the cavity in the radiographs on an average was found to be 1 year. George et al in his study of osteolytic lesions of proximal femur, all achieved partial or complete consolidation within 12 months. Partial consolidation was defined as more than 50% radio-opacity of the defect and full consolidation as 100% radio-opacity.[35]

The average time for consolidation in our study is 18 weeks which correlates with the study of San Julian Aranguren et al 83 massive bone allografts in 79 patients with malignant bone tumours: osteosarcoma 57; Ewing's sarcoma 8; malignant fibrous histiocytoma 3; chondrosarcoma 4; fibrosarcoma 5; and giant cell tumours 2. The

mean consolidation time for metaphyseal and diaphyseal osteotomies was 6.5 and 16 months respectively.[31]

KRIEG et al. in their study on 30 cases where the bone defect was bridged with non vascularised fibula, found equally good results with only slight increase in time to union.

In this study population, fibular graft was used as a single, double or triple strut stabilised with plate, screws or merely wedged in the bone. In all the patients good functional activity was observed postoperatively with a mean time to consolidation of 6 months.[12]

In our study 10 patients post curettage and fibular graft cavities were filled completely with grade 1 modified neer's score. In one patient, the cavity was filled incompletely with grade 2 modified neer's score was only 6 months post surgery and there was no graft resorption till now .[95,96]

There were neither signs of knee instability nor progression to varus on weight bearing.

Based on the Knee Society Scoring, 6 patients (40%) had an excellent outcome scoring more than 90. 3 patients (50%) had a good outcome with a score above 80. Two patient had a fair outcome with a score below 80. The low Knee Society Score was due to the poor range of knee movement post operatively.

One patient had an episode of deep seated infection with Acinetobacter which was refractory to i.v. antibiotics. The patient was taken up for wound debridement and antibiotic beads were placed which were subsequently removed at 6 weeks post operative. The patient consequently recovered well.

Another patient could only achieve a knee flexion of 45 degree post operatively. The patient was a middle aged female with low compliance levels and poor family support.

LIMITATIONS OF THE STUDY

Our study had several limitations like:

- Failure to achieve the sample size of 15.
- Short duration of follow up.

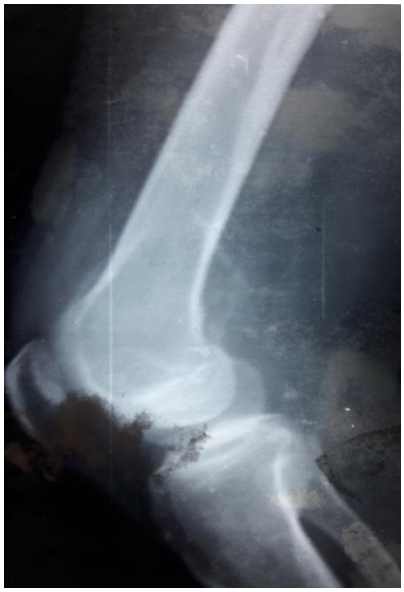
CONCLUSION

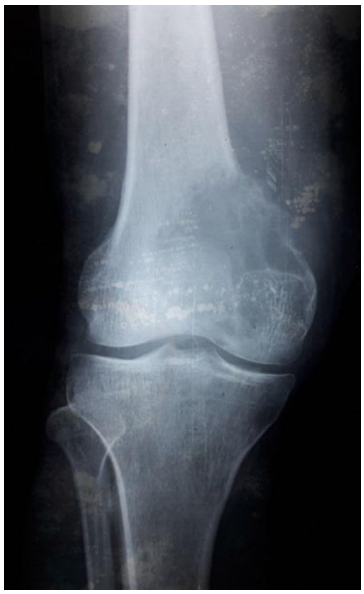
Our study demonstrates that tumor volume of less than 92 cm^3 consolidated earlier at an average period of less than 18 weeks. Tumor volume of more than 92 cm^3 consolidated after 18 weeks with maximum period of 24 weeks. There was no collapse of the cavity in our serial follow up despite filling the cavity only with fibular strut graft .Neither bone cement nor cancellous bone graft were used**.** High quality, efficient healing and nil recurrence of Giant cell tumor were achieved after treating with curettage and fibular strut graft with zoledronic acid adjuvant.

CASE ILLUSTRATION: 1

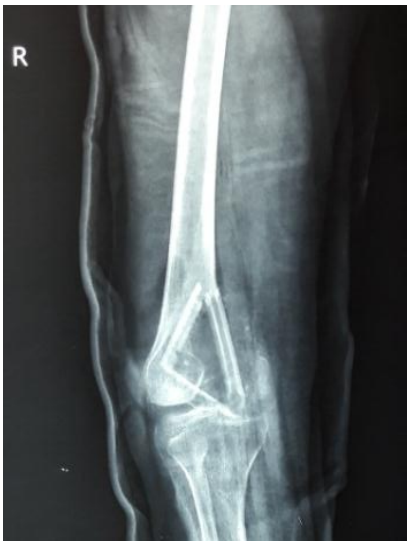
Name : Mr. A
Age : 28 years
Diagnosis : Primary Giant cell tumor – Right distal femur
Tumor volume: 77.5 cm^3
Time taken for consolidation: 16 weeks

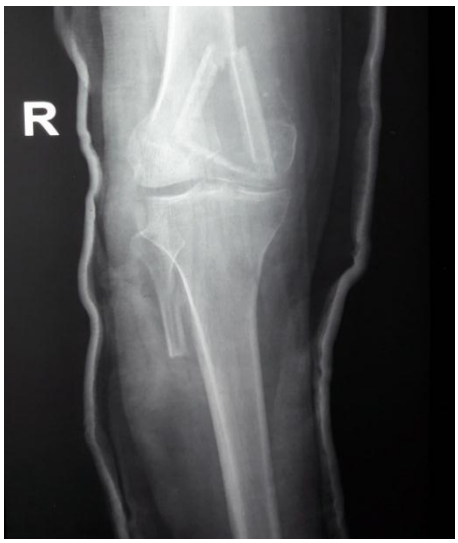
PRE – OPERATIVE X RAYS



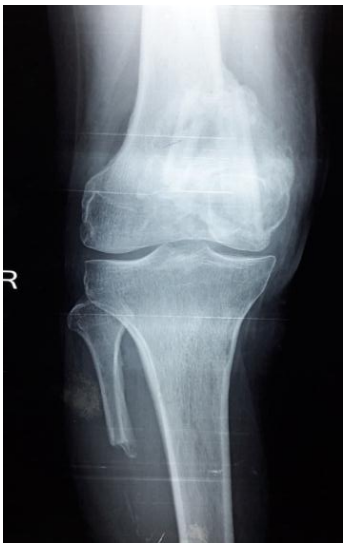


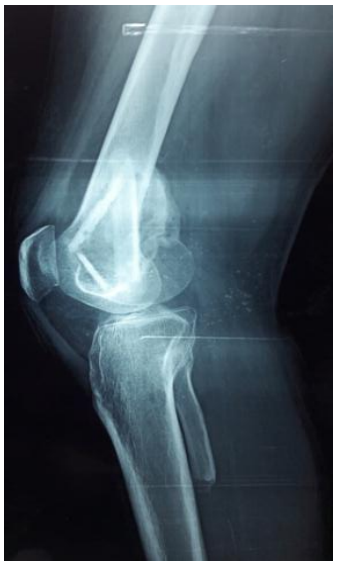
IMMEDIATE POST OP X RAYS



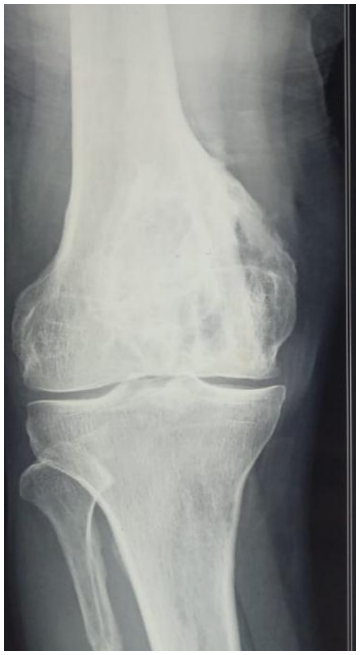


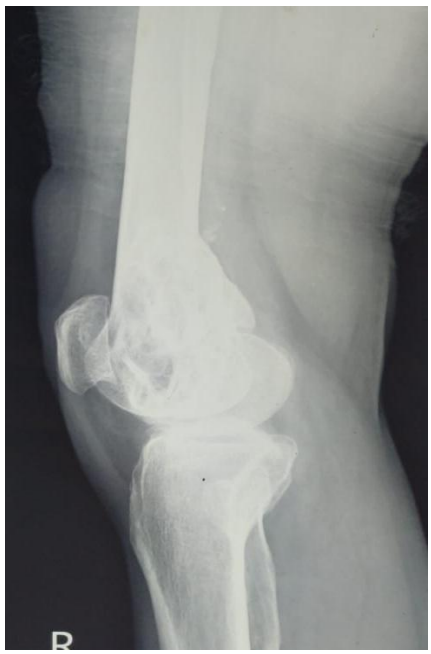
16 WEEKS POST OP XRAYS SHOWS CONSOLIDATION OF THE FIBULAR GRAFT



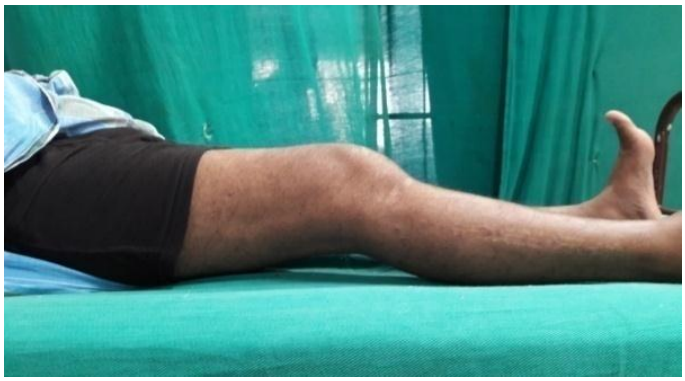


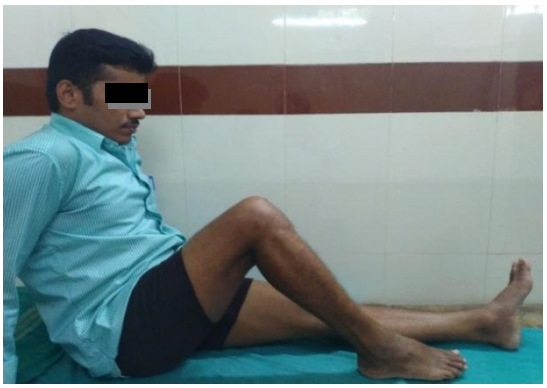
2 ½ YEARS FOLLOW UP





KNEE FUNCTION

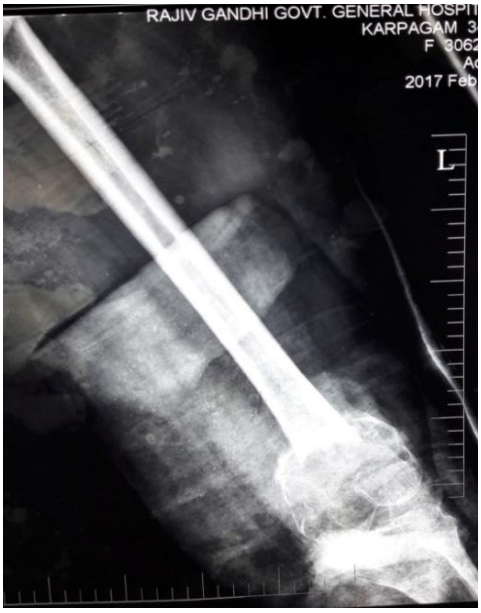


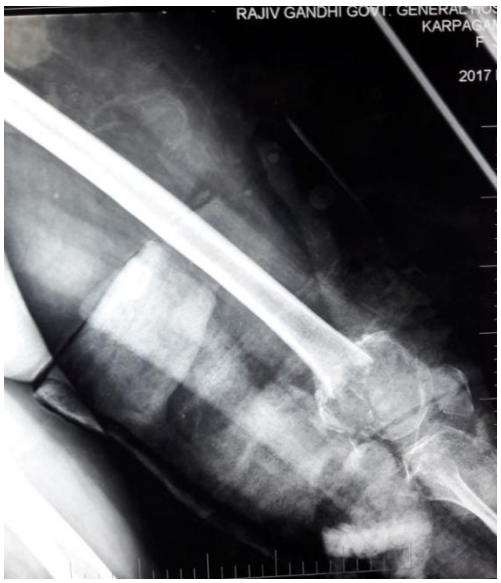


CASE ILLUSTRATION: 2

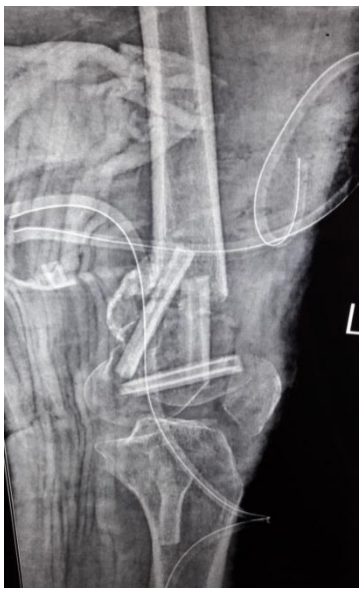
Name : Mrs. A
Age : 34 years
Diagnosis : Primary Giant cell tumor – Right distal femur
Tumor volume: 132.37 cm^3
Time taken for consolidation: 20 weeks

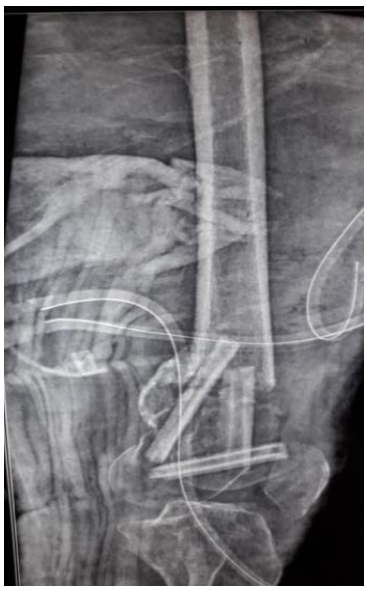
PRE – OPERATIVE X RAYS



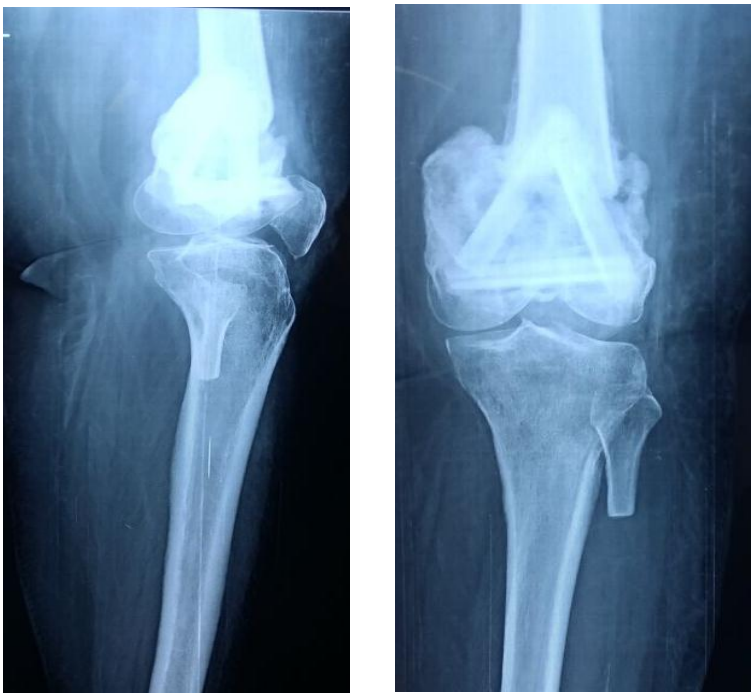


IMMEDIATE POST OP X RAYS

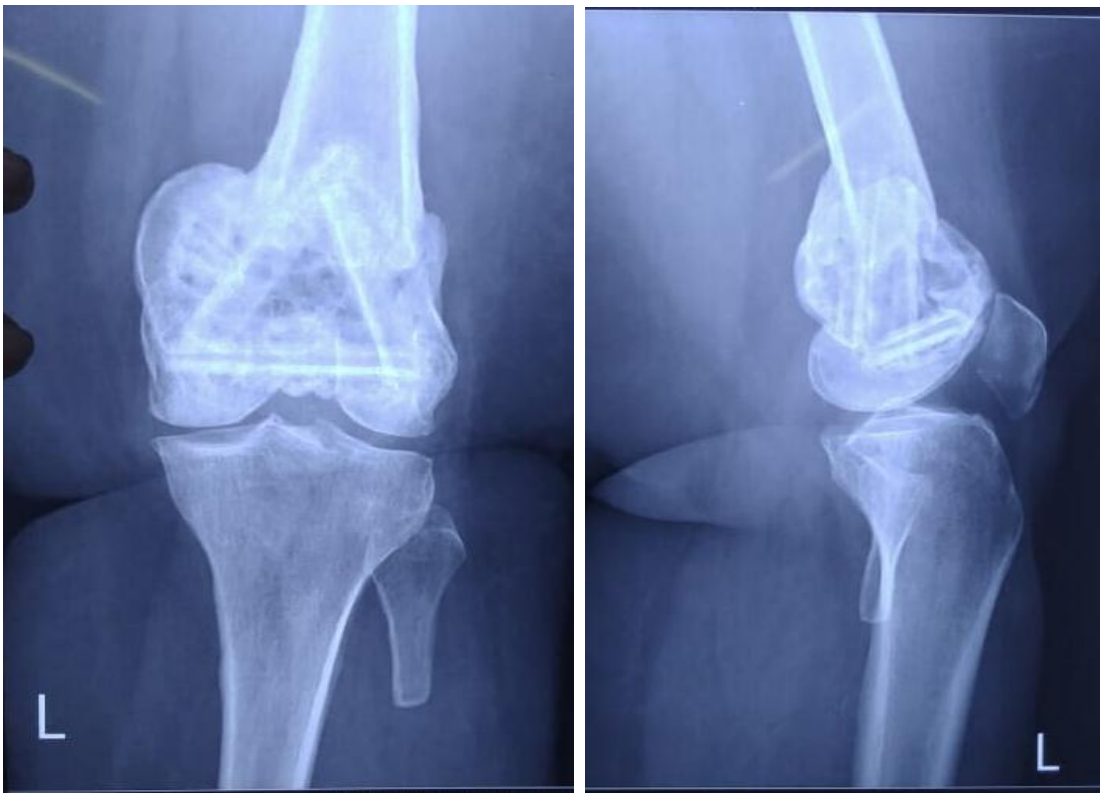




20 WEEKS POST OP X RAYS SHOWS CONSOLIDATION OF THE FIBULAR GRAFT



2 ½ YEARS FOLLOW UP

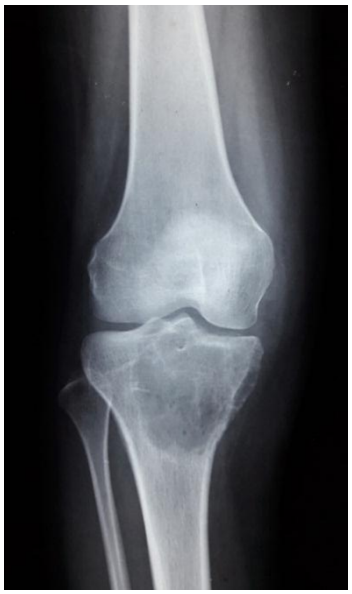
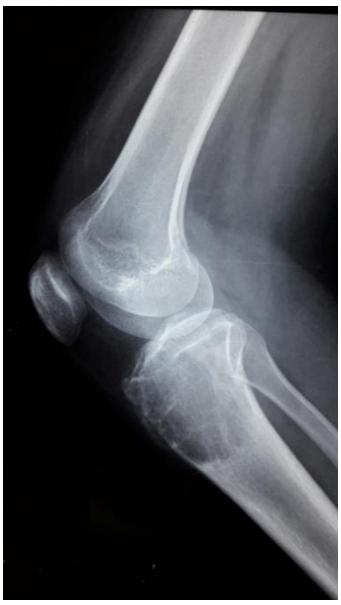


KNEE FUNCTION

CASE ILLUSTRATION: 3

Name : Ms. A
Age : 18 years
Diagnosis : Primary Giant cell tumor – Right proximal tibia
Tumor volume: 40 cm^3
Time taken for consolidation: 16 weeks

PRE – OPERATIVE X RAYS

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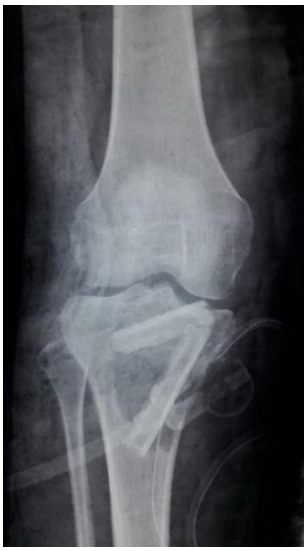
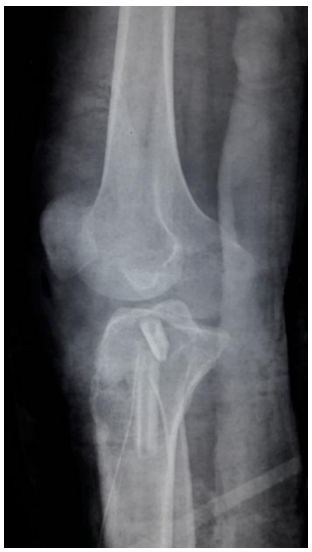
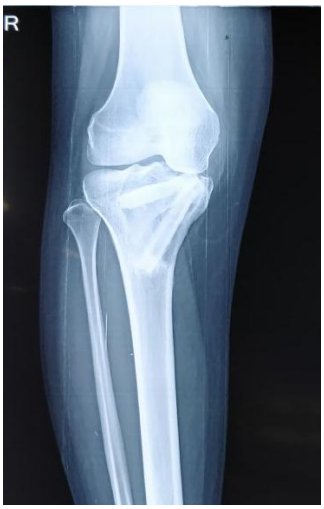
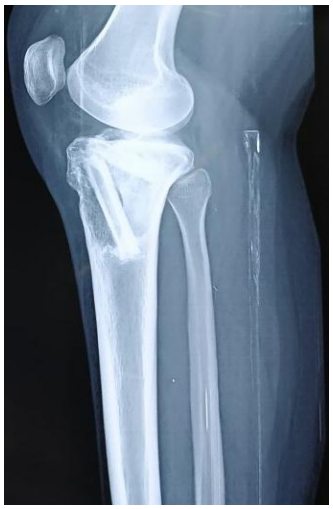
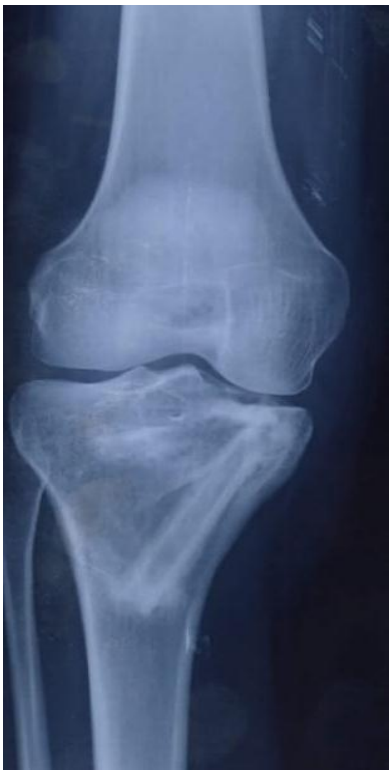



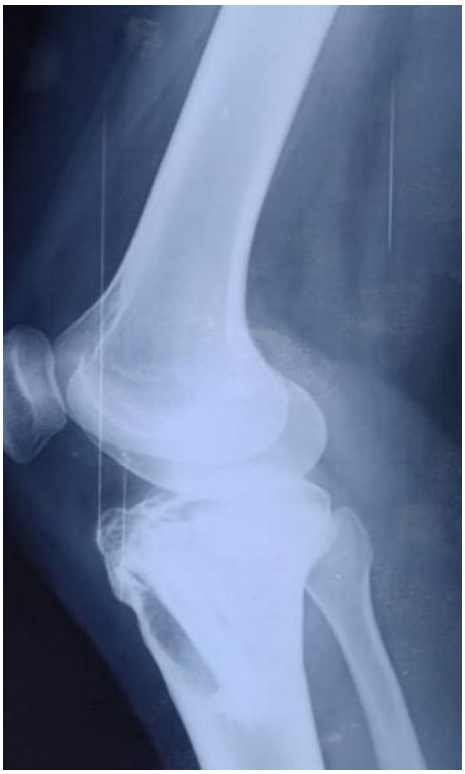
16 WEEKS POST OP X RAYS SHOWS CONSOLIDATION OF THE FIBULAR GRAFT





1½ YEARS FOLLOW UP



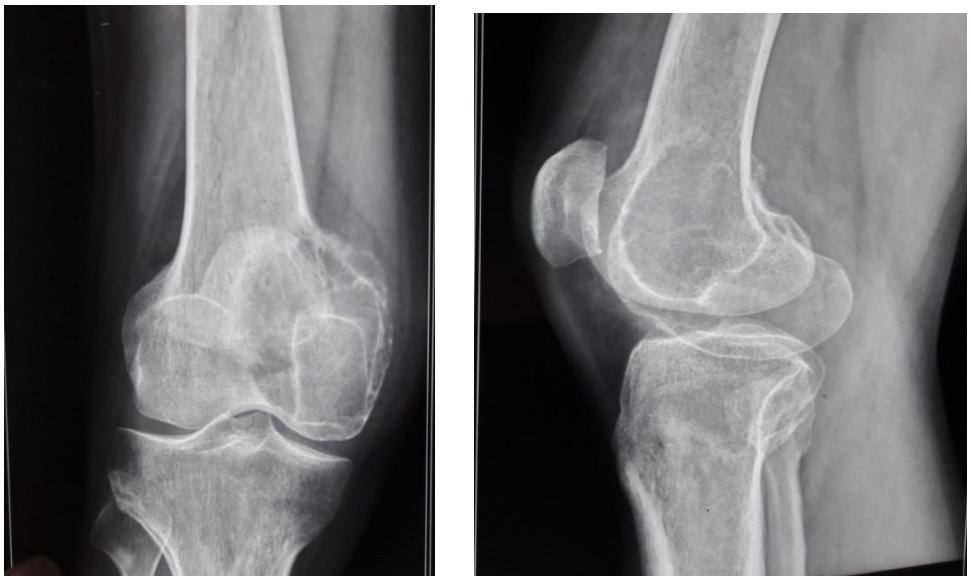


KNEE FUNCTION

CASE ILLUSTRATION: 4

Name : Mr. A
Age : 39 years
Diagnosis : Primary Giant cell tumor – Right distal femur
Tumor volume: 80.95 cm^3
Time taken for consolidation: 14 weeks

PRE – OPERATIVE X RAYS



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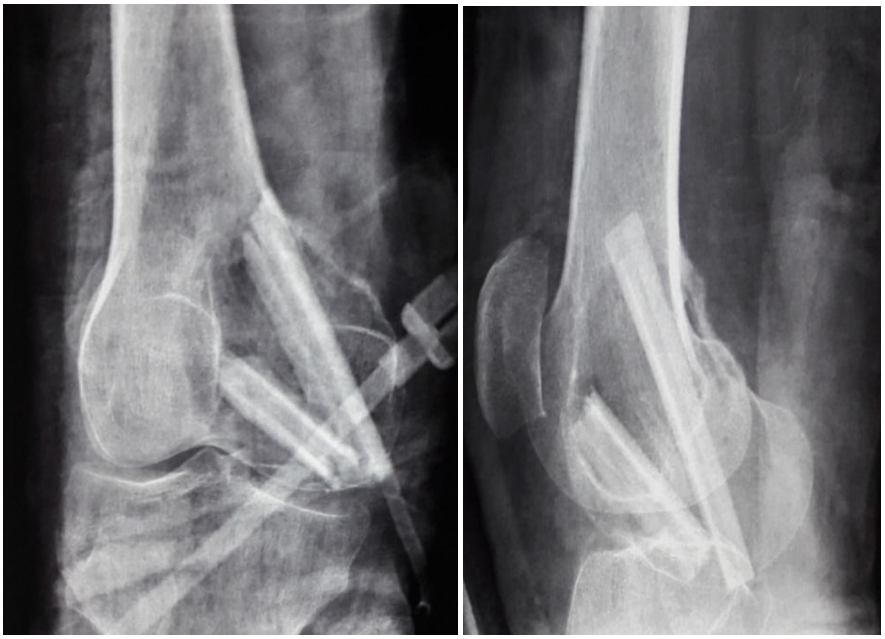
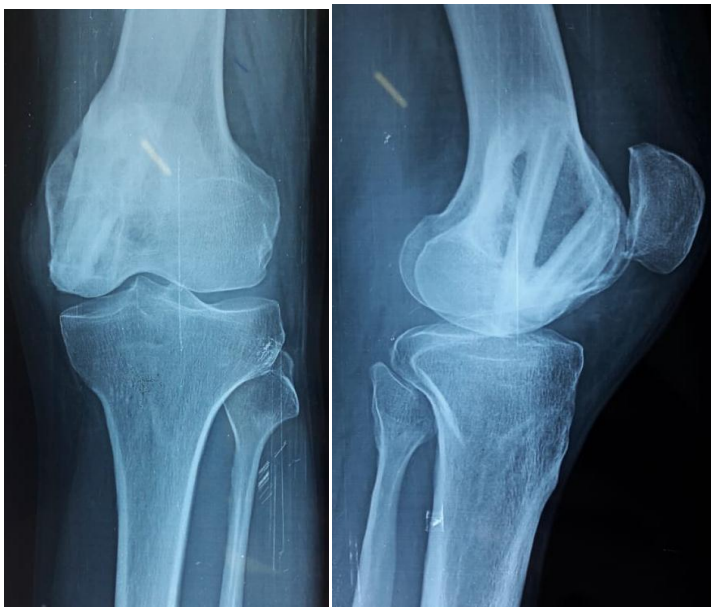
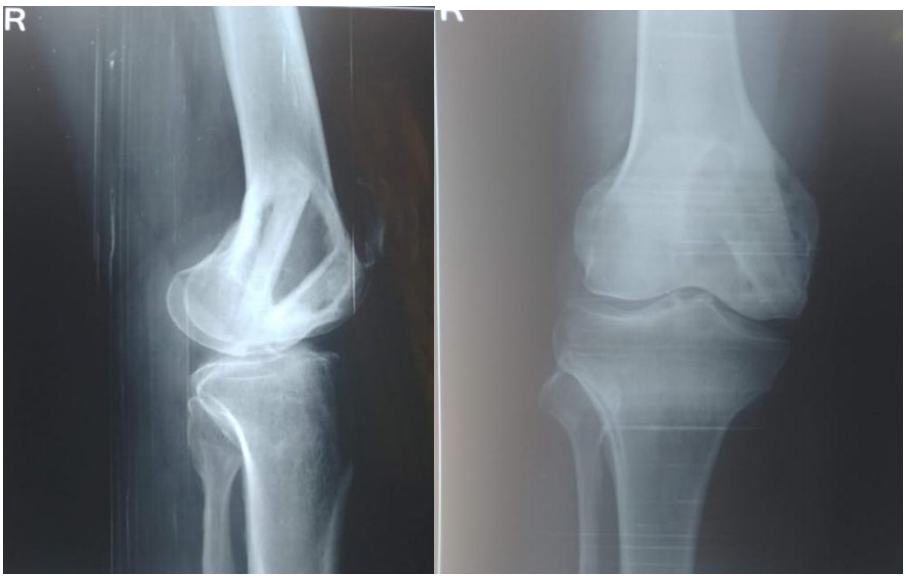


14 WEEKS POST OP X RAYS SHOWS CONSOLIDATION OF THE FIBULAR GRAFT



1 ½ YEARS FOLLOW UP



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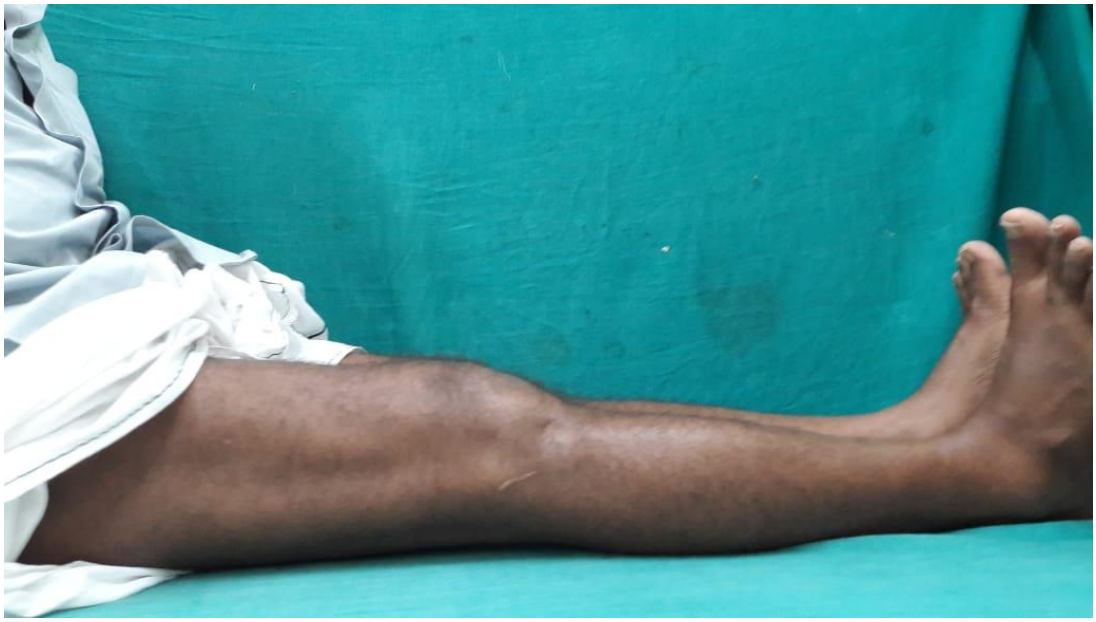
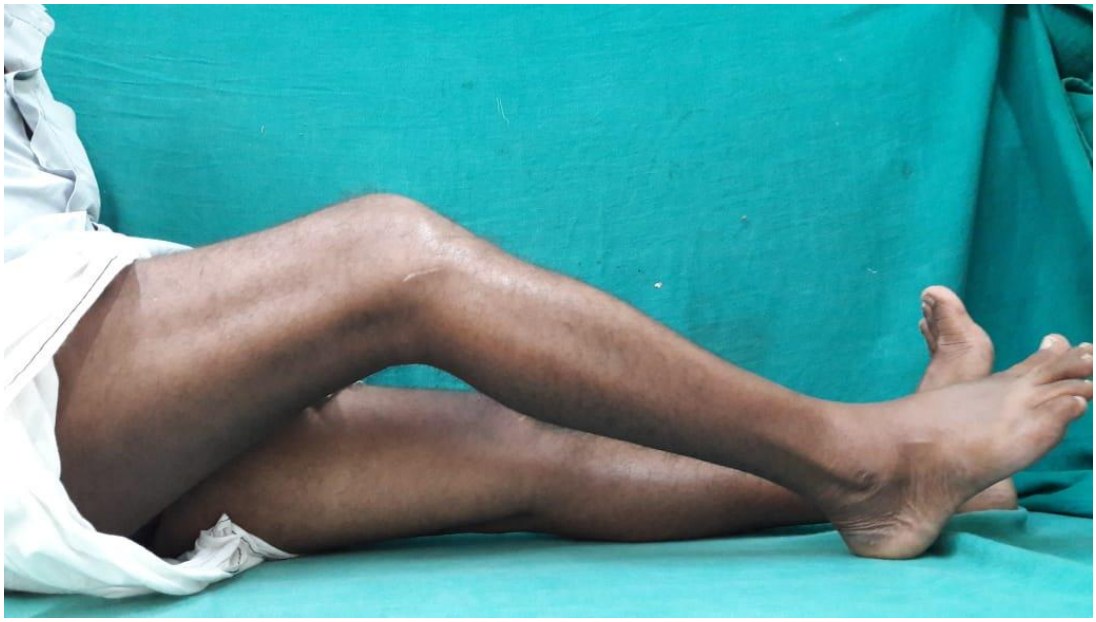
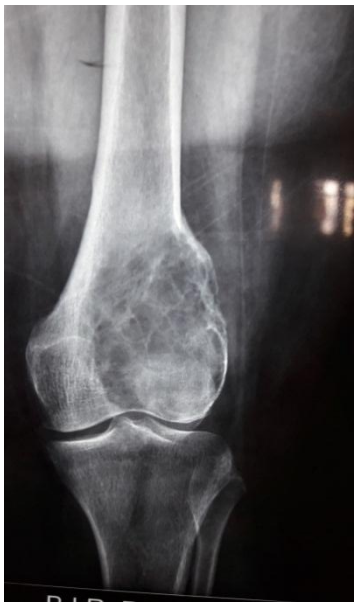


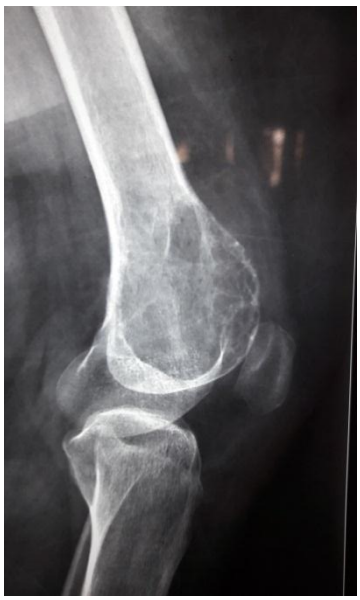


CASE ILLUSTRATION: 5

Name : Mrs. A
Age : 23 years
Diagnosis : Primary Giant cell tumor – Left distal femur
Tumor volume: 111.38 cm^3
Time taken for consolidation: 18 weeks

PRE – OPERATIVE X RAYS





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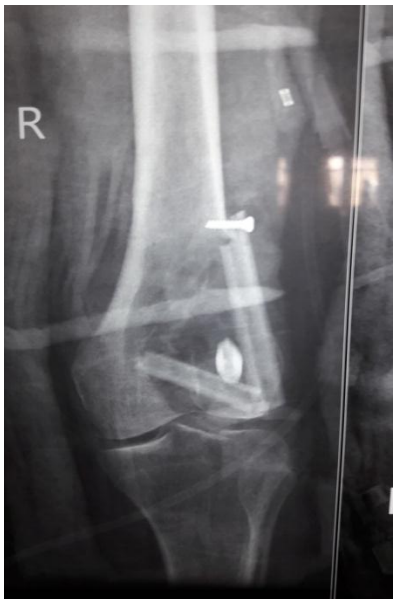
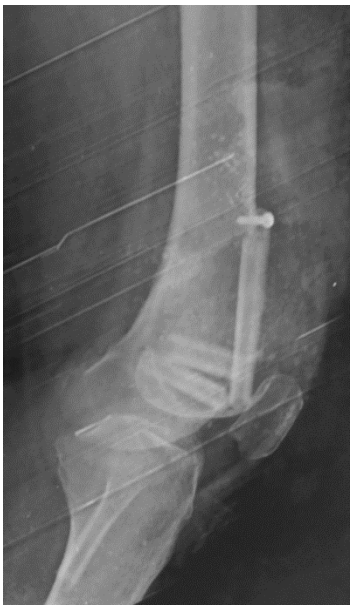
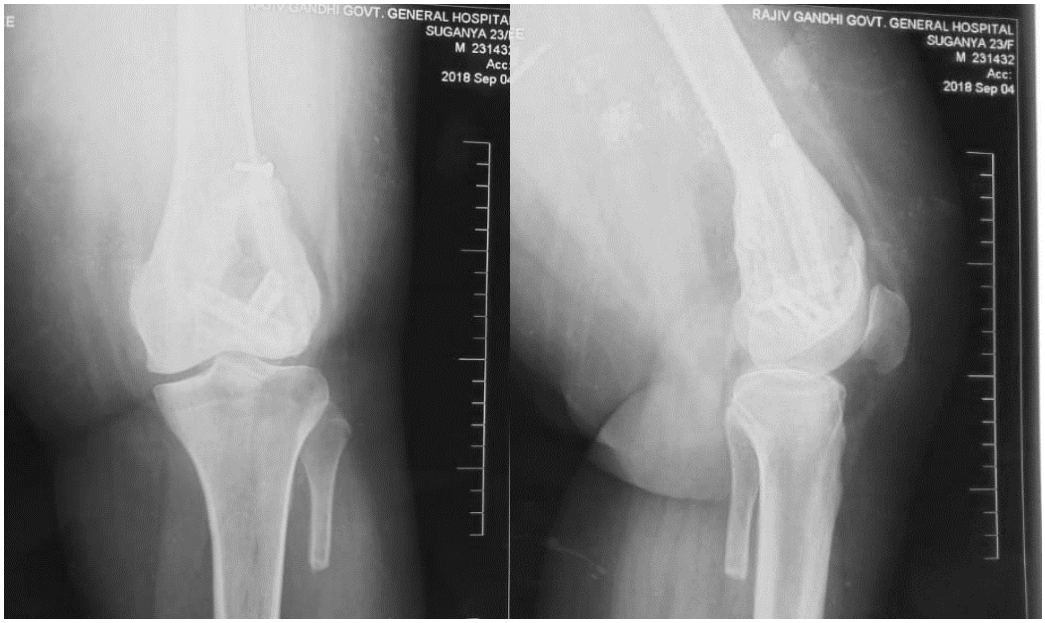
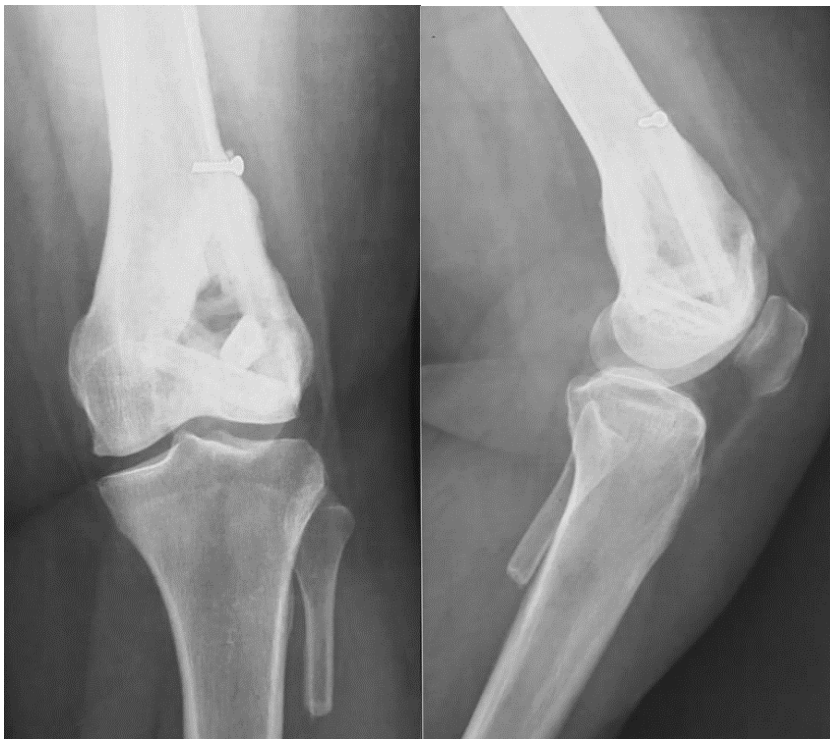




18 WEEKS POST OP X RAYS SHOWS CONSOLIDATION OF THE FIBULAR GRAFT



2 YEARS FOLLOW UP



KNEE FUNCTION

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Po-Kuei Wu . Cheng-Fong Chen , Chao-Ming Chen , Shang-Wen Tsai, Yu-Chi Cheng , Ming-Chau Chang , Wei-Ming Chen .
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PATIENT CONSENT FORM

Study Detail: "A PROSPECTIVE STUDY OF UTILITY OF WEIGHT BEARING X-RAYS IN AIDING THE MANAGEMENT OF ISOLATED LATERAL MALLEOLAR FRACTURES"

Study Centre: Rajiv Gandhi Government General Hospital, Chennai.

- Patient's Name :
- Patient's Age :
- In Patient's Number :
- Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the Ethics committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or ❑

unusual symptoms.

I hereby consent to participate in this study ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests and to undergo treatment ☐

Signature/thumb impression Signature of Investigator

Patient's Name and Address: Study Investigator's Name: Dr. Govindaraju.M

INFORMATION SHEET

Principle Investigator Name: Participant Name:

We are conducting a study on **"PROSPECTIVE AND RETROSPECTIVE STUDY OF FUNCTIONAL OUTCOME AND TIME TAKEN FOR CONSOLIDATION IN GIANT CELL TUMOR AFTER FIBULAR STRUT GRAFTING BASED ON INTRATUMOR CAVITY VOLUME"** among patients attending the Institute of Orthopaedics & Traumatology, Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to evaluate and analyze the functional outcome.

We are selecting certain cases and if you are found eligible, we may be using your radiographs, blood samples, CT, MRI to evaluate the outcome of the treatment which in any way does not affect your final report or management.

All the procedures are free of cost and there will not be any side effects.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the Participant Signature of Investigator

Date and Place :

PROFORMA

Name :

Age / Sex :

I.P. Number :

Address :

Occupation :

Date of Admission :

Complaints :

Co – morbidities :

Haemoglobin :

Serum creatinine :

Creatinine Clearance :

Blood Urea :

CT / MRI finding :

Tumor volume :

Biopsy :

Pre Operative ZA :

Diagnosis :

Procedure Done :

Date of Surgery :

Post Operative ZA :

Renal parameters at each visit :

Duration of immobilisation :

Mobilisation started on :

Range of knee motion :

Weight bearing started on :

Time taken for consolidation :

Duration of Follow up :

Knee Society Score at

6 months :

1 year :

Complications :

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு:

"இராட்சச அணு கட்டியினை அகற்றி காலின் முழங்கால் சிற்றெலும்பினை பொருத்திய பின்பும் மற்றும் Zolodronic Acid அமிலம் கொடுத்த பின்பும் இராட்சச அணுகட்டியின் பரும அளவினை ஒப்பிட்டு எலும்பு வளரும் கால அளவினை அறியும் ஆய்வு"

ஆய்வாளர் பெயர் : மரு. M.கோவிந்தராஜு

ஆய்வு நிலையம் : விபத்து மற்றும் முடநீக்கியல் பிரிவு

சென்னை மருத்துவக் கல்லூரி, சென்னை-3

இந்த ஆய்வில் தங்களை பங்கேற்ற அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆராய்ச்சியில் பங்கேற்கலாமா வேண்டாமா என்பதை முடிவு செய்ய உதவியாக இருக்கும். இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை நீங்கள் தயங்காமல் கேட்கலாம்.

நீங்கள் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனையின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம்

தேதி:

பங்கேற்பாளர் கையொப்பம்/

இடது கட்டை விரல் ரேகை

தேதி:

ஆய்வு ஒப்புதல் படிவம்

ஆய்வு தலைப்பு

"இராட்சச அணு கட்டியினை அகற்றி காலின் முழங்கால் சிற்றெலும்பினை பொருத்திய பின்பும் மற்றும் Zolodronic Acid அமிலம் கொடுத்த பின்பும் இராட்சச அணுகட்டியின் பரும அளவினை ஒப்பிட்டு எலும்பு வளரும் கால அளவினை அறியும் ஆய்வு"

பெயர் :

தேதி:

வயது :

வெளிநோயாளி எண்:

பால் :

ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறென்.

நான் ஆராய்ச்சியாளருடன் ஒத்துழைப்பென் என்றும், எனக்கு ஏற்படக்கூடிய ஆசாதாரண நிகழ்வுகள் பற்றியும் உடனடியாக ஆராய்ச்சியாளரிடம் தெரிவிப்பேன் என்று உறுதி கூறுகிறேன். இந்த ஆய்விலிருந்து எப்போது வேண்டுமானாலும் எக்காரணமும் கூறாமல் என்னை விடுவித்துக் கொள்ளலாம் என்பதை அறிவேன்.

என்னிடம் இருந்து பெறப்படும் தகவல்களை அரசு, வரைமுறை அதிகாரிகள் ஆகியோர்களுடன் பகிர்ந்துகொள்ள ஆராய்ச்சியாளருக்கு அனுமதி அளிக்கிறேன். என்னுடைய சிகிச்சைக் கட்டுகளை பார்வையிட உரிமை உண்டு. என்னுடைய தகவல்களின் அடையாளம் இரகசியமாக வைக்கப்படும் என்பதை அறிவேன்.

இந்த ஆராய்ச்சியில் பங்கேற்க தன்னிச்சையாக முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் / ரேகை

ஆய்வாளர் கையொப்பம்

பங்கேற்பவர் பெயர்

ஆய்வாளர் பெயர்

இடம்:

இடம்:

தேதி:

தேதி:

URKUND

Urkund Analysis Result

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Submitted By:	drgovimmc@gmail.com
Significance:	5 %

Sources included in the report:

GIANT CELL TUMOR TREATED BY CURETTAGE AND ZOLEDRONIC ACID WITH STRUCTURAL SUPPORT BY FIBULAR CORTICAL STRUTS.docx (D43116466)
Thesis write up latest again for print.docx (D31767872)
Functional outcome of management of giant cell tumor around the knee joint.docx (D42782048)
thesis final numbers.docx (D42634683)
https://www.sicot-j.org/articles/sicotj/full_html/2017/01/sicotj170044/sicotj170044.html
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018195/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6348933/
https://www.nature.com/articles/s41598-017-09486-6
https://www.researchgate.net/publication/49666048_Treatment_of_Gaint_cell_tumor_of_bone_current_Concepts
https://www.researchgate.net/publication/50832219_Local_recurrences_after_curettage_and_cementing_in_long_bone_giant_cell_tumor
https://www.researchgate.net/publication/24039985_Custom_prosthetic_replacement_for_distal_radial_tumours
https://www.researchgate.net/publication/38068192_Giant_Cell_Tumour_of_the_Distal_Radius_Wide_Resection_and_Reconstruction_by_Non-vascularised_Proximal_Fibular_Autograft

Instances where selected sources appear:

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr. M. GOVINDARAJU
I Yr. MS ORTHOPAEDICS
INSTITUTE OF ORTHOPAEDICS & TRAUMATOLOGY
MADRAS MEDICAL COLLEGE
CHENNAI

Dear Dr. M. GOVINDARAJU,

The Institutional Ethics Committee has considered your request and approved your study titled **"FUNCTIONAL OUTCOME AND TIME TAKEN FOR CONSOLIDATION IN GIANT CELL TUMOR AFTER FIBULAR STRUT GRAFT BASED ON INTRA TUMOR CAVITY VOLUME" - NO.34032018**

The following members of Ethics Committee were present in the meeting held on **27.03.2018** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar	:Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH	: Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
9. Prof. S. Purushothaman, Associate Professor of Pharmacology, MMC,Ch-3	: Member
10.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
11.Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3	: Member
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
14.Thiru K.Ranjith, Ch- 91	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MASTER CHART

S.No.	Name	Age / Sex	Diagnosis	Campanacci Grading	Tumor volume in cm3	Appearance of callus in radiograph	Partial weight bearing	Time to full weight bearing	Duration of follow up	Knee flexion	Time taken for consolidation	Knee soceity score	Time taken for 100% opacification in radiograph
1.	Murugan	35 M	Primary GCT left proximal tibia	III	177.94	12 weeks	16 weeks	22 weeks	1 1/2 years	120 degree	22 weeks	84	1 year
2.	Vediyappan	34 M	Primary GCT left distal femur	II	203.27	16 weeks	16 weeks	24 weeks	3 years	6o degree	24 weeks	62	1 year 8 months
3.	Nagaraj	28 M	Primary GCT right distal femur	III	77.5	10 weeks	10 weeks	16 weeks	2yrs 9 months	110 degree	16 weeks	82	9 months
4.	Karpagam	34 F	Primary GCT right distal femur	III	132.37	9 weeks	14 weeks	20 weeks	2 yrs 9 months	80 degree	20 weeks	76	1 year
5.	Menaka	28 F	Primary GCT right proximal tibia	II	46.2	10 weeks	10 weeks	18 weeks	2 ½ years	45 degree	18 weeks	64	1 1/2 year
6.	Manimegalai	18 F	Primary GCT right proximal tibia	II	40	8 weeks	10 weeks	16 weeks	2 ½ years	120 degree	16 weeks	84	1 year
7.	Suresh Kumar	38 M	Recurrent GCT right proximal tibia	-	27.8	6 weeks	4 weeks	12 weeks	2 1/2 years	75 degree	12 weeks	75	1 year

MASTER CHART

8.	Saranya	23 F	Recurrent GCT right proximal tibia	-	37.05	6 weeks	6 weeks	18 weeks	2 years 3 months	110 degree	18 weeks	82	7 months followup Partial consolidation
9.	Rajkumar	39 M	Primary GCT right distal femur	II	80.95	8 weeks	8 weeks	14 weeks	2 years	100 degree	14 weeks	80	11 months
10.	Suganya	23 F	Primary GCT left distal femur	II	111.38	8 weeks	8 weeks	18 weeks	2 years	110 degree	18 weeks	82	9 months
11	Priyanka	17 F	Primary GCT left proximal tibia	II	80.08	10 weeks	10 weeks	16 weeks	6 months	90 degree	16 weeks	78	-