CLINICORADIOLOGICAL OUTCOME IN PATIENTS UNDERGOING LIMB SALVAGE OPERATION FOR OSTEOSARCOMA OF THE DISTAL FEMUR AND PROXIMAL TIBIA

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT OF THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, TAMIL NADU, CHENNAI FOR THE AWARD OF M.S. ORTHOPAEDICS DEGREE TO BE HELD IN APRIL 2016.

ENDORSEMENT BY THE PRINCIPAL OF THE MEDICAL COLLEGE

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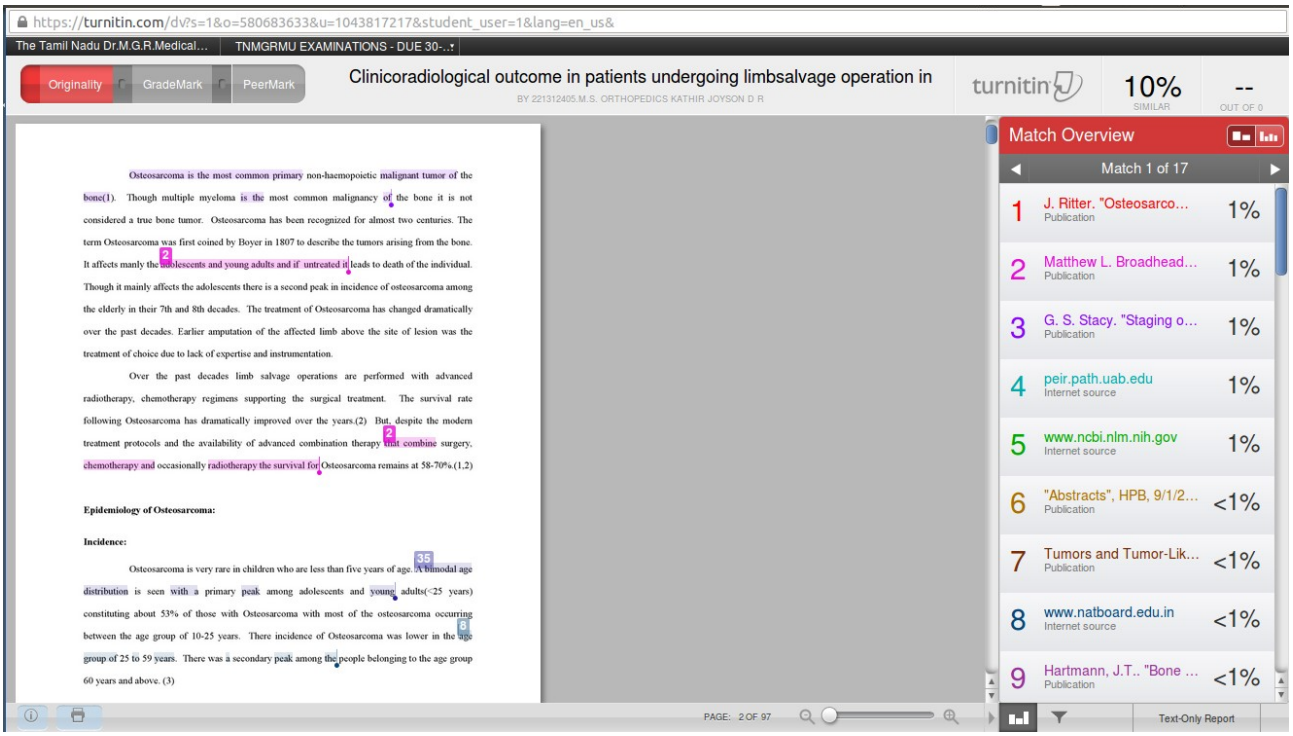
Introduction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Over the past decades limb salvage operations are performed with advanced radiotherapy, chemotherapy regimens supporting the surgical treatment. The survival rate following Osteosarcoma has dramatically improved over the years.(2) But, despite the modern treatment protocols and the availability of advanced combination therapy that combine surgery, chemotherapy and occasionally radiotherapy the survival for Osteosarcoma remains at 58-70%.(1,2)
Epidemiology of Osteosarcoma:
Incidence:
Osteosarcoma is very rare in children who are less than five years of age. A bimodal age distribution is seen with a primary peak among adolescents and young adults(<25 years) constituting about 53% of those with Osteosarcoma with most of the osteosarcoma occurring between the age group of 10-25 years. There incidence of Osteosarcoma was lower in the age group of 25 to 59 years. There was a secondary peak among the people belonging to the age group 60 years and above. (3)
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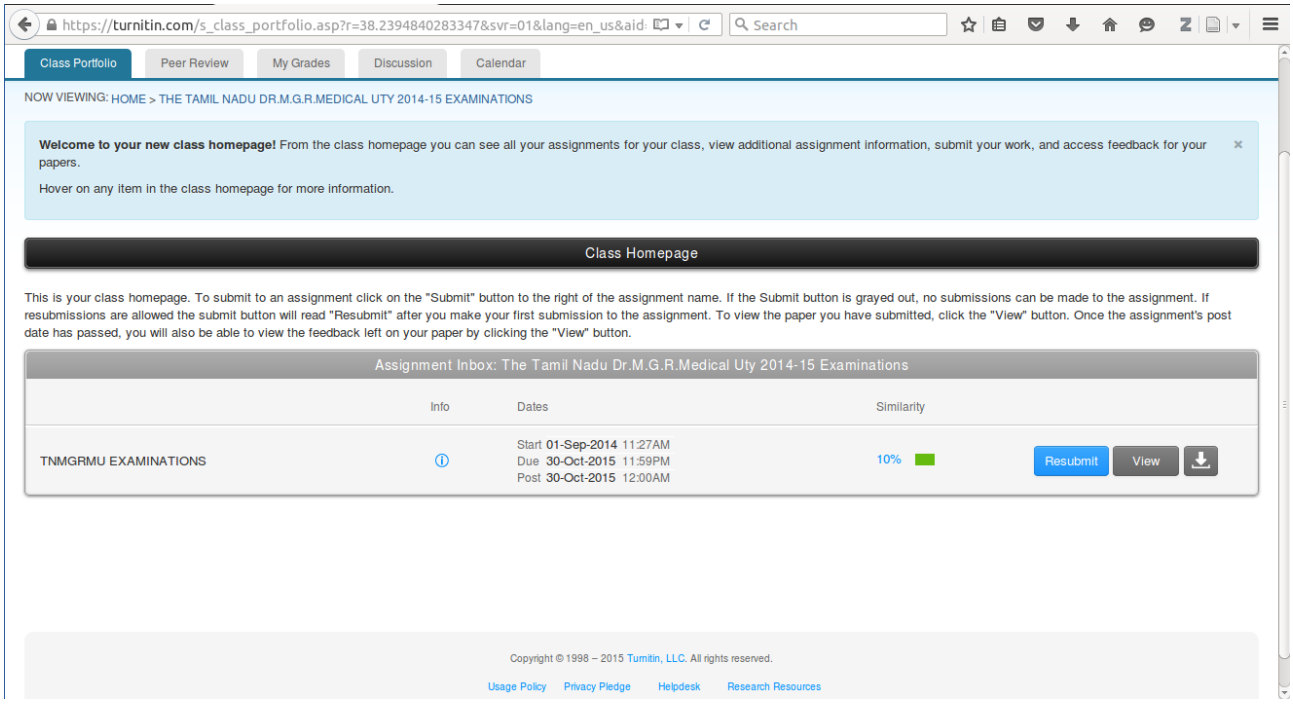
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ABSTRACT

Title: CLICORADIOLOGICAL OUTCOME IN PATIENTS UNDERGOING LIMB SALVAGE OPERATION FOR OSTEOSARCOMA OF THE DISTAL FEMUR AND PROXIMAL TIBIA

Department : Department of Orthopedics Unit II

Candidate : Dr. Kathir Joyson D R

Degree : Master of Surgery - Orthopedics

Guide : Dr. V. T. K. Titus

Objectives: To measure the clinico radiological out come in patients undergoing tumour excision and mega-prosthesis for osteosarcoma of the proximal tibia and distal femur in terms of survival and local recurrence.

Methods: Patients who underwent tumour excision and mega-prosthesis for osteosarcoma of the proximal tibia or distal femur from January 2010 to October 2014 were included in the study. The patients records were used to finding out the local recurrence, occurrence of metastasis and to determine the survival of the patient. Phone calls were used for patients who had not come for follow up. Data regarding age, sex, value of alkaline phosphatase at diagnosis, time of metastasis, time of local recurrence, range of motion Tumor volume, tumour depth, Blackburne-Peel ratio, percentage of resection were collected from the patients records and appropriate imaging.

Results: Among our patients the over all survival was 66% and the incidence of local recurrence was 20%. Most tumours belong to high grade and had large volume. Tumour volume and tumour depth were significantly associated with overall survival. Tumour volume, tumour depth and administration of radiotherapy were significantly associated with local recurrence. Tumour volume and radiotherapy were independently associated with time to local recurrence. Blackburne-Peel ratio was significantly associated decreased lag but the extent of resection of the femur or tibia did not have any functional significance. Wound infection was noted in 9 patients and 8 patients eventually underwent amputation.

Key words: Local recurrence, Survival, Radiotherapy

INDEX

Introduction

Osteosarcoma is the most common primary non-haemopoietic malignant tumor of the bone(1). Though multiple myeloma is the most common malignancy of the bone it is not considered a true bone tumor. Osteosarcoma has been recognized for almost two centuries. The term Osteosarcoma was first coined by Boyer in 1807 to describe the tumors arising from the bone. It affects manly the adolescents and young adults and if untreated it leads to death of the individual. Though it mainly affects the adolescents there is a second peak in incidence of osteosarcoma among the elderly in their 7th and 8th decades. The treatment of Osteosarcoma has changed dramatically over the past decades. Earlier amputation of the affected limb above the site of lesion was the treatment of choice due to lack of expertise and instrumentation.

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Epidemiology of Osteosarcoma:

Incidence:

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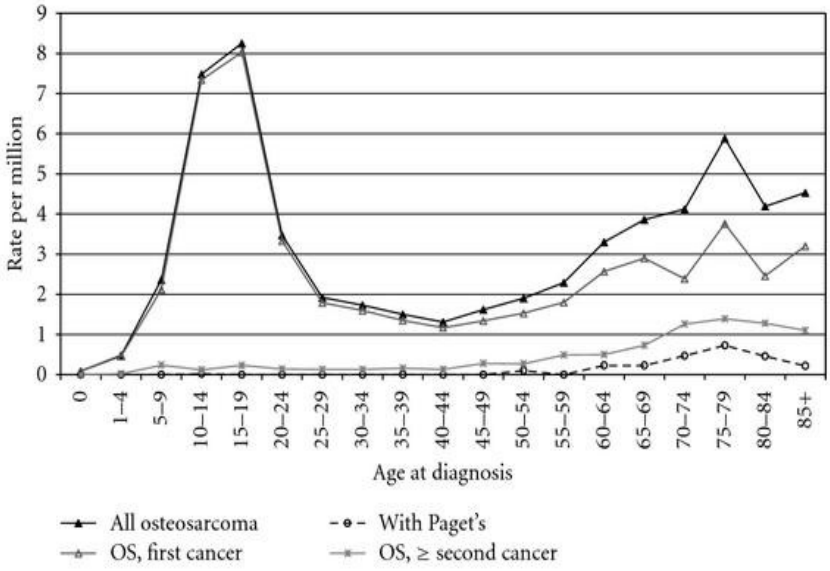
As we move the age group over 60 years only 13-30% constitute the patients with Osteosarcoma. The incidence of Osteosarcoma is slightly more in males than in females. The

overall male to female including all the age groups was 1.22:1. But among the patients below 15 years of age more girls were affected than the boys. There peak incidence was found to be earlier among the girls. Being 12 years, when compared with 16 years in boys.(3)



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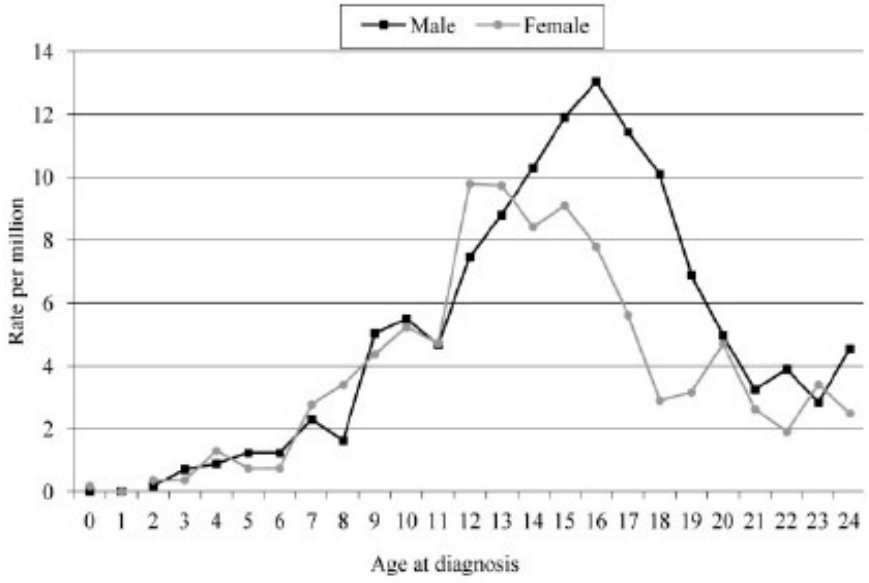


Source:Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004. Cancer. 2009;115(7):1531–43.

REVIEW OF LITERATURE

Anatomical site and location:

Osteosarcoma usually arises in the metaphysis of long bone inside the medullary cavity. It then penetrates the cortex of the bone. After breaching the cortex it then involves the soft tissue around the metaphyseal region. As the tumour grows a pseudo-capsule is formed around the tumour which aggressively penetrates into the soft tissue. Though Osteosarcoma can occur in any bone it most commonly occurs in the long bones near the metaphyseal growth plate of the appedicular skeleton.

Most of the Osteosarcoma originate around the knee accounting for about 60% of the Osteosarcoma occurring in humans. In femur it affects the distal femur in 75% of the individuals with Osteosarcoma of the femur. While in tibia, 80% of the time it originates in the proximal tibia. The humerus constitutes to about 10% of the Osteosarcoma with 90% of them originating in the proximal humerus.(5)

Among the Osteosarcoma which originate in the long bone 90% occur in the metaphyseal region, 9% in the diaphyseal region and very rarely in the epiphyseal region.(6) But as we look separately at the patients above 60 years of age the axial skeleton was the most commonly affected (27%), in addition to the craniofacial bones (13%) and extra skeletal sites (11%).(7) Compared to the younger population where Osteosarcoma occurs more in the sites of rapid growth such as the metaphyseal region only 14.5% of the older patients with Osteosarcoma had the tumor originating from such sites.(7)

Bone	**Percentage(5)**
Femur	42%
Tibia	19%
Humerus	10%
Skull and jaw	8%

Pelvis	8%

Etiological associations of Osteosarcoma:

Environmental exposures:

Exposure to radiation has been associated with increased risk of Osteosarcoma. The patient who have undergone treatment with radium for conditions such as ankylosing spondylitis were found to be at increased risk of bone sarcomas.(8) Survivors of Hodgkins lymphoma who had undergone radiation as a part of treatment were also found to be at higher risk of Osteosarcoma.(9)

Varying results have been obtained when comparing exposure to fluoride and its association with Osteosarcoma. It was found that there was an association between fluoride levels in drinking water in childhood and incidence of Osteosarcoma. This association was only noticed in males.(10) This finding was not consistent among females. Other studies have shown that there is no association between fluoride exposure and Osteosarcoma.(11) Radium in drinking water was associated with increased risk of Osteosarcoma among youth.(12) Radium dial painters are also found to have increased incidence of Osteosarcoma.(13)

Growth:

Osteosarcoma has been found to have an increased incidence in the pubertal age group. It is a age group when the remodeling of bone and bone growth is very active. Various hormones have been found to be at increased levels and play a role in this stage. At puberty the levels of insulin-like growth factor 1(IGF1), sex hormones, and growth hormones are found to be high. Insulin lie growth factors have been implicated as possible agents in the development of Osteosarcoma.(14) In patients with acromegaly there have been case reports of Osteosarcoma.(15) Though the incidence of Osteosarcoma has not been quantified among patient with acromegaly its been hypothesized that prolonged exposure to growth hormone may play a role. Single nucleotide polymorphisms of IGF2R have also been associated with increased risk of Osteosarcoma.(16)

Height:

Height has been counted as a risk factor for Osteosarcoma. Some studies have shown as

association and other have not. The largest cohort of patients with Osteosarcoma studied showed that the patients under 18 years who had Osteosarcoma were taller that normal.(17) Another meta-analysis showed an association between height at diagnosis and Osteosarcoma.(18) It is thought that children having faster growth spurts during puberty are exposed to higher levels of the growth hormones and factors probably leading to a increased risk of developing Osteosarcoma.

Birth weight:

Varied results have been published about the association between birth weight and Osteosarcoma. Higher birth-weight has also been associated, thought weakly, with increased incidence of Osteosarcoma. A recent meta-analysis done showed children with birth-weight more that 4046g having an elevated risk of Osteosarcoma.(18) It has been postulated that birth weight may have a role by its association with intrauterine growth factor levels that the baby is exposed to.

Pagets disease:

Pagets disease has also been considered as one of the risk factors for Osteosarcoma. Though the exact incidence has not been elucidated the incidence of Osteosarcoma among patient with Pagets disease is thought to be <1%.(19) Though the association and the reason behind the increased incidence is not well explained the outcome for these patients who develop osteosarcoma remains bleak.

Genetic factors:

The presence of chromosomal aneuploidy in osteosarcoma indicates the possible role played by chromosomal instability in putting a patient at risk of osteosarcoma. Thought studies have elaborated on the possible role of chromosomal instability, no single consistent definite association has been found between any specific changes so far. Single nuclear polymorphisms of Tumor Necrosis Factor-α (TNF), Vitamin D Receptor (VDR), Estrogen Receptor (ESR1), Collagen 1α1 (COL1A1), Tumor Protein p53 (TP53), Insulin-like Growth Factor 2 Receptor (IGF2R), Fas (TNF receptor super-family, member 6; FAS), Mdm2 p53 binding protein homo-log (MDM2),

Transforming growth factor beta receptor 1 (TGFBR1) and 8q24 region have been studied and have been associated with a increased risk of developing osteosarcoma.

Moreover various syndromes have been associated with the increased risk of Osteosarcoma. Though they are rare they help us in understanding the disease more. Table illustrates the various syndromes that have been associated with Osteosarcoma. Li-fraumeni Syndrome is caused by a germ-line mutation in the TP 53 gene which encodes for p53 protein. This protein has been found to be of importance in DNA repair, normal cell growth and various other mechanisms of the cell.

Retinoblastoma is caused by mutations in the RB1 tumor suppressor gens. Among patients with Retinoblastoma, Osteosarcoma is the second most common tumour. It has been shown that patient with hereditary retinoblastoma are at a higher risk of osteosarcoma than those with sporadic retinoblastoma. (20) The children with this gene mutations are at high risk for developing retinoblastoma and usually present at an age of than 5 years.

Blooms syndrome is caused by mutation in the BLM helicase gene. Though the incidence of Osteosarcoma is not very high in these patients it is still higher than the general population.

Werner's syndrome is associated with an increase risk of osteosarcoma. It is caused by mutations in the WRN DNA helicase gene. The patients typically are describe to have short stature, bird facies, parental history of consanguinity, atrophic skin, premature atherosclerosis and early cataracts.

Diamond Blackfan Anemia is an inherited disorder where the patient presents with inherited red cell aplasia. Identifiable mutations in the gene important for ribosomal functions are found in around 40% of patients. Though the involvement of these mutations is not fully understood the increased incidence of osteosarcoma among these patients is notable.

Disorder	Chromosome	Gene	Inheritance pattern
Li-Fraumeni Syndrome	17p13.1	TP53	Dominant
Rothmund Thomson syndrome	8q24.3	REQL4	Recessive
Retinoblastoma	13q14.2	RB1	Dominant

Bloom Syndrome	15q261	BLM	Recessive
Diamond Blackfan Amnemia	Multiple	RPS19, RPL5, RPL11,RPL35A, RPS24, RPS17,RPS7	Dominant
Werner Syndrome	8p12	WRN	Recessive

Pathogenesis of Osteosarcoma:

As mentioned above bone growth, various environmental factors, genetic factors etc. have been shown to play a role in the pathogenesis of Osteosarcoma. There factors play a role at the molecular level leading to rapid tumour growth and metastasis.

Growth factors:

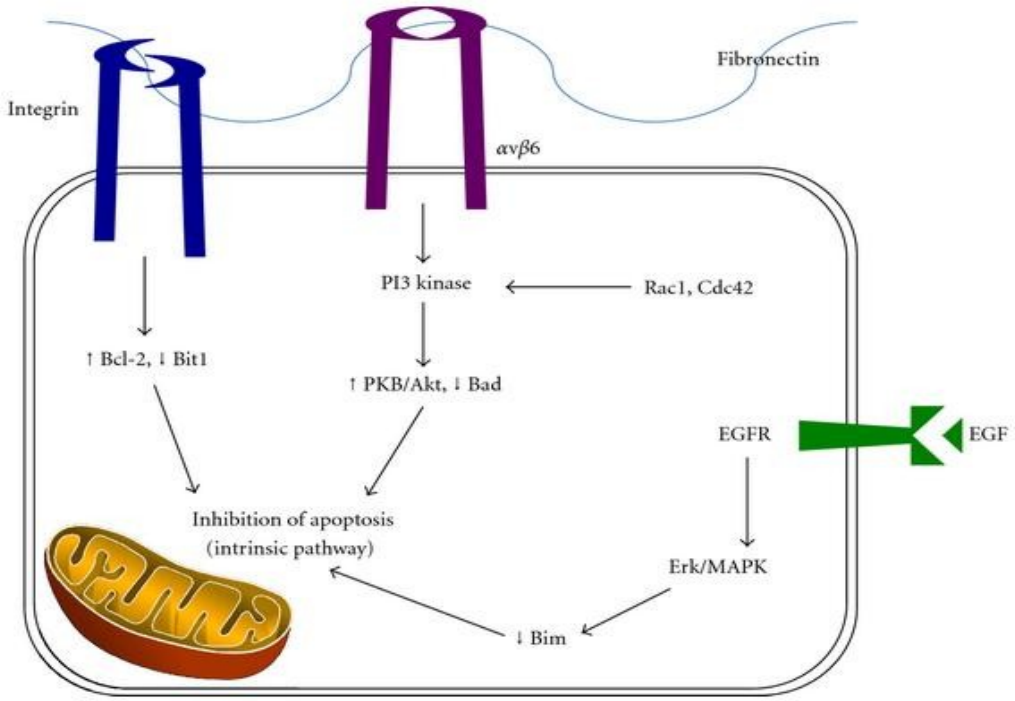
Osteosarcoma cells produces a variety of growth factors. These factors have their autocrine and paracrine effects on the cells. Moreover there is dis-regulated expression of these growth factors and there is also a over activated signal transduction associated with these receptors.

Some growth factors that have been implicated are transforming growth factor, insulin-like growth factor and connective tissue growth factor. This leads to rapid proliferation of cells. Parathyroid hormone and parathyroid hormone related peptide and the receptor have been associated with Osteosarcoma metastasis and progression. It was found that there was increased proliferation, invasion through Matrigel and increased motility when the Osteosarcoma cells were over expressed with parathyroid hormone related peptide 1.

Failure of apoptosis:

Apoptosis plays an important role in the death of the cells that turn rogue. Cancer cells find ways to circumvent pathways that bring about apoptosis and avoid their elimination. Hence they proliferate without any restriction. Apoptosis has two steps which are initiation and execution. In the initiation phase Capsases are activation and in the execution phase these activated capsases execute the actual process of hydrolysis and cell death. The cells that are no longer attached to a

basement membrane or a matrix undergo apoptosis under normal circumstances. This process is termed as Anoikis. It has been shown that Osteosarcoma cells are anoikis resistant and in-spite of the deranged cell-cell and cell matrix attachments they proliferate, which is termed as anchorage independent growth. The picture below summarizes the various pathways that disrupt anoikis.



Broadhead ML, Clark JCM, Myers DE, Dass CR, Choong PFM. The Molecular Pathogenesis of Osteosarcoma: A Review. Sarcoma. 2011;2011:1–12.

Tumour angiogenesis:

The tumour tissue is in a pro-angiogenic state due to the acidotic micro-environment, tissue hypoxia, loss of tumour suppressor gene function, oncogene activation. There is also down regulation of the anti-angiogenic factors such as thrombospondin 1, TGF-β, troponin I, pigment epithelial-derived factor etc. The Von Hippel lindau protein releases hypoxia inducible factor–1a which then binds to vascular endothelial growth factor gene and then up-regulates it. This leads to stimulation of the endothelial cell proliferation, migration and blood vessel maturation. Moreover vasodialation and increased vascular permeability is caused by nitric oxide released by the endothelial cells. Eventually with the involvement of various intermediate factors a immature, irregular and leaky vascular network results.

Cell migration:

Osteosarcoma has a very high metastatic potential. This requires the Osteosarcoma cells to detach from the area of the tumour, then adhere to the extracellular matrix. Following adhesion to the extracellular matrix the cell goes through local migration and invasion through the stroma, intravasation and extravasation. The complex cell to cell and cell to matrix interactions that occur facilitates this process. The various proteins involved in this process include those in the extracellular matrix such as fibronectin, proteoglycans, laminins, collagen and those receptor proteins in the cell surface such as the integrins. The interactions between the proteins of the tumour cells and the extracellular matrix causes conformational changes in the architecture of the cell leading to the formation of membrane ruffles. These changes help in cell migration and metastasis.

Invasion of the tumour cells and destruction of bone matrix:

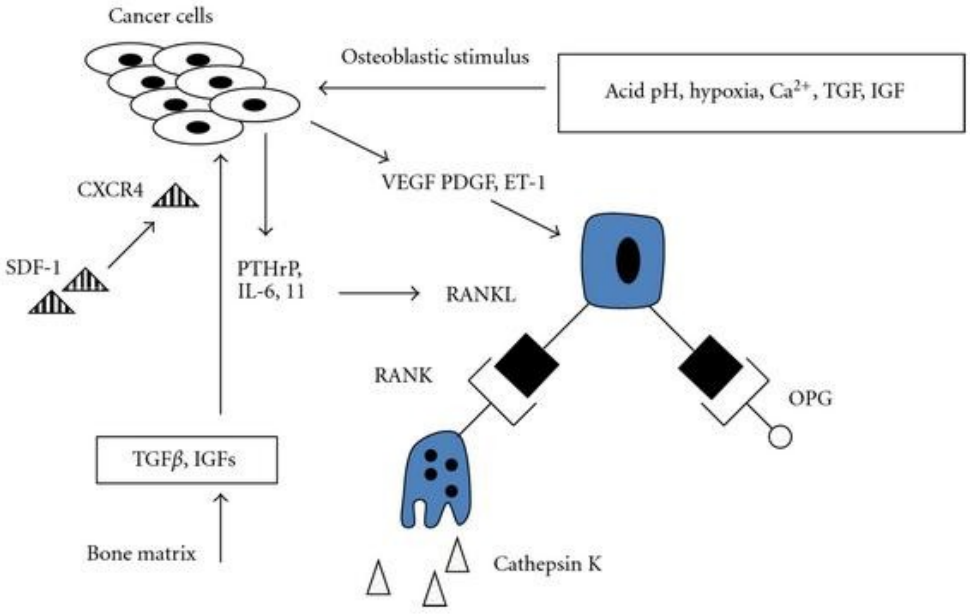
Degradation of the extracellular matrix is essential for the osteosarcoma to invade into the surrounding tissues. This is facilitated by the family of Matrix metalloproteinases which include stromeolysins, gelatinases and collagenases. These matrix metalloproteinases clear the pathway for the cells to grow into the surrounding tissues. Moreover the matrix metalloproteinases also facilitate angiogenesis. While acting on the extracellular matrix the matrix metalloproteinases release Vascular endothelial growth factor which in-turn further up-regulates the matrix metalloproteinases. Another pathway which plays a role in osteosarcoma invasion is urokinase plasminogen activator system. In this pathway plasminogen is broken down to plasmin which then breaks down the extracellular matrix and also leads to further activation of the pro-matrix metalloproteinases. Hence a cascade of activation is established.(21,22)

The invasion of the osteosarcoma cells also depends on the interactions between osteosarcoma cells, osteoclasts, and the matrix of the bone. The degraded bone matrix releases transforming growth factor-β which then stimulates the osteosarcoma cells to release parathyroid hormone-related peptide, interleukin-11 and interleukin-6. The osteoclasts are stimulated by these

cytokines released by the osteosarcoma cells in turn stimulates the osteoclasts to release pro-resorptive cytokines which leads to further invasion. The osteoblasts also function as mediators in bone resorption by the increased receptor activator of nuclear factor κB ligand expression which in turn activates the osteoclasts which in-turn released proteases which resorb the unmineralized part of bone. One among the proteases is Cathepsin K and its been found that patients with low levels of Cathepsin K at diagnosis have better prognosis. (23)

Receptor activator of nuclear factor κB ligand plays a central role in the activation of osteoclasts and invasion of bone. Osteoprotegerin a decoy receptor for receptor activator of nuclear factor κB ligand if found to suppress the differentiation of osteoclasts. In rodent models it was shown that osteoprotegerin gene transfer prevented the formation of osteolytic lesions, decreased tumour incidence, decreased tumour growth and increased survival.(24)

The following picture explains this complex interactions that occur leading to invasion of the Osteosarcoma cell and metastasis.



Broadhead ML, Clark JCM, Myers DE, Dass CR, Choong PFM. The Molecular Pathogenesis of Osteosarcoma: A Review. Sarcoma. 2011;2011:1–12.

Histopathology:

Osteosarcoma is named so because of the presence of osteoid or the ability of the tumour cells to produce osteoid. Though the name Osteosarcoma gives a implication for the tumour to be of osteblastic origin there is no evidence for the same. This is implied well in the term osteogenic sarcoma, a terminology used earlier to describe Osteosarcoma. It is also noted that the tumour produces variable quantities of fibrous tissue and cartilage matrix. The proportion of the cartilage matrix, osteoid, fibrous tissue sometimes vary significantly that it might be difficult to make a diagnosis of Osteosarcoma. It has also been seen that osteosarcoma produce different amounts of matrix which might be cartilage or fibrous tissue. Sometimes the fibrous tissue or the cartilage may be in such high proportion that it might be needed to seek out the osteoid matrix to make a diagnosis of Osteosarcoma.

Traditionally osteosarcoma have been subdivided into three types

1. Osteoblastic
2. Fibroblastic
3. Chondroblastic

Though the classification into any of these types is arbitrary it generally signifies at-least a 50% predominance of the particular histological type. Based on the site of origin they can be intramedullary, surface osteosarcoma or extra-skeletal. Intramedullary tumour are generally high grade and surface osteosarcoma are generally low grade.

Sometimes the tumour can have high grade and low grade components in the same tumour and in such a case the tumour generally behaves similar to the higher grade of sarcoma present among the tumour contents.

Osteosarcoma can be classified based on the anatomical location of the tumour or the pathology of the tumour.

The following tables classifies them based on the anatomical location of the tumour. (25)

Classification of Osteosarcoma based on anatomical location	
Osseous	Surface
	Gnathic
	Central
	Multi-focal
Soft tissue	Intramuscular
	Other

The following table classifies Osteosarcoma based on the histopathology of the tumour.(25)

Types of Osteosarcoma		
Central	High grade	Conventional
		Telangiectatic
		Small cell
		Epithelioid
		Osteoblastoma-like
		Chondroblastoma-like
		Chondroblastoma-like
		Fibrohistiocytic
		Giant cell-rich
	Low-grade	Desmoplastc fibroma -like
		Fibrous dysplasia - like
Surface	High-grade	De-differentiated parosteal
		High-grade surface
	Intermediate-grade	Periosteal
	Low-grade	Parosteal
Gnathic		
Intra cortical		
Extra-skeletal	High-grade	
	Low-grade	

Histological grading of Osteosarcoma:

The histological grading of Osteosarcoma is based on the grading of squamous cell carcinoma of the lip as described by Broders et al.(26) In this grading the tumors are graded in a scale based on the amount of anaplasia in the tumour. In this grading system it is assumed that cytological atypia is the most important factor that determines the grade of the tumour. Hence any area of significant anaplasia will switch the tumour to a higher grade of 4.

The problem with this grading system arises when there is a normalization effect seen as in sclerosing osteosarcoma.

Histological grading of Osteosarcoma	
Grade	Percentage of anaplasia
Grade I	<25%
Grad II	25-50%
Grade III	50-75%
Grade IV	75%-100%

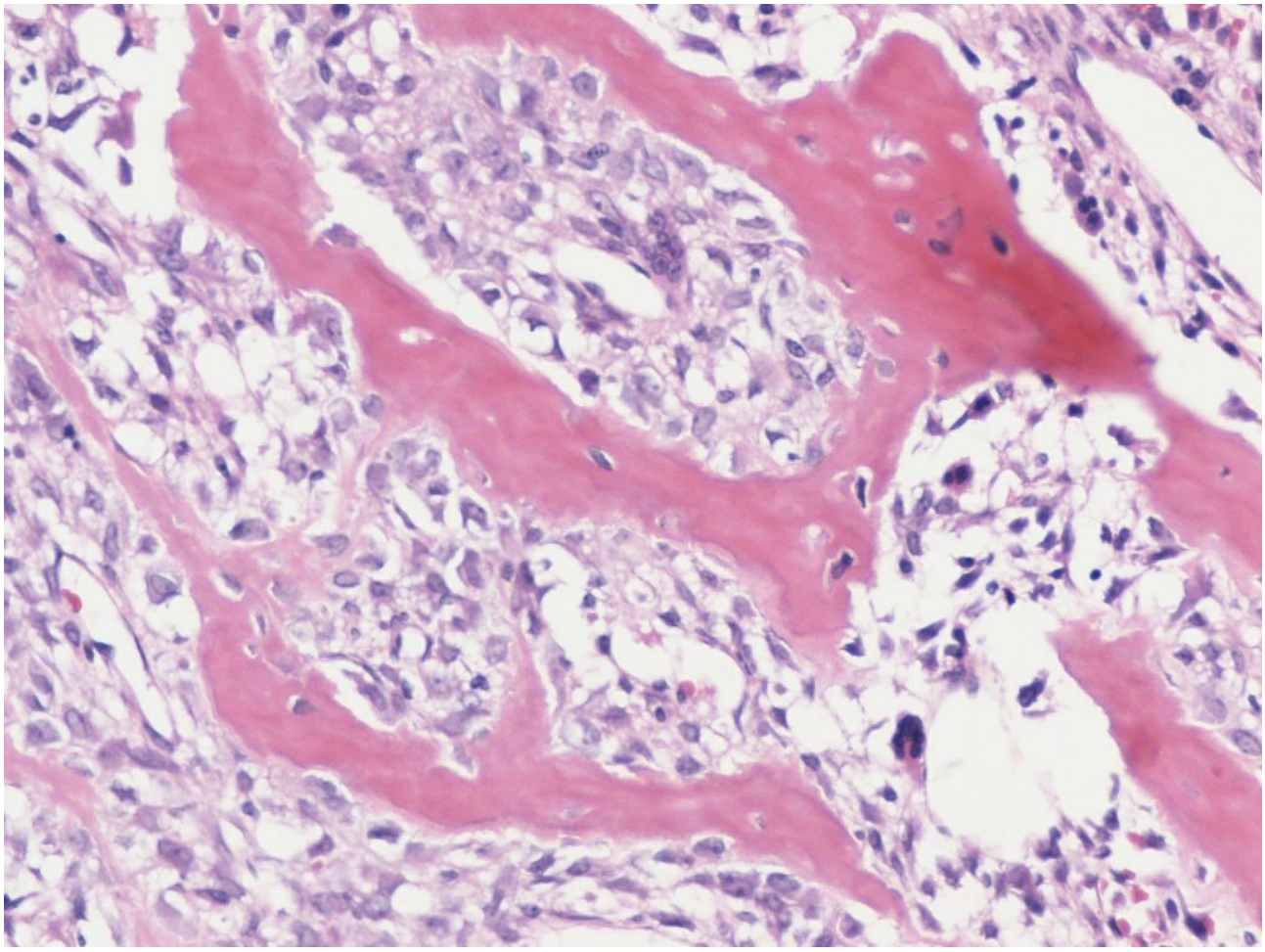
In clinical practice conventional osteosarcoma usually fall under either a grade 3 or 4 and hence they are considered high grace and surface osteosarcoma are low grade. Hence usually for most practical purposes there are two tiers of grading ie. High-grade and low grade. When the tumour does not fit into either a high-grade or a low-grade then a third tier is added and it is classified as an intermediate grade tumour.

Conventional Osteosarcoma:

This is the classic form of Osteosarcoma and they are easily diagnosed where they are in their classic form. Mitotic cells are easily seen with the presence of atypical mitotic cells. The cells may be polyhedral or spindle shaped and with a hyper-chromatic pleomorphic nuclei. The cells also produce osseous, fibrous or cartilaginous matrix in varying proportions. Though conventional osteosarcoma have been divided as osteoblastic, chondroblastic and fibroblastic there is no statistical difference in the survival rates of the patients with high-grade tumors of these

different sub-types.

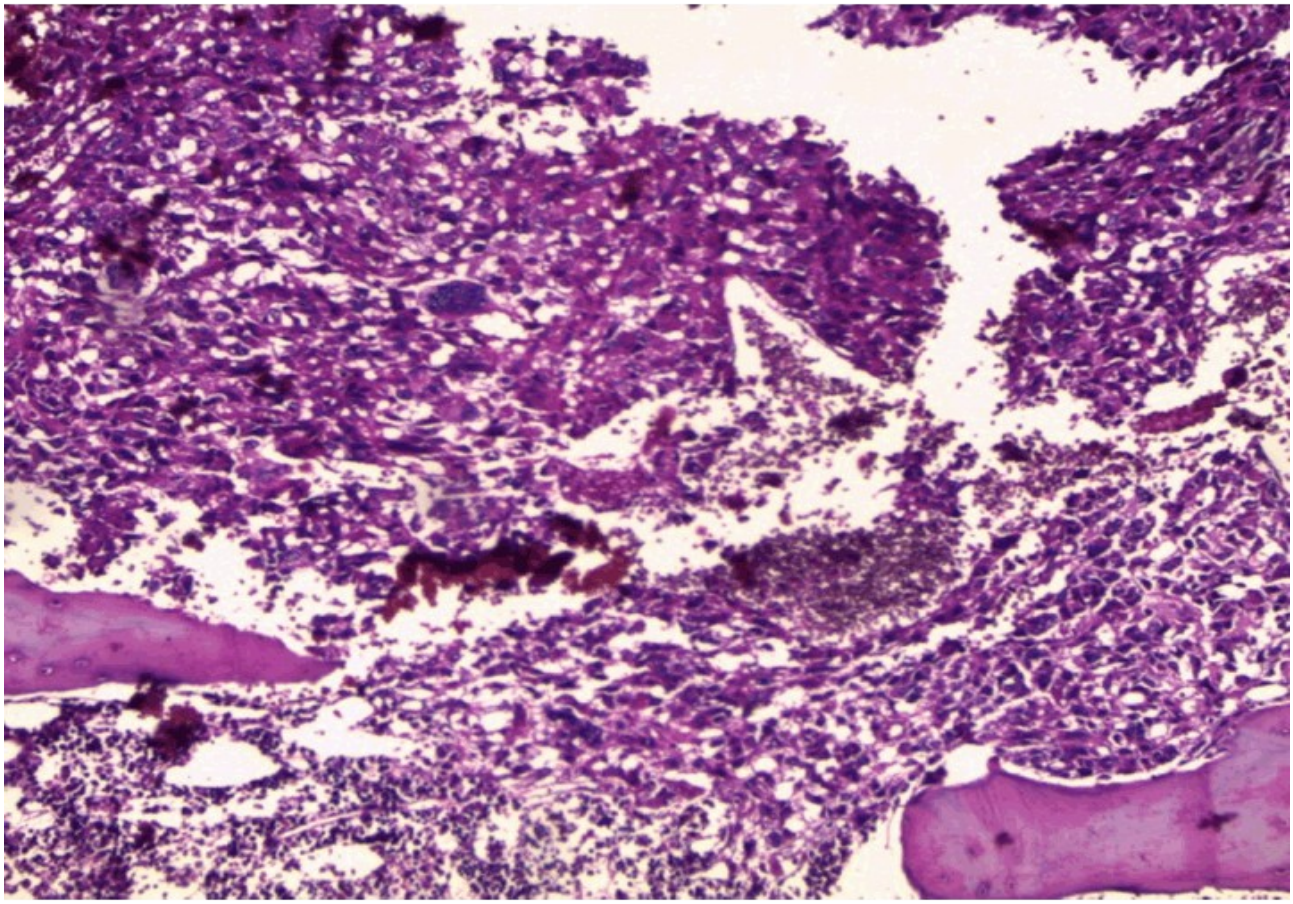
In the purely sclerosing Osteosarcoma the tumour cells get incorporated into the bone matrix and hence it is difficult to identify the cellular component. But the cellular component can be easily visualized at the advancing edge of the tumour. In some patients with sclerosing osteosarcoma the bone matrix grows between the adipocytes along the interseptal spaces. This may appear as if the lesion is non malignant. In such cases clinico-radiological correlation will help to clinch the diagnosis. Moreover there would be microscopic soft tissue involvement that would be evident though the gross section may appear uninvolved.



Source : N F, Lc M. Primary malignant giant cell tumour of the proximal tibia: a case report. Journal of Cancer Research & Therapy. 2013 Aug 1;1(6):174–7.

Telangiectatic Osteosarcoma:

This is a type of osteosarcoma which resembles aneurysmal bone cyst both radio-graphically and histologically. It produces a asymmetric expansile lesion with associated radio-lucent bone destruction. Interrupted periosteal reaction is seen and since there is little bone formation conventional radiographs may not show bone formation. With the advent of computed tomography some bone matrix is detected in at-least 85% of the telangiectatic osteosarcoma. Magnetic resonance imaging of the tumour shows blood filled sinusoids which are multiple in number with little soft tissue content. Though on a low power microscopic evaluation it appears as much as an aneurysmal bone cyst, the high mitotic rate and the presence of pleomorphic nuclei helps to differentiate the two. Moreover there is local destruction and permeation into the cortical haversian canal or the adjacent marrow.(25)

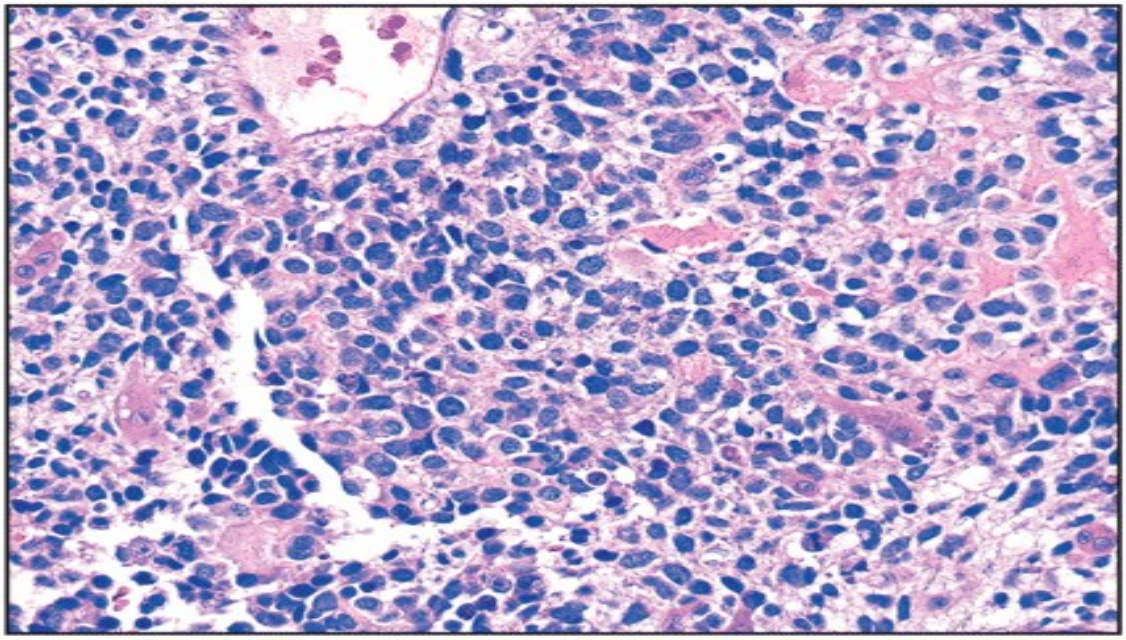


Source: Mahdi Y, Rouas L, Amrani A, Malihy A, Lamalmi N, Alhamany Z. Neglected telangiectatic osteosarcoma of the femur presenting as surgical emergency. International Journal of Case Reports and Images. 2014;5(5):391.

It has also been noted that telangiectatic osteosarcoma have foci of osteoclastic giant cells. Earlier it was found that outcome for telangiectatic osteosarcoma was poor compared to the conventional osteosarcoma. With the advent of Chemotherapy this has changed and outcomes for telengiectatic osteosarcoma are considered equivalent or better compared to osteosarcoma.

Small cell Osteosarcoma:

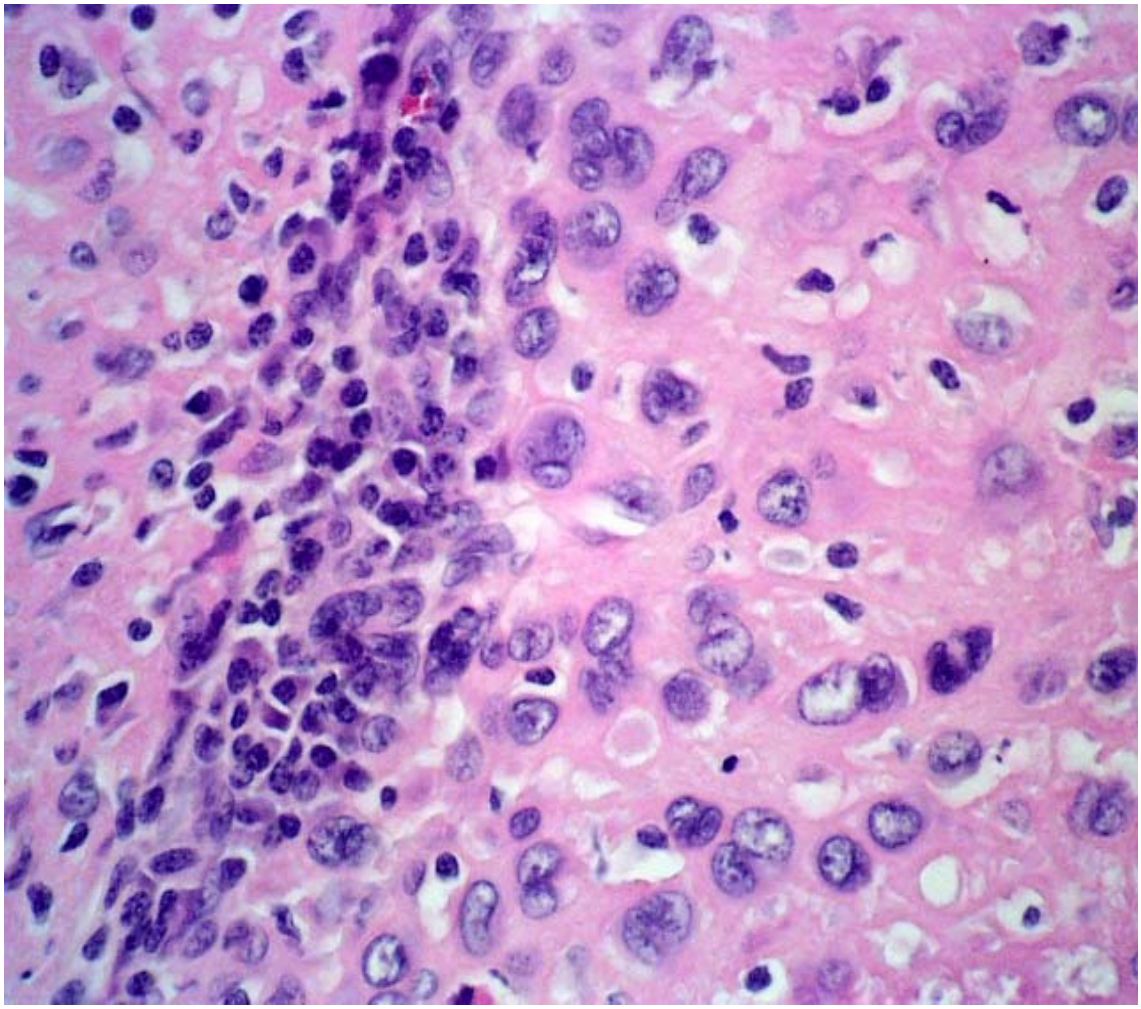
It is rare variant of osteosarcoma constituting about 1-2% of all osteosarcoma. Though this tumour resembles Ewing's sarcomas in its immunological profile by the positivity of CD 99, it differs by the production of osteoid. Histologically it resembles Ewing's sarcoma by the presence of small round cell with hyper-chromatic nuclei. The nuclear pleomorphism in small cell osteosarcoma is much less compared to conventional osteosarcoma. The reciprocal trans-location between the chromosomes 11 and 22 most commonly reported in Ewing's sarcoma has also been occasionally reported in Small cell Osteosarcoma. All this similarity with Ewing's sarcoma makes it a controversial diagnosis with some authors contenting to consider them as Ewing sarcoma/PNET.



Bishop JA, Shum CH, Sheth S, Wakely PE, Ali SZ. Small Cell Osteosarcoma Cytopathologic Characteristics and Differential Diagnosis. AJCP. 2010 Jan 5;133(5):756–61.

Epithelioid Osteosarcoma:

Epithelioid osteosarcoma are called so due to the difficulty in differentiating whether the tumour is a sarcoma or carcinoma. The diagnosis becomes difficult especially when there is little osteoid productions and the tumour cells resemble epithelial cells. There may be gland like structures and the cells may be arranged as papillary structures. When these tumors are seen in the younger age group osteosarcoma must be considered. In case of older patients metastatic carcinoma must be considered. Immuno-histochemical analysis might be positive for keratins though the tumour may be an osteosarcoma. Hence a careful search must be made for osteoid formation especially in younger age group.



Source: http://www.orthopaedicsone.com/display/PORT/Epithelioid+Sarcoma

Kyoji et al. described subtype of rosette forming epithelioid osteosarcoma with very aggressive clinical behavior.(27)

Giant cell rich Osteosarcoma:

Giant cells have been noted in as many as 25% of all osteosarcoma. Sometimes the presence of giant cell make diagnosis difficulty especially in areas where giant cell tumour is more common that Osteosarcoma, such as the sacrum. But giant cell tumors arises in skeletally mature people. Moreover periosteal reaction is generally absent in giant cell tumour the exception being a associated pathological fracture. Hence the presence of a giant cell rich lesion with associated periosteal reaction in a immature skeleton must be carefully evaluated to rule out the presence of osteosarcoma.

Gnathic Osteosarcoma:

The osteosarcoma of the mandible and maxilla usually present with pain and swelling. Conventional radiographs show radio-lucent area or a mixture of radio-dense and radio-lucent areas. They are predominantly chondroblastic osteosarcoma. But other types such as osteoblastic, fibroblastic and small cell osteosarcoma have been reported. They are usually high-grade tumors and leads to uncontrolled local disease. Osteosarcoma occurring in the other craniofacial bones generally occur among the older age group and is usually associated with conditions such as Pagets disease, past exposure to radiation etc.

Chondroblastoma like and osteoblastoma like osteosarcoma:

Osteoblastoma like osteosarcoma appears similar to osteoblastoma by producing similar microtrabecular bone which are lined by osteoblasts. But radiologic appearance can help to differentiate a malignant tumour. But this differentiation may be absent as osteoblastoma can have atypical radiological appearance. Some times osteoblastoma may also contains atypical cells and this makes differentiating a malignant lesion from a benign lesion extremely difficult. The presence of aneuploid mitotic activity and permeation of the normal bone at the tumour bone interface helps

to differentiate a malignant lesion.

Chondroblastoma like osteosarcoma is a very rare tumour. It may be present in the epiphyseal region. The presence of the tumour in the epiphysis makes diagnosis very difficult as the features cannot be distinguished exclusively. But the presence of osteoid, atypical cell and permeation of the trabeculae helps to differentiate from the benign counterpart.

Low grade Central Osteosarcoma:

Low grade central osteosarcoma are quite uncommon compared to the high grade counterpart. The osteoid formation is scant and it has a bland fibrous stroma contained the microtrabecular bony matrix. Though they mimic benign lesions such as fibrous dysplasia the presence of dense sclerosis, indistinct zone of transition, interrupted periosteal reaction and cortical infarction helps us to differentiate from them. Sections of the interface between the tumour and the normal bone shows fibrous tissue inside the haversian canals and between the mature trabecular bone and this confirms it as a malignancy. Though these lesions have good outcome with surgical treatment alone it has been reported that some of the patients developed secondary high-grade osteosarcoma at the same site.

Surface osteosarcoma:

They are osteosarcoma whose epicenters are away for the underlying cortex. They arise from the cortex of the bone or the periosteum without involving the medullary cavity or involving the medullary cavity minimally. There occur in the third or the fourth decade compared to the conventional osteosarcoma which occur in adolescence. They are predominantly low grade tumours with low risk of distant metastasis. But they have a propensity towards local recurrence. Around 10% of the surface osteosarcoma are high grade in nature.

Parosteal osteosarcoma:

This is the most common form of surface osteosarcoma. It accounts for less that 1 out of 20

osteosarcoma that are diagnosed. It was first described by Geschicter and Copeland. Its incidence is around a decade after the age group for conventional osteosarcoma. About 75-80% of the parosteal osteosarcoma arise from the distal posterior femur. It usually presents as a fullness over the popliteal region or it might restrict full flexion. Conventional radiographs show a lesion of non uniform radio-density, being more radio-dense centrally than peripherally and the lesion is not continuous with adjacent cortex nor the medullary cavity thus differentiating from osteochondroma. On radiographs a thin radio-lucent line separates the tumour from the adjacent cortex. When resected and examined this correlates with the periosteum of the bone and the tumour is attached to the periosteum at some point. Periosteal reaction is absent as this tumour does not lift the cambium layer off the cortex. Histological examination shows steamers of trabecular bone which are arranged in parallel orientation similar to a periosteal new bone formation. Mira et al. described this appearance a a flowing steel wool appearance. About 25-30% of the cases have a cellular cartilage cap outside the bony portion of the lesion. Most of the parosteal osteosarcoma are associated with outer fibrous layer of the periosteum and hence they do not produce typical periosteal reactions. Sometimes these tumors may break through the periosteum and the cortex though it might be low grade. But it has been noted that invasion of the cortex does not worsen the prognosis as long the tumor is low grade in nature.

Periosteal Osteosarcoma:

This is a intermediate grade osteosarcoma first describe by Unni et al.(28) The incidence of this tumour is much less common compared to the parosteal osteosarcoma. It arises between the cambium layer and the bony cortex and hence is associated with vivid periosteal reaction. The underlying cortex is either thickened or eroded but it never extends into the endosteum.

Dedifferentiated parosteal osteosarcoma:

It was first described by Wold et al.(29) Though following the first series that was published it was thought that the tumour occurs as a recurrent disease following a previous low-grade

parosteal osteosarcoma, it is now considered that these dedifferentiated areas are present in the initial resection of parosteal osteosarcoma itself. This dedifferentiated area can be grossly distinguished from the sclerotic ares of the parosteal osteosarcoma. Histologically it contains areas of low grade parosteal osteosarcoma and high-grade parosteal osteosarcoma. Though the prognosis is poorer than typical parosteal osteosarcoma it is better than high-grade parosteal osteosarcoma. Bertoni et al reported that this dedifferentiation occurs in one in four cases of parosteal osteosarcoma.(30)

High-grade parosteal osteosarcoma:

This is a surface bone lesion and it has a histological high-grade. Radio-graphic appearance may vary from features of parosteal osteosarcoma to mixed features or presence of large soft tissue component. Its has a accelerated growth compared to parosteal osteosarcoma and it is more aggressive. CT and MRI may show foci of marrow infiltration occasionally. It is differentiated from a conventional osteosarcoma by it having a epicenter outside the bone and by the absence of periosteal reaction.

Intra-cortical osteosarcoma:

This is a very rare variant of Osteosarcoma described by Jaffe et al. and it occurs as a area of lucency within the bony cortex with surrounding sclerosis.(31,32) Abundant osteoid formation is present histologically. It behaves like a conventional osteosarcoma and hence it must be treated aggressively. The other lesions that may be confused with this are osteoid osteoma or a osteoblastoma.

Multi-focal osteosarcoma:

This is a very rare condition which affects multiple bone either at the same time or at varying intervals. Based on this they can be

1. Synchronous
2. Metachronous

The synchronous form generally occurs in children, being symmetric and radio-dense, it is quickly fatal. The metachronous form, being asymmetric with variable sclerosis generally occurs in adults with varying disease free intervals. Though metastases is a differential diagnosis the longer survival associated with the patients speak that these are a different class of tumors.

Extra-skeletal osteosarcoma:

It accounts for less than 2% of soft tissue sarcomas. It occurs in the 5h to 7th decade and it arises in the deep soft tissues mainly in the arm, buttock and in the retro-peritoneal region. Radiographs show mineralization of the tumour and it can be better appreciated on a computed tomograph. All histological types can occur and the prognosis depends mainly on the grade of the tumour. High grade tumors have high mortality while low grade tumour though rare have better survival rates.

Clinical features:

Most patients with osteosarcoma present with localized pain which lasts for several months. The most common sites involved are the distal femur, proximal tibia, proximal humerus, proximal femur followed by other regions. They generally do not have any fever, weight loss, malaise or any other systemic symptoms. Widhe et al. found that 87% of the patients presented with pain associated with strain. Intermittent pain at rest was also common. But only 21% of the patients with osteosarcoma had night cries. 47% of the Osteosarcoma had history of trauma at the onset of the symptoms and 58% of male patients and 35%of female patients were involved in sports. (33)

Among the patients regional pain alone was the main complaint that brought the patients to the hospital in 70% of the patients and pain and palpable mass were the initial complaints in 25% of the patients.

Angela et al. noted that 78% of the patients had pain, 62% had difficulty in walking, 50% had swelling, 38% had edema, 10% had warmth and 8% had erythema. (34)

The most important finding on clinical examination is a palpable mass with associated tenderness which arises from the bone. There might be associate compression of the vessels and nerves depending on the size of the mass. Pathological fractures can also be present at initial presentation. Angela et al. found that 42% of the patients had pathological fractures at presentation.

Widhe et al. showed that the following physical findings were present at the first visit among the 102 patients with Osteosarcoma he studied.

Physical findings at the first visit(33)	
Local tenderness	92%
Painful joint movement	39%
Mass on palpation	39%
Movement restriction of the joint	23%
Limp while walking	31%
Muscle atrophy	5%
Fever	3%

About 10-20% of the patients with osteosarcoma have demonstrable macro-metastasis at presentation. Though these metastases most commonly involve the lung, bone involvement is also noted.

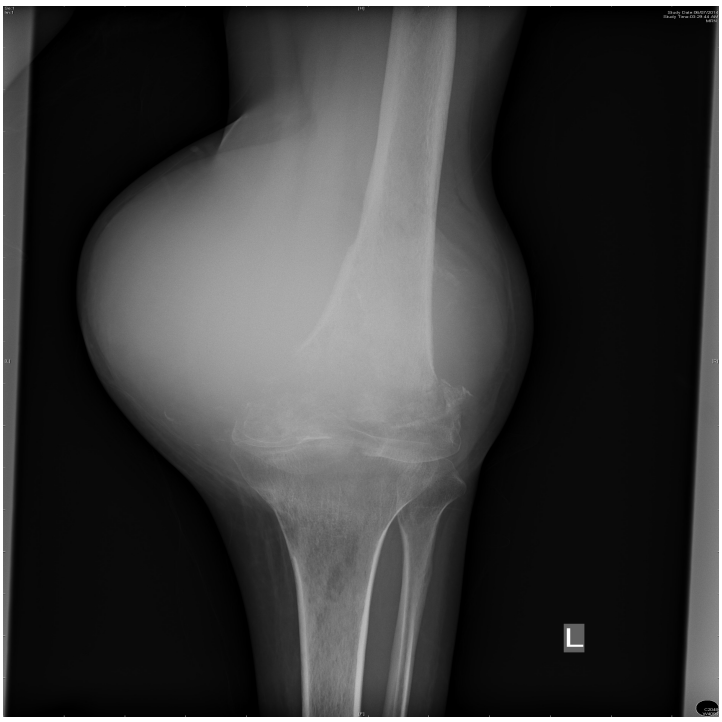
Investigations:

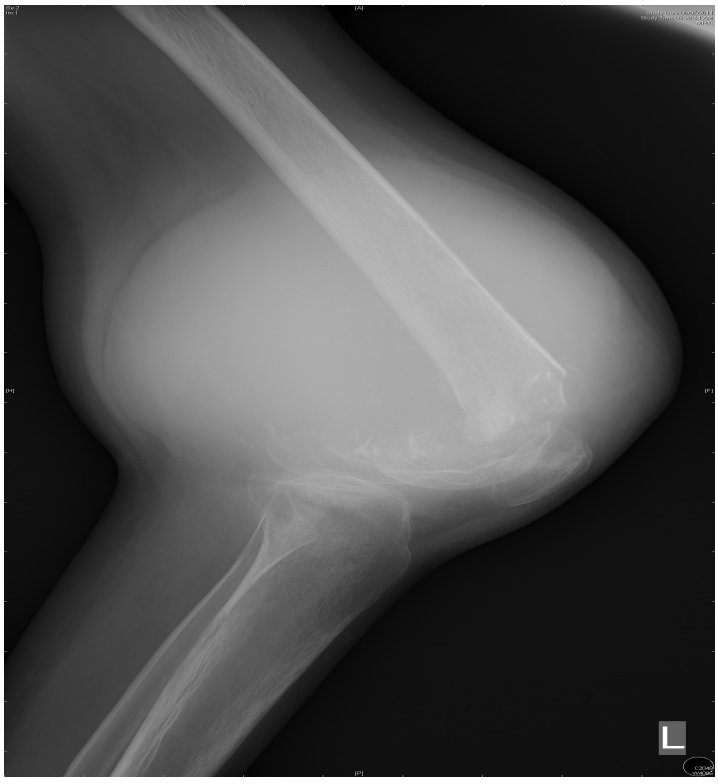
Various modalities of investigations are used to diagnose and stage osteosarcoma. They are detailed as below.

According to the appropriateness criteria of American College of Radiology plain radiographs must be the initial modality of evaluation for a bone lesion. They are inexpensive and features noted on the plain radiographs help in the diagnosis of the lesion. Moreover they also help to decide on the need for further evaluation and imaging.

Osteosarcoma shows features of a aggressive lesions such as wider zone of transition, cortical destruction, periosteal new bone formation and associated soft tissue mass. The periosteal reaction is typically described as codman's triangle or sunburst appearance, hair on end appearance etc. Osteolysis is more of a feature of the telangiectatic osteosarcoma and sclerosis is more seen in the sclerosing type. In patients in whom the physis is still active it generally acts as a barrier but aggressive tumors can cross the physis.

But lytic lesions will not be detected on the plain radiographs until 30-50% demineralization of the bone. If the radiographs are normal and the patient persists to have symptoms then he must be evaluated with further imaging. The most preferred imaging in such a setting is a MRI as it detects marrow lesions much better than other modalities. Moreover it also helps to know whether if there are any other modalities apart from the bone. MRI though expensive is preferred because of its superior soft tissue definition, demarcation of the neurovascular bundle, marrow and joint involvement and the presence of skip lesions.(35) MRI has also been used to predict the effect of neoadjuvant chemotherapy as it detects the decreased neo-angiogenesis following chemotherapy. (36)





Osteosarcoma of the distal femur with Pathological fracture AP/Lateral views

Another study showed that diffusion weighted imaging is a good non-invasive predictor of the response to neoadjuvant chemotherapy as it detects the early changes in the cells following chemotherapy.(37) Some proponents of diffusion weighted imaging advocate the usage of it as a surrogate marker for estimating the response the chemotherapy.

Gillespy el al concluded that MRI is extremely accurate in measuring the intramedullary extent of osteosarcoma.(38) Schima et al. showed MRI is extremely accurate in predicting joint involvement.(39)

If the patient has pain that cannot be localized the bone scan would be a better option. Technitium 99m diphosphate is administered at a dose of 20mCi and the scan is done in three phases: the flow phase, blood pool phase and the delayed phase. The flow phase images are obtained one minute after the injection of Tc99m diphosphate and blood pool phase is obtained at 5 min after injection. The delayed phase is obtained 2-4 hours after injection of Tc99m diphosphate. The flow phase illustrates increased blood flow to a area, the blood pool phase illustrated a increased blood pooling in a area by capillary leakage etc and bone images are obtained in the delayed phase.

Chest X ray helps to pick up the presence of metastasis and the it is typically described as canon ball like lesions. More over bone scan would be needed to stage the disease and rule out any distant metastases. The patient also needs spiral computed tomography of the thorax to rule out metastatic lesions of the lung.

PET/CT scanning has been evaluated for its use in tumour detection, grading, tumour staging, monitoring following therapy, prognostication and as guide for obtaining biopsy. In this a positron emitter which is preferentially taken up by tumor tissue is used. F18-deoxyglucose is injected into the patient which is taken up by tumour tissue. Dual photons are released following the annihilation reaction between the positron released from F18-deoxyglucose and an electron. These dual proton events are detected by the detectors which are placed around the patient. (40,41)

But it has been found that though PET/CT can be helpful in the above mentioned situation, it is less cost effective and provides very little additional information most of the time. Histological examination is the gold standard for obtaining tumour grade, tumour staging is best done using a conventional CT to avoid the false positive provided by PET/CT. PET/CT might have some usefulness in patients with non-pulmonary metastases and for monitoring response following therapy. But it needs further research and standardization before it becomes the standard of care. The following table summarizes the pros and cons of PET/CT.(40)

Pros and cons for PET/CT	
Pros	**Cons**
Allows biopsy guidance to active metabolic areas	Clinical suspicion of aggressive-appearing lesions directs physicians to re-sample equivocal biopsy Results
Allows evaluation of chemotherapy response before resection and histologic examination	Cutoffs for stopping chemotherapy by PET/CT are poorly defined
Allows for evaluation of lymph nodes and non-pulmonary sites of metastatic disease	PET/CT has false-positives that cause unnecessary biopsies and procedures to be performed
Allows for noninvasive grading of tumors	PET/CT does not obviate biopsy, which is the gold standard for tumor grading

As per the ESMO Guidelines Working Group the following are considered as requirements for the diagnostic work-up of patients with Osteosarcoma.

Diagnostic work-up for osteosarcoma patients(42)	
Primary tumor	
Plain radiographs	Tumor localization in two planes - whole extremity p/a
Magnetic resonance imaging Metastases	Whole extremity/tumor region
99mTc bone scan	Whole skeleton
Computed tomography	Chest
Organ function	
Heart	Echo-cardiogram, electrocardiogram
Hearing	Audiogram
Kidney	Creatinine (including estimated clearance)
	Tubular function tests
Liver	Liver function tests
Other laboratory	

Alkaline phosphatase in serum
Lactate dehydrogenase in serum

Alkaline phosphatase is found to be increased in some patients with patient with osteosarcoma. One study which included 560 patients with high-grade osteosarcoma noted that alkaline phosphatase was normal in 54% of the patients with osteosarcoma and it was high in 46%. (43) Some studies have shown that the level of alkaline phosphatase at diagnosis has prognostic significance with higher levels alkaline phosphatase having poorer outcomes.(43,44) Another study noted a positive correlation between decrease in bone alkaline phosphatase and the response to chemotherapy.(45)

The patient also needs investigation to evaluate his fitness for neoadjuvant or adjuvant chemotherapy and also for a baseline recording of his heart, ear and renal functions before starting chemotherapy.

Biopsy:

Biopsy is most essential for diagnosis of osteosarcoma and is considered the final diagnostic procedure. A biopsy that it inadequately performed will lead to failure or delay in diagnosis and there by alter the prognosis of the patient and also may lead to amputation due to inability to attempt a limb salvage operation. All patients with bone lesions that are suspicious of osteosarcoma must undergo a biopsy. Lesions which appear benign clinically and radio logically need not need a biopsy. On the other hand lesions that appear malignant, aggressive or with doubtful appearance need a biopsy. Biopsy must be done in a center with the adequate reliable diagnostic facilities where the patient must be able to undergo operative treatment and other modalities of treatment required for his condition. It was found that biopsies done at smaller ill equipped centers had a complication in 15.9% of patients, diagnostic errors in 13.5 of patients and 3% of patients underwent amputation which were deemed unnecessary.(46,47) It was the same in a study done by the same author in 1982 and it did not change considerably when he studied it again in 1996.

The location of the biopsy tract has also become important with the increased number of limb salvage operations that are being performed as it requires the excision of the biopsy tract in-toto with the tumour to avoid recurrence of the tumour due to spillage at the biopsy site. A well performed biopsy helps to know the histological type of the tumour and the grade of the tumour. Earlier open biopsies were performed and spillage of the tumour did not matter as amputation was the treatment of choice. Nowadays per-cutaneous biopsies with core-cut needle are being performed and it decreases the incision size and the tumour spillage without decreasing the biopsy yield. Core needle biopsy is done using a 14-gauge needle. It was found that core of maximum length of 20 mm, was more than 90% accurate in differentiating malignant from benign lesions.(48) In case of lesions where the diagnosis in inconclusive or in lesions where the core biopsy does not correlate with radiologic and clinical findings an open biopsy is advised. While performing a open biosy the incision must be made longitudinally and must be preferably performed by the surgeon performing the definitive procedure. If the biopsy requires a window to be made in the bony cortex it must be made in a oblong shape longitudinally as this helps to prevent pathological fractures following the biopsy. A study which compared the residual bone strength following biopsy showed that a rectangular hole with square corners or rectangular hole with rounded corners had less residual bone strength to resist fractures in comparison to a oblong hole with rounded end.(49)

Fine needle aspiration cytology has also been used in the diagnosis of osteosarcoma and it has been found to be effective and quick method of diagnosing osteosarcoma.(50) But it requires the expertise of a pathologist well experienced in fine needle aspiration cytology. Another study showed that fine needle aspiration cytology can obviate the need for open biopsy in patient with high-grade osteosarcoma demonstrating typical radiological features.(51)

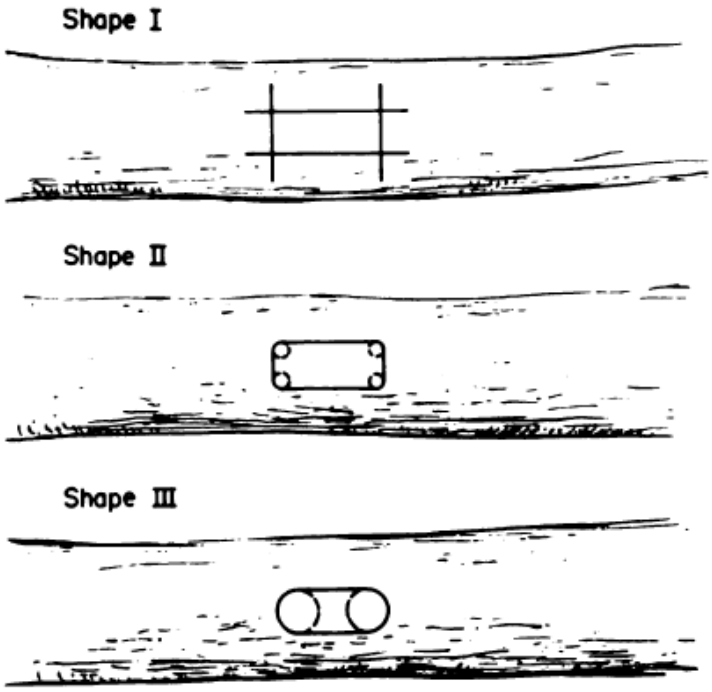
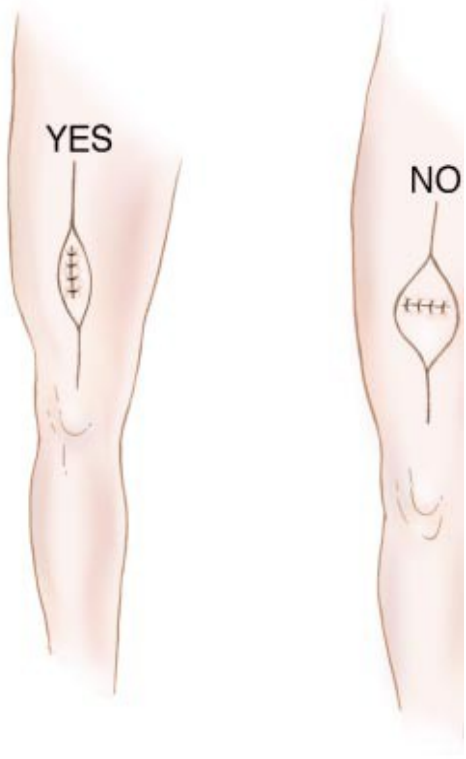


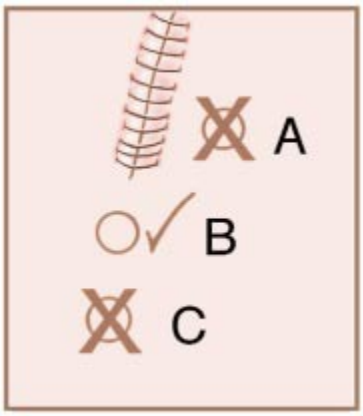
FIG. 1

The three types of biopsy-hole shape used in the first part of our study. Shape I, rectangular hole with square corners; Shape II, rectangular hole with rounded corners; and Shape III, oblong hole with rounded ends.

Clark CR, Morgan C, Sonstegard DA, Matthews LS. The effect of biopsy-hole shape and size on bone strength. J Bone Joint Surg Am. 1977 Mar;59(2):213–7.



Incision for open biopsy



Drain site following open biopsy

Staging of Osteosarcoma:

Staging of osteosarcoma involves the staging of the primary tumour and the systemic staging. Local staging of the tumour is done with the help of plain radiographs of the involved region in two planes. MRI helps to look at the soft tissue involvement and extent and also the bone marrow involvement and extent.

Systemic staging of osteosarcoma involves evaluation of the lung and skeleton for any metastases and most metastases occur in the lung or in the bone. Spiral CT done during a single breath-hold with a collimation of less than 5 mm helps to rule in or out lung metastasis. Tc99m diphosphate bone scan with the help of plain radiographs helps to rule out bony metastasis.

Two main systems of staging are under use for staging of Osteosarcoma. One is the Musculoskeletal society scoring system, adopted from the Enneking staging system and the other is the American Joint committee on cancer staging system. The Musculoskeletal tumour society staging system has been widely used for many years and it classically divides a malignancy into two grades ie. high grade and low grade and whether the tumour is contained within the compartment or whether the tumour has breached the compartment.

Enneking staging system for Primary Malignant Tumors of Bone			
Stage	**Tumor**	**Metastases**	**Grade**
IA	T1	M0	G1
IB	T2	M0	G1
IIA	T1	M0	G2
IIB	T2	M0	G2
III	T1 or T2	M1	G1 or G2
T1 – Tumour is intra-compartmental			
T2 – Tumour is extra-compartmental			
M0 – No regional or distant metastasis			
M1 – Regional or distal metastasis			
G1 – Low grade			
G2 – High grade			

The second staging system is the AJCC staging system or the TNM staging system. The following table elaborates the AJCC staging system.

American Joint Committee on Cancer Staging System for Primary Malignant Tumors of Bone for Those Tumors Diagnosed on or After January 1, 2003				
Stage	**Tumor**	**Lymph Node**	**Metastases**	**Grade**
IA	T1	N0	M0	G1 or G2
IB	T2	N0	M0	G1 or G2
IIA	T1	N0	M0	G3 or G4
IIB	T2	N0	M0	G3 or G4
III	T3	N0	M0	Any G
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
IVB	Any T	Any N	M1b	Any G
Tx - primary tumor cannot be assessed			M0 - no distant metastasis	
T0 - no evidence of primary tumor			M1 - distant metastasis	
T1 - tumor 8 cm or less in greatest dimension			M1a - lung	
T2 - tumor more than 8 cm in greatest dimension			M1b - other distant sites	
T3 - discontinuous tumors in the primary Bone			Gx - grade cannot be assessed	
Nx - regional lymph nodes not assessed			G1 - well differentiated (low grade)	
N0 - no regional lymph node metastases			G2 - moderately differentiated (low grade)	
N1 - regional lymph node metastasis			G3 - poorly differentiated high grade)	
Mx - distant metastasis cannot be assessed			G4 - undifferentiated (high grade)	

Treatment of Osteosarcoma:

The treatment of Osteosarcoma has evolved over the past 3 decades. It requires a multidisciplinary treatment model. It has been noticed that 89-90% of the patients with apparent localized disease eventually develop metastases predominantly in the lungs when chemotherapy is not administered. If chemotherapy is not instituted early on in the course of the disease these patients will die of metastases. Randomized trails done showed the improved survival due to chemotherapy.

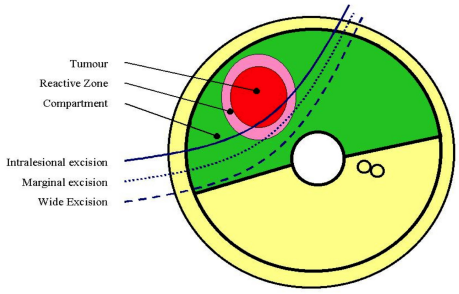
Current treatment regimens include the following modalities

1. Surgery
2. Chemotherapy
3. Radiotherapy

This multidisciplinary treatment has improved the survival among patient with osteosarcoma to about 60-70%.

The objective of operative management of osteosarcoma is complete removal of the tumour. Operative management must aim to get at-least a wide margin during the operation. A wide margin implies that the tumour and the biopsy tract must be removed with cuff of healthy tissue that is not violated.

Enneking criteria for surgical margins in musculoskeletal Tumors(52)	
Margin	**Dissection**
Intralesional	Within the lesion
Marginal	Through the pseudo-capsule or reactive tissue
Wide	Lesion (including biopsy scar), pseudo-capsule and/or reactive zone, and an unviolated cuff of normal tissue completely surrounding the mass removed as a single block
Radical	Entire anatomic compartment containing the tumor removed as one block



Earlier amputation was the most common operative procedure done for osteosarcoma. But with improved expertise and prosthesis limb sparing operations are being performed more commonly. These limb sparing operations have been supported by advances in biomedical engineering, imaging techniques with improved understanding of neoadjuvant chemotherapy.

Various techniques have been used to reconstruct the limb following the tumour excision. Some of them are

1. Turn-up Plasty(53,54)
2. Endoprosthetic reconstruction
3. Allograft reconstruction
4. Van Nes rotationplasty

Though various advances have been made in the surgical management of Osteosarcoma recurrence of the tumour still continues to be a dreaded complication. Due to the various complication that occur after operation these extensive operations must be attempted by a surgeon who is aware of the various surgical techniques and is capable of implementing them for the appropriate patient.

Amputations:

Currently amputations are employed only for those patients with significant neurovascular infiltration or poor function of the distal extremity. Other indications include failed limb salvage attempts, recurrent local recurrence of the tumour. Contamination of the soft tissue associated with large hematomas is also considered an indication for amputation.

Tumors involving the knee joint the which require a limb ablation procedure require a above knee amputation or a hip dis-articulation procedure. The ideal optimal level as described for a above knee amputation is considered at a level 15 cm above the knee joint line or 25 cm distal to the greater trochanter.(55) The patient undergoing amputation generally has extensive disease and will require complex bony and soft tissue resection. In such complex tumour resections this may not always be possible and the stump might be much shorter and such patients would benefit from a hip

dis-articulation.

Van nes rotationplasty is another alternative for preserving as much function as possible in patients with distal femur osteosarcoma.(56) This is done in skeletally immature individuals. This procedure helps to get a functional limb that will act as a Below knee stump. Here the femoral resection is done as proximal as possible and the disease free tibia is rotated by 180 degree and it functions as the new knee joint.(57) It has bee found that the functional results following this procedure are adequate and there have no adverse psychological outcomes.

Limb salvage procedures:

Many recent studies show that limb-preserving operations are preferred to limb ablations operations. In a multi-centric study among 227 patient who underwent either a limb salvage procedure, above knee amputation or hip disarticulation it has been shown that limb-salvage procedures do not compromise the disease free interval or the long term survival of the patients. (58)

An important factor while attempting limb salvage operations is the adequacy of surgical margins. It is considered that in case of high-grade tumors a wide margin would achieve satisfactory local control in 95% of the patients. Sluga et al showed that in patient in whom wide or radical margins can be achieved there was no significant difference in outcome between amputation and limb preserving operations.(59)

Limb-preserving operations can be broadly classified as

1. Joint preserving - Arthroplasty
2. Joint ablating - Arthrodesis

Arthrodesis is usually achieved using allografts and vascularised autografts. It provides a durable, stable reconstruction of the limb postoperatively and is resistant to the physical stress during the routine day to day activities. Moreover it is usually a one time procedure and does not

require any further procedures once the bone unites. But it has its limitations due to its changes in gait, sitting and also due the increased stress on the spine and hip.

On the other hand joint preserving operations are done using a allograft or a endoprosthesis. Structural cadaveric allografts are used for reconstruction. Re-implantation of the autoclaved resected bone has also been reported.(60,61) Allografts are associated with high complication rate and significant morbidity.

The common complication associated with allografts are non union, post operative infection and secondary fractures. These complications have been noted in almost half the patient undergoing such procedures.

Micro-vascular free fibula grafts have also been used to reconstruct the bony defect.(62,63)

Endoprosthetic reconstruction is the most common joint preserving reconstruction following a tumour resection operation. This is done with use of modular/custom made prosthesis. Earlier custom made prosthesis lead to increased manufacturing delays and decreased flexibility during operation. With the availability of modular prosthesis this disadvantage has been negated.

The joint is usually a rotating hinge and gives good mobility though it is more constrained compared to a normal knee. The complication associated with a endoprosthetic reconstruction include excessive wear, loosening, knee stiffness and failure of the endoprosthesis.

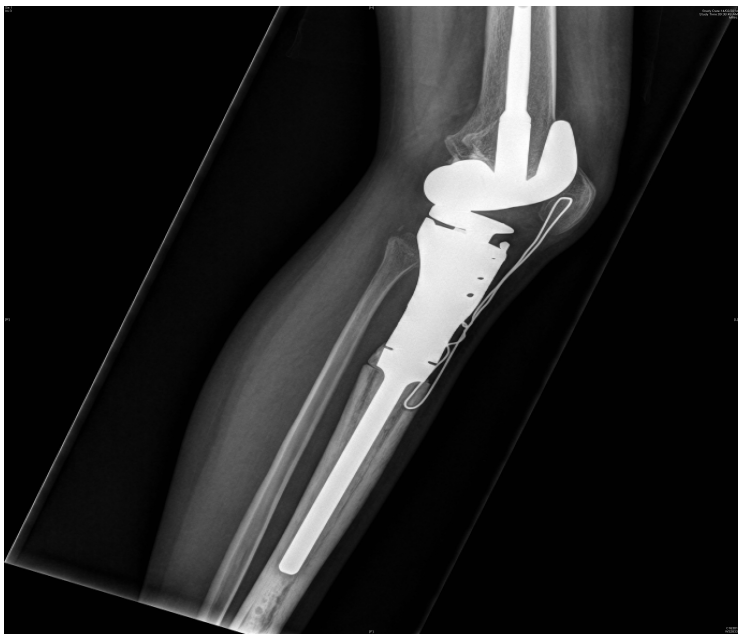
A newer development in a endoprosthetic reconstruction is the availability of expandable endoprosthesis for patients with immature skeleton. This is useful when the growth plate is involved or when the growth plate is resected along with the tumour. The usage of expandable prosthesis helps to compensate the normal distal femoral growth of 1.6 cm per year. Thus it helps to prevent gait disturbances, compensatory scoliosis and low back pain. Some examples are the Phenix Growing Prosthesis (Phenix Medical, Paris, France) and Stanmore expandable prosthesis (Stanmore Implants, Stanmore Middlesex, United Kingdom). (64,65)

Reconstruction of the patella tendon or the extensor mechanism is a challenging procedure

following tumour resection. Kendall et al showed by their functional analysis that compromised extensor mechanism was the main deterrent in achieving adequate function after tumour resection of the knee.(66) In the study by Grimer et al the extension lag of 30° was noted.(67) Another study showed a lag of 15.5° ± 7.6° at 12 months after reconstruction.(68) The proximal tibia being the second most common site for bony tumors, resection of tumors with adequate surgical margins will most often lead to sacrificing the tibial tuberosity and the patella tendon attachment. Moreover highest rate of complications following limb salvage operations is noted among patients with tumors of the proximal tibia. Various techniques have been described for reconstruction of the extensor mechanism following mega-prosthetic replacement.

Bickels et al. described a technique in which the patellar tendon remnant was attached to the prosthesis with a Dacron tape which was reinforced by autologous bone graft. This reconstruction was covered by a gastronemius flap.(69) Among the 55 patients studied 48 patient had a functional outcome that was good to excellent, in 6 patients it was fair and outcome was poor in 1 patient. Eight patients required procedures for secondary reinforcement of the patella tendon.

Titus et al. reported the usage of a method of protection of the extensor mechanism reconstruction following the attachment of the patella tendon after proximal tibia resections. In this method the patella tendon was attached to the anterior surface of the proximal aspect of the prosthesis with sutures without the use of any additional flaps. This reconstruction was then protected by the use of a cerclage wire between the patella and the proximal aspect of the prosthesis thereby protecting the repaired ligament. It was found that though wire breakage was noted in six of the ten patients they persisted to have good functional outcome.(70)



Extensor mechanism reconstruction following tumour resection and endoprosthesis

Various other methods done for the reconstruction of patellar tendon include Trevira tube and flap, Gore-Tex tube and flap, ligament augmentation device and flap, quadriceps turn down and flap.

Radiotherapy:

Osteosarcoma was considered a radio-resistant tumour and hence radiotherapy was not commonly employed in the treatment. A study done by the Cooperative Osteosarcoma Study Groups showed that radiotherapy has an influence on local control when combined with surgery. (71) Another study done by the same group in patients with osteosarcoma of the pelvis showed that the patient who underwent radiotherapy had better survival compared to those who did not.(72) High-Dose Samarium-153 Ethylene Diamine Tetramethylene Phosphonate has been used as a mode of targeted radiotherapy in patients with osteosarcoma.(73) But its role and its benefit in patients with osteosarcoma is yet to be delineated.(74)

Chemotherapy:

Osteosarcoma is considered a systemic disease at diagnosing with microscopic metastases occurring early on in the disease. Chemotherapy has been well studied and has been proven to

improve the survival of the patient in osteosarcoma.

Chemotherapy in osteosarcoma can be broadly divided as

1. Adjuvant
2. Neoadjuvant

Both adjuvant and neoadjuvant chemotherapy has been found to improve the overall survival of the patients with osteosarcoma.(75–77)

Various agents have used in the systemic therapy of osteosarcoma. Cisplatin, doxorubicin,high-dose methotrexate with leukovorin-rescue and ifosfamide are commonly used in the various regimens and are considered as the agents that are most active against osteosarcoma. The ideal effective combination is yet to be defined. Among the current protocols most of them include a period of neoadjuvant (preoperative) chemotherapy and a period of adjuvant (postoperative) chemotherapy. The addition of preoperative chemotherapy has not found to add any survival benefit over postoperative chemotherapy alone.(78) But the administration of preoperative chemotherapy has become the standard protocol as it gives the following advantages:(79,80)

1. It provides better delineation of the tumour and hence better surgical margin
2. The percentage of tumour necrosis following neoadjuvant chemotherapy offers prognostic information
3. It provides valuable time for planning for the definitive limb-preserving procedure

Another study evaluated the effect of chemotherapy alone in the treatment of osteosarcoma. But it was found that only 3 out of 31 patients who underwent this modality of treatment survived without recurrence of the disease.(81)

Treatment of relapse or primary metastatic disease:

Treatment of metastatic osteosarcoma can be broadly divided into curative and palliative. Curative management can be offered to patients with primary metastatic osteosarcoma and it is similar to that of the treatment of localized disease. It has been found that when curative therapy is

administered to patients with primary metastatic disease 30-40% of them might become long term survivors. (82,83)

Relapse of osteosarcoma is associated with poor prognosis with the survival rate less than 20%. But studies have shown that if surgical remission is achievable in patients with relapse more than one third of these patients will survive more that 5 years.(84)

Second line chemotherapy is administered to patients who have a relapse of the disease or occurrence of metastases following initial treatment. Various agents have been tried but the outcome following relapse persists to be poor. The common agents used are ifosfamide, high-dose methotrexate, cyclophosphamide, etoposide topotecan, gemcitabine, pirarubicin and docetaxel.(85) He et al found that pirarubicin based therapy was as effective as gemcitabine-docetaxel with lesser toxicity when administered as a second line treatment for osteosarcoma.(86) It has also been shown that the use of chemotherapy prolonged the survival in patients with relapse of osteosarcoma.(87)

Supportive care:

With multi-modal therapy becoming the cornerstone of treatment of osteosarcoma adequate supportive care is essential for a successful outcome. The various drugs used in chemotherapy can be fatal unless the patient is carefully monitored. The use of serotonin antagonists, dexamethasone to control chemotherapy induced emesis, opioid for pain relief and hematopoietic growth factors for severe granulocytopenia induced by chemotherapy has made chemotherapy must safer and acceptable than it earlier was.

Follow-up:

Follow up of patient undergoing treatment for osteosarcoma is very essential. A detailed history and physical examination must be done at each visit with evaluation of the blood counts. Chest X-ray must be done and if it is inconclusive or doubtful it must be followed up by a CT of the

thorax.

The following table summarizes the various investigations and the recommended time-line for follow-up of patient treated for osteosarcoma :

Suggestions for follow-up investigations after multi-modal therapy for osteosarcoma

Time	Tumor directed	Late effects
Baseline	X-ray chest and CT	Echo-cardiogram, audiogram, liver and kidney function, hepatitis B/C and HIV serology
	X-ray and (CT)/MRI primary site	
Years 1 and 2	X-ray chest every 6–12 weeks	
	X-ray primary site every 4 months	Echo-cardiogram every 1–2 years, audiogram, liver and kidney function Audiogram and liver function need not be repeated if normal at 1 year
Years 3 and 4	X-ray chest every 2–4 months	Echo-cardiogram every 1–2 years
	X-ray primary site every 4 months	
Years 5–10	X-ray chest every 6 months Some groups recommend annual radiographs of the primary site until year 10	Echo-cardiogram every 2–4 years
Thereafter	(Few) relapses reported as late as two decades after treatment. Discuss with patient whether to continue chest X-ray every 6–12 months	Echo-cardiogram every 2–4 years

Survival and outcomes:

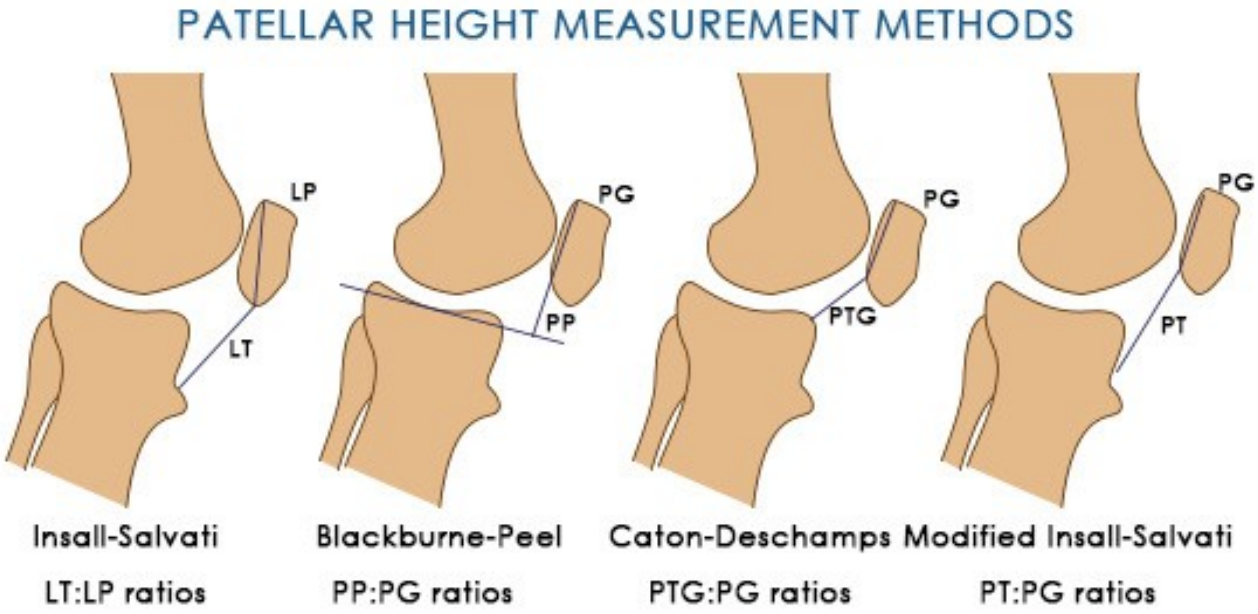
The survival in osteosarcoma among patients has greatly improved with the initiation of the multi-modal therapy. Before the onset of multidisciplinary treatment and the introduction of chemotherapy the overall survival of patients with osteosarcoma at 2 years was 15-20%. The outcome also varies when the patient with classical osteosarcoma and non classical osteosarcoma are compared. Classical osteosarcoma generally carries a better prognosis at it generally presents without metastasis at presentation and as it occurs in the younger age group.

Currently the survival of the patients with multi-modal therapy has increased to 60-70%. Among the patients belonging to the age group above 40 years, who are more prone to non-classical osteosarcoma, the five year survival rate was 46%.(88)

Among the patients with Pagets disease who develop Osteosarcoma the survival remains poor. Mankin et al. found that the survival among this subset of patients was only 14% at 2.5 years. (87)

Patella position:

Patella position is a important factor playing an important role in the normal functioning of the knee joint.(90) Various methods have been described to evaluate the patellar position. Some of them are Insall-Salvati ratio, Blackburne-peel method, Caton-Deschamps ratio, Labelle-Laurin method and Linclau method. In a study done by Eugene et al. they found that the Blackburne-Peel ration reproduced the patellar height index most consistently.(91) They also noted that the values did not change significantly between 30° to 50° of knee flexion. Rogers et al found that using Blackburne-peel method decreased the inter-observer variability compared to Insall-Salvati index in patient who underwent total knee arthroplasty.(92)



Complications:

Limb-preserving operations are associated with higher risk of complications when compared to the limb ablation procedures.(93) The complications may be immediate or late complications. Immediate complications include wound dehiscence, wound necrosis, periprosthetic hematoma, persistent wound drainage and delayed wound healing. The common delayed complications noted are aseptic loosening, implant breakage, bushing failure, superficial and deep infections, dislocation, and periprosthetic fracture. These complications have been reported in as much as 40% of the patients in a series of patient.(94) About 29% of patients had implant failure and almost 13% of the patients developed infections.

Wound infection following mega-prosthesis is a well known complication.(95) The extensive dissection involved especially with the removal of large tumors and the dead space left behind after tumour resection with the presence of a metallic implant might assist the formation of bacterial bio-films leading to the occurrence of infections in patients undergoing tumour resection and mega-prosthesis. The incidence of wound infection following limb salvage operations is reported to be around 11%-20% in most studies.(96–98) Among the patient undergoing endoprosthetic reconstruction wound infection have been found to be more in patients undergoing proximal tibial resection compared to the distal femur resections..(99) Among the patient devolving infection 37% to 87% of the patient ended up having an amputation.(97,98,100)

Local recurrence of osteosarcoma has increased with the increased number of limb salvage operations being performed. Limb salvage has become the standard of care for the patient with osteosarcoma whenever it is possible. Local recurrence following limb salvage operation has been reported from 2..4% to 16%.(101–103)

Prognostic factors:

Various factors have been found to be helpful to prognosticate the outcome in patients with osteosarcoma. These include disease specific factors and treatment related factors. The disease

specific factors include sex, metastasis at presentation, level of alkaline phosphatase, tumour volume and treatment related factors include amount of tumour necrosis and surgical margins.(104)

Presence or absence of metastases at presentation was found to be the most important prognostic indicator in the survival of patients with osteosarcoma as the presence of metastasis decreased the overall survival significantly.(104–106)

Male sex was also found to have a poorer prognosis compared to their female counterparts. (104) In the study published by the Scandinavian sarcoma group male sex had a increased risk of 4.1 compared to the female counterparts.(105)

The level of alkaline phosphatase has been associated with prognosis of the patient with osteosarcoma. Increased pretreatment level of alkaline phosphatase in patients with osteosarcoma is associated with poor outcome and increase chance of recurrence compared to the patients whose levels are normal.(43,107) Other studies did not show any association between the level of alkaline phosphatase and prognosis.(75)

The initial tumour volume has also been associated with outcome of patients with osteosarcoma.(108) Patients with large tumors at presentation had a less favorable outcome. Among the patients studied under Scandinavian sarcoma group tumour volume above 190 ml was associated with poor outcome.(105) Kim et al showed that a larger tumour was associated with poor histological response and poor outcome.(108) Kaste et al showed that absolute tumour volume at diagnosis was significantly associated with event free survival and over all survival among patients with non-metastatic osteosarcoma.(109,110) Another study showed that an absolute tumour volume of less than100 ml was associated with better outcomes.(111)

Histological grade of the osteosarcoma has also been found to have prognostic implications. Most conventional osteosarcoma belong to high grade. Tumors with a low or intermediate grade have been found to be associated with better event free survival, overall survival and decreased

incidence of metastases.

Tumor necrosis following neoadjuvant chemotherapy has been found to have significant prognostic association. As per Rosen et al. the tumour is graded as four grades. Grade I and II corresponded to poor histological response and grade III and IV corresponded to good histological response.(112) In another study done by Picci et al. a necrosis of greater than 80% was considered as good, 50% - 80% was considered fair and a necrosis of less than 50% was considered poor.(113)

Rosen grades(114)	
Grade	Percentage of tumor necrosis
I	Very little necrosis
II	Necrosis more than 50%
III	Necrosis more than 90%
IV	No viable tumor cells seen

Poor histological response has been associated with decreased event free survival and decreased overall survival among patients with osteosarcoma.(106,112,115) Response to chemotherapy was found to have the strongest association with local recurrence.

Surgical margin has been found to have prognostic role in osteosarcoma. Earlier studies showed that surgical margins were associated with risk of local recurrence and poor prognosis. (104,115) A study done by Kong et al showed that marginal or intralesional excision was associated with decreased metastases free survival.(116) Local recurrence of the tumour has also been related to the adequacy of the surgical margin.(117) A recent study evaluated the advantage provided by amputation in patients with close margins and poor necrosis. It was found that amputation did not offer any survival benefit in such patients though it offers a wide local clearance. (118)

METHODOLOGY

Aims:

The aim of this study was to follow up patients with osteosarcoma of the distal femur and proximal tibia who underwent mega-prosthesis of the knee in our institution.

Objectives:

1) The main objective of the study was to evaluate the clinico-radiological outcome in among patients with osteosarcoma of the distal femur or proximal tibia, who underwent tumour excision and mega-prosthesis of the knee in our institution between January 2010 and October 2014.

2) To evaluate the relationship between tumour volume, tumour grade. tumour necrosis, alkaline phosphatase levels and the prognosis among the patients with osteosarcoma of the knee who underwent tumour excision and mega-prosthesis of the knee in our institution between January 2010 and October 2014.

3) To evaluate the patella position following tumour reconstruction and the effectiveness of the simple method of reconstruction of the extensor mechanism.

Materials and methods:

This was a ambidirectional cohort study. We studied the patients who underwent tumour excision and mega-prosthesis of the knee from January 2010 till October 2014. There patients were on follow up in the outpatient clinic following the operation. The hospital records of these patients were accessed and they relevant data pertaining to the study were collected. The patients were followed up until the latest follow up in the outpatient clinic or they were followed up until their death. The patients who did not come for follow up following the surgery and those who stopped follow up after a certain period were contacted via the telephone calls from the numbers stored in the hospital information system. Apart from the patients whose death was confirmed earlier via the hospital record all patients were contacted via phone and survival or death was confirmed. The

time of death of the patient was also found out from the patients records or from the patients relatives during the phone call.

Treatment Protocol
Preoperative:
Detailed clinical examination
Blood investigations
Plain radiographs – two views
Biopsy
Chest X ray(CT thorax/PET imaging if required)
MRI(For all patients)
Bone scan
Multidisciplinary Tumour Board(MDTB) – Decision on preop Chemo/RT
Neoadjuvant Chemotheraphy(if decided by the MDTB)
Repeat radiographs of the lesion
Surgery
Postoperative:
Knee ROM in the immediate post operative period as wound heals
Multidisciplinary Tumour Board(MDTB) – Decision on postop Chemo/RT
Adjuvant Chemotheraphy(as decided by the MDTB)
Radiotheraphy(as decided by the MDTB)

Followup protocol
Every 3 months in the first year
Every 4 months in the second year
Every 6 months for the next 2 years
Yearly follow up for atleast 10 years
Investigation done at followup:
Detailed history and clincal examination
Plain radiographs – two views
Chest X ray
Ultrasound(if required)
CT Thorax – If there is any doubt on Chest – Xray
Bone scan if suspision of bony metastasis
Special investigation: Echo, Audiogram(if required)
Indication for CT Thorax:
Suspicious nodue on Chest X ray
Indication for PET imaging:
Non specific pain with normal plain radiographs and bone scan

Inclusion criteria:

All patient who underwent tumor excision and mega-prosthesis of the knee for osteosarcoma of the distal femur or proximal tibia in our institution from January 2010 till October 2014 as decided in the multidisciplinary tumor board meeting.

Exclusion criteria:

1. Presence of metastasis .
2. Patient with infected or fungating tumour
3. Any large tumour requiring amputation
4. Osteosarcoma of the fibula
5. Not a definite diagnosis of osteosarcoma
6. Large tumours requiring a total femur or tibia replacement

Sample size:

Using the incidence of local recurrence from the previous dissertation, 9% the sample size was(Confidence level 95% and margin of error at 5%)

$$N=\frac{1.96^2 \times 0.09 \times 0.91}{0.10^2} = 125$$

Defining variables:

Tumour necrosis was classified as per the criteria by Rosen et al and then sub-classified as per the description of Bacci et al.(112,114) As from the previous studies tumour necrosis of >90% was considered as good and a tumour necrosis of <90% was considered as poor. Hence all patient with tumour necrosis of <90% were considered to have a poor necrosis and the patients who had tumour necrosis above 90% were classified as good necrosis.

Histological the grade of the tumour were classified based on histological criteria. Lesions with cellular atypia, marked vascularity increased mitosis and increased necrosis associated with poor differentiation are found have a higher likelihood of metastases.(119). The American joint committee on cancer classified osteosarcoma into four, grade 1 is moderately well

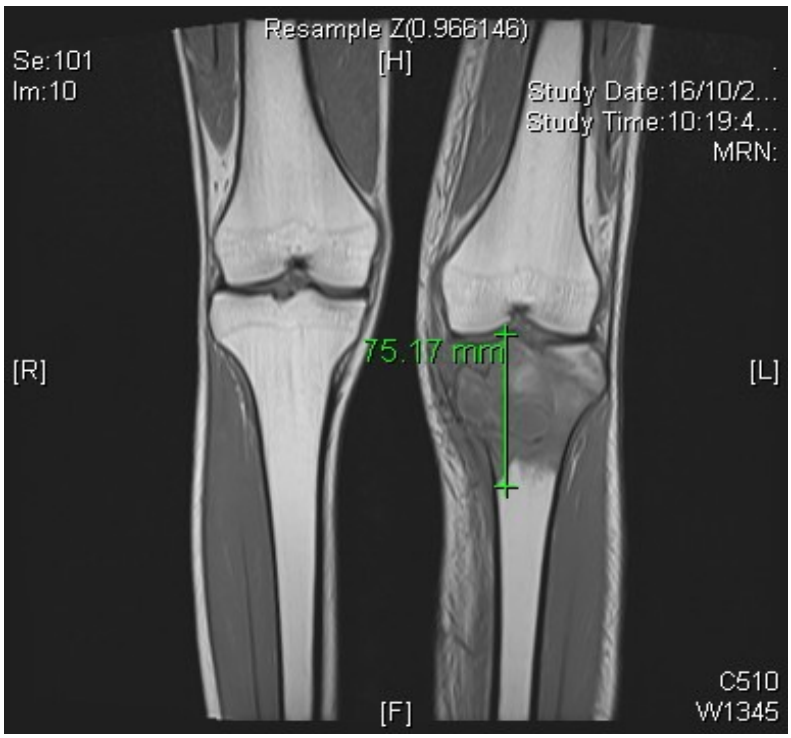
differentiated, grade 2 is poorly differentiated, grade 3 is poorly differentiated, grade 4 is undifferentiated. Though the tumour is classified as four grades they are essentially grouped into two grades. Tumors belonging to grade 1 and 2 are considered as low grade and tumors belonging to grade 3 and 4 are considered as high grade. At times when the tumor cannot be fully classifies as either high grade or low grade a new group is added and the tumour is classified as intermediate grade.(119)

Histological grading	
Osteosarcoma Grade	**Histological grade**
Low-grade	Grade 1 and 2
High-grade	Grade 3 and 4
Intermediate grade	Tumors between high and low grade

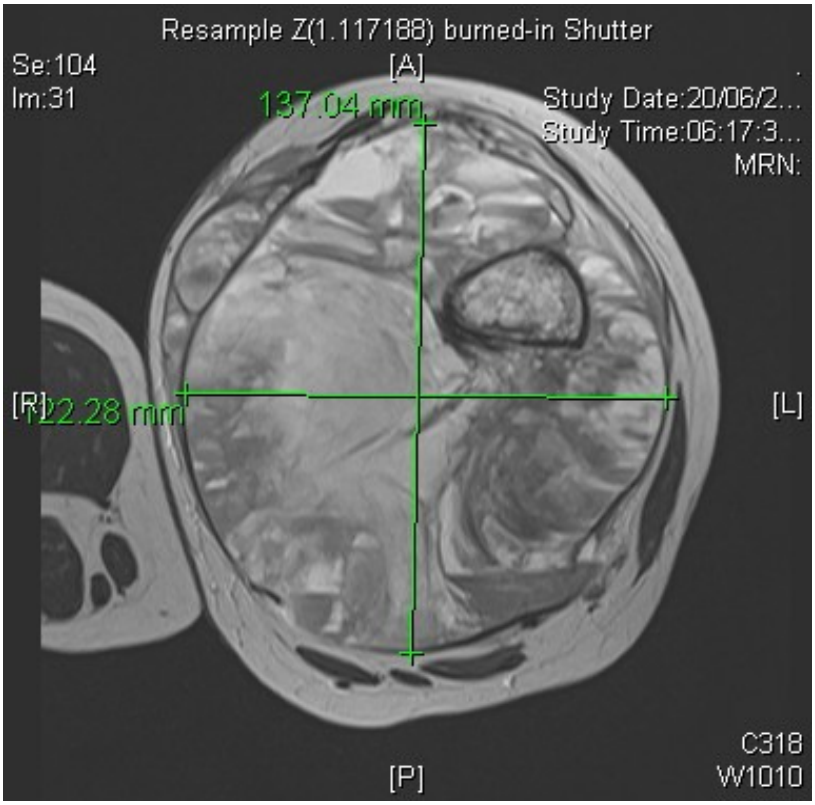
The grade of the tumour was tumour and percentage of the tumour necrosis were retrieved from the histopathological reports of the patients stored in the electronic records of the patients. But the sub-types could not be retrieved as the reporting in out institution did not routinely involve reporting of the histological sub-type. Tumor margins were also retrieved from the histopathology reports of the patient who were enrolled in the study from the electronic records of the respective patients. All patient had tumour margins that were reported in the histopathology reports. If all margins were negative it was classified as clear margins and the positivity or involvement of any one of the tumour margins was classified as involved tumour margin.

Tumor volume has been associated with prognosis in patients with osteosarcoma. In a study done at St. Jude Children's Research Hospital, Tennessee, it was showed that a tumour volume more than 150 cm^3 was associated with increased risk of death compared to patient with lesser tumour volumes.(109) Tumor length, breadth and depth were calculated from the MRI of the patients by using the Centricity software(GE Healthcare)..

We measured the tumour volume by the ellipsoid formula(120,121)



Measurement of the tumour length in a osteosarcoma of proximal tibia(Male, 17 yrs)



Measurement of the tumour width and depth in a distal femur osteosarcoma (Female, 7 yrs)

Level of alkaline phosphatase among children and adolescents. Source: Turan S, Topcu B, Gökçe I, Güran T, Atay Z, Omar A, et al. Serum Alkaline Phosphatase Levels in Healthy Children and Evaluation of Alkaline Phosphatase-scores in Different Types of Rickets. J Clin Res Pediatr Endocrinol. 2011 Mar;3(1):7–11.

Tumour Volume $= 4\pi/3(abc)$

$= (4\pi/3)\,X\,0.5\,X\,ATL\,X\,0.5\,X\,ATW\,X\,0.5\,X\,ATD$

$= 0.52\,X\,ATL\,X\,ATW\,X\,ATD$

In the above formula a, b, c are the radii of the length, width and height of the tumour.

Tumor depth is calculated as the depth of the tumor extending from the anterior extent of the tumor to the posterior extent of the tumor on the MRI.

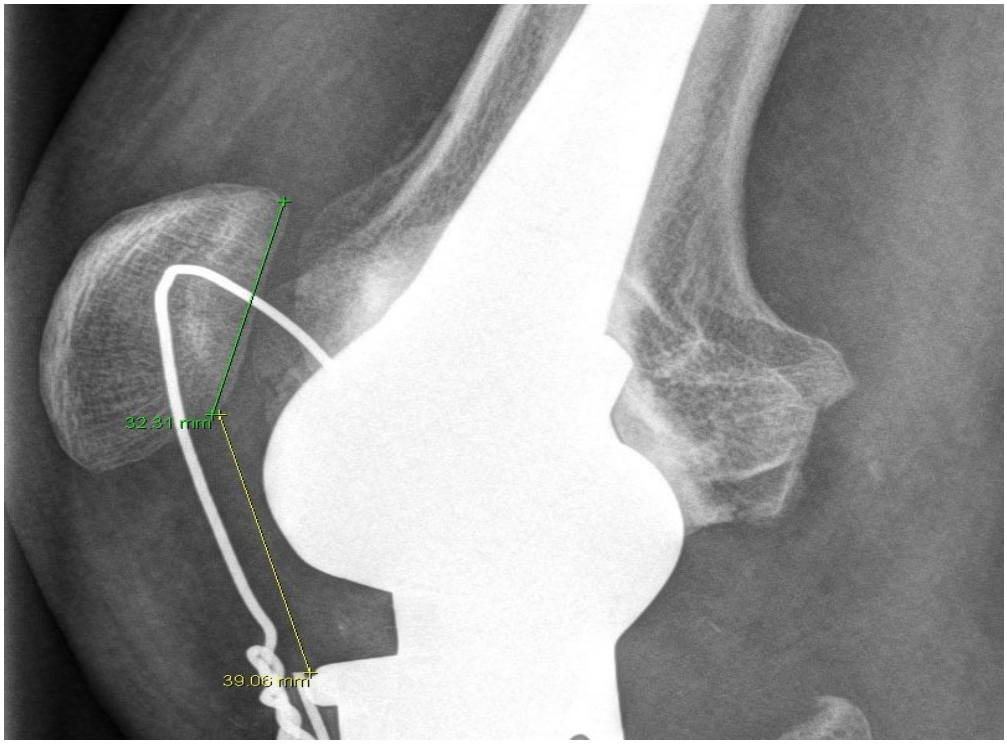
Alkaline phosphatase values for the patients included in out study were collected form the patient record. The level of alkaline phosphatase before the onset of treatment ie. before chemotherapy or surgical excision of the tumour was found. Though studies have shown that the level of alkaline phosphatase at diagnosis correlates with the outcome and the risk of metastases, other studies have shown that the level of alkaline phosphatase may not be of any value. With this controversy over the value of alkaline phosphatase we sought to find if there is any relation with the outcome in the patients included in the study. Another issue with alkaline phosphatase was the normal increase that is noted during the pubertal growth spurt. A study published earlier classified the mean values and the normal ranges of alkaline phosphatase in the respective age groups among children and adolescents.(122) In the adults an alkaline phosphatase level of 40-125U/L was considered as normal. Using the values published we classified the patients into those with high alkaline phosphatase and those with normal levels.

Females (age groups)	N	-2SD	Mean	+2SD	SQR-Mean	SQR-SD
0-6 months	90	355	663	1037	25.5	3.3
6 -12 months	40	350	563	812	23.6	2.4
1 year	79	311	570	884	23.7	3.0
2-3 years	62	265	526	849	22.7	3.2
4-5 years	74	294	516	783	22.6	2.7
6-7 years	97	255	473	738	21.6	2.8
8-9 years	116	326	530	769	22.9	2.4
10-11 years	100	328	587	899	24.0	3.0
12-13 years	99	204	515	924	22.3	4.0
14-15 years	97	82	282	564	16.4	3.7
16-17 years	50	88	180	293	13.3	1.9
Males (age groups)	**N**	**-2SD**	**Mean**	**+2SD**	**SQR-Mean**	**SQR-SD**
0-6 months	86	297	746	1178	25.8	4.3
6 -12 months	36	299	611	998	24.4	3.6
1 year	61	327	664	1118	25.8	3.8
2-3 years	48	319	509	734	22.5	2.3
4-5 years	64	273	485	755	22.0	2.7
6-7 years	96	388	570	785	23.9	2.1
8-9 years	89	241	458	743	21.4	2.9
10-11 years	92	400	641	938	25.3	2.7
12-13 years	91	286	596	1000	24.3	3.7
14-15 years	108	164	559	1000	22.2	4.7
16-17 years	66	68	210	430	14.5	3.1

SQR: square root, SD: standart deviation, ALP: alkaline phosphatase

The Blackburne-Peel index is the ration between length of the line projected from the distal part of the joint surface of the patella anteriorly to the tibial plateau surface and the length of the articular surface of the patella.(123) The radiographs of all patients include in the study were accessed via the hospital information system. All radiographs were reviewed and all the patients who had the radiographs taken with the knee at 30° of flexion were included in the study. The distance between the upper surface of the anterior tibial component was measured and the length of the articular surface was measured. These measurements were made on the radiographs with the help of the Centricity software(GE Healthcare)

A

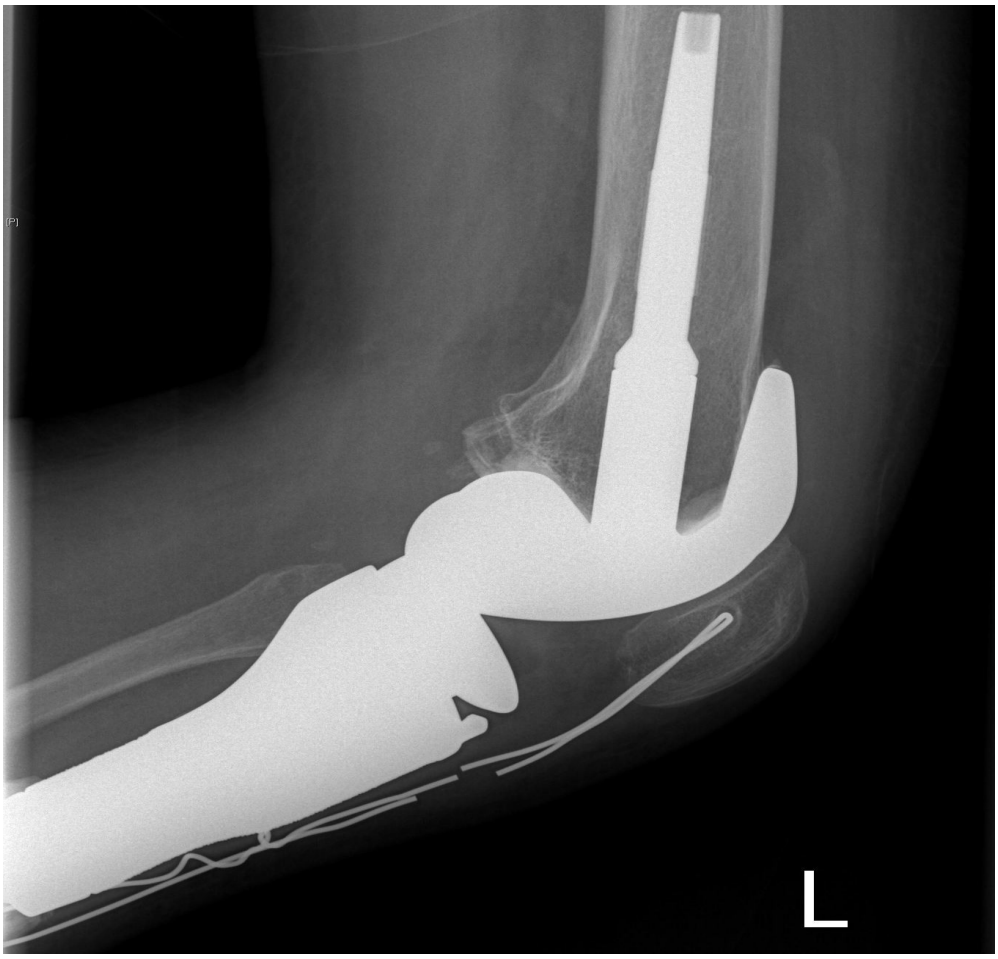


Blackburne-peel ration of less than 0.8 was considered as patella infera, 0.8-1 was considered as normal and a ratio of greater than 1 was considered was patella alta.(90)

Blackburne-peel ratio	
Type of patella	***Range***
Patella infera	<0.8
Patella norma	0.8-1
Patella alta	>1

We at our hospital used the simple method of reconstruction of the patella tendon

reconstruction as described by Titus et al.(70) Wire breakage was a expected occurrence in the patients undergoing this procedure. Even in the study published by Titus et al six out of 10 patients developed wire breakage though it did not affect the function. (70)



Brocken cerclage wire as seen on the followup radiograph of the patient

This method of reconstruction was routinely done in the patients who underwent resection of the tumour of the proximal tibia. We evaluated the radiographs at follow up to look at the breakage of the wire and the approximate time period when the wire breakage occurred.

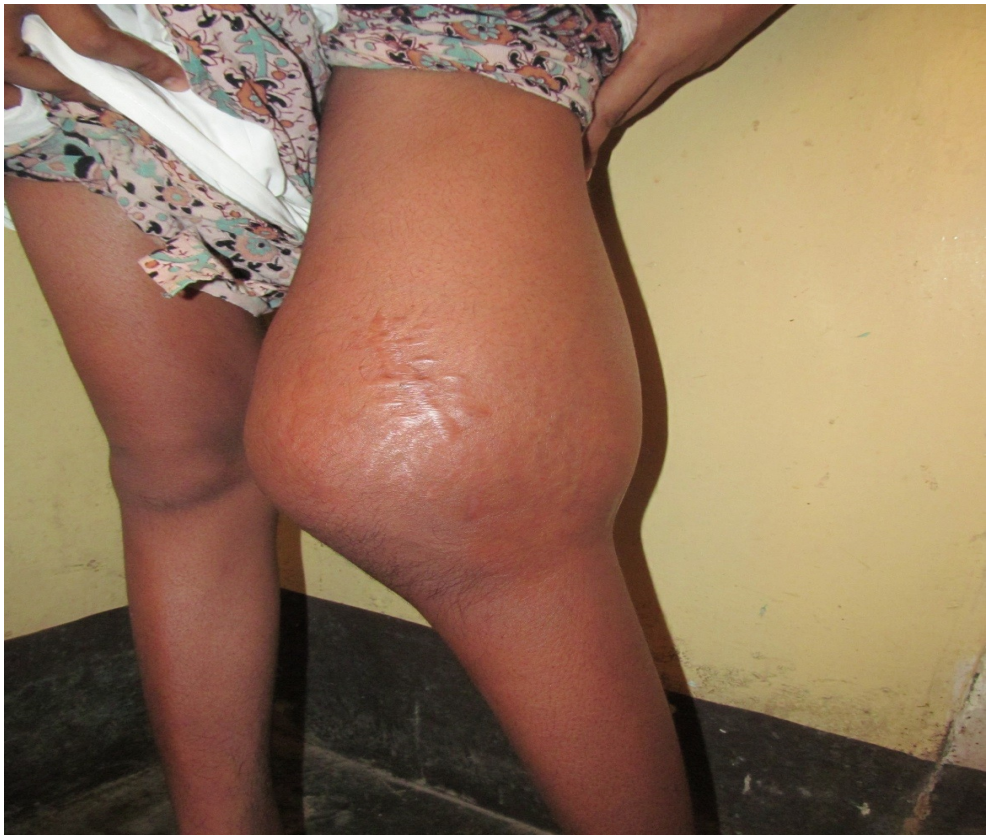
The occurrence of local recurrence, bony metastasis, wound infection, need for wound suturing, time of wire breakage were also collected from the records of the patient.

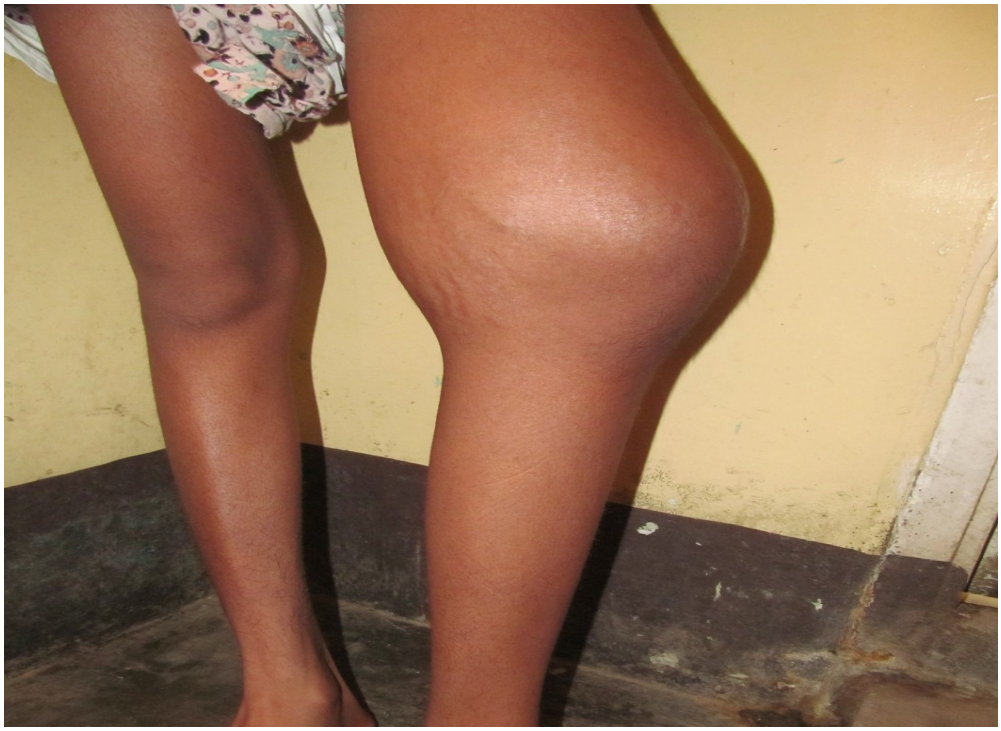
Statistical Analysis:

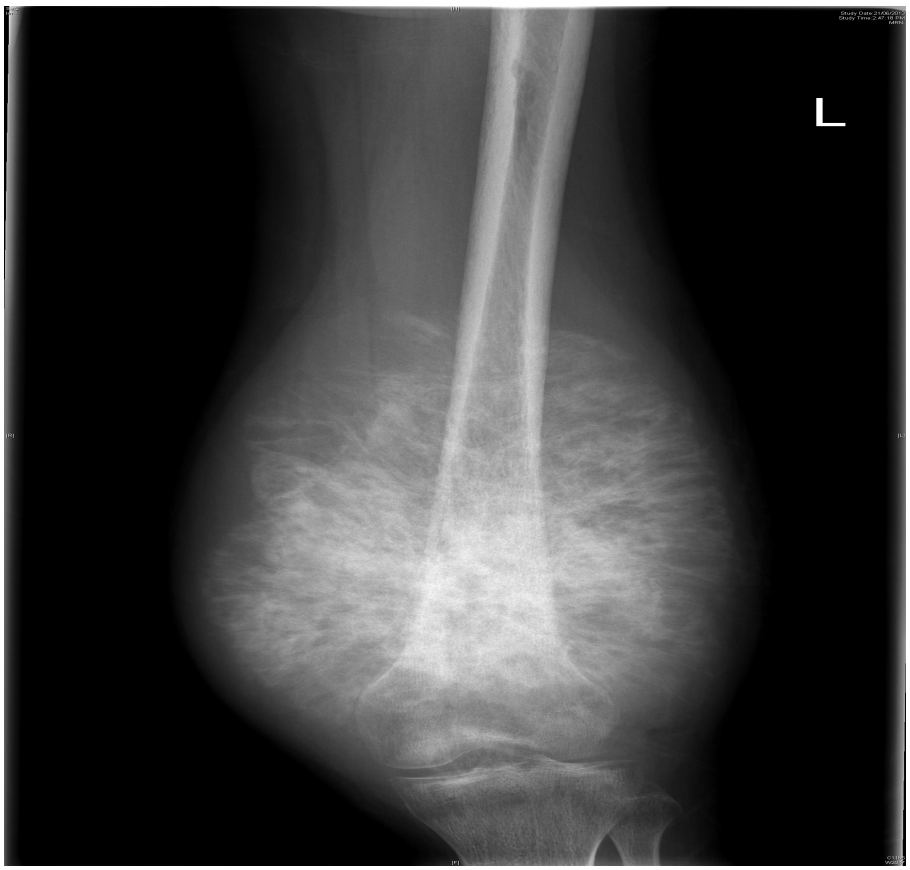
Data entry was done with the help of LibreOffice Spreadsheet V 3.5(The Document Foundation) and all statistical analysis were done with the help of SPSS(IBM SPSS v20). Survival and local recurrence were found out for patients included in our study. Kaplan- Meier method was used for calculating the overall survival and effect of other factors on time to local recurrence and the significance of the other factors affecting local recurrence.

Pre-op, Intraop and Post-op images of a patient

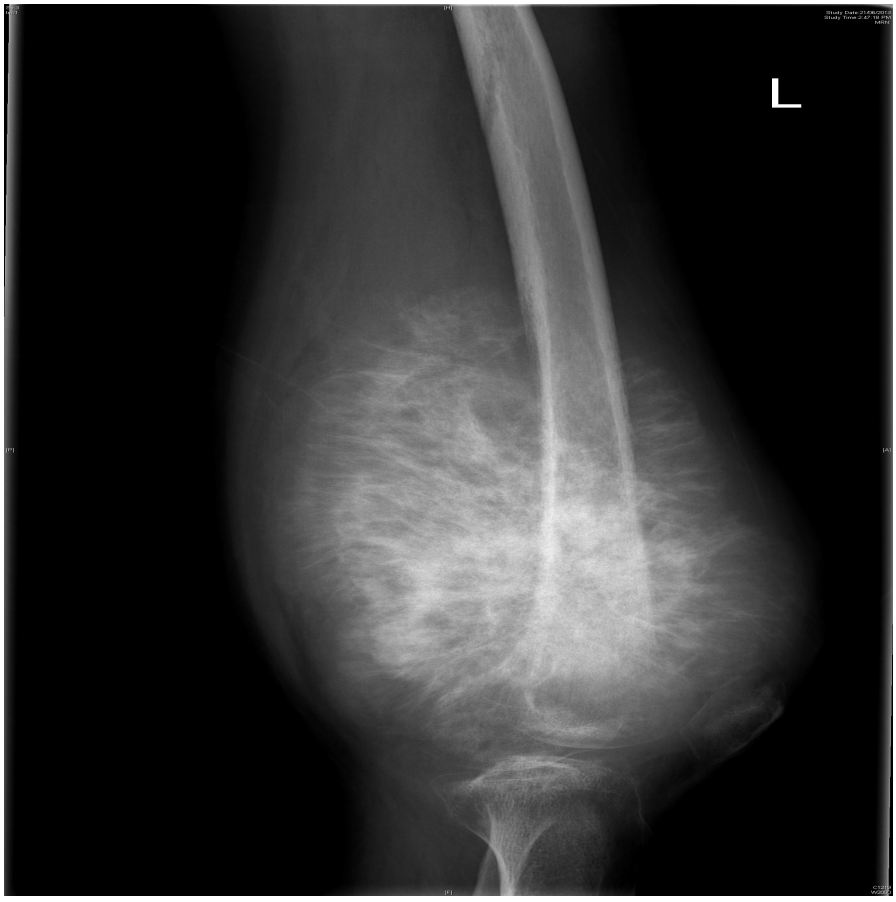
Clinical photographs: DS, 18, F

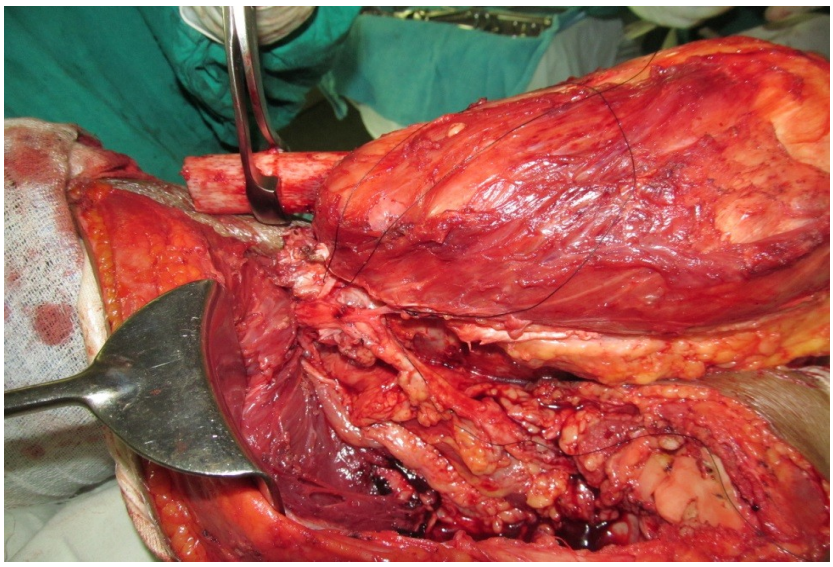


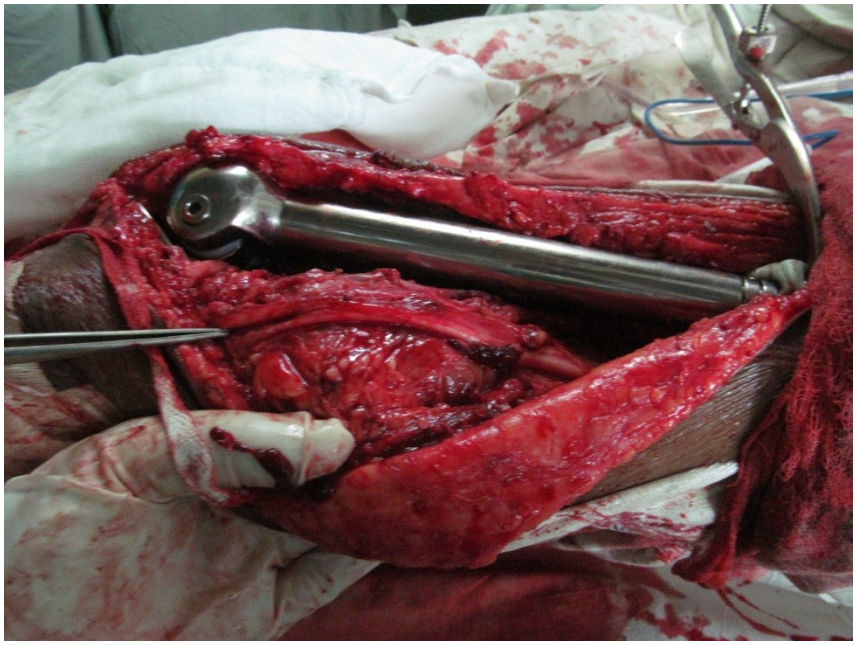


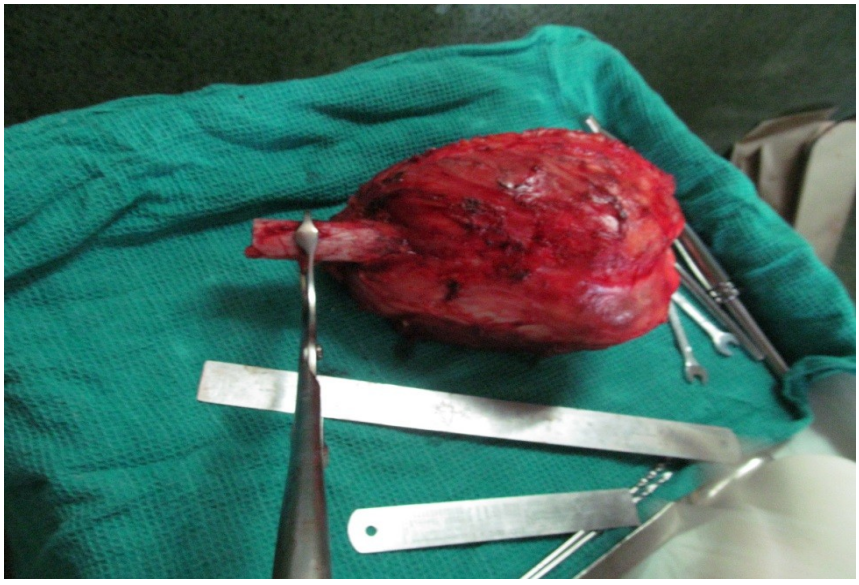


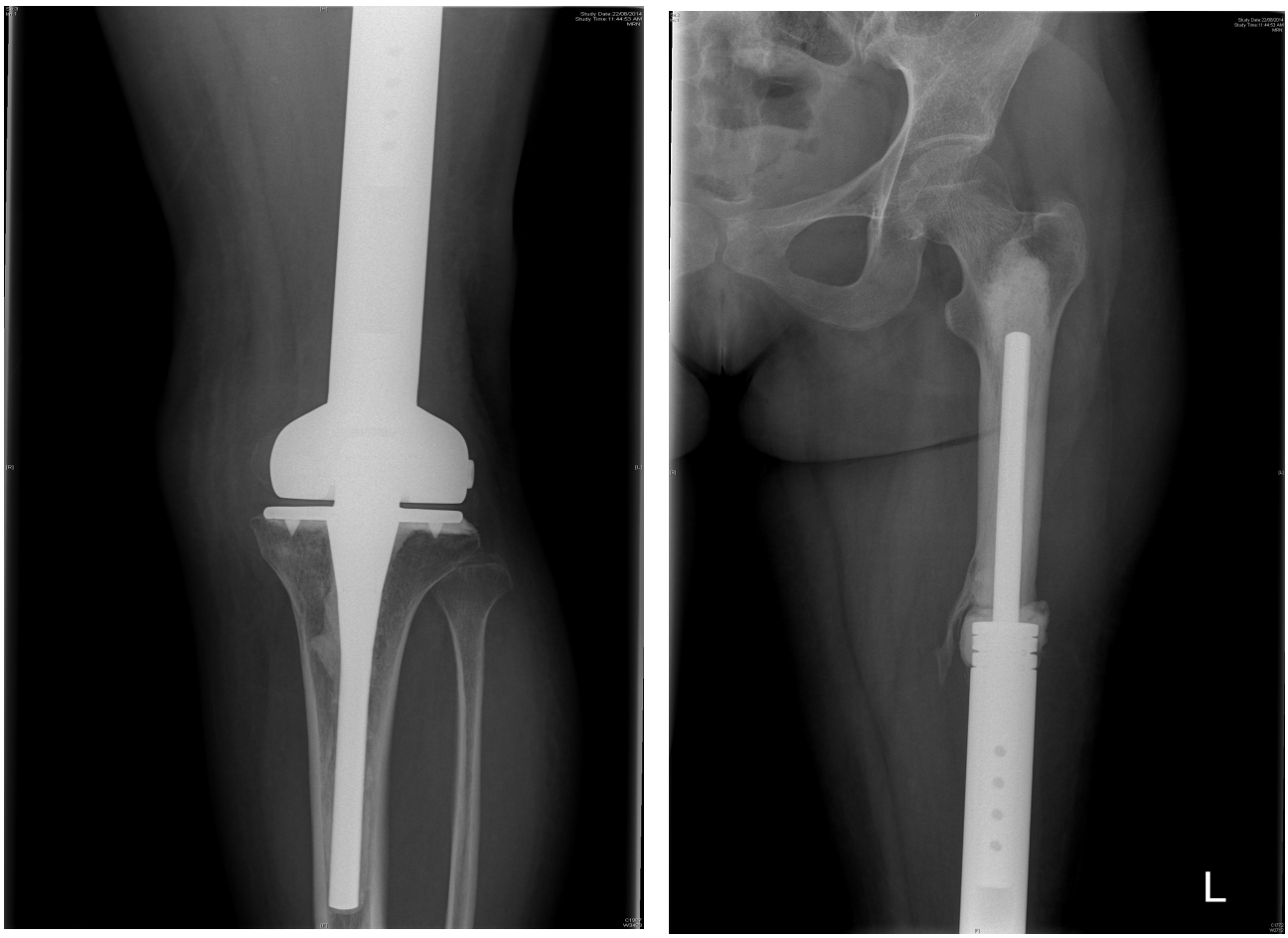
Preoperative radiographs



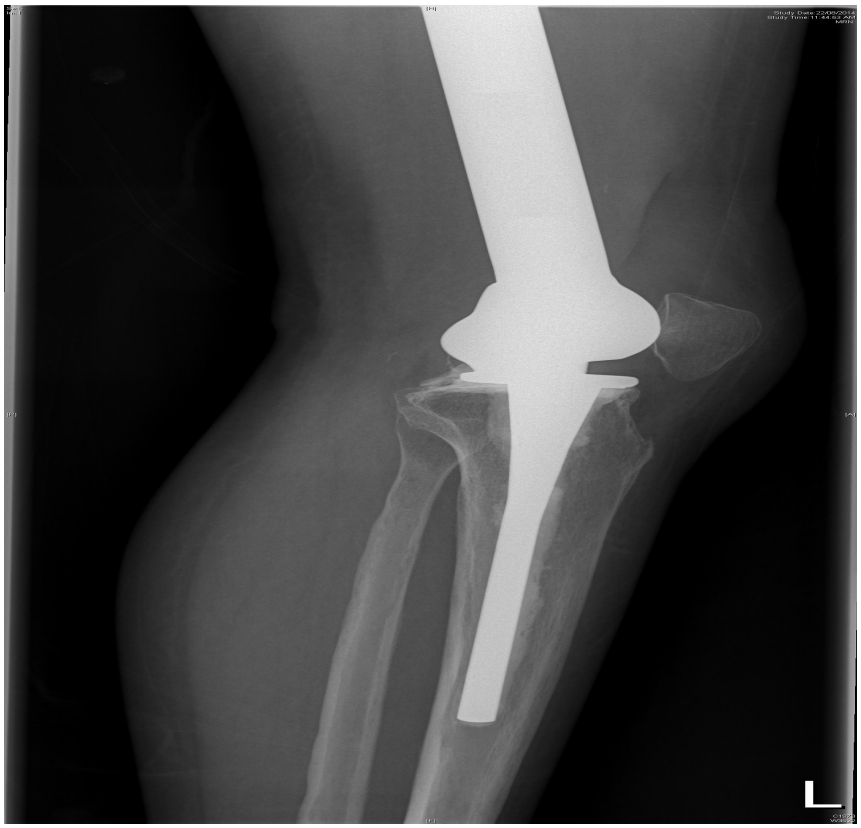




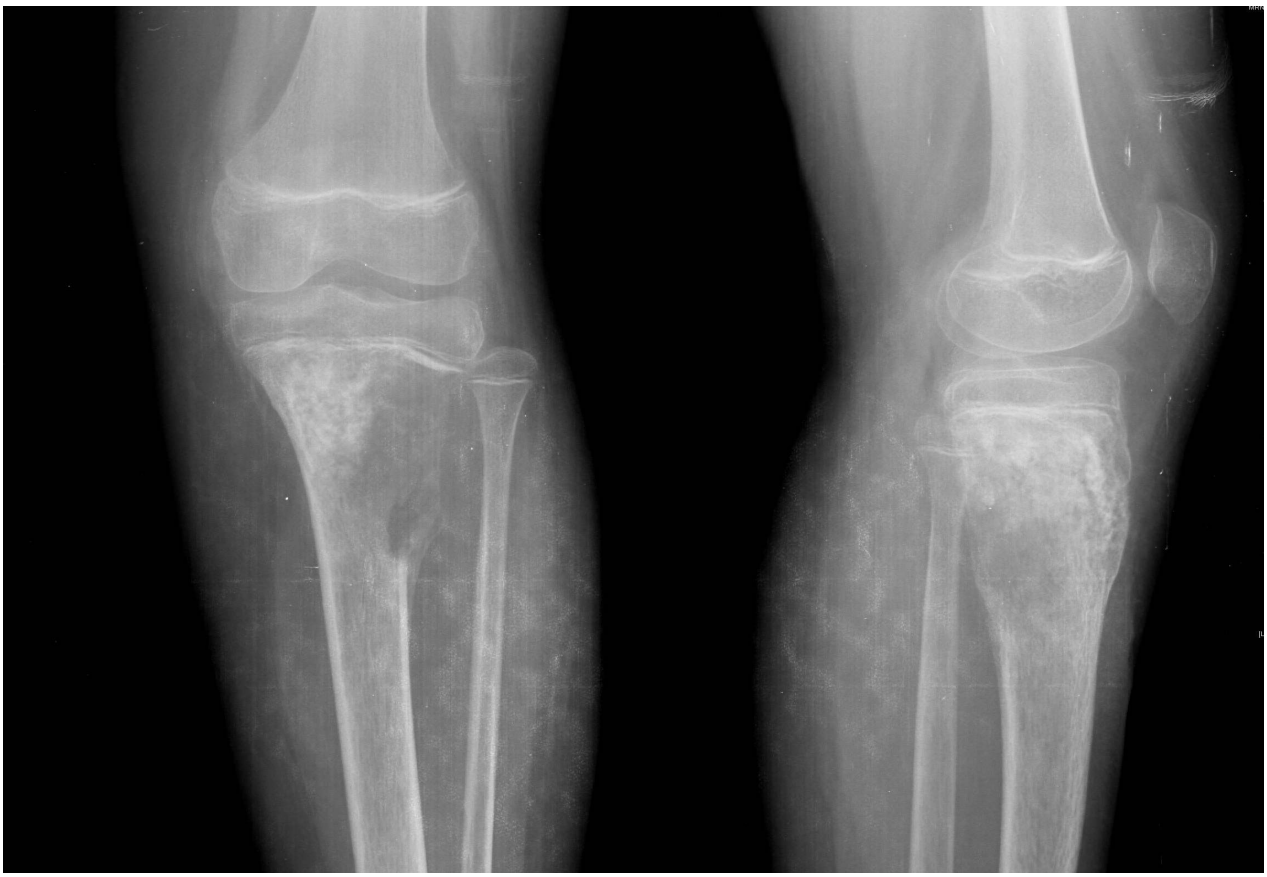


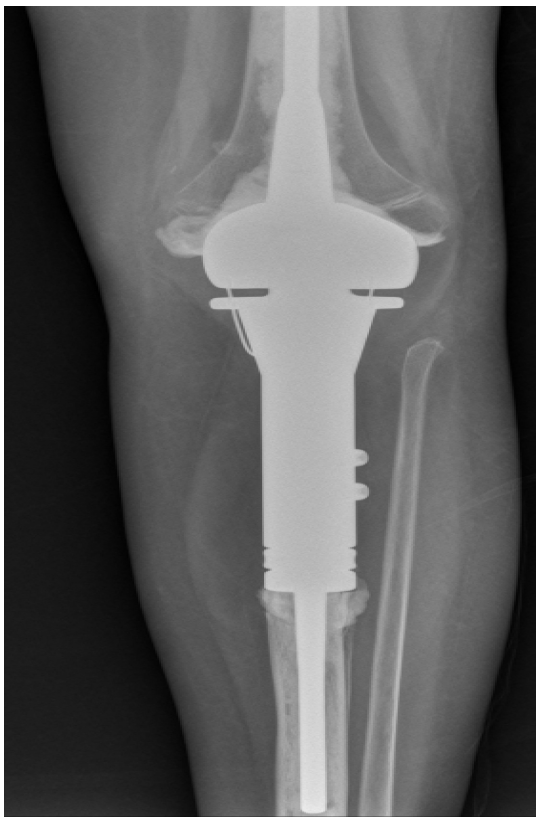


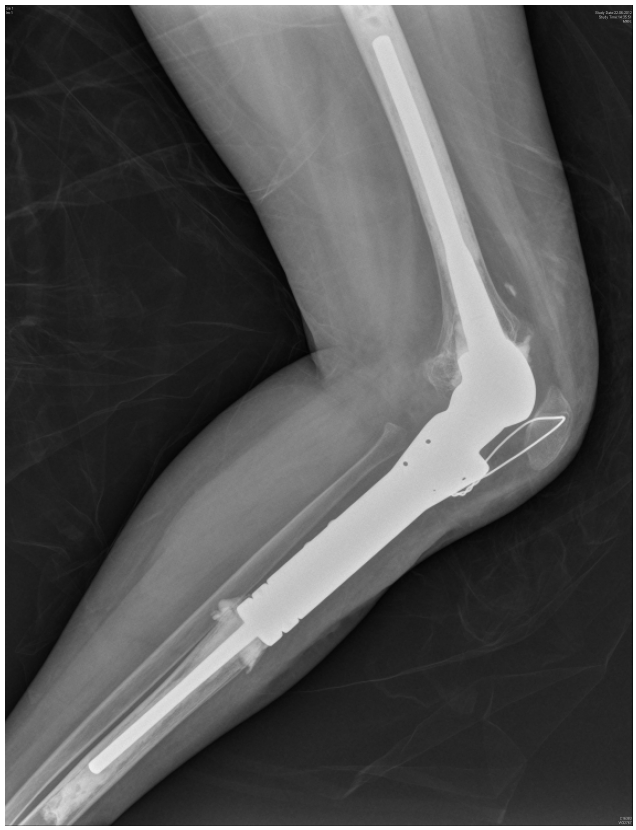
Postoperative radiographs



AT, 14 yrs, F, Proximal tibia





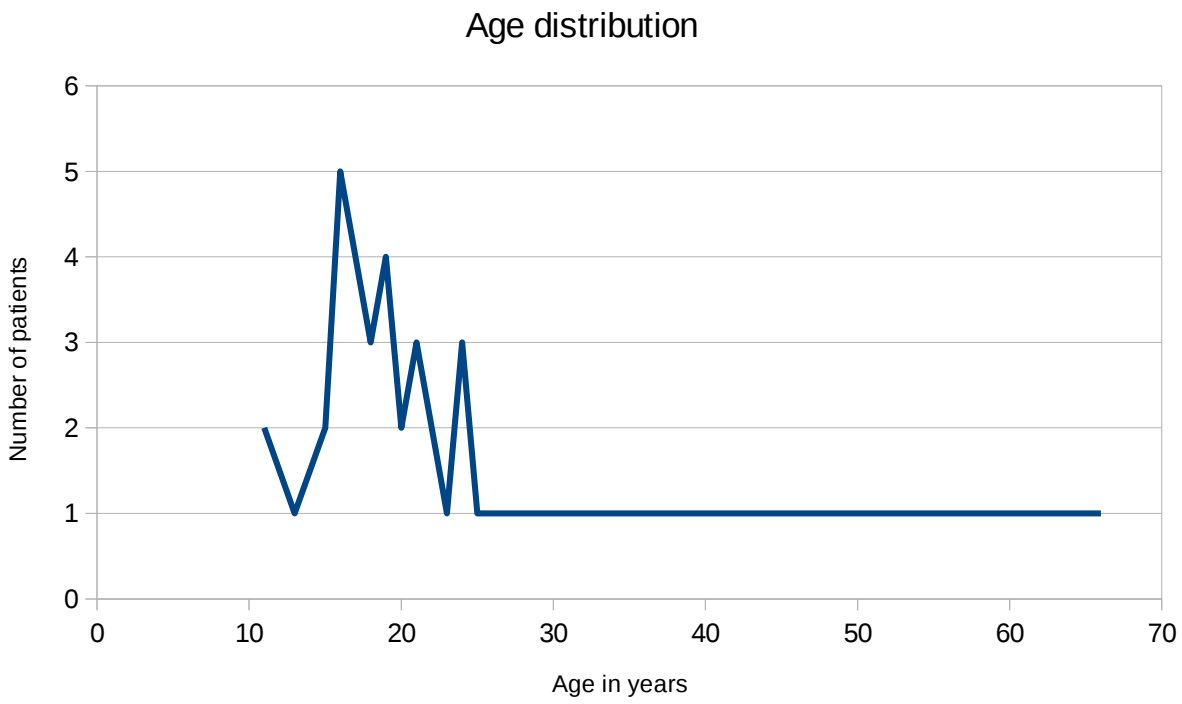


Results

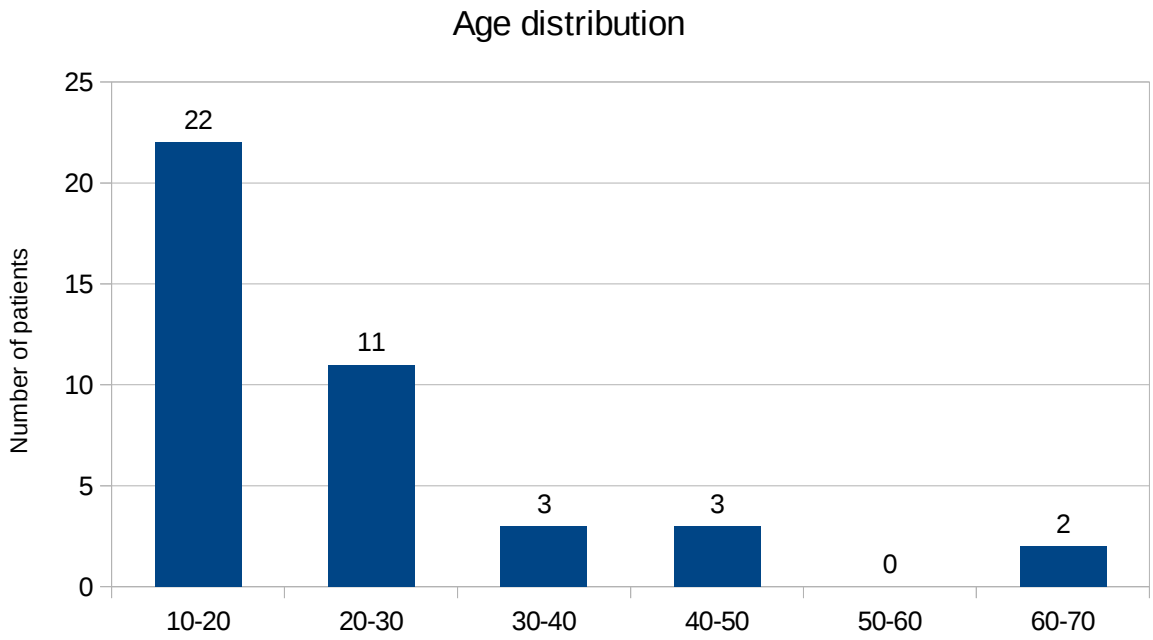
Results:

From the year January 2010 to October a total of forty one patients who were diagnosed with osteosarcoma of the distal femur or proximal tibia and underwent mega-prosthesis of the knee were found to be eligible to be enrolled into the study, as per the inclusion and exclusion criteria.

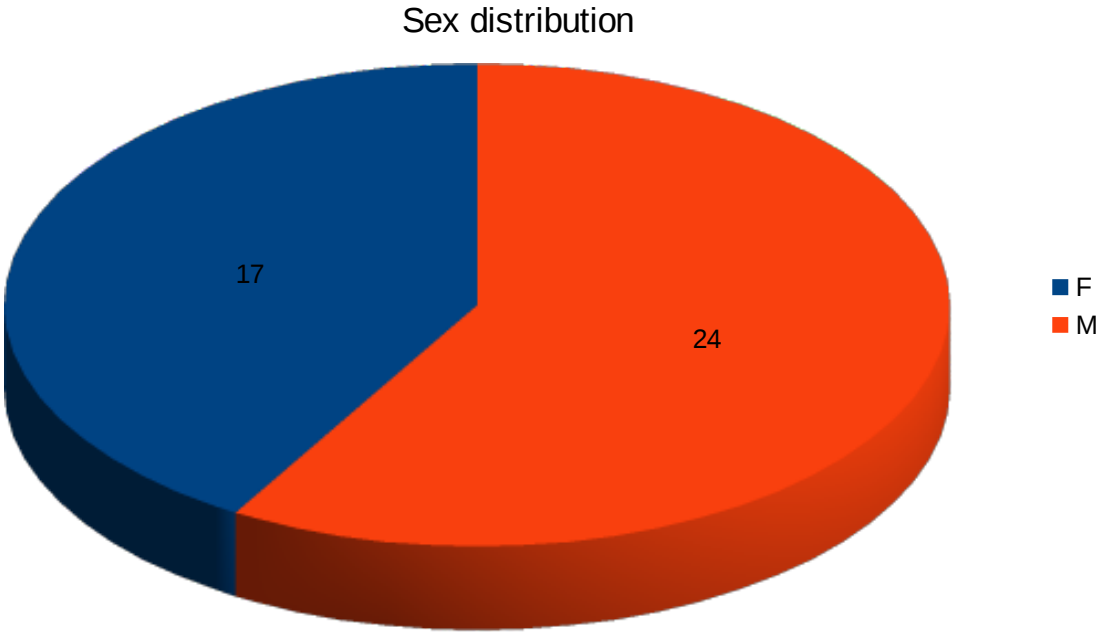
The average age of the patient included in the study was 24 years(11-66 years). Out of the patients 41 patient 21 (51.2%) patients were below or at 19 years of age, another 15 (36.4%) were between 19 and 40 years and 5(12.2) patients were above 40 years.

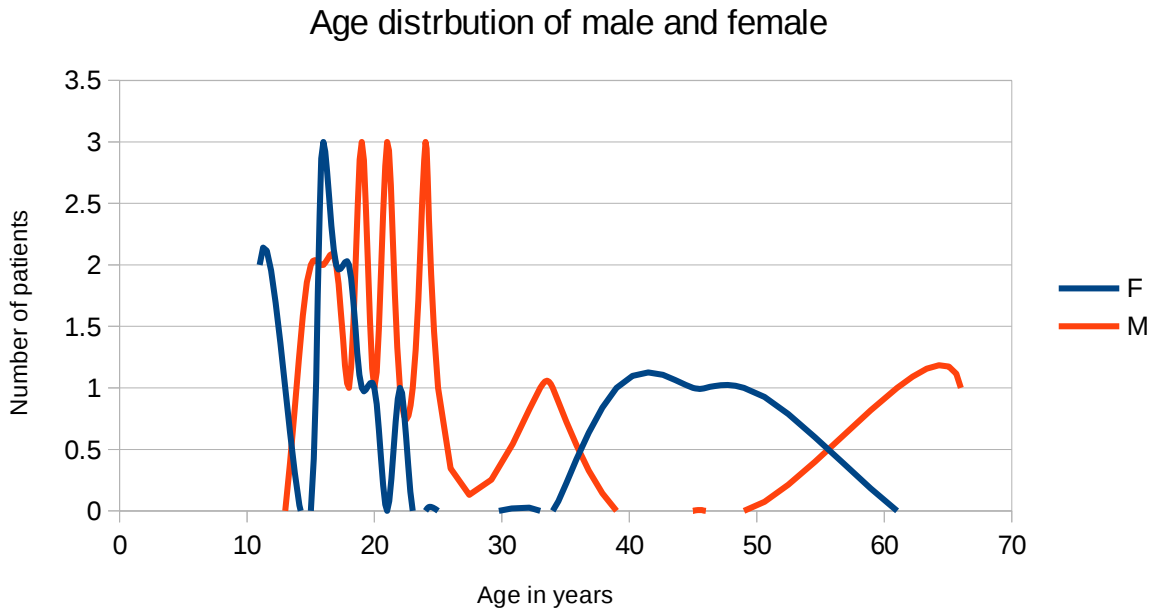


As shown in the chart above most patients in our group fell in the age group between 10-25 years of age.

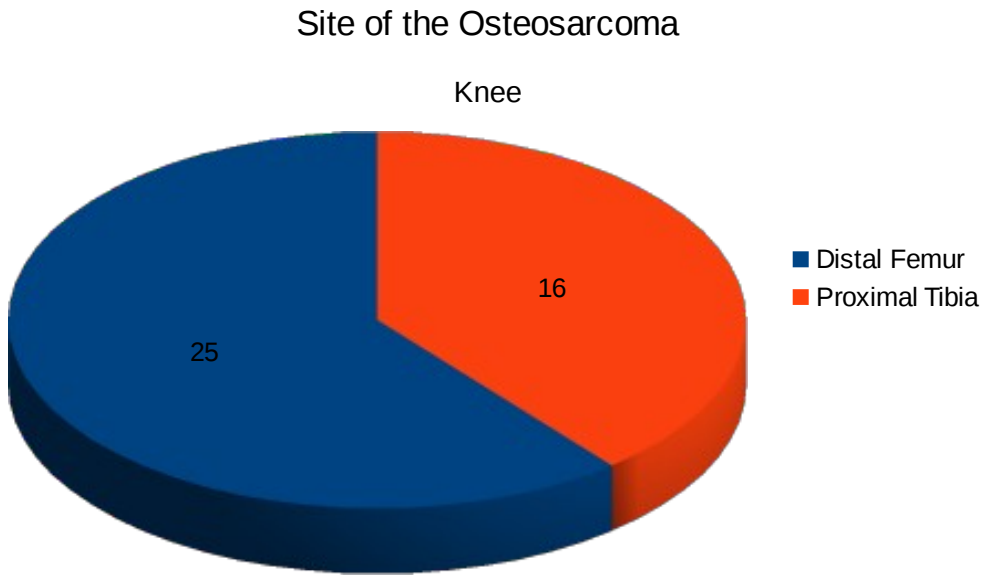


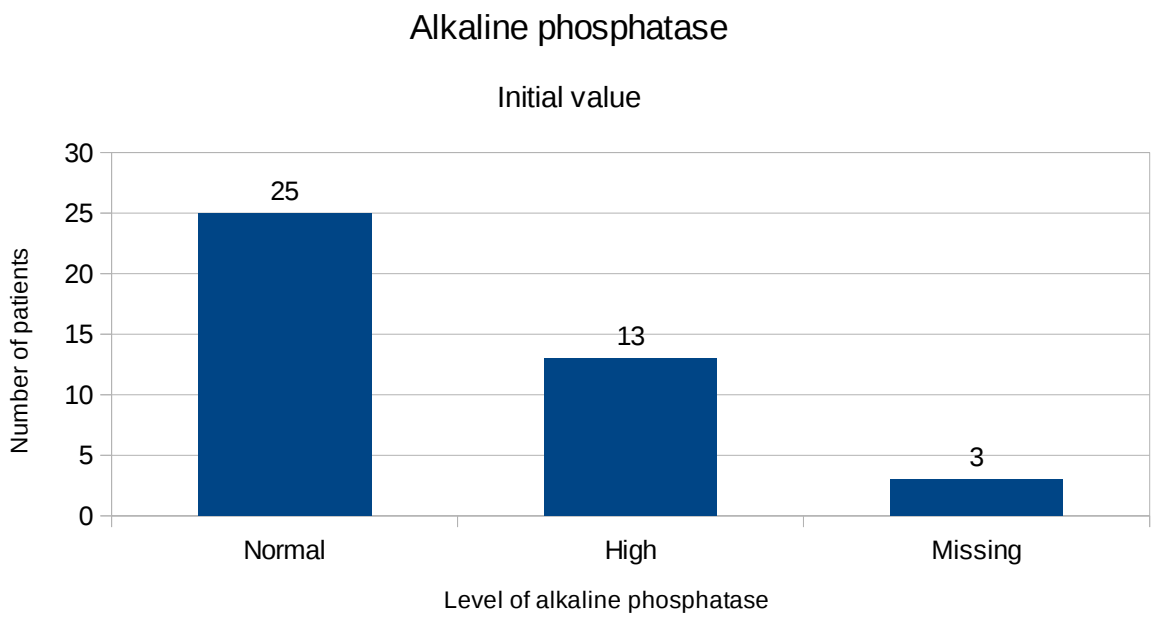
There were 24 males and 17 females among the 41 patients included in this study.

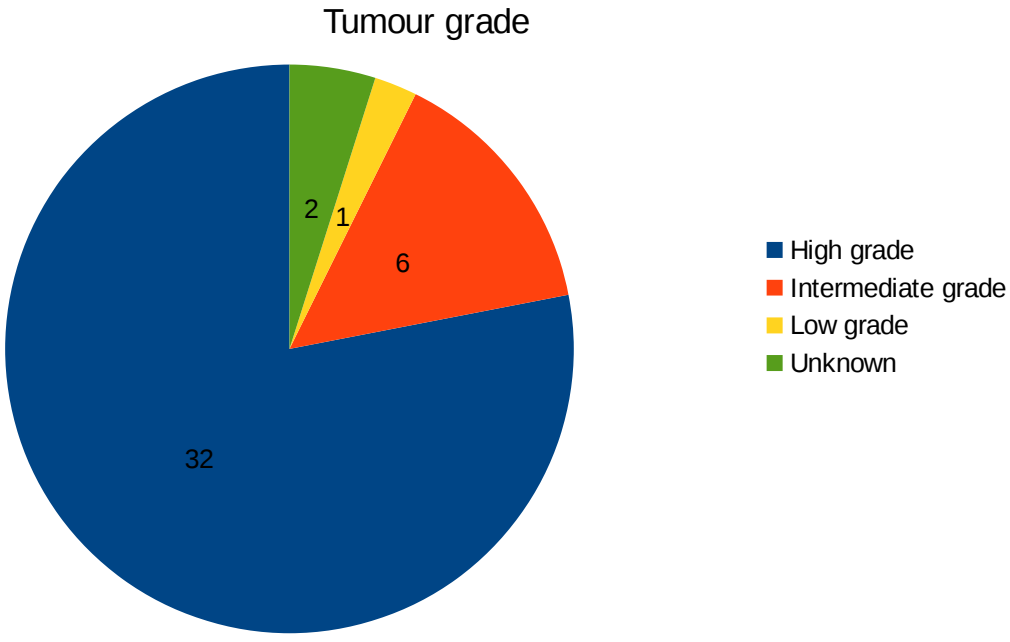


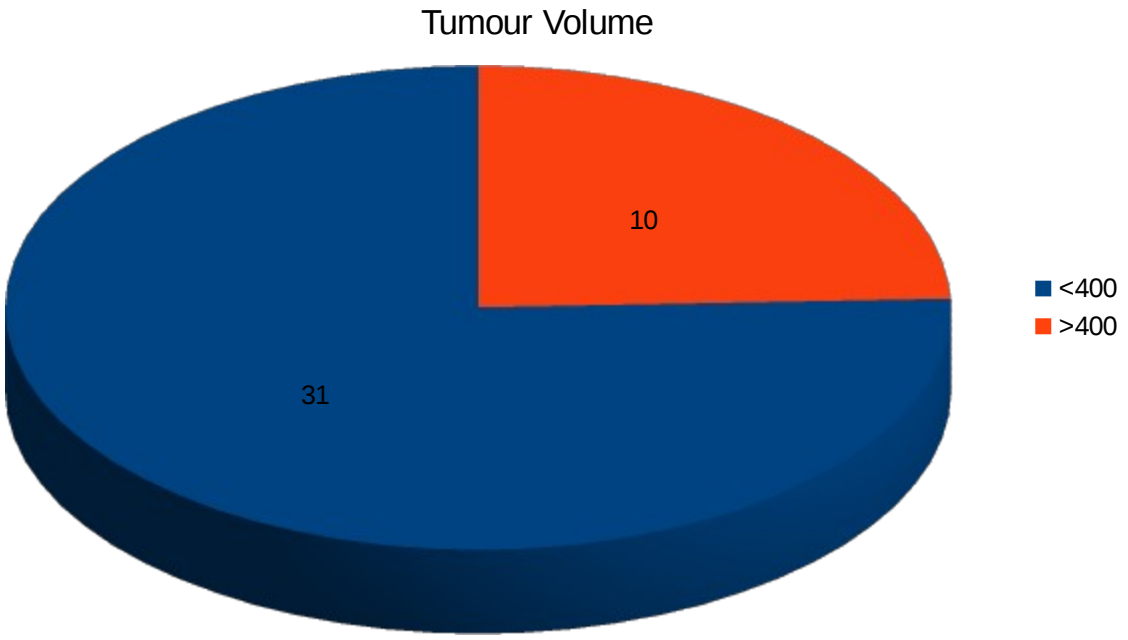


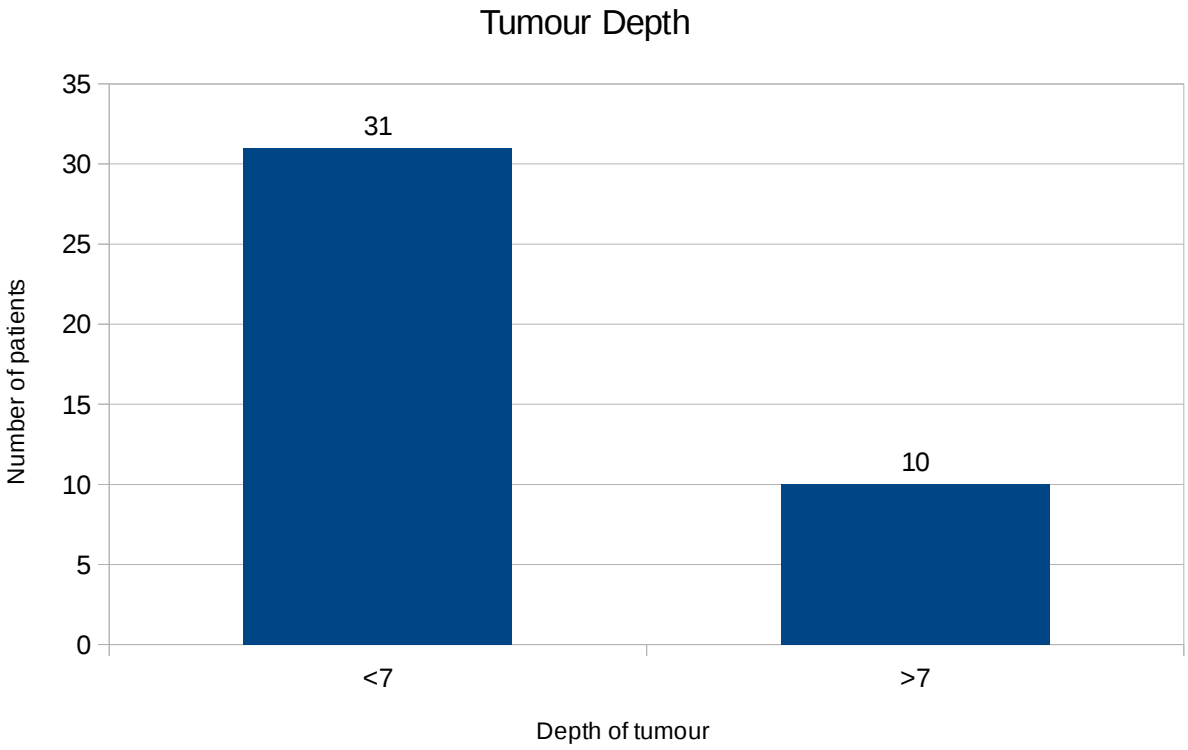
On plotting the age group of the patients in relation to the sex of the patients the peak in the number of female patient occurred earlier than the peak in the number of the female patients.

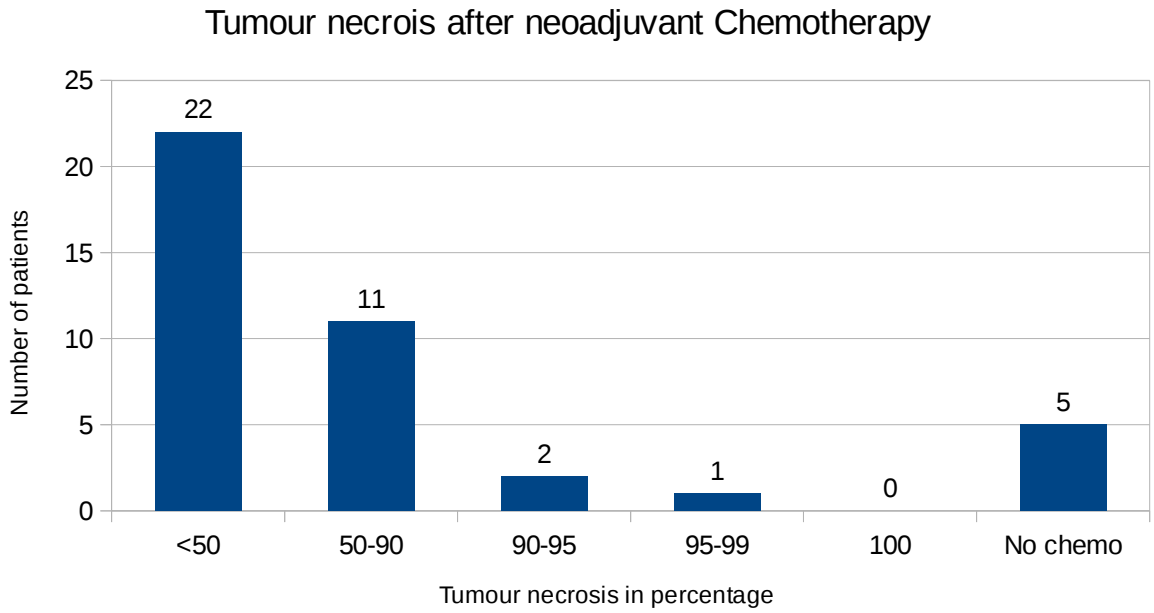


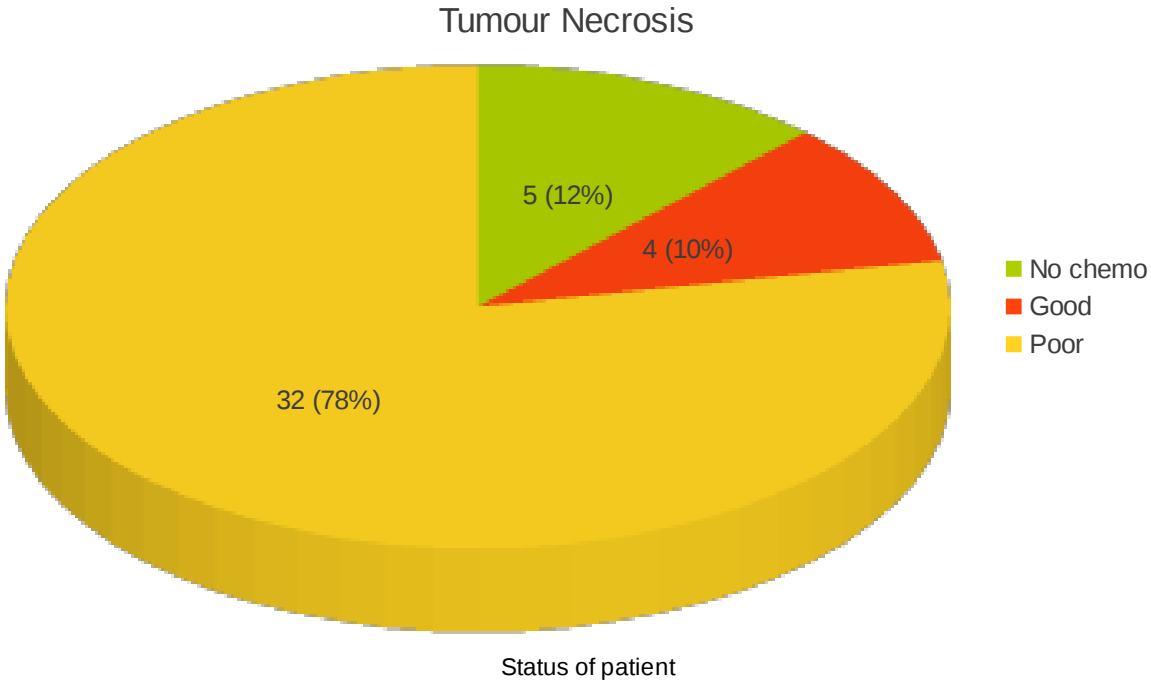

Alkaline phosphatase
Initial value
Number of patients
30
25
20
15
10
5
0
25
13
3
Normal
High
Missing
Level of alkaline phosphatase

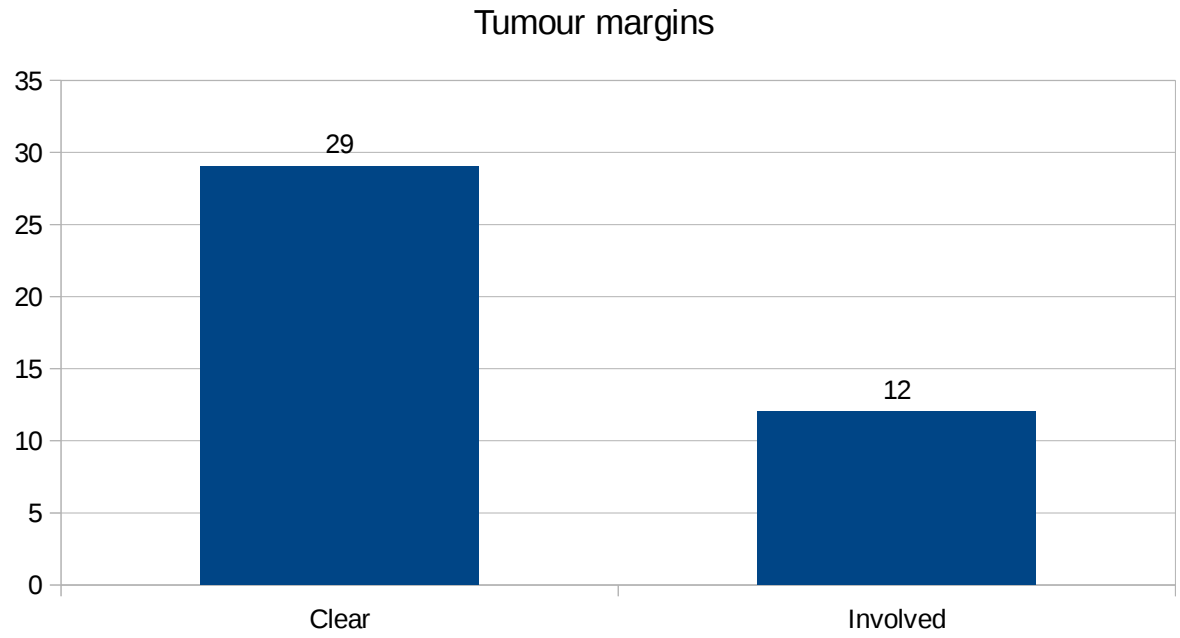

Tumour grade
2
1
6
32
High grade
Intermediate grade
Low grade
Unknown

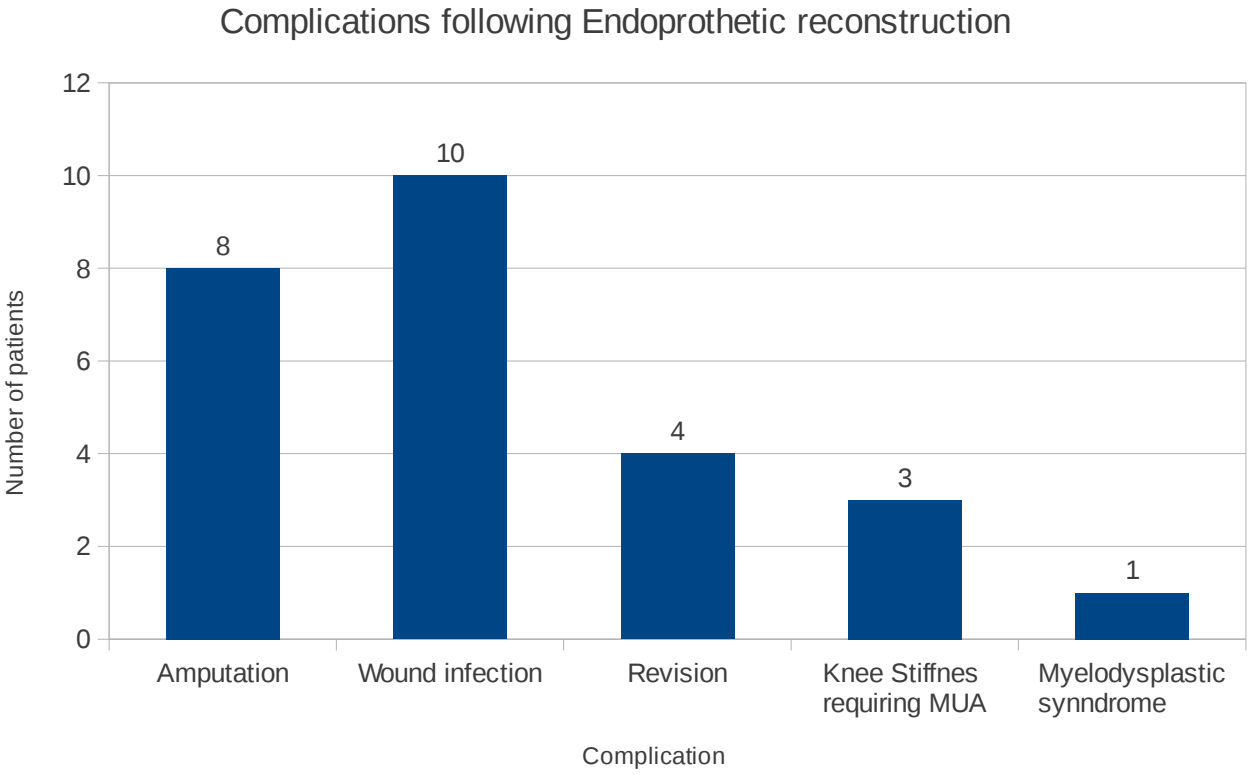

Tumour Volume
10
31
<400
>400

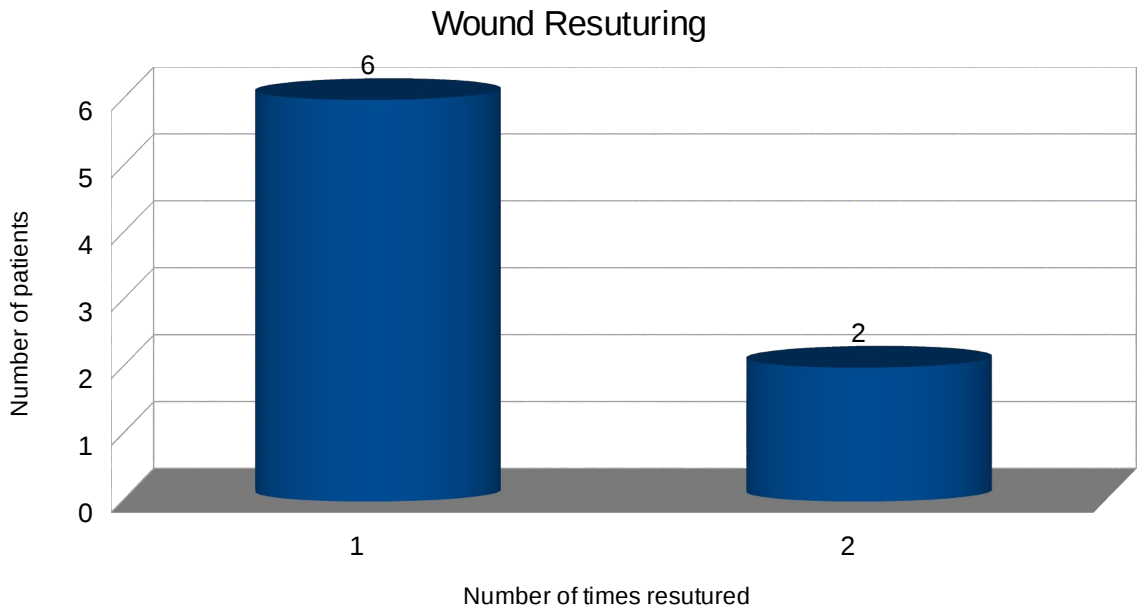

Tumour Depth
35
30
25
20
15
10
5
0
31
10
<7
>7
Number of patients
Depth of tumour


Tumour necrois after neoadjuvant Chemotherapy
Number of patients
25
20
15
10
5
0
22
11
2
1
0
5
<50
50-90
90-95
95-99
100
No chemo
Tumour necrosis in percentage


Tumour Necrosis
5 (12%)
4 (10%)
32 (78%)
No chemo
Good
Poor
Status of patient


Tumour margins
35
30
25
20
15
10
5
0
29
12
Clear
Involved


Complications following Endoprothetic reconstruction
Number of patients
12
10
8
6
4
2
0
8
10
4
3
1
Amputation
Wound infection
Revision
Knee Stiffnes requiring MUA
Myelodysplastic synndrome
Complication



The minimum follow up of the patients was 3 months and the maximum follow up of the patient included was 67 months. The mean follow up of the patients included in the study was 31 months.

The distal femur was the site for osteosarcoma in 25 of the patients and the proximal tibia was the site for osteosarcoma in the rest patients.

Tumour grade was not reported for two patients. Most patients fell in the high grade group(80%) compared to the intermediate grade(15% and low grade(3%).

Only 36 patients recruited in this study received preoperative chemotherapy. The others did not receive preoperative chemotherapy. Among the 36 patients who received neoadjuvant chemotherapy tumour necrosis was found to be good(more than 90%) in only 4 patients and the rest 32 patients had a poor necrosis or a necrosis percentage less that 90%.

Tumour volume was less than 400 cm3 in 30 patients and the in 11 patients it was more than 400 cm3. Tumour volume more than 400 cm3 was found to be associated with decreased survival and this difference was significant(p=0.009). The mean survival in patients with tumor

volume more than 400 cm^3 was 24.8 months compared to 55 months among patients who have tumor volume of less than 400 cm^3.

Tumor depth was found to be less than 7 cm in 30 patients and more than 7 cm in 11 patients. Tumor depth more than 7 cm was found to be associated with decreased overall survival and this difference was statistically significant (p = 0.009). The mean survival among the patients with tumor depth more than 7 cm was 23.7 months compared to 56.2 months in patients whose tumor depth was less than 7 cm.

Alkaline phosphatase levels before the onset of treatment were not available for 3 patients. 25 patients had normal alkaline phosphatase levels and 13 patients had high alkaline phosphatase levels. Higher levels of alkaline phosphatase was associated with decreased over all survival. The mean survival in patients with normal alkaline phosphatase was 52 months compared to 36 months among the patients with normal alkaline phosphatase levels. But this difference was not statistically significant.(p=0.092)

Tumor margins were positive for 12 patients and the remaining 29 patients had margins that were clear of the tumor. Out of the 12 patient one patient had three margins involved, 5 patients had two margins that were involved and six patients had a single margin that was involved. But there was no significant association with overall survival among the patients studied.

Seven patients who were included in this study developed local recurrence. In one patient the local recurrence developed within a month. In the other patient 3 patients developed local recurrence at 3 months after surgery, 2 patients developed local recurrence at 5 months after surgery. One patient developed local recurrence 35 months after surgery. Local recurrence was associated with poor survival and this association was statistically significant.(p=0.005)

Local recurrence was significantly lower in patient s who received postoperative radiotherapy compared to the patients who did not under go radiotherapy.

Eight patients had wound dehiscence and skin necrosis requiring re-suturing in the operation

theater. Out of the 8 patients 6 of them underwent re-suturing once and the 2 of them required re-suturing twice.

The complications noted were amputation, wound infection, aseptic loosing, knee stiffness and implant failure.

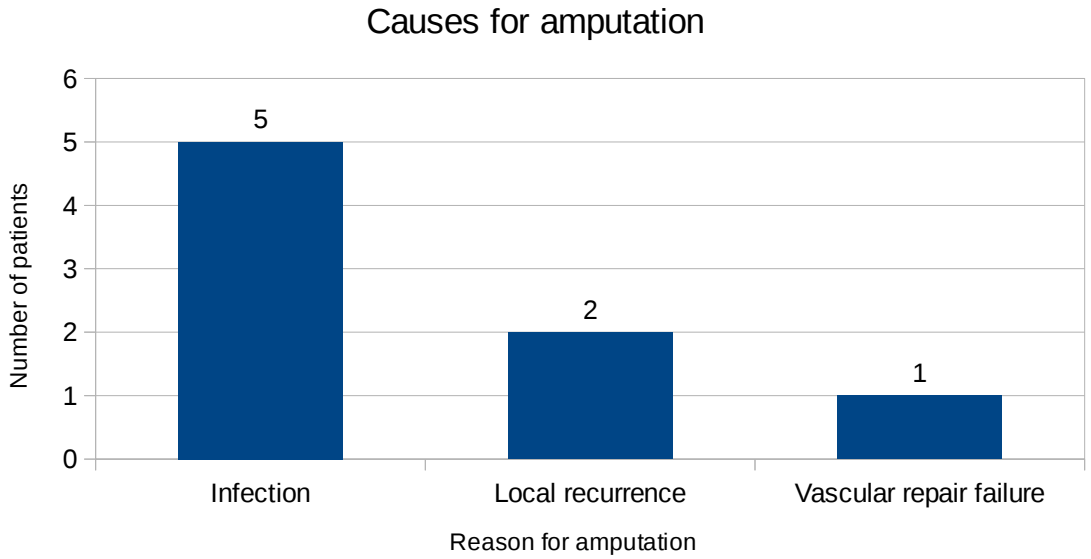
8 patient among the patients included in our study eventually required amputation. One patient in our study developed a avascular limb following a extensive tumor resection and vascular reconstruction and hence underwent amputation. The other reasons for amputation were infection in 5 patients and local recurrence in 2 patients. There was a association between amputation and tumour necrosis, alkaline phosphatase level at diagnosis and tumour margins. But this association was not statistically significant. Tumour volume of more than 400 ml was associated with increased risk of amputation and this association was statistically significant.(p=0.049)

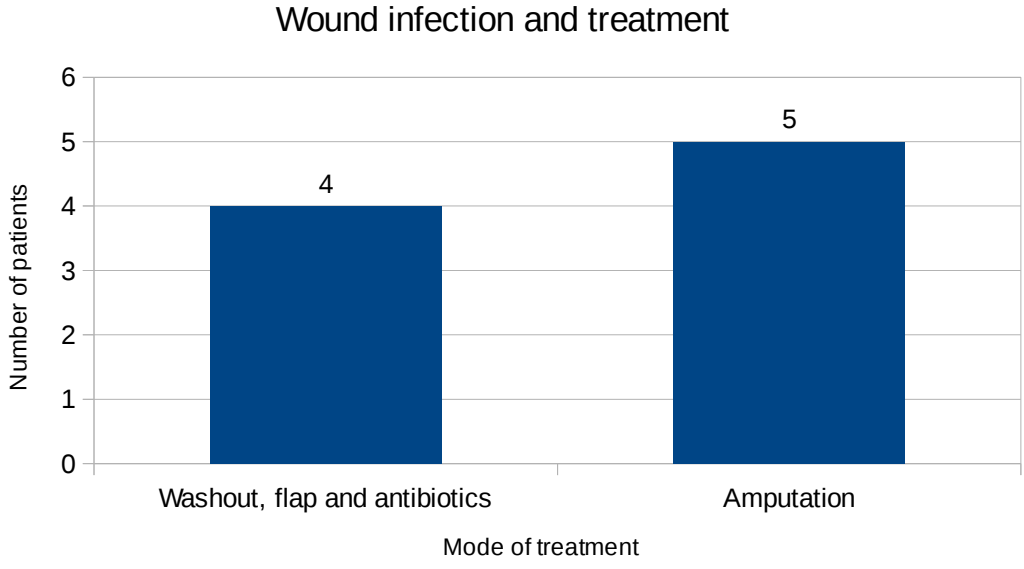
	Amputation			
Tumour grade	**No**	**Yes**	**Total**	**P value**
High	24	8	32	0.777
Intermediate	5	1	6	
Low	1	0	1	
Total	30	9	39	

	Amputation			
Tumour necrosis	**No**	**Yes**	**Total**	**P value**
Poor	24	8	32	0.345
Good	4	0	4	
Total	28	8	36	

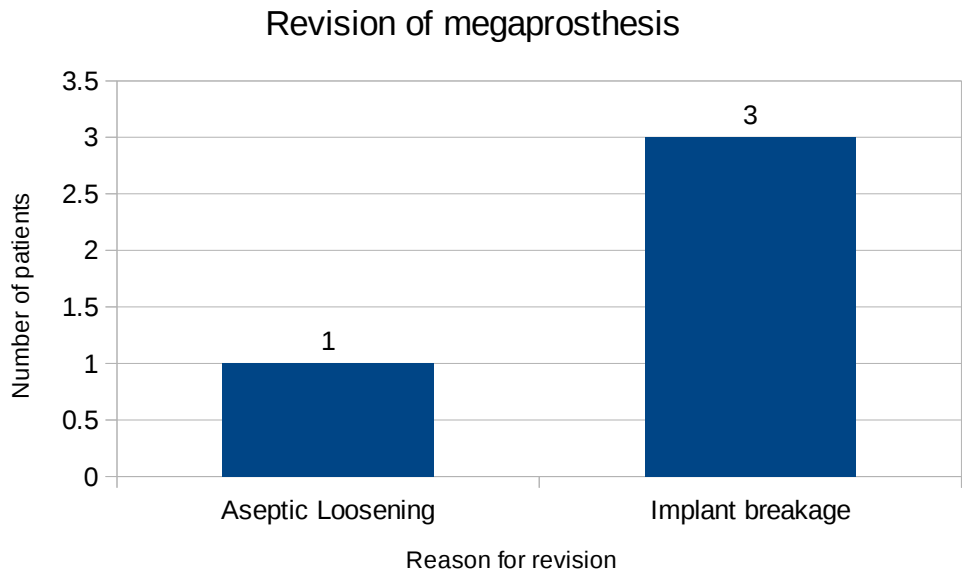
	Amputation			
Margin	**No**	**Yes**	**Total**	**P value**
Clear	23	6	29	0.53
Positive	9	3	12	
Total	32	9	41	

Tumour volume	Amputation		Total	P value
	No	Yes		
<400	26	4	30	0.049
>400	6	5	11	
Total	32	9	41	





Wound infection was noted in 10 patients. 5 patients who developed wound infection underwent amputation and the other five patients were treated with wound washout, muscle flap and IV antibiotics.



Revision of mega-prosthesis was done in 4 patients included our study. One patient developed aseptic loosening and hence underwent revision and the others had implant breakage and hence required revision.

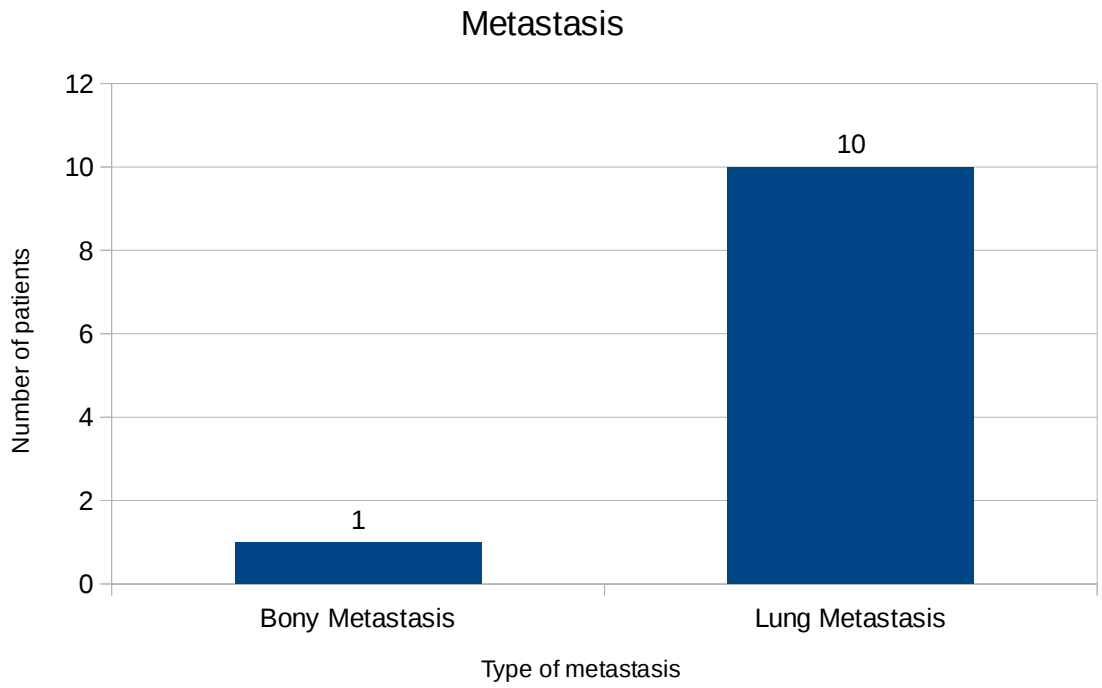
Out of the 41 patients who underwent mega prosthesis 3 patients developed significant knee stiffness postoperative and hence required manipulation under anesthesia. All of them attained good flexion following the manipulation under anesthesia but one patient later developed lung metastasis and died.

One patient developed chemotherapy induced Myelodysplastic syndrome at one year following operation and was on treatment for the same.

Out of the 41 patients studied 12 patients had died and 24 patients were alive. 5 patients were lost to follow up. The mean survival time was 49 months. Overall survival was significantly

associated with local recurrence, development of metastasis, tumor volume more than 400 ml and tumour depth more than 7 cm.

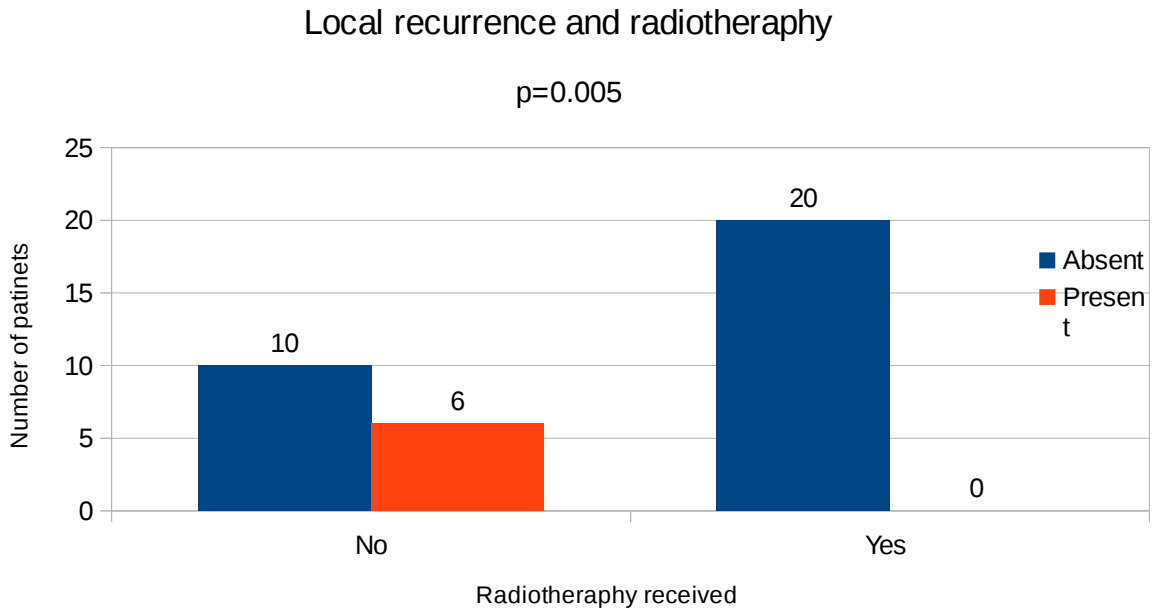
Though the sex, site of the tumour, level of alkaline phosphatase at diagnosis, tumour necrosis showed association with survival the association was not statistically significant.



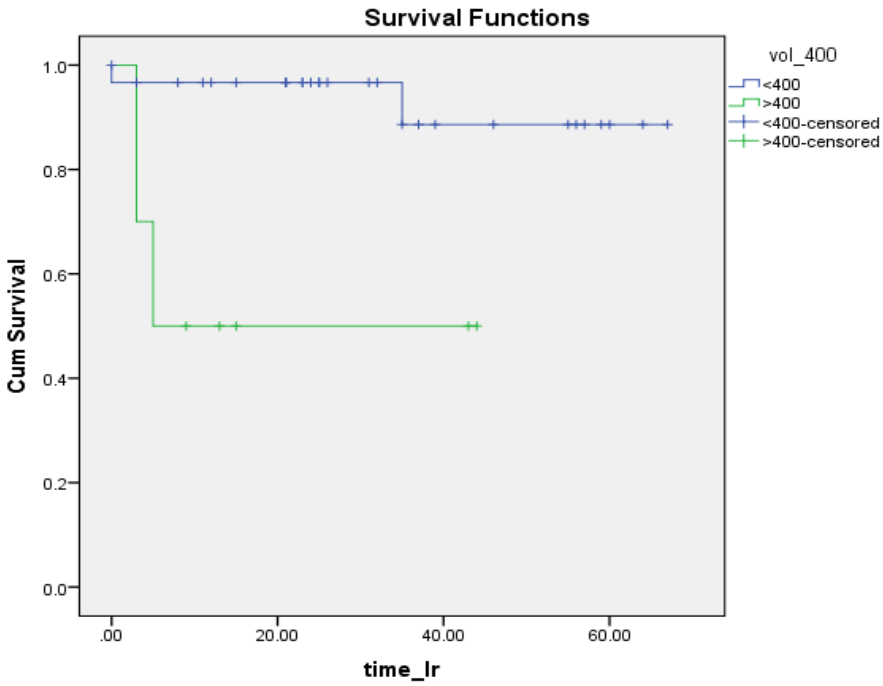
Among our patients 11 patient developed metastasis. 10 patients developed lung metastasis and one patient developed bony metastasis. Among those who developed metastasis the patient with bony metastasis and 4 patients with lung metastasis died. 3 patients with lung metastasis are alive and are on follow-up. All the patients who are alive were recently diagnosed to have metastatic disease.

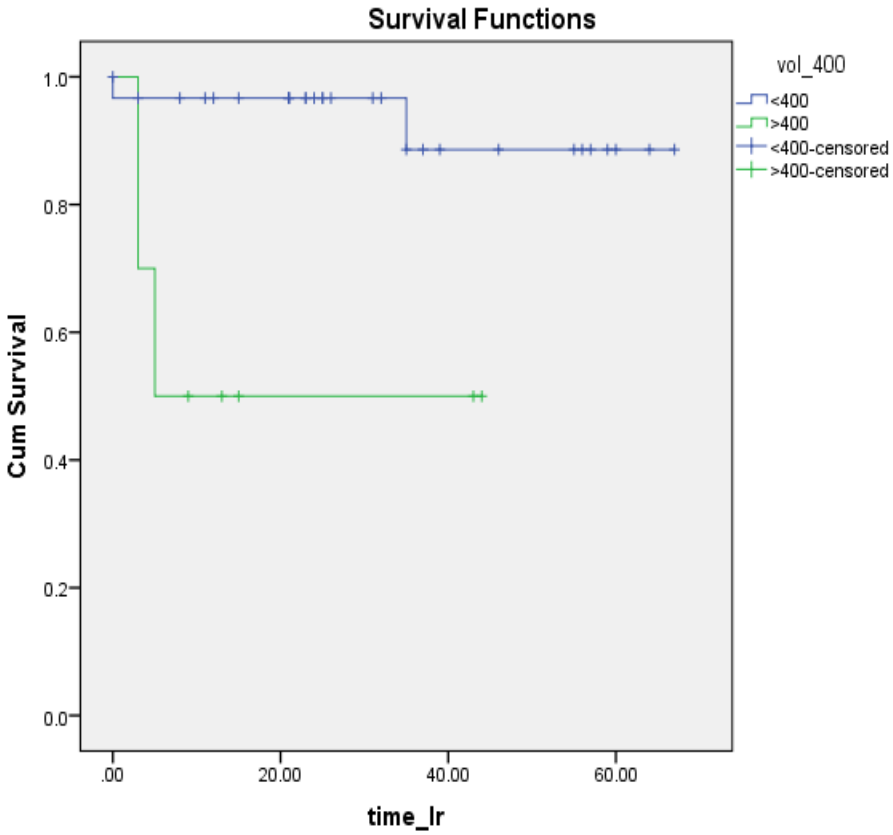
Local recurrence was noted in 7 of the 41 patients included in the study. Local recurrence was significantly associated with tumor volume more than 400 ml($p=0.006$), tumour depth more than 7cm($p=0.006$) and radiotherapy(0.005). Tumour volume and tumour depth increased the risk of local recurrence while radiotherapy was associated with decreased local recurrence.

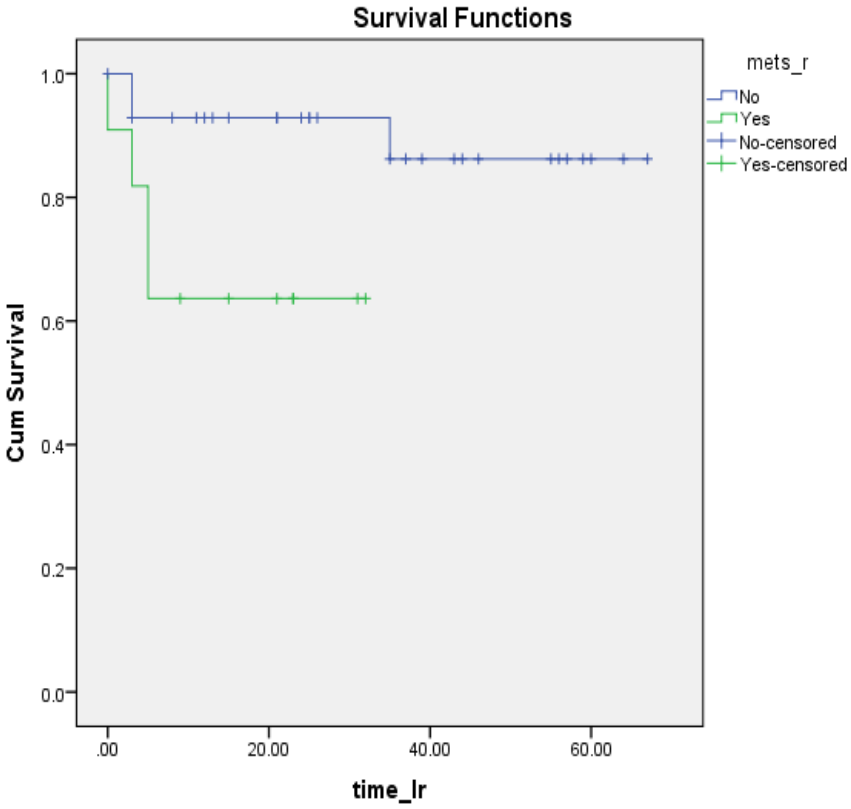
The was no significant statistically significant association between tumour necrosis, margin, level of alkaline phosphatase and local recurrence of the tumour.



The time to local recurrence was also significantly associated with tumour volume(0.001), tumour depth(p=0.001) and the development of metastatic disease(0.025).




Survival Functions
vol_400
<400
>400
<400-censored
>400-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
time_lr

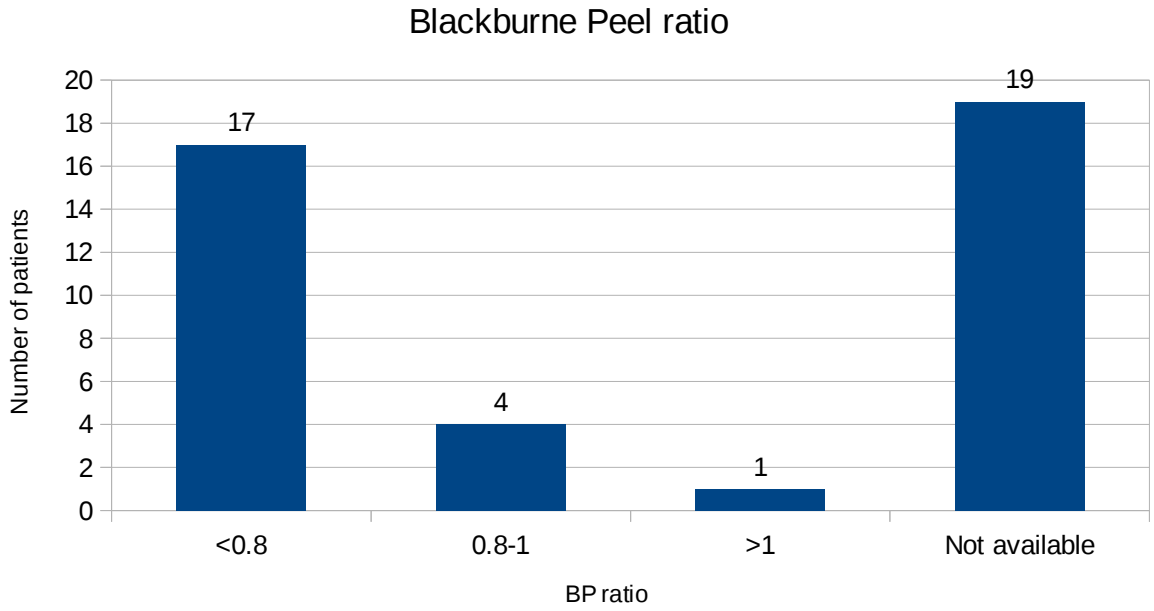

Survival Functions
mets_r
No
Yes
No-censored
Yes-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
time_lr

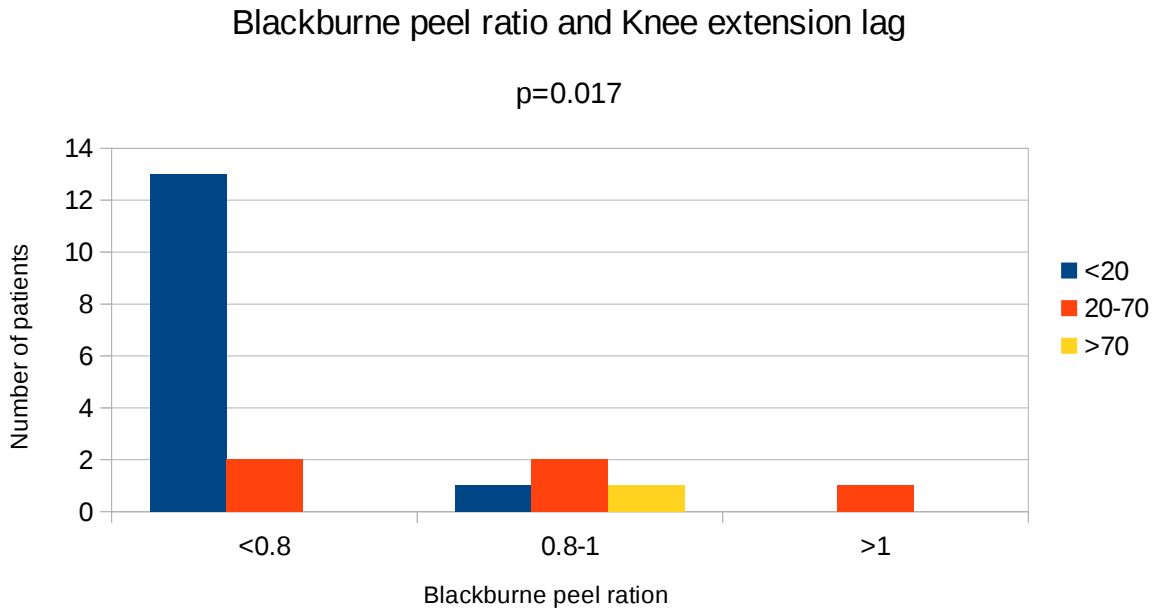
Blackburne-peel ratio was calculated for 22 patients for whom radiographs were available at 30 degree flexion. 18 patients did not have radiographs at 30 degree and hence were excluded. The Blackburne-peel ratio was significantly associated with lag noticed postoperatively.(p=0.017) But it did not have any significant effect on the flexion of the patients.

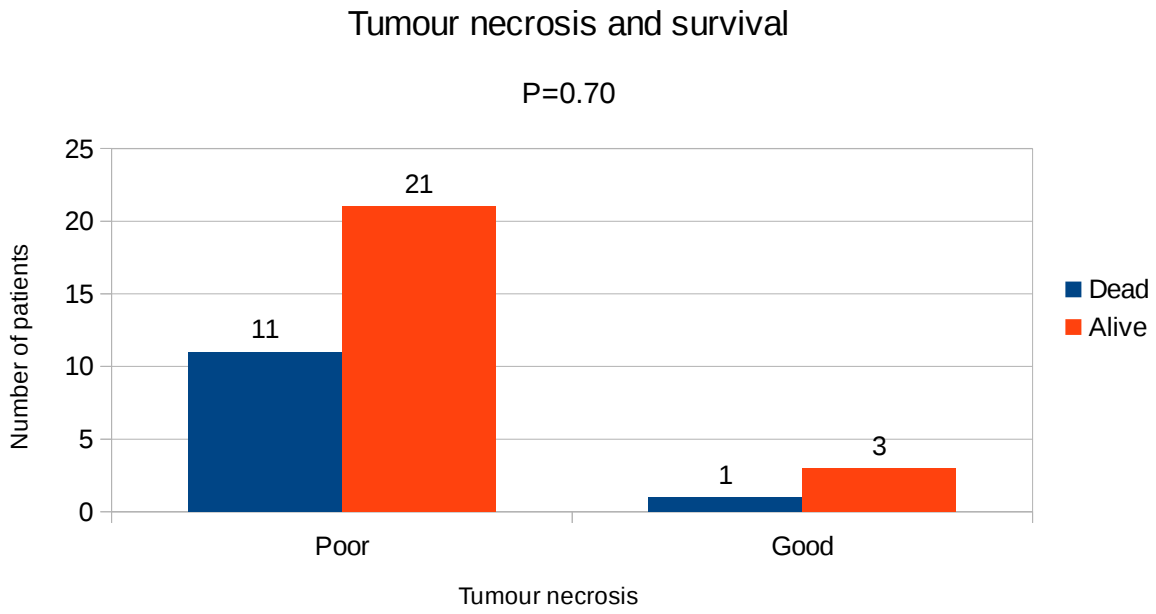
There were 16 patients in whom the method of extensor mechanism reconstruction as described by Titus et was was done. The wire broke in 5 and in 11 it remained intact at the last follow-up. Among the 11 patients with intact wires only one patient had a intact wire still functioning at follow up. All other patients with intact wires either underwent amputation or died before the wire broke. The presence of absence of a intact wire did not affect the extension lag in the knee.

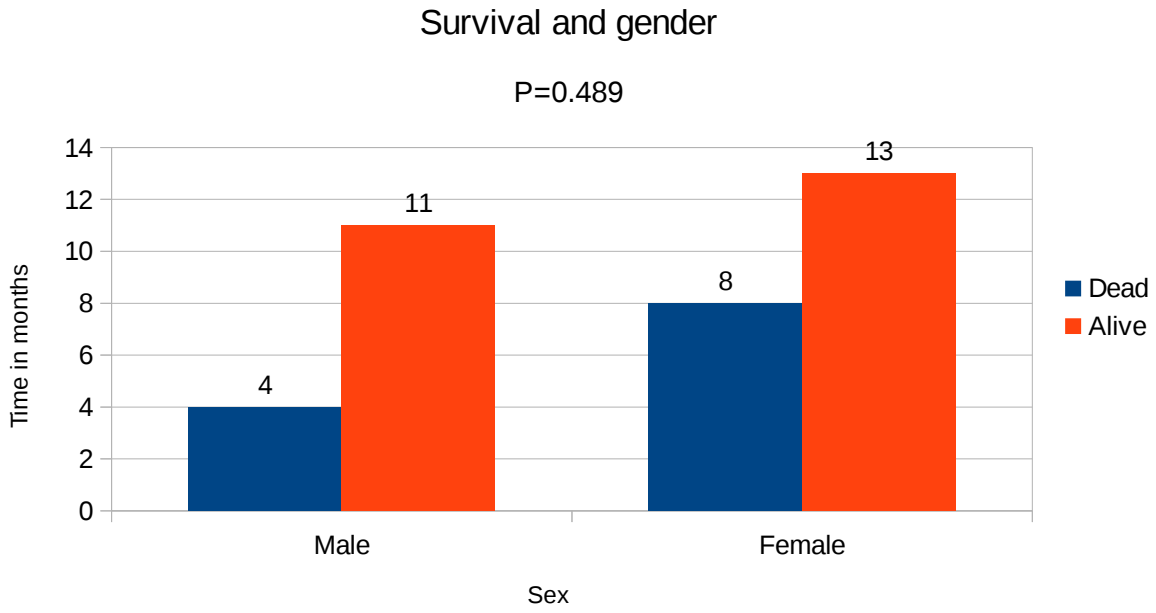
The volume of the tumour resected did not have any statistically significant effect on flexion or extension lag noticed in the patients.

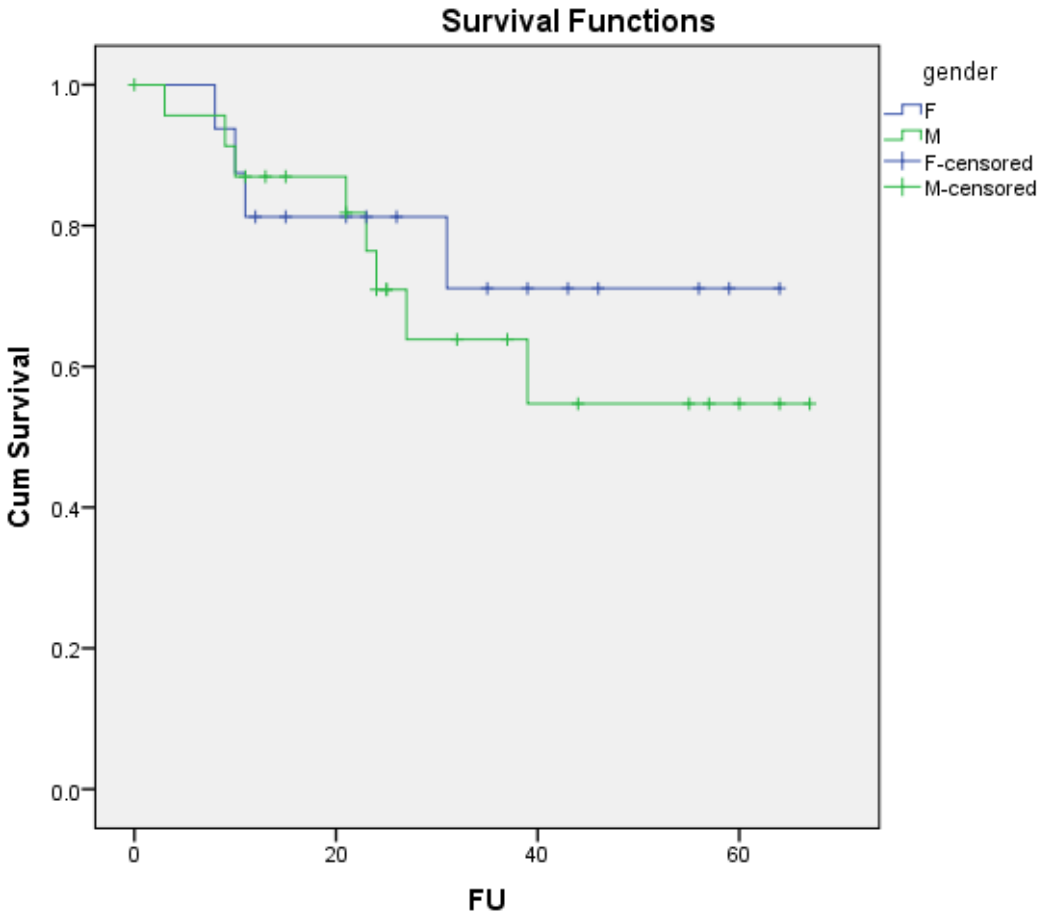
The length of resection on the tibia and femur also did not show any association with knee flexion or extension lag postoperatively.

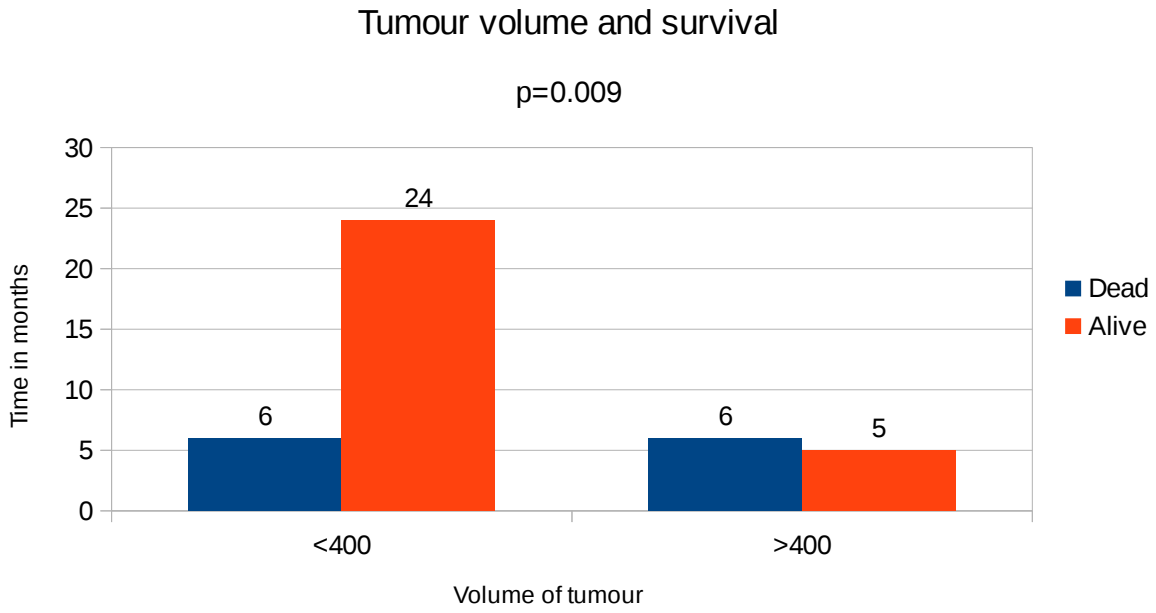


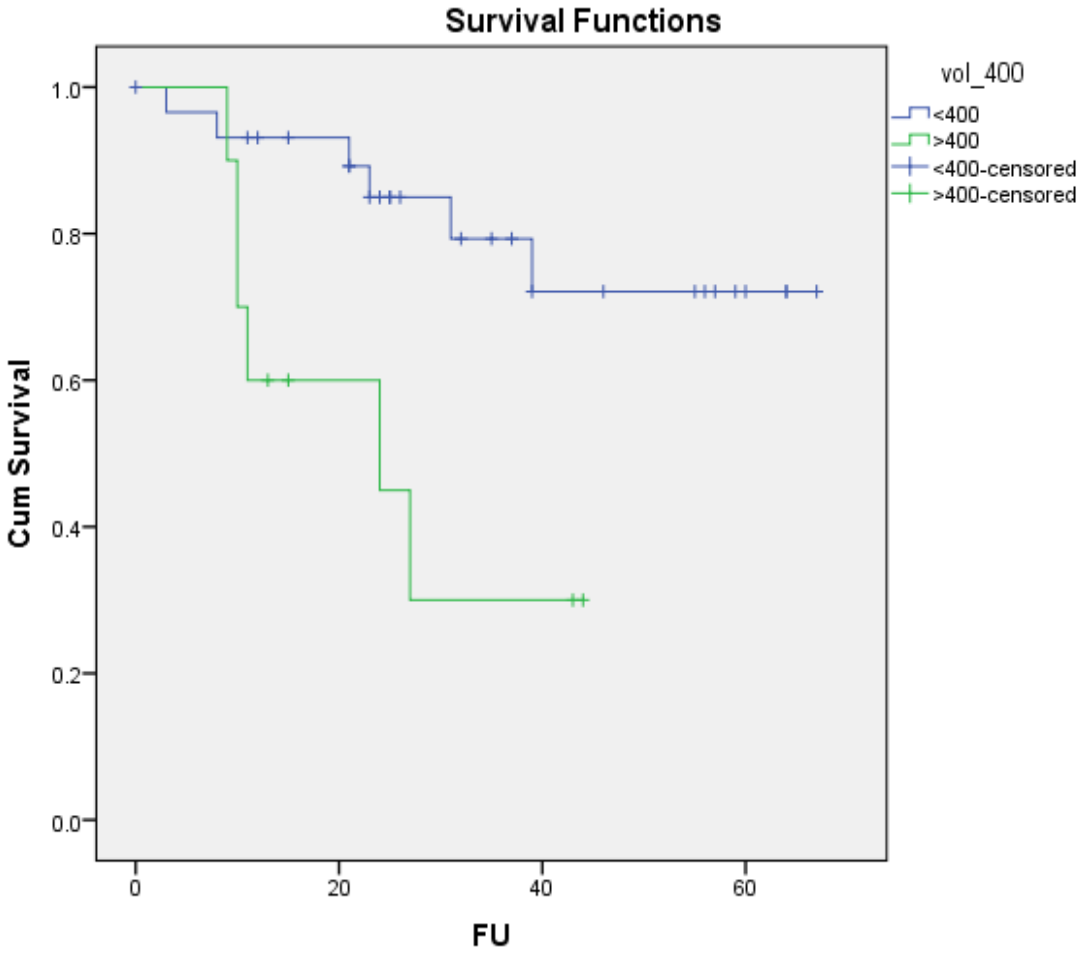

Blackburne peel ratio and Knee extension lag
p=0.017
Number of patients
14
12
10
8
6
4
2
0
<0.8
0.8-1
>1
Blackburne peel ration
<20
20-70
>70

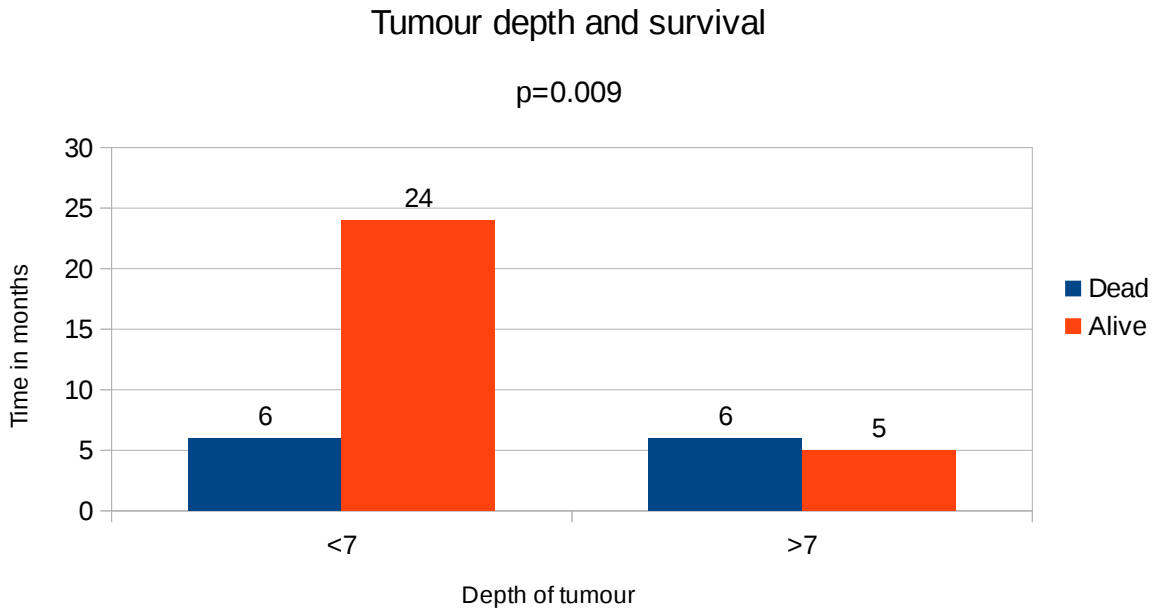

Tumour necrosis and survival
P=0.70
Number of patients
25
20
15
10
5
0
11
21
1
3
Poor
Good
Tumour necrosis
Dead
Alive

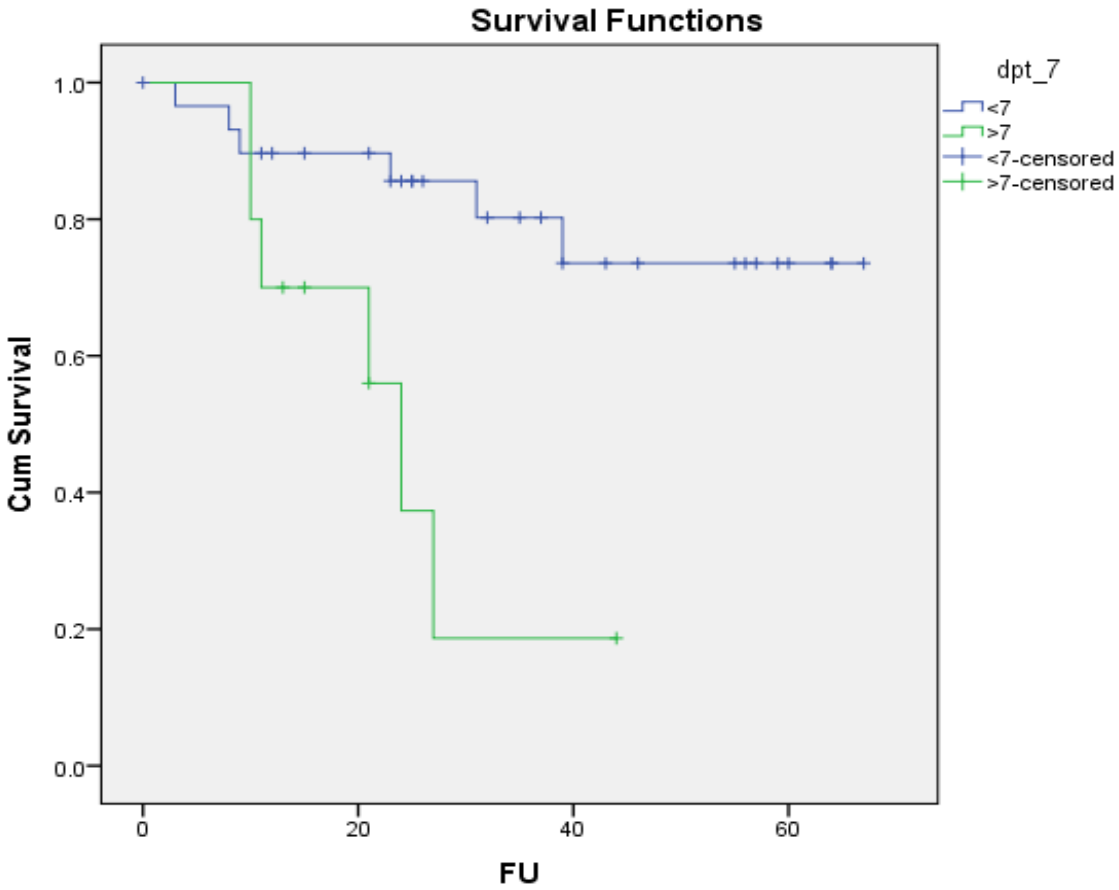

Survival and gender
P=0.489
14
12
10
8
6
4
2
0
Time in months
4
11
8
13
Male
Female
Sex
Dead
Alive


Survival Functions
1.0
0.8
0.6
0.4
0.2
0.0
Cum Survival
0
20
40
60
FU
gender
F
M
F-censored
M-censored


Tumour volume and survival
p=0.009
30
25
20
15
10
5
0
Time in months
24
6
6
5
<400
>400
Volume of tumour
Dead
Alive

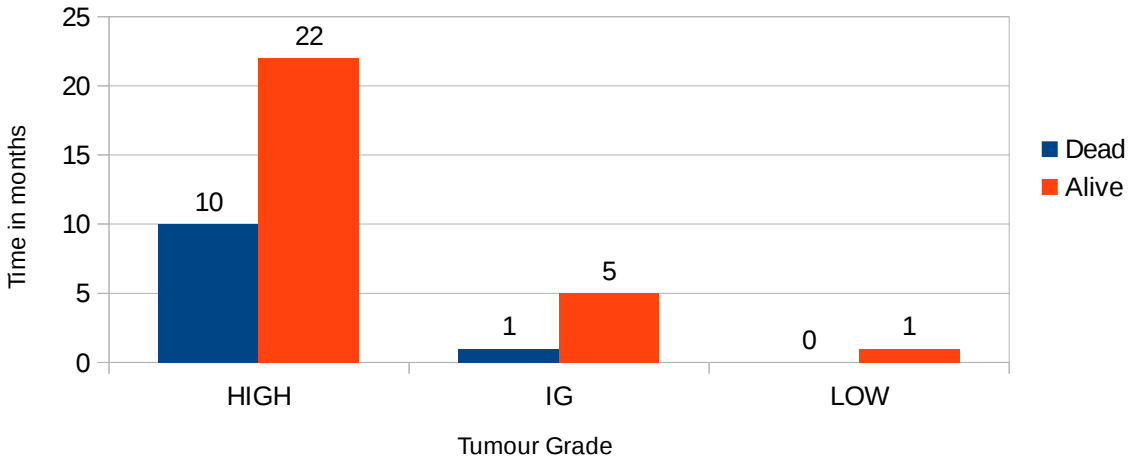

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
FU
vol_400
<400
>400
<400-censored
>400-censored

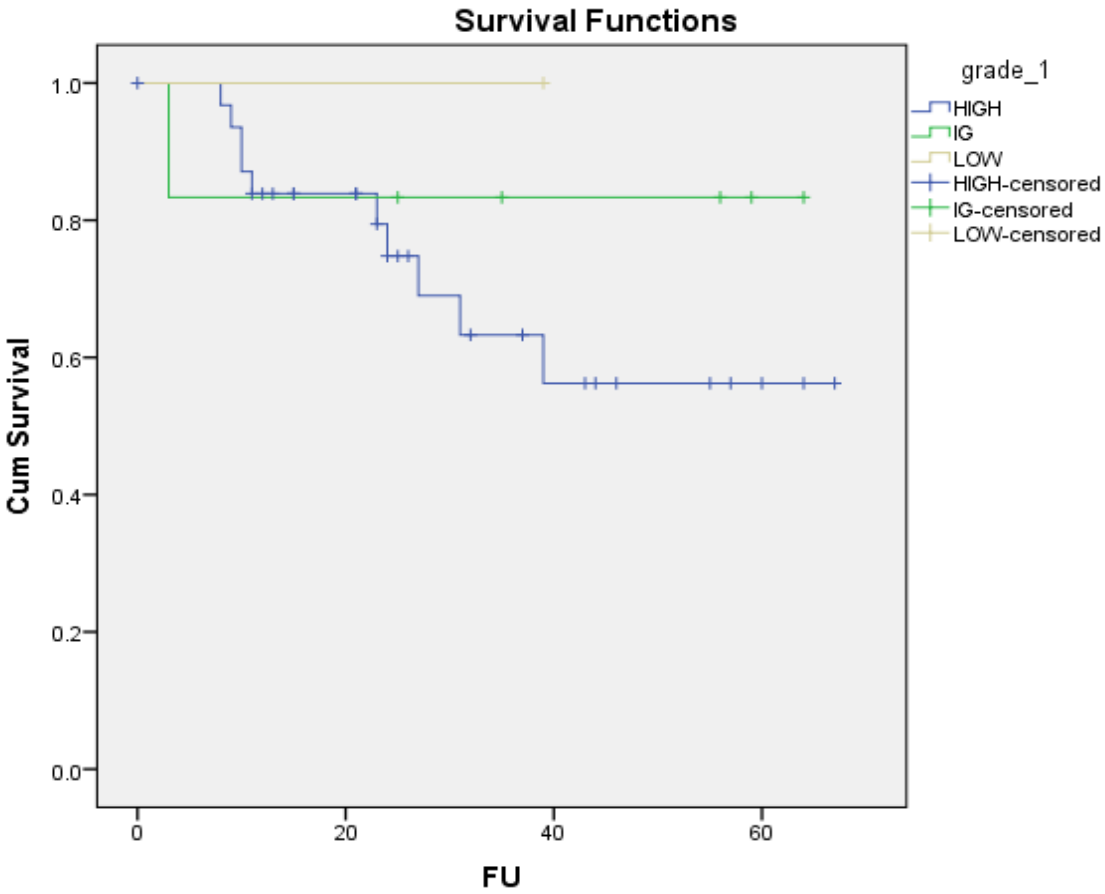

Tumour depth and survival
p=0.009
30
25
20
15
10
5
0
Time in months
24
6
6
5
<7
>7
Depth of tumour
Dead
Alive

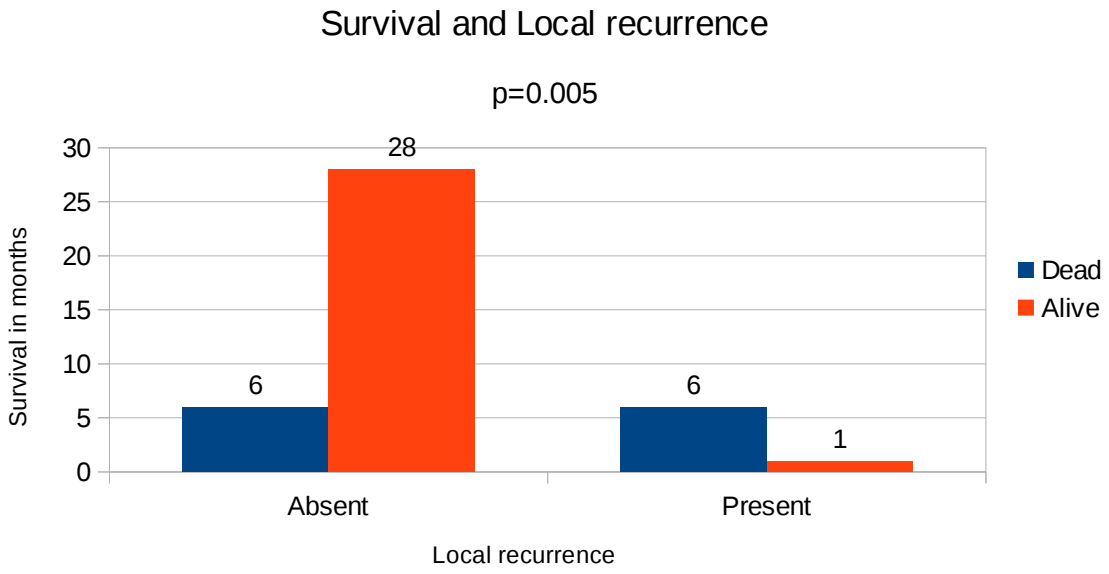

Survival Functions
dpt_7
<7
>7
<7-censored
>7-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
FU

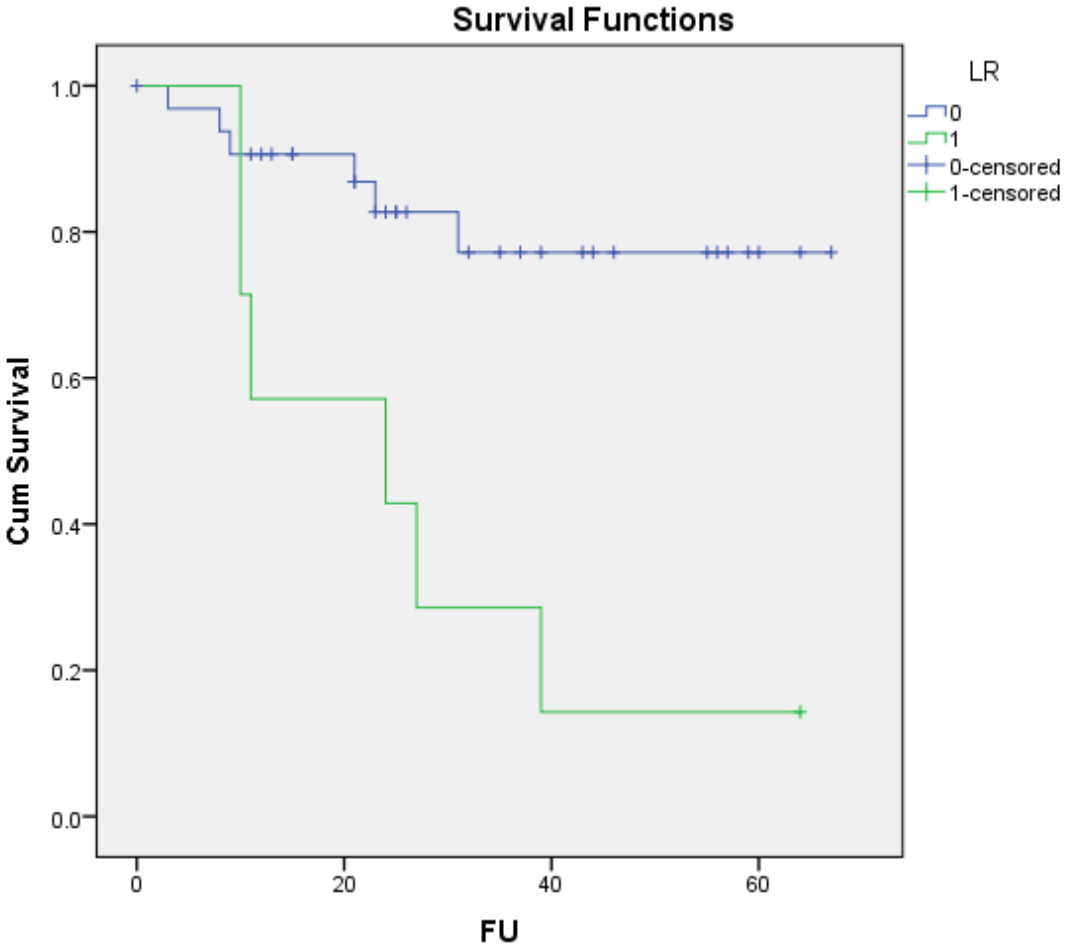
Tumour Grade and survival

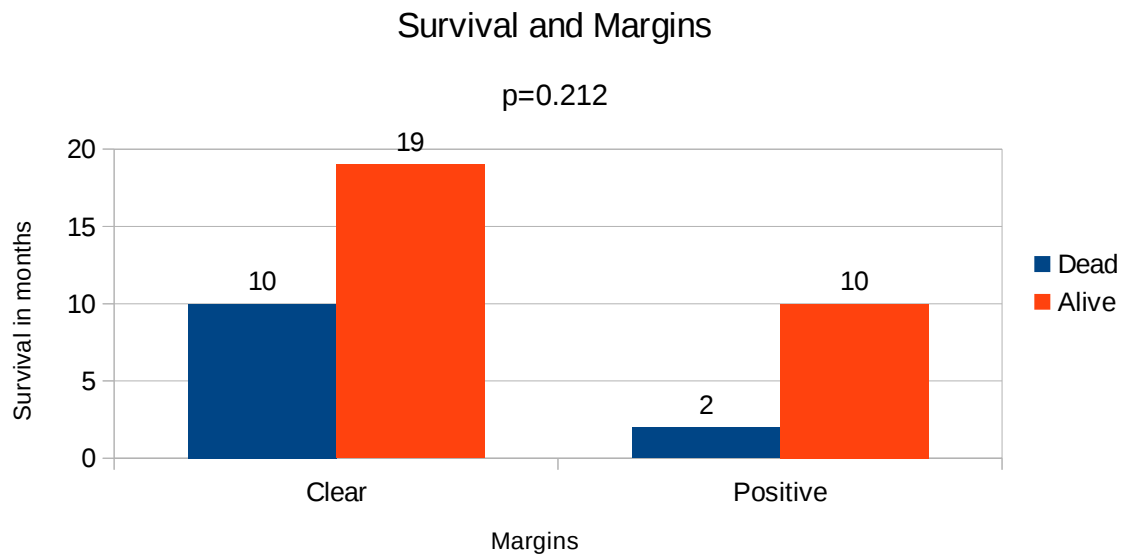
p=0.627

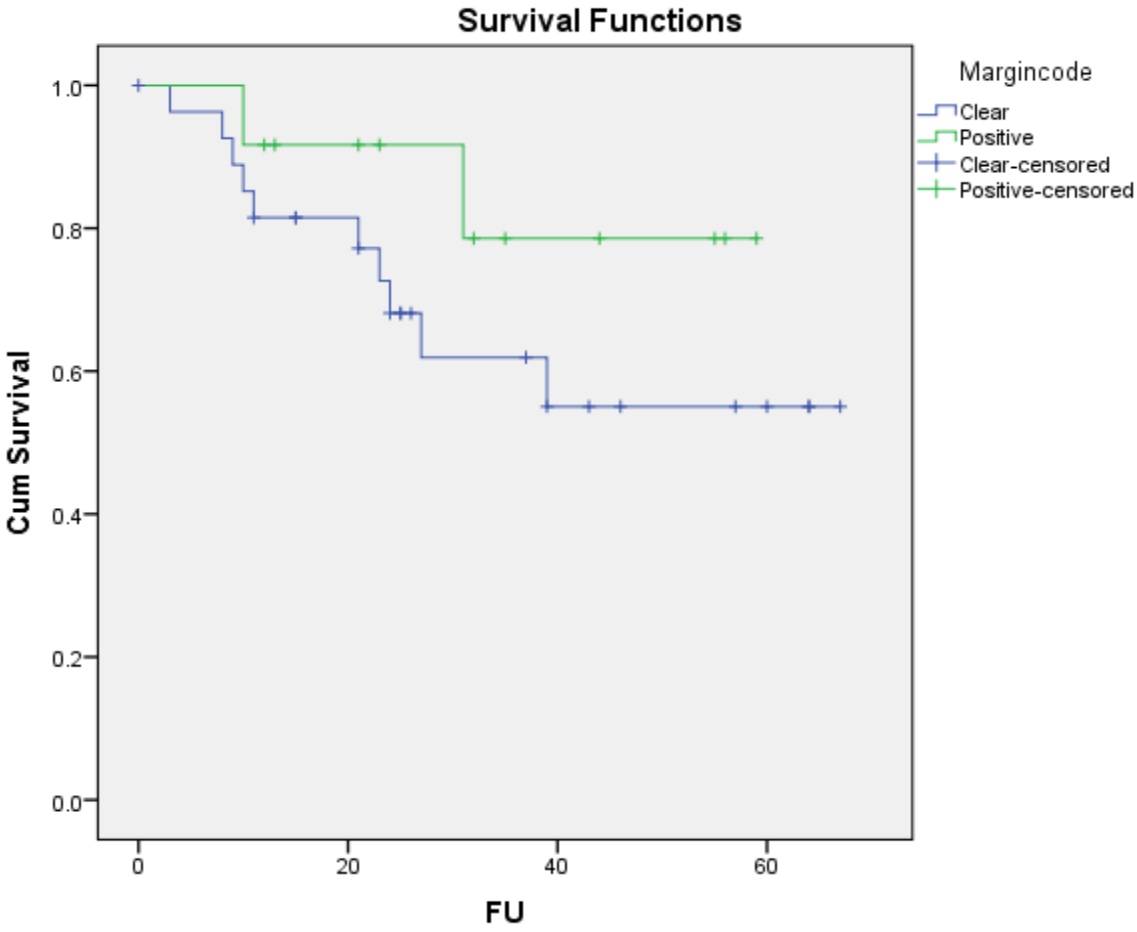


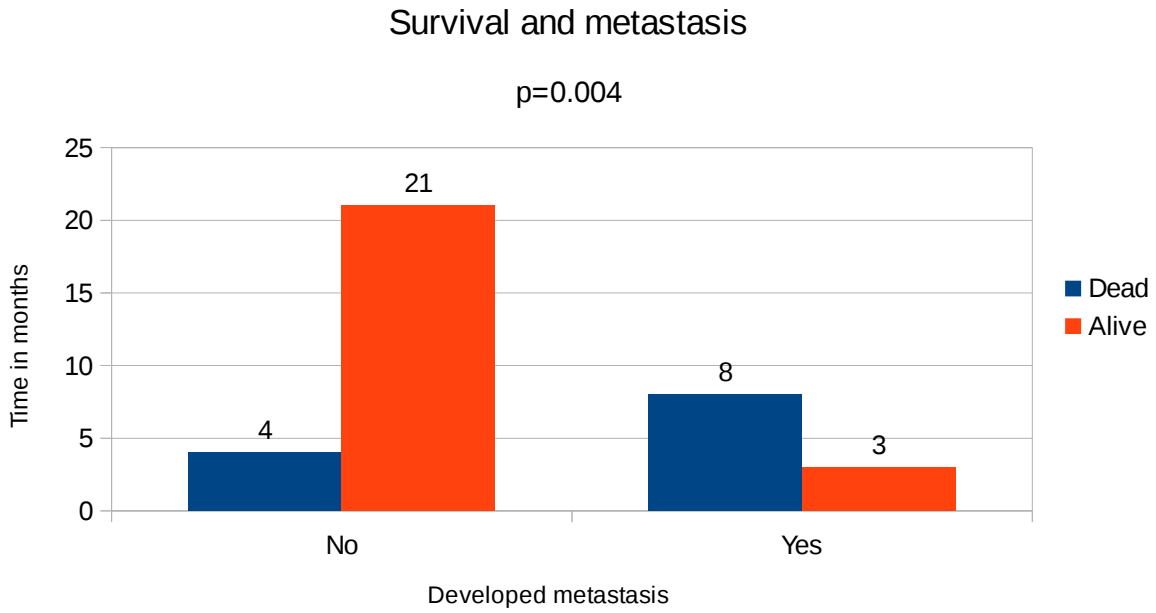


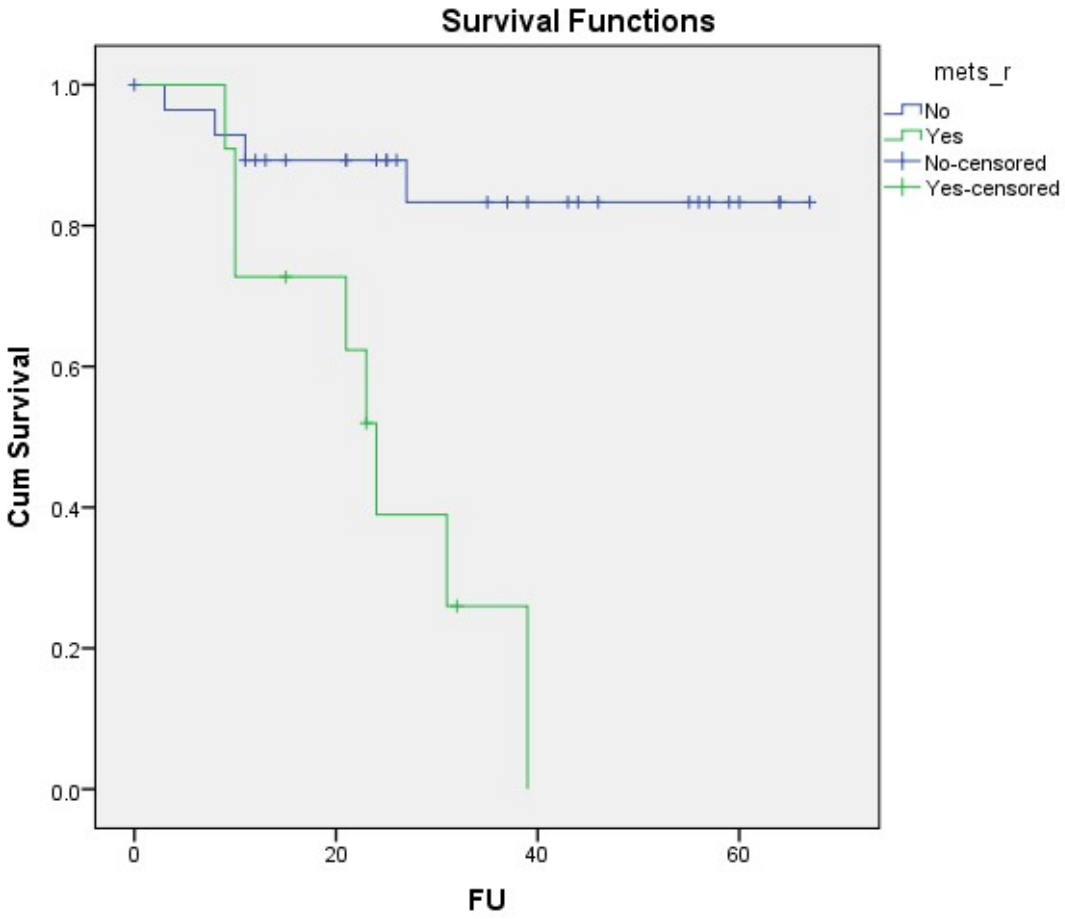

Survival and Local recurrence
p=0.005
Survival in months
30
25
20
15
10
5
0
28
6
6
1
Absent
Present
Local recurrence
Dead
Alive

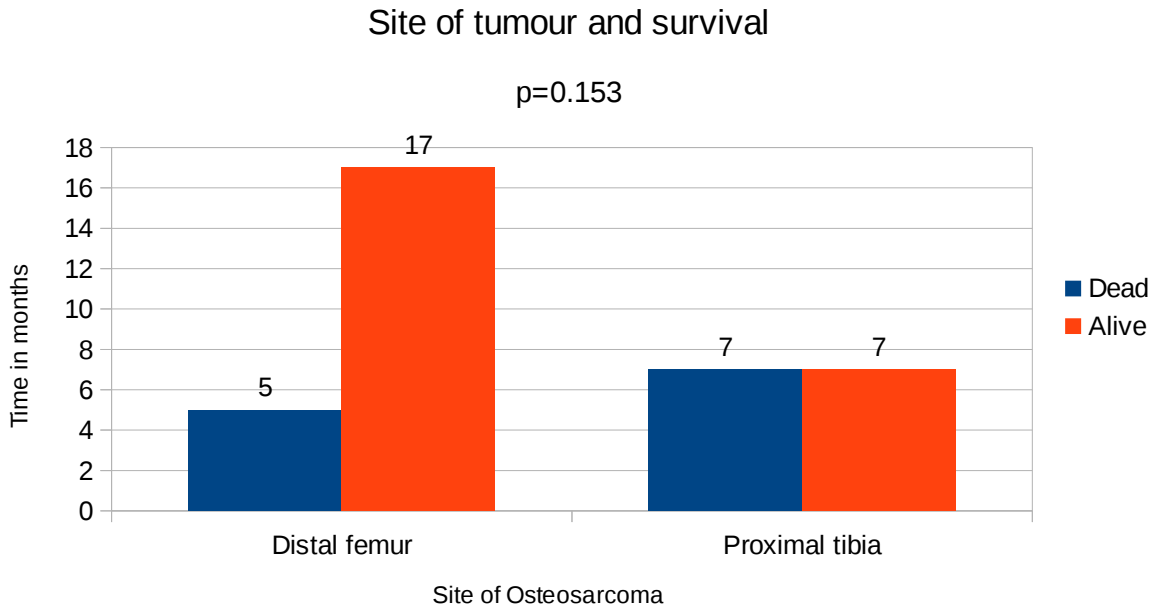

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
FU
LR
0
1
0-censored
1-censored

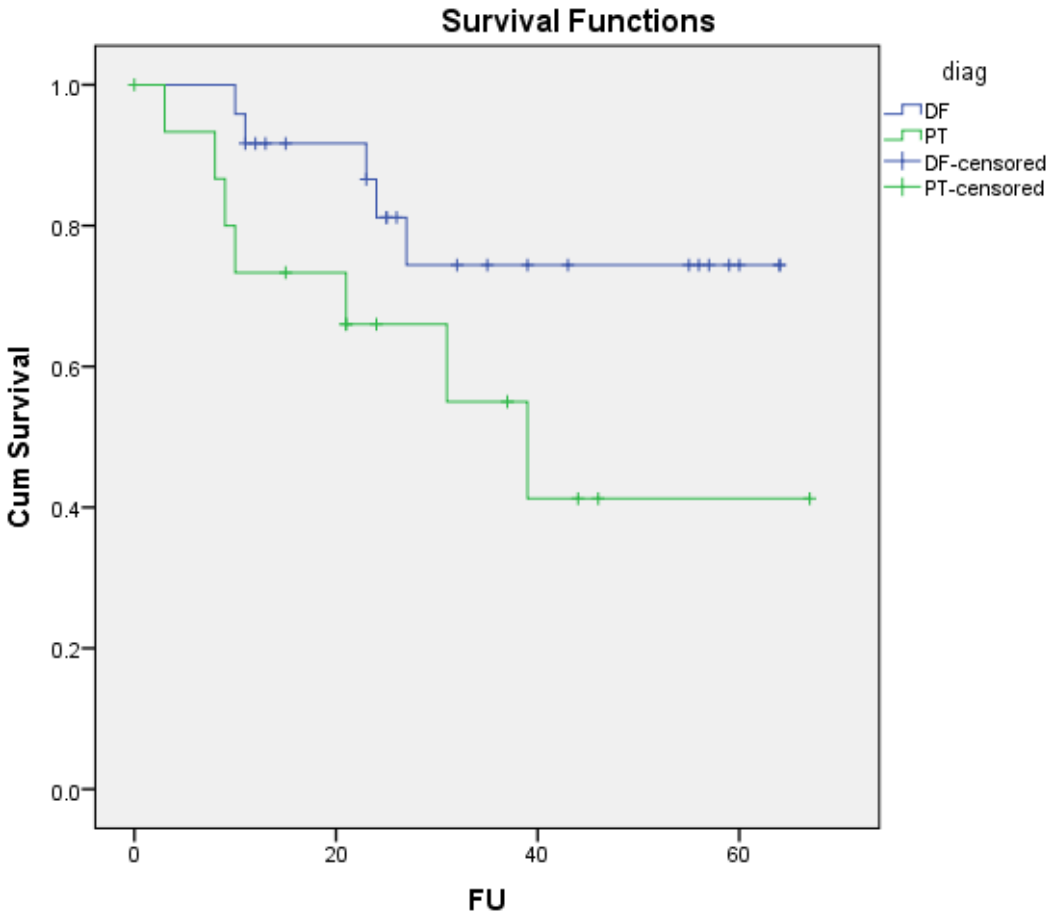

Survival and Margins
p=0.212
Survival in months
20
15
10
5
0
19
10
10
2
Clear
Positive
Margins
Dead
Alive

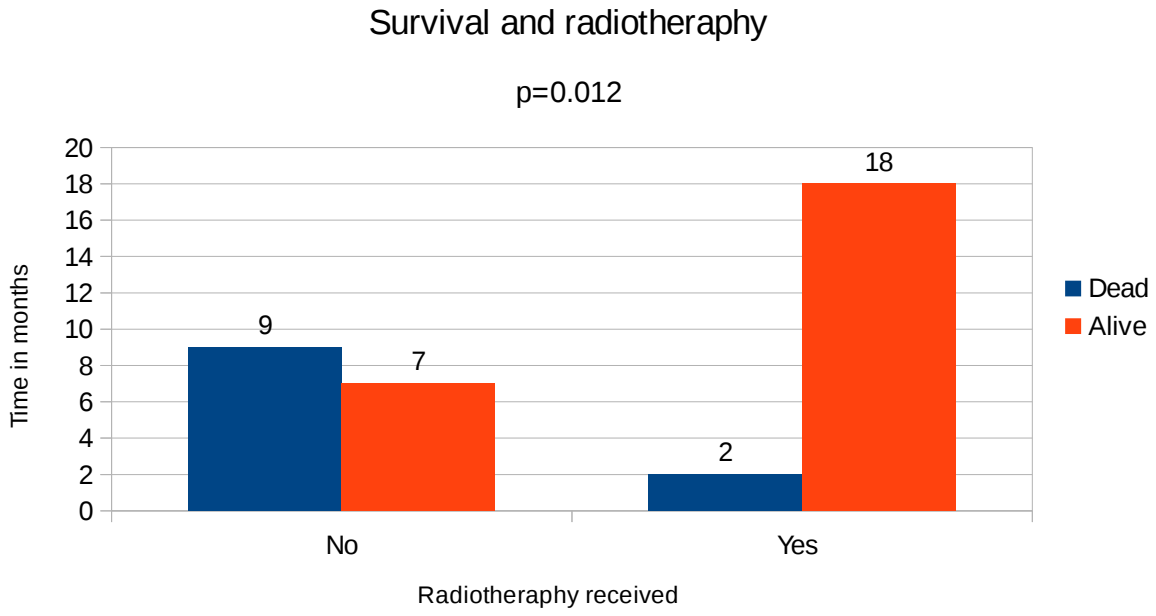

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
FU
Margincode
Clear
Positive
Clear-censored
Positive-censored

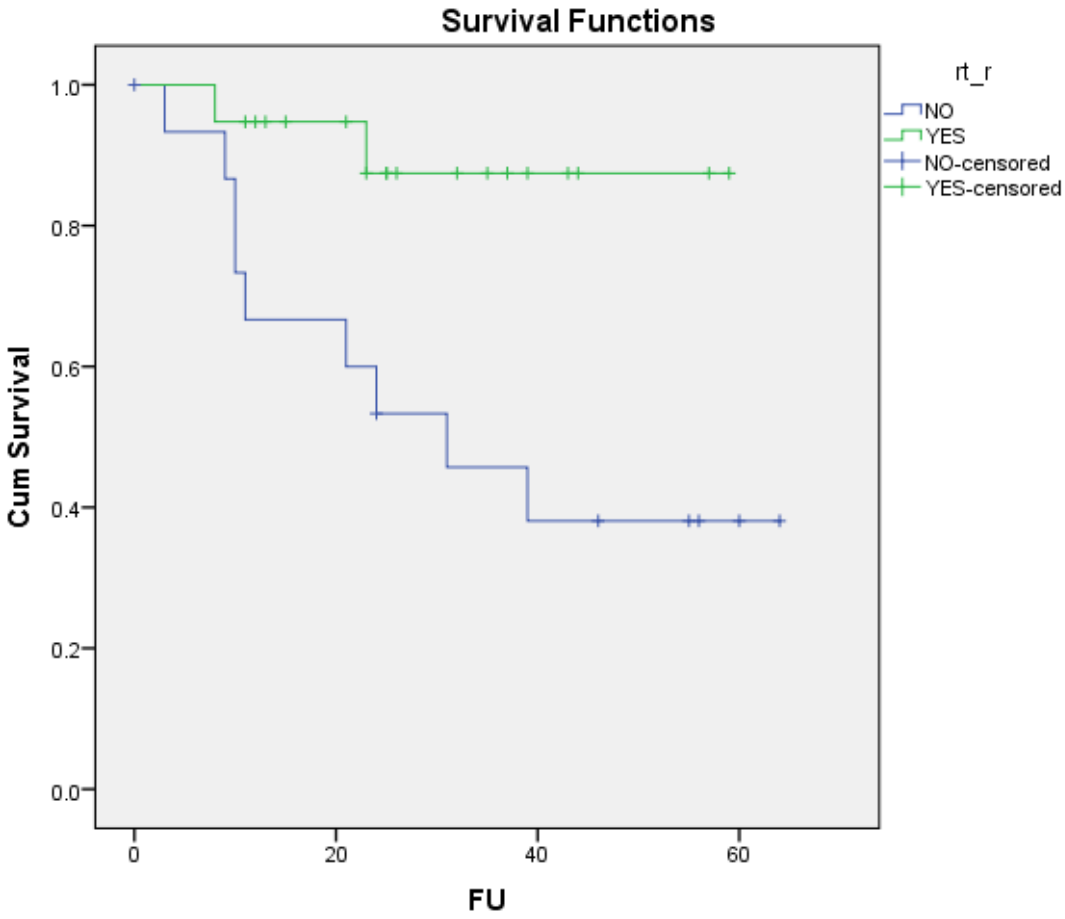

Survival and metastasis
p=0.004
Time in months
25
20
15
10
5
0
21
4
8
3
No
Yes
Developed metastasis
Dead
Alive

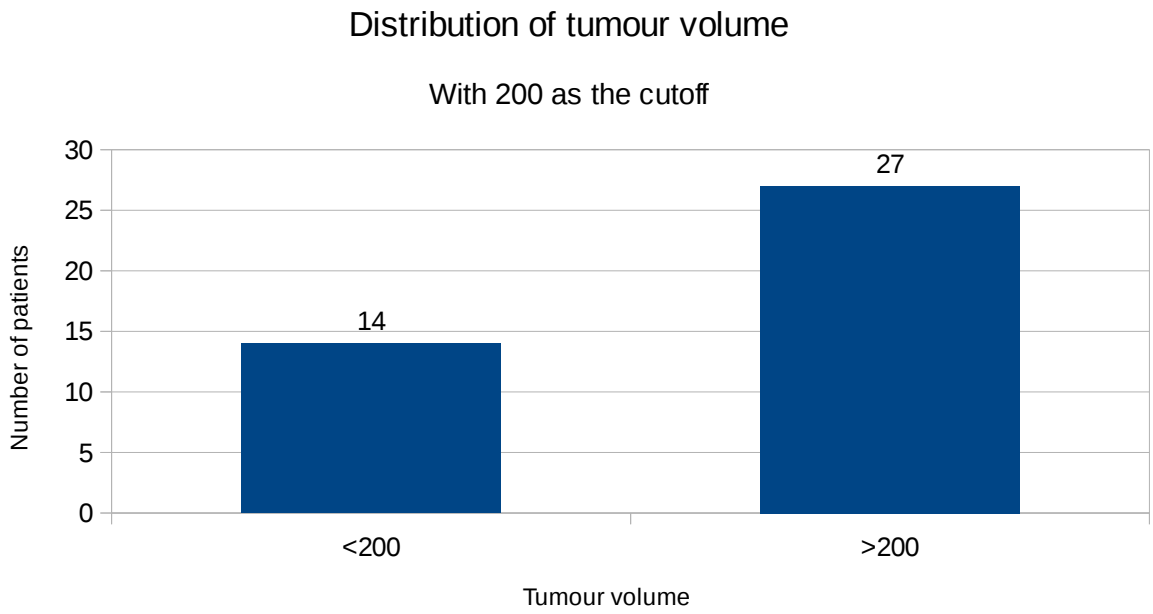

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
FU
mets_r
No
Yes
No-censored
Yes-censored


Site of tumour and survival
p=0.153
Time in months
18
16
14
12
10
8
6
4
2
0
17
5
7
7
Distal femur
Proximal tibia
Site of Osteosarcoma
Dead
Alive


Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
FU
diag
DF
PT
DF-censored
PT-censored


Survival and radiotheraphy
p=0.012
Time in months
20
18
16
14
12
10
8
6
4
2
0
9
7
2
18
No
Yes
Radiotheraphy received
Dead
Alive


Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
FU
rt_r
NO
YES
NO-censored
YES-censored


Distribution of tumour volume
With 200 as the cutoff
Number of patients
30
25
20
15
10
5
0
14
27
<200
>200
Tumour volume

Discussion

Discussion:

Osteosarcoma though known for 2 centuries is associated with significant morbidity and mortality. Though multi-modal treatment has improved the survival and outcome for the patients with osteosarcoma survival rates have not significantly improved over the last two decades. In our country, during the 1990s, before mulitmodal treatment ie. limb salvage surgery, chemotherapy, radiotherapy was introduced the only treatment available offered was amputation. The western data available with such an approach, in the prechemotheraphy, preradiotherapy and preprosthesis time, had a survival of 20%. Hence any improvement in survival is an improvement in prognosis. In our institution tumour staging is done with the help of Chest x ray and bone scan due to financial constraints. CT Thorax is a confirmatory investigation for decision between limb-salvage. amputation or no surgery. We also have had patients in whom PET scan and CT scan have missed metastasis. Generally amputation is offered only as a curative operation in non-metastatic lesions and for better quality of life in patients with metastatic disease. Patients with metastatic disease who sustain a pathological fracture are offered palliative surgery.

In our study we noted a overall survival rate of 67% among the patient undergoing multi-modal therapy for osteosarcoma of the proximal tibia or distal femur that are treated with tumour excision and mega-prosthesis. Survival rates of osteosarcoma have been reported from 58 -70%. (1,2,112) and our study also notes survival rates as has been reported in other studies.

We also noted that tumour volume was associated with survival. Various studies have noted different volumes and tried to find any correlation that might be present. Various cut off that have bee used include 150mll(112), 190 ml(105) and 150$cm^{3(121)}$. We found out, among our patients a cut off of 400cm^3 was significantly associated with overall survival, local recurrence and time to local recurrence. We also found that in our patients the tumour volume was significantly high. 11 (27%) patients in this study had a tumour volume greater than 400cm^3. In an earlier study done by Kaste et al a tumour depth of 5 cm was found to be associated with over all survival. In our study we

noted a tumour depth of 7 cm to be significantly associated with survival.(121)

Many earlier studies have shown that a positive tumour margin was associated with tumour recurrence and poor survival.(104,116) Some studies found that positive tumour margin was associated increased risk of local recurrence.(117,124) Another study noted that amputation did not affect the outcomes in patient who were found to have positive surgical margins.(118) Thus the role of margins though well proven in earlier is still being evaluated for better understanding of its role. In our study we did not find any association between tumour margin and over all survival or recurrence of the tumour. In our study we had 12 patients who had positive margins.

Tumour necrosis after chemotherapy has been found to have prognostic significance in many studies and it use as to tool to prognosticate outcome in osteosarcoma.(101,104,112,125) But in our study we found that though it was associated with survival the association did not reach statistical significance. This may be because of the small number of patients we had while dividing into subgroups. Another factor is that most of the tumours were large in size. 27 patients had tumour volume that was more that 200 cm^3 and among them 11 of them had volume more than 400cm^3. It has been shown in earlier studies that tumour volume by itself is an independent prognostic factor and this might have played a confounding the role with regards to tumour necrosis.

Histological grade of the tumour has been associated with survival of the patients in osteosarcoma. Traditionally grade I and II are considered to be low grade and grade III and IV are considered as high-grade. The overall survival rate for low grade osteosarcoma is 90%(126,127) while the overall survival rate for high grade osteosarcoma is about 60-70%(1). Low grade osteosarcoma are associated with better outcomes than high grade sarcoma as noted in previous studies. Among our patient we did notice an association between survival and tumour grade with the lower grades having better survival. But this association did not reach statistical significance.

High levels of alkaline phosphatase have been associated with poorer outcomes in patient in

earlier studies.(128,129) They have also been shown to have prognostic significance. In our patients higher level of alkaline phosphatase was associated with decreased over all survival. But this association did not reach statistical significance.

Though osteosarcoma was considered to be a radio-resistant tumour earlier studies have shown that radiotherapy, when employed along with surgery and chemotherapy, decreased the local recurrence and gave better local control of the tumour.(71) In our study we also noted that radiotherapy was associated with decreased local recurrence. There was significant reduction in the number of local recurrences in the patients who under radiotherapy compared to those who did not. But radiotherapy after surgery is associated with increased wound complications. In our study though radiotherapy was associated with increased wound complication, the association did not reach statistical significance.

The mean time for the recurrence of osteosarcoma has been noted to be 11 months.(130) Late recurrence of osteosarcoma has been noted in other studies even after 20 years.(131) In our study we noted that the mean time for local recurrence was 7.5 months. Except for one patient who had a recurrence at 3 years all other patients had local recurrence in the first year in our study. This is in accordance with the notion that most recurrences in osteosarcoma occur in the first year after surgery.(132) We also noted that tumour volume, tumour depth and metastases were found to have significant associated with time to local recurrence of the tumour.

The median time for metastases was reported to be 10 months by Aljubran et al.(133) In our patients we found that the median time to metastasis was 8 months(range 5-26 months).

We also noted that 8 patients included in our study required re-suturing of the wound and 2 of them required re-suturing twice. The indication was necrosis of the wound edges in all the cases. This might be due to large size of the tumours that were associated with those patients. Though re-suturing was associated with higher tumour volumes the association did not reach statistical significance.

Conclusion

Conclusion:

The over all survival of our patients was 67%. Local recurrence of associated with decreased over all survival among our patients. Local recurrence was noted in 20% of our patients. Survival rate and local recurrence were better than what we expected as we considered the large size of the tumour. We found that tumour volume and tumour depth are associated with local recurrence among patients and have significant effect on the over all survival of the tumour. This is well known in earlier studies that have been published. Moreover patients come with larger tumour volumes due to the delay in seeking medical attention and the difficulty in accessing tertiary care centers which offer multi modal treatment for osteosarcoma as most of the secondary care centers offer amputation as the primary treatment option.

Though osteosarcoma is the commonest primary true bone malignancy, mainly affecting the children and adolescents the outcome for osteosarcoma has not significantly improved over the last decade in the western countries.

1) Our study shows comparable clinico-radiological results with regard to local recurrence and survival when compared with the available published literature.

2)Local recurrence of the tumour, tumour volume and tumour depth, radiotherapy, metastasis are significantly associated with over all survival. Tumour volume, tumour depth and radiotherapy are significantly associated with local recurrence. Though the site of tumour and tumour necrosis were associated with over all survival the association did not reach statistical significance.

3)The position of the patella as measured by Blackburne-peel ratio was significantly associated with knee lag noted postoperaviely.

4)We did not find any association between tumour grade and survival or local recurrence. It might be due to reason that 80% of the tumours were high grade tumours.

The introduction of adjuvant chemotherapy increased the survival dramatically but after that the survival of osteosarcoma has plateaued. This is not the case with developing countries as access

to affordable healthcare is still a difficulty. Ours institution is the second tumour center and our series probable has the largest number of large tumours that have been studied. With more researchers studying the genetic basis of osteosarcoma and the molecular pathogenesis, this might help in making the next big leap in tackling osteosarcoma and improving the survival.

Limitations:

In our study the number of patients were small and the number became even smaller when they were divided into subgroups for analysis. Moreover large number of patients included in our study had larger tumour volume that might introduce a bias. Most of the data was collected retrospectively from the inpatient and outpatient records and also from the electronic database. We could not find the survival of all the patients as 5 patients were lost to followup.

Bibliography:

1. Broadhead ML, Clark JCM, Myers DE, Dass CR, Choong PFM. The Molecular Pathogenesis of Osteosarcoma: A Review. Sarcoma. 2011;2011:1–12.

2. Sampo MM, Tarkkanen M, Kivioja AH, Taskinen MH, Sankila R, Böhling TO. Osteosarcoma in Finland from 1971 through 1990: a nationwide study of epidemiology and outcome. Acta Orthop. 2008 Dec;79(6):861–6.

3. Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004. Cancer. 2009;115(7):1531–43.

4. Savage SA, Mirabello L. Using Epidemiology and Genomics to Understand Osteosarcoma Etiology. Sarcoma. 2011 Mar 8;2011:e548151.

5. Goes M. Knochenwachs tum und osteogenes sarckom. Strahlenther 89194-210.
6. Tsuneyoshi M, Dorfman HD. Epiphyseal osteosarcoma: distinguishing features from clear cell chondrosarcoma, chondroblastoma, and epiphyseal enchondroma. Hum Pathol. 1987 Jun;18(6):644–51.

7. Huvos AG. Osteogenic sarcoma of bones and soft tissues in older persons. A clinicopathologic analysis of 117 patients older than 60 years. Cancer. 1986 Apr 1;57(7):1442–9.
8. Ron E. CANCER RISKS FROM MEDICAL RADIATION. Health Phys. 2003 Jul;85(1):47–59.

9. Metayer C, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, et al. Second Cancers Among Long-Term Survivors of Hodgkin's Disease Diagnosed in Childhood and Adolescence. J Clin Oncol. 2000 Jun 12;18(12):2435–43.

10. Bassin EB, Wypij D, Davis RB, Mittleman MA. Age-specific Fluoride Exposure in Drinking Water and Osteosarcoma (United States). Cancer Causes Control. 2006 May 1;17(4):421–8.

11. Gelberg KH, Fitzgerald EF, Hwang SA, Dubrow R. Fluoride exposure and childhood osteosarcoma: a case-control study. Am J Public Health. 1995 Dec;85(12):1678–83.

12. Finkelstein MM, Kreiger N. Radium in drinking water and risk of bone cancer in Ontario youths: a second study and combined analysis. Occup Environ Med. 1996 May;53(5):305–11.

13. Guse CE, Marbella AM, George V, Layde PM. Radium in Wisconsin Drinking Water: An Analysis of Osteosarcoma Risk. Arch Environ Health Int J. 2002 Jul 1;57(4):294–303.

14. Pollak MN, Polychronakos C, Richard M. Insulinlike Growth Factor I: A Potent Mitogen for Human Osteogenic Sarcoma. J Natl Cancer Inst. 1990 Feb 21;82(4):301–5.

15. Lima G a. B, Gomes EMS, Nunes RC, Neto LV, Sieiro AP a. V, Brabo EP, et al. Osteosarcoma and acromegaly: A case report and review of the litereture. J Endocrinol Invest. 2014 Apr 9;29(11):1006–11.

16. Savage SA, Woodson K, Walk E, Modi W, Liao J, Douglass C, et al. Analysis of Genes Critical for Growth Regulation Identifies Insulin-like Growth Factor 2 Receptor Variations with

Possible Functional Significance as Risk Factors for Osteosarcoma. Cancer Epidemiol Biomarkers Prev. 2007 Aug 1;16(8):1667–74.

17. Longhi A, Pasini A, Cicognani A, Baronio F, Pellacani A, Baldini N, et al. Height as a risk factor for osteosarcoma. J Pediatr Hematol Oncol. 2005 Jun;27(6):314–8.

18. Mirabello L, Pfeiffer R, Murphy G, Daw NC, Patiño-Garcia A, Troisi RJ, et al. Height at diagnosis and birth-weight as risk factors for osteosarcoma. Cancer Causes Control. 2011 Jun;22(6):899–908.

19. Hansen MF, Seton M, Merchant A. Osteosarcoma in Paget's Disease of Bone. J Bone Miner Res. 2006 Dec 1;21(S2):P58–63.

20. Marees T, Moll AC, Imhof SM, Boer MR de, Ringens PJ, Leeuwen FE van. Risk of Second Malignancies in Survivors of Retinoblastoma: More Than 40 Years of Follow-up [Internet]. [cited 2015 Jun 27]. Available from: http://jnci.oxfordjournals.org

21. Choong PF, Fernö M, Akerman M, Willén H, Långström E, Gustafson P, et al. Urokinase-plasminogen-activator levels and prognosis in 69 soft-tissue sarcomas. Int J Cancer J Int Cancer. 1996 Aug 22;69(4):268–72.

22. Pillay V, Dass CR, Choong PFM. The urokinase plasminogen activator receptor as a gene therapy target for cancer. Trends Biotechnol. 2007 Jan;25(1):33–9.

23. Husmann K, Muff R, Bolander ME, Sarkar G, Born W, Fuchs B. Cathepsins and osteosarcoma: Expression analysis identifies cathepsin K as an indicator of metastasis. Mol Carcinog. 2008 Jan 1;47(1):66–73.

24. Lamoureux F, Richard P, Wittrant Y, Battaglia S, Pilet P, Trichet V, et al. Therapeutic relevance of osteoprotegerin gene therapy in osteosarcoma: blockade of the vicious cycle between tumor cell proliferation and bone resorption. Cancer Res. 2007 Aug 1;67(15):7308–18.

25. Klein MJ, Siegal GP. Osteosarcoma: anatomic and histologic variants. Am J Clin Pathol. 2006 Apr;125(4):555–81.

26. Unni KK. Osteosarcoma of bone. J Orthop Sci. 1998 Sep;3(5):287–94.

27. Okada K, Hasegawa T, Yokoyama R. Rosette-forming epithelioid osteosarcoma: A histologic subtype with highly aggressive clinical behavior. Hum Pathol. 2001 Jul;32(7):726–33.

28. Unni KK, Dahlin DC, Beabout JW. Periosteal osteogenic sarcoma. Cancer. 1976 May;37(5):2476–85.

29. Wold LE, Unni KK, Beabout JW, Sim FH, Dahlin DC. Dedifferentiated parosteal osteosarcoma. J Bone Joint Surg Am. 1984 Jan;66(1):53–9.

30. Bertoni F, Bacchini P, Staals EL, Davidovitz P. Dedifferentiated parosteal osteosarcoma: the experience of the Rizzoli Institute. Cancer. 2005 Jun 1;103(11):2373–82.

31. Jaffe HL. Intracortical osteogenic sarcoma. Bull Hosp Joint Dis. 1960 Oct;21:189–97.

32. Picci P, Gherlinzoni F, Guerra A. Intracortical osteosarcoma: Rare entity or early manifestation of classical osteosarcoma? Skeletal Radiol. 1983 May;9(4):255–8.

33. Widhe B, Widhe T. Initial Symptoms and Clinical Features in Osteosarcoma and Ewing Sarcoma*. J Bone Jt Surg. 2000 May 1;82(5):667–667.

34. Angela Rech. Clinical features in osteosarcoma and prognostic implications. J Pediatr (Rio J). 80:65–70.

35. Aisen A, Martel W, Braunstein E, McMillin K, Phillips W, Kling T. MRI and CT evaluation of primary bone and soft-tissue tumors. Am J Roentgenol. 1986 Apr 1;146(4):749–56.

36. Bajpai J, Gamnagatti S, Kumar R, Sreenivas V, Sharma MC, Khan SA, et al. Role of MRI in osteosarcoma for evaluation and prediction of chemotherapy response: correlation with histological necrosis. Pediatr Radiol. 2010 Oct 27;41(4):441–50.

37. Wang C-S, Du L-J, Si M-J, Yin Q-H, Chen L, Shu M, et al. Noninvasive Assessment of Response to Neoadjuvant Chemotherapy in Osteosarcoma of Long Bones with Diffusion-Weighted Imaging: An Initial In Vivo Study. Loeb D, editor. PLoS ONE. 2013 Aug 26;8(8):e72679.

38. Gillespy T, Manfrini M, Ruggieri P, Spanier SS, Pettersson H, Springfield DS. Staging of intraosseous extent of osteosarcoma: correlation of preoperative CT and MR imaging with pathologic macroslides. Radiology. 1988 Jun 1;167(3):765–7.

39. Schima W, Amann G, Stiglbauer R, Windhager R, Kramer J, Nicolakis M, et al. Preoperative staging of osteosarcoma: efficacy of MR imaging in detecting joint involvement. Am J Roentgenol. 1994 Nov 1;163(5):1171–5.

40. Becher S, Oskouei S. PET Imaging in Sarcoma. Orthop Clin North Am. 2015 Jul;46(3):409–15.

41. Brenner W, Bohuslavizki KH, Eary JF. PET Imaging of Osteosarcoma. J Nucl Med. 2003 Jun 1;44(6):930–42.

42. Bielack S, Carrle D, Casali PG, Group O behalf of the EGW. Osteosarcoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009 May 1;20(suppl 4):iv137–9.

43. Bacci G, Longhi A, Ferrari S, Lari S, Manfrini M, Donati D, et al. Prognostic significance of serum alkaline phosphatase in osteosarcoma of the extremity treated with neoadjuvant chemotherapy: recent experience at Rizzoli Institute. Oncol Rep. 2002 Feb;9(1):171–5.

44. Levine AM, Rosenberg SA. Alkaline phosphatase levels in osteosarcoma tissue are related to prognosis. Cancer. 1979 Dec;44(6):2291–3.

45. Yang Z, Huo Y, Sun G, Li J, Li X. Measurement of bone alkaline phosphatase and relative study with osteosarcoma. Front Med China. 2007 Feb 1;1(1):54–7.

46. Mankin HJ, Mankin CJ, Simon MA. The Hazards of the Biopsy, Revisited. For the Members of the Musculoskeletal Tumor Society*. J Bone Jt Surg Am. 1996 May 1;78(5):656–63.

47. Mankin HJ, Lange TA, Spanier SS. The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J Bone Jt Surg Am. 1982 Oct 1;64(8):1121–7.

48. Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF. Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol. 1997 Aug;4(5):425–31.

49. Clark CR, Morgan C, Sonstegard DA, Matthews LS. The effect of biopsy-hole shape and size on bone strength. J Bone Joint Surg Am. 1977 Mar;59(2):213–7.

50. Kilpatrick SE, Ward WG, Bos GD, Chauvenet AR, Gold SH. The role of fine needle aspiration biopsy in the diagnosis and management of osteosarcoma. Pediatr Pathol Mol Med. 2001 Jun;20(3):175–87.

51. Söderlund V, Skoog L, Unni KK, Bertoni F, Brosjö O, Kreicbergs A. Diagnosis of High-Grade Osteosarcoma by Radiology and Cytology: A Retrospective Study of 52 Cases. Sarcoma. 2004;8(1):31–6.

52. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop. 1980 Dec;(153):106–20.

53. Tate R a, Gerrand C a, Hale J b. Tibial turn-up procedure as an alternative to rotationplasty in a 4-year-old with osteosarcoma of the distal femur. [Miscellaneous Article]. J Pediatr Orthop B. 2015 Jan;24(1):50–5.

54. Wieder HS, Nicholson JT. Total Resection of Femur with “Turn-up Plasty” of Tibia and Prosthetic Replacement of Hip Joint. Ann Surg. 1956 Aug;144(2):271–6.

55. Rizzo RL, Matsumoto T. Above vs. below knee amputations: a retrospective analysis. Int Surg. 1980 Jun;65(3):265–7.

56. Van Nes CP. 12.full-text.pdf. Rotat-Plasty Congenit Defects Femur Mak Use Shortened Limb Control Knee Jt Prosthes. 1950;(32B):12–6.

57. Lindner NJ, Ramm O, Hillmann A, Roedl R, Gosheger G, Brinkschmidt C, et al. Limb salvage and outcome of osteosarcoma. The University of Muenster experience. Clin Orthop. 1999 Jan;(358):83–9.

58. Simon MA, Aschliman MA, Thomas N, Mankin HJ. Limb-salvage treatment versus amputation for osteosarcoma of the distal end of the femur. J Bone Joint Surg Am. 1986 Dec;68(9):1331–7.

59. Sluga M, Windhager R, Lang S, Heinzl H, Bielack S, Kotz R. Local and systemic control after ablative and limb sparing surgery in patients with osteosarcoma. Clin Orthop. 1999 Jan; (358):120–7.

60. Khattak MJ, Umer M, Haroon-ur-Rasheed null, Umar M. Autoclaved tumor bone for reconstruction: an alternative in developing countries. Clin Orthop. 2006 Jun;447:138–44.

61. Umer M, Umer HM, Qadir I, Rashid H, Awan R, Askari R, et al. Autoclaved Tumor Bone for Skeletal Reconstruction in Paediatric Patients: A Low Cost Alternative in Developing Countries,

Autoclaved Tumor Bone for Skeletal Reconstruction in Paediatric Patients: A Low Cost Alternative in Developing Countries. BioMed Res Int BioMed Res Int. 2013 Dec 18;2013, 2013:e698461.

62. Germain MA, Dubousset J, Mascard E, Kalifa C. [Vascularized peroneal reconstruction after bloc resection of tumors or congenital malformations of the upper limb in children]. Bull Académie Natl Médecine. 2000;184(8):1671–84; discussion 1685–6.

63. Malizos KN, Zalavras CG, Soucacos PN, Beris AE, Urbaniak JR. Free vascularized fibular grafts for reconstruction of skeletal defects. J Am Acad Orthop Surg. 2004 Oct;12(5):360–9.

64. Marulanda GA, Henderson ER, Johnson DA, Letson GD, Cheong D. Orthopedic surgery options for the treatment of primary osteosarcoma. Cancer Control J Moffitt Cancer Cent. 2008 Jan;15(1):13–20.

65. Marulanda GA, Henderson ER, Palumbo BT, Alexander GE, Cheong D, Letson GD. Use of extendable prostheses: a limb-salvaging alternative for patients with malignant bone tumors. Expert Rev Med Devices. 2008 Jul;5(4):467–74.

66. Kendall SJ, Singer GC, Briggs TW, Cannon SR. A functional analysis of massive knee replacement after extra-articular resections of primary bone tumors. J Arthroplasty. 2000 Sep;15(6):754–60.

67. Grimer RJ, Carter SR, Tillman RM, Sneath RS, Walker PS, Unwin PS, et al. Endoprosthetic replacement of the proximal tibia. J Bone Joint Surg Br. 1999 May;81(3):488–94.

68. Shimose S, Sugita T, Kubo T, Matsuo T, Ochi M. Reconstructed Patellar Tendon Length after Proximal Tibia Prosthetic Replacement. Clin Orthop. 2005 Oct;439:176–80.

69. Bickels J, Wittig JC, Kollender Y, Neff RS, Kellar-Graney K, Meller I, et al. Reconstruction of the extensor mechanism after proximal tibia endoprosthetic replacement. J Arthroplasty. 2001 Oct;16(7):856–62.

70. Titus V, Clayer M. Protecting a Patellar Ligament Reconstruction after Proximal Tibial Resection: A Simplified Approach. Clin Orthop. 2008 Jul;466(7):1749–54.

71. Schwarz R, Bruland O, Cassoni A, Schomberg P, Bielack S. The role of radiotherapy in oseosarcoma. Cancer Treat Res. 2009;152:147–64.

72. Ozaki T, Flege S, Kevric M, Lindner N, Maas R, Delling G, et al. Osteosarcoma of the Pelvis: Experience of the Cooperative Osteosarcoma Study Group. J Clin Oncol. 2003 Jan 15;21(2):334–41.

73. Franzius C, Bielack S, Flege S, Eckardt J, Sciuk J, Jürgens H, et al. High-activity samarium-153-EDTMP therapy followed by autologous peripheral blood stem cell support in unresectable osteosarcoma. Nukl Nucl Med. 2001 Dec;40(6):215–20.

74. High-Dose Samarium-153 Ethylene Diamine Tetramethylene Phosphonate: Low Toxicity of Skeletal Irradiation in Patients With Osteosarcoma and Bone Metastases [Internet]. [cited 2015 Sep 28]. Available from: http://jco.ascopubs.org/content/20/7/1953.full?ijkey=55382f02bee985a694fbe09354605c5292d4196d&keytype2=tf_ipsecsha

75. Bacci G. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. Ann Oncol. 2003 Jul 1;14(7):1126–34.

76. Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S, Goodnight J. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol. 1987 Jan 1;5(1):21–6.

77. Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med. 1986 Jun 19;314(25):1600–6.

78. Goorin AM, Schwartzentruber DJ, Devidas M, Gebhardt MC, Ayala AG, Harris MB, et al. Presurgical Chemotherapy Compared With Immediate Surgery and Adjuvant Chemotherapy for Nonmetastatic Osteosarcoma: Pediatric Oncology Group Study POG-8651. J Clin Oncol. 2003 Apr 15;21(8):1574–80.

79. Carrle D, Bielack SS. Current strategies of chemotherapy in osteosarcoma. Int Orthop. 2006 Aug 3;30(6):445–51.

80. Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, Huvos AG. Primary osteogenic sarcoma. The rationale for preoperative chemotherapy and delayed surgery. Cancer. 1979 Jun 1;43(6):2163–77.

81. Jaffe N, Carrasco H, Raymond K, Ayala A, Eftekhari F. Can cure in patients with osteosarcoma be achieved exclusively with chemotherapy and abrogation of surgery? Cancer. 2002 Nov 15;95(10):2202–10.

82. Kager L, Zoubek A, Pötschger U, Kastner U, Flege S, Kempf-Bielack B, et al. Primary Metastatic Osteosarcoma: Presentation and Outcome of Patients Treated on Neoadjuvant Cooperative Osteosarcoma Study Group Protocols. J Clin Oncol. 2003 May 15;21(10):2011–8.

83. Briccoli A, Rocca M, Salone M, Guzzardella GA, Balladelli A, Bacci G. High grade osteosarcoma of the extremities metastatic to the lung: long-term results in 323 patients treated combining surgery and chemotherapy, 1985-2005. Surg Oncol. 2010 Dec;19(4):193–9.

84. Ferrari S, Briccoli A, Mercuri M, Bertoni F, Picci P, Tienghi A, et al. Postrelapse Survival in Osteosarcoma of the Extremities: Prognostic Factors for Long-Term Survival. J Clin Oncol. 2003 Feb 15;21(4):710–5.

85. Xiao X, Wang W, Wang Z. The role of chemotherapy for metastatic, relapsed and refractory osteosarcoma. Paediatr Drugs. 2014 Dec;16(6):503–12.

86. He A, Qi W, Huang Y, Sun Y, Shen Z, Zhao H, et al. Comparison of pirarubicin-based versus gemcitabine-docetaxel chemotherapy for relapsed and refractory osteosarcoma: a single institution experience. Int J Clin Oncol. 2013 Jun;18(3):498–505.

87. Bielack SS, Kempf-Bielack B, Branscheid D, Carrle D, Friedel G, Helmke K, et al. Second and Subsequent Recurrences of Osteosarcoma: Presentation, Treatment, and Outcomes of 249

Consecutive Cooperative Osteosarcoma Study Group Patients. J Clin Oncol. 2009 Feb 1;27(4):557–65.

88. Grimer RJ, Cannon SR, Taminiau AM, Bielack S, Kempf-Bielack B, Windhager R, et al. Osteosarcoma over the age of forty. Eur J Cancer Oxf Engl 1990. 2003 Jan;39(2):157–63.

89. Mankin HJ, Hornicek FJ. Paget's sarcoma: a historical and outcome review. Clin Orthop. 2005 Sep;438:97–102.

90. Anagnostakos K, Lorbach O, Reiter S, Kohn D. Comparison of five patellar height measurement methods in 90° knee flexion. Int Orthop. 2011 Dec;35(12):1791–7.

91. Berg EE, Mason SL, Lucas MJ. Patellar Height Ratios A Comparison of Four Measurement Methods. Am J Sports Med. 1996 Mar 1;24(2):218–21.

92. Rogers BA, Thornton-Bott P, Cannon SR, Briggs TWR. Interobserver variation in the measurement of patellar height after total knee arthroplasty. J Bone Joint Surg Br. 2006 Apr 1;88-B(4):484–8.

93. Wu X, Cai Z, Chen Z, Yao Z, Zhang G. A Preliminary Evaluation of Limb Salvage Surgery for Osteosarcoma around Knee Joint. PLoS ONE. 2012 Mar 23;7(3):e33492.

94. Shehadeh A, Noveau J, Malawer M, Henshaw R. Late Complications and Survival of Endoprosthetic Reconstruction after Resection of Bone Tumors. Clin Orthop Relat Res. 2010 Jul 13;468(11):2885–95.

95. Racano A, Pazionis T, Farrokhyar F, Deheshi B, Ghert M. High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. Clin Orthop. 2013 Jun;471(6):2017–27.

96. Tiwari A, Jain S, Mehta S, Kumar R, Kapoor G, Kumar K. Limb salvage surgery for osteosarcoma: Early results in Indian patients. Indian J Orthop. 2014;48(3):266–72.

97. Jeys LM, Grimer RJ, Carter SR, Tillman RM. Periprosthetic infection in patients treated for an orthopaedic oncological condition. J Bone Joint Surg Am. 2005 Apr;87(4):842–9.

98. Graci C, Maccauro G, Muratori F, Spinelli MS, Rosa MA, Fabbriciani C. Infection following Bone Tumor Resection and Reconstruction with Tumoral Prostheses: A Literature Review. Int J Immunopathol Pharmacol. 2010 Oct 1;23(4):1005–13.

99. Hardes J, Gebert C, Schwappach A, Ahrens H, Streitburger A, Winkelmann W, et al. Characteristics and outcome of infections associated with tumor endoprostheses. Arch Orthop Trauma Surg. 2006 Apr 21;126(5):289–96.

100. Bickels J, Wittig JC, Kollender Y, Henshaw RM, Kellar-Graney KL, Meller I, et al. Distal femur resection with endoprosthetic reconstruction: a long-term followup study. Clin Orthop. 2002 Jul;(400):225–35.

101. Bacci G, Ferrari S, Lari S, Mercuri M, Donati D, Longhi A, et al. Osteosarcoma of the limb. Amputation or limb salvage in patients treated by neoadjuvant chemotherapy. J Bone Joint Surg Br. 2002 Jan;84(1):88–92.

102. Rastogi S. Limb salvage In osteogenic Sarcoma: An Indian Perspective. Indian Journal of Medical and Paediatric Oncology [Internet]. 2004 [cited 2014 Dec 8];25. Available from: http://medind.nic.in/ias/t04/s2/iast04s2p46g.pdf

103. Bacci G, Ferrari S, Bertoni F, Ruggieri P, Picci P, Longhi A, et al. Long-Term Outcome for Patients With Nonmetastatic Osteosarcoma of the Extremity Treated at the Istituto Ortopedico Rizzoli According to the Istituto Ortopedico Rizzoli/Osteosarcoma-2 Protocol: An Updated Report. J Clin Oncol. 2000 Dec 15;18(24):4016–27.

104. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol Off J Am Soc Clin Oncol. 2002 Feb 1;20(3):776–90.

105. Smeland S, Wiebe T, Böhling T, Brosjö O, Jonsson K, Alvegård TA. Chemotherapy in osteosarcoma. The Scandinavian Sarcoma Group experience. Acta Orthop Scand Suppl. 2004 Apr;75(311):92–8.

106. Janeway KA, Barkauskas DA, Krailo MD, Meyers PA, Schwartz CL, Ebb DH, et al. Outcome for adolescent and young adult patients with osteosarcoma: a report from the Children's Oncology Group. Cancer. 2012 Sep 15;118(18):4597–605.

107. Levine AM, Rosenberg SA. Alkaline phosphatase levels in osteosarcoma tissue are related to prognosis. Cancer. 1979 Dec;44(6):2291–3.

108. Kim MS, Lee S-Y, Cho WH, Song WS, Koh J-S, Lee JA, et al. Initial tumor size predicts histologic response and survival in localized osteosarcoma patients. J Surg Oncol. 2008 Apr 1;97(5):456–61.

109. Kaste SC, Liu T, Billups C a., Daw N c., Pratt C b., Meyer W h. Tumor size as a predictor of outcome in pediatric non-metastatic osteosarcoma of the extremity. Pediatr Blood Cancer. 2004 Dec 1;43(7):723–8.

110. Bieling P, Rehan N, Winkler P, Helmke K, Maas R, Fuchs N, et al. Tumor size and prognosis in aggressively treated osteosarcoma. J Clin Oncol Off J Am Soc Clin Oncol. 1996 Mar;14(3):848–58.

111. Rehan N, Bieling P, Winkler P, Helmke K, Maas R, Baldini N, et al. Die prognostische Bedeutung des Tumorvolumens beim Osteosarkom unter neoadjuvanter Chemotherapie. Klin Pädiatr. 1993 Jul;205(04):200–9.

112. Bacci G, Bertoni F, Longhi A, Ferrari S, Forni C, Biagini R, et al. Neoadjuvant chemotherapy for high-grade central osteosarcoma of the extremity: Histologic response to preoperative chemotherapy correlates with histologic subtype of the tumor. Cancer. 2003 Jun 15;97(12):3068–75.

113. Picci P, Bacci G, Campanacci M, Gasparini M, Pilotti S, Cerasoli S, et al. Histologic evaluation of necrosis in osteosarcoma induced by chemotherapy regional mapping of viable and nonviable tumor. Cancer. 1985 Oct 1;56(7):1515–21.

114. Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, Cacavio A, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer. 1982 Mar 15;49(6):1221–30.

115. Picci P, Sangiorgi L, Rougraff BT, Neff JR, Casadei R, Campanacci M. Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. J Clin Oncol Off J Am Soc Clin Oncol. 1994 Dec;12(12):2699–705.

116. Kong C-B, Song WS, Cho WH, Oh JM, Jeon D-G. Local recurrence has only a small effect on survival in high-risk extremity osteosarcoma. Clin Orthop. 2012 May;470(5):1482–90.

117. R J Grimer AMT. Surgical outcomes in osteosarcoma. J Bone Joint Surg Br. 2002;84(3):395–400.

118. Reddy KIA, Wafa H, Gaston CL, Grimer RJ, Abudu AT, Jeys LM, et al. Does amputation offer any survival benefit over limb salvage in osteosarcoma patients with poor chemonecrosis and close margins? Bone Jt J. 2015 Jan;97-B(1):115–20.

119. Peabody TD, Gibbs CP, Simon MA. Evaluation and staging of musculoskeletal neoplasms. J Bone Joint Surg Am. 1998 Aug;80(8):1204–18.

120. Göbel V, Jürgens H, Etspüler G, Kemperdick H, Jungblut RM, Stienen U, et al. Prognostic significance of tumor volume in localized Ewing's sarcoma of bone in children and adolescents. J Cancer Res Clin Oncol. 1987 Apr;113(2):187–91.

121. Kaste SC, Liu T, Billups C a., Daw N c., Pratt C b., Meyer W h. Tumor size as a predictor of outcome in pediatric non-metastatic osteosarcoma of the extremity. Pediatr Blood Cancer. 2004 Dec 1;43(7):723–8.

122. Turan S, Topcu B, Gökçe I, Güran T, Atay Z, Omar A, et al. Serum Alkaline Phosphatase Levels in Healthy Children and Evaluation of Alkaline Phosphatasez-scores in Different Types of Rickets. J Clin Res Pediatr Endocrinol. 2011 Mar;3(1):7–11.

123. Gracitelli GC, Pierami R, Tonelli TA, Falótico GG, Silva FD, Nakama GY, et al. Assessment of patellar height measurement methods from digital radiography. Rev Bras Ortop. 2012 Apr;47(2):210–3.

124. Bertrand TE, Cruz A, Binitie O, Cheong D, Letson GD. Do Surgical Margins Affect Local Recurrence and Survival in Extremity, Nonmetastatic, High-grade Osteosarcoma? Clin Orthop. 2015 May 27;

125. Li X, Ashana AO, Moretti VM, Lackman RD. The relation of tumour necrosis and survival in patients with osteosarcoma. Int Orthop. 2011 Feb 26;35(12):1847–53.

126. Menna C, Grimer RJ, Carter SR, Tillman RM, Abudu A, Jeys L. Low Grade Central Osteosarcoma – Difficult to Diagnose, Easy to Treat! J Bone Joint Surg Br. 2011 Jan 1;93-B(SUPP I):81–81.

127. Malhas AM, Sumathi VP, James SL, Menna C, Carter SR, Tillman RM, et al. Low-Grade Central Osteosarcoma: A Difficult Condition to Diagnose, Low-Grade Central Osteosarcoma: A

Difficult Condition to Diagnose. Sarcoma Sarcoma. 2012 Jul 16;2012, 2012:e764796.

128. Bacci G, Picci P, Ferrari S, Orlandi M, Ruggieri P, Casadei R, et al. Prognostic significance of serum alkaline phosphatase measurements in patients with osteosarcoma treated with adjuvant or neoadjuvant chemotherapy. Cancer. 1993 Feb 15;71(4):1224–30.

129. Bacci G, Longhi A, Ferrari S, Lari S, Manfrini M, Donati D, et al. Prognostic significance of serum alkaline phosphatase in osteosarcoma of the extremity treated with neoadjuvant chemotherapy: Recent experience at Rizzoli Institute. Oncol Rep [Internet]. 2002 Jan 1 [cited 2015 Sep 28]; Available from: http://www.spandidos-publications.com/10.3892/or.9.1.171

130. Glasser DB, Lane JM, Huvos AG, Marcove RC, Rosen G. Survival, prognosis, and therapeutic response in osteogenic sarcoma. The Memorial Hospital experience. Cancer. 1992 Feb 1;69(3):698–708.

131. Lau TW, Wong JWK, Yip DKH, Chien EP, Shek TWH, Wong LLS. Local recurrence of parosteal osteosarcoma adjacent to a prosthesis after 20 years: a case report. J Orthop Surg Hong Kong. 2004 Dec;12(2):263–6.

132. Ellegast J, Barth TFE, Schulte M, Bielack SS, Schmid M, Mayer-Steinacker R. Metastasis of Osteosarcoma After 16 Years. J Clin Oncol. 2011 Jan 20;29(3):e62–6.

133. Aljubran AH, Griffin A, Pintilie M, Blackstein M. Osteosarcoma in adolescents and adults: survival analysis with and without lung metastases. Ann Oncol. 2009 Jun 1;20(6):1136–41.

ANNEXURES

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Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
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Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC	Internal, Clinician
Dr. Jacob John	MBBS, MD	Associate Professor, Community health	Internal, Clinician
Dr. Rajesh Kannangai	MD, Ph D.	Professor & In-charge Retrovirus Laboratory (NRL under NACO), Department of Clinical Virology, CMC, Vellore	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Simon Pavamani	MBBS, MD,	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Dept of Biostatistics, CMC, Vellore	Internal, Statistician
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
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Mrs. Sheela Durai	MSc Nursing	Addl. Deputy Nursing Superintendent, Professor of Nursing in Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. C. Sampath	BSc, BL	Legal Expert, Vellore	External, Legal Expert
Rev. Joseph Devaraj	B. Sc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. Nihal Thomas,	MD, MNAMS, DNB(Endo), FRACP(Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

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January 21, 2015

Dr. Kathir Joyson D. R
PG Registrar
Department of Orthopedics
Christian Medical College, Vellore 632 004

Sub: **Fluid Research Grant Project:**
To calculate the reduction in local recurrence rate of Osteosarcoma of knee (distal femur or proximal) tibia by using newer techniques.
Dr. Kathir Joyson D. R, Dr. V. T. K. Titus, Orthopedics, CMC, Vellore.

Ref: IRB Min No: 9206 [OBSERVE] dated 08.12.2014

Dear Dr. Kathir Joyson D. R,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "To calculate the reduction in local recurrence rate of Osteosarcoma of knee (distal femur or proximal) tibia by using newer techniques." on December 08th 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Kathir Joyson D. R, V. T. K. Titus
3. Informed Consent form (English, Hindi, Telugu & Bengali)
4. Information Sheet (English, Hindi, Telugu & Bengali)
5. Proforma
6. No of documents 1-5

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on December 08th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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Participant information sheet

This study is being carried out by the Orthopedics Unit II, Christian Medical College Hospital, Vellore. It is being conducted by Dr. Kathir Joyson under the guidance of Dr. V. T. K. Titus. Recurrence of tumour after the tumour resection surgery is a known complication. By this study we are trying to find the efficacy of the techniques that are currently being followed in the department of Orthopedics II to reduce the chance of tumour coming back. The patient as per his usual treatment plan undergoes tumor operation in which the knee with cancer is replaced with metal knee after excision of the tumor. After the operation the patient will be required to follow-up regularly as advised as per the usual follow up plan for all patients undergoing such operations to look for any local recurrence or metastasis. While on follow up the patient will be asked about his ability to do the day to day activities. Moreover the data from the MRI, X ray and clinical records will be accessed . All data collected as a part of this study will be kept confidential and will be used only for research purposes. The patient can willingly take part in the study and can also decide against doing so at his/her own will.

Does this study put the patient at any increased risk for complication?

No. In this study we observe the patient as he goes through his treatment and look at his outcome. This study does not modify the patient's treatment plan in any way.

Can the patient withdraw from the study after it starts?

The patient is free to withdraw from the study at any time he feels to do so. It will not have any bearing on the treatment he receives from the caregivers and he will continue to get the best possible care required for his condition in our hospital.

Is there any extra cost involved in taking part in the study?

There is no extra cost in taking part in the study. The patient will undergo the routine investigations required for his condition and if any additional investigations are required as a part of the study it will be done free of cost for the patient.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

For doubts and queries:

Orthopedics II office,
Department of Orthopedics,
Paul brand building 1st floor,
CMCH Vellore. Phone:04162282091

பங்கேற்பவர் தகவல் படிவம்

இந்த ஆராய்ச்சி கிறிஸ்தவ மருத்துவர் கல்லூரியில் உள்ள எலும்புமூட்டு பிரிவு II - ஆல் நடத்தபடுகிறது. இவ்வாராய்ச்சி மருத்துவர் V. T. K. டைடஸ் அவர்களின் வழிகாட்டுதலின் கீழ் மருத்துவர் கதிர் ஜாய்சன் - ஆல் நடத்தப்படுகிறது. கால்முட்டின் புற்றுநோய்க்கான அறுவை சிகிச்சைக்கு பின், புற்றுநோய் கட்டி மீண்டும் உருவாகுவது அறியப்பட்ட சிக்கல்களில் ஒன்றே. இவ்வாறு கட்டி மீண்டும் உருவாகாமல் இருக்க சில புதிய நுட்பங்கள் இப்பொழுது பயன்படுத்தப்பட்டு வருகின்றன. இந்த ஆராய்ச்சியின் மூலம் இப்புதிய நுட்பங்களின் திறனை கண்டறிய முற்படுகிறோம்.

புற்றுநோயில் முட்டு மாற்று அறுவை சிகிச்சையின்பொது நோயாளியின் மூட்டு மாற்றப்பட்டு உலோக மூட்டு பொருத்தபடுகிறது. அறுவை சிகிச்சை முடிந்தபின் நோயாளி வழக்கமான முறையின் படி மருத்துவரை தொடர்ந்து வந்து சந்திக்க வேண்டும். இந்த சந்திப்பின் பொது நோயாளியிடம் அனுதின செயல்பாடுகள் குறித்தும் அதில் ஏற்படும் தடங்கல்களை குறித்தும் தகவல்கள் சேகரிக்கப்படும். மேலும் MRI, எக்ஸ்ரே மற்றும் மருத்துவ பதிவேடுகள் இந்த ஆராய்ச்சிக்கு பயன் படுத்தப்படும். இவ்வாறு சேகரிக்கும் தகவல்கள் அனைத்தும் இவ்வாராய்ச்சிக்கு மட்டுமே பயன்படுத்தப்படும். மேலும் இவை இரகசியமாக பாதுகாக்கப்படும். இந்த ஆராய்ச்சியில் நோயாளி தங்கள் சொந்த விருப்பத்தின் பேரில் பங்குகொள்ளவோ விலகிகொள்ளவோ முடியும்.

இவ்வராய்ட்சியினால் ஏதேனும் பின் விளைவுகள் வர வாய்ப்புள்ளதா?

இவ்வராய்ட்சியினால் பின் விளைவுகள் எதுவும் வராது. இவ்வராய்ட்சியினால் மருத்துவ சிகிட்சையில மாற்றங்கள் எதுவும் செய்யப்பட மாட்டாது.

இவ்வராய்ட்சியினால் கூடுதல் செலவினம் எதாவது வருமா?

இல்லை. பொதுவாக செய்யப்பட்டும் பரிசோதனைகள் தவிர்த்து வேறு பரிசோதனைகள் செய்யும் நிலை உருவானால் அவை இலவசமாக செய்யப்படும்.

இவ்வராய்ட்சியில் சேர்ந்த பின்னர் விலகிக்கொள்ளலாமா?

இவ்வராய்ட்சியிலிருந்து சொந்த விருப்பத்தின் பேரில் எஃபொழுது வேண்டுமானாலும் விலகி கொள்ளலாம். இதனால் மருத்துவ சிகிட்சை எந்த விதத்திலும் பாதிக்கப்படாது.

மேலும் விவரங்களுக்கு:

எலும்புமூட்டு பிரிவு II அலுவலகம்,
எலும்புமூட்டு துறை,
பால் பிராண்ட் கட்டடம் - முதல் மாடி ,
கிறிஸ்தவ மருத்துவ கல்லூரி மருத்துவமனை, வேலூர்.

Informed Consent form

Patient's Name: _____

Hospital No. _____

(i) I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signatory's name: Date: _____/_____/_____	Signature (or Thumb impression) of the Subject/Legally Acceptable
Stydy investigator's Name Date: _____/_____/_____	Signature of the Investigator:
Name of the Witness: Date: _____/_____/_____	Signature (or Thumb impression) of the Witness:

ஒப்புதல் படிவம்

நோயாளியின் பெயர்:
மருத்துவமனை எண்:

(i) மேலே உள்ள ஆய்வு தகவல் தாளை நான் படித்து புரிந்து கொண்டேன் என்றும் கேள்விகள் கேட்க வாய்ப்பு கிடைத்தது என்று உறுதி செய்கிறேன்.[ ]

(ii) இந்த ஆய்வில் பங்கேற்பது என் விருப்பம் என்றும், நான் எந்த நேரத்திலும் எந்த காரணமும் கொடுக்காமல், என் மருத்துவ தேவைகள் மற்றும் சட்ட உரிமைகள் பாதிக்காமல் விலகிக்கொள்ள முடியும் என்று புரிந்துகொள்கிறேன்.[ ]

(iii) நெறிமுறைகள் குழு மற்றும் கட்டுப்பாட்டு அதிகாரிகள் தற்போதைய ஆய்விற்க்கும் மேலும் எதிர்கால ஆராய்ச்சிகள் தொடர்பாக என் மருத்துவ பதிவுகளை பார்க்க என் அனுமதி தேவையில்லை என்று புரிந்துகொள்கிறேன். நான் இந்த அணுகலுக்கு ஒப்புக்கொள்கிறேன். எனினும், என் அடையாளம் மூன்றாவது நபர்களுக்கு வெளியிடப்படாது என்பதை புரிந்துகொண்டேன்.[ ]

(iv) இந்த ஆய்வில் எழும் எந்த முடிவுகளை நான் அறிவியல் நோக்கத்திற்காக பயன்படுத்த எனக்கு தடை இல்லை.[ ]

(v) இந்த ஆய்வில் பங்கேற்க நான் ஏற்கிறேன்.[ ]

பெயர்:
தேதி:
கையொப்பம்/அல்லது கைநாட்டு:

விசாரணை செய்பவரின் பெயர்:
தேதி:
கையொப்பம்:

சாட்சியின் பெயர்:
தேதி:
கையொப்பம்:

Nam	AGE	SEX	Hospita	ALIV	Time o	ALP	AL	Previous	BPTP	BPPP	BPM	wire	TWI	DEG	diag	date of s	Grade	FEM	TIBL	FERE	TIB R	IMFE	IM TI	CEMF	CEM	Marg	TN	TN co	TIME	Resu	WOUN	LR	TIM	MET	TIM	FLA	AMP	REA	MUA	REV	REAS
MD	34	M	583055	A		75	N	23/01/14				NA		40,20	PT	###	HIGH		35.4		10.4		8.1		5.7	C	20	Poor	5Y3M	0	0	0				0	0		0	1	IMPF
ANC	24	M	678410	A		133	H	04/08/15	32.8	39.8	24	NA		30,50	DF	###	HIGH	51.7		18.8		13.4		12.9		C	40	Poor	5Y	0	0					0	0		0	1	ASL
JAY	49	F	700654	A		50	N	31/05/13	1.6	24.5	4	IA		30	DF	###	IG	12.7		17.3		10.9		9.9		C	no ch	9999	5Y	0	0	1	35			0	1	LR	1	0	
SUD	22	M	723662	D	11/12	396	H	07/02/11	16.6	35.8	2	NA		30, 40	DF	###	HIGH	50.5		17.1		11.6			13	C	30-40	Poor	4Y10	0	0	1	3			0	0		0	0	
SUF	15	M	726260	A		211	N	09/12/14	2.5	33.9	14	NA		50,30	DF	###	HIGH	46.3		17.4		11.6		9.6		C	70	Poor	4Y8M	0	0					0	0		0	1	IMPF
ALP	45	F	807085	NC		77	N	14/01/13	20.5	34.2	1D	NA		30,50	DF	02/11/10	IG	42.6		16.3		13.1		9.4		A	99	Good	4Y7M	0	0					0	0		0	0	
RAS	23	M	827477	D	09/12	305	H	08/04/11	6.4	35	5	I		30	PT	###	UNKNOWN	9999		13.8		12.1		###	C	60-70	Poor	4Y6M	0	0	0		LM	6	0	0		0	0	
KAN	24	M	804878	NC		205	H	26/09/11				NA		50	DF	18/01/11	HIGH	51		18.7		18		7.2		C	95	Good	4Y5M	0	0	0				0	0		0	0	
DIP	39	F	823177	A		76	N	19/03/11	33	28.3	1D	NA		30	DF	01/03/11	IG	9999		15.3		13.9		3.5		M	no ch	9999	4Y3M	0	0	0				0	0		0	0	
SAI	61	M	891986	A		78	N	02/04/13	23.3	36.2	3	NA		30	DF	17/03/11	HIGH	9999		13.6		15.5		9999		MLI	no ch	9999	4Y3M	0	1	0				1	0		0	0	
MOI	21	M	889750	D	02/12	285	H	20/01/12				IA		15	PT	17/05/11	HIGH		36.5		23.6		10.1		0	C	80-85	Poor	4Y1M	1	1	0		LM	8	0	1	IN	0	0	
NAY	15	M	888092	D	08/11	147	N	23/06/11				NA		8	PT	24/05/11	IG	46.7		15.4		11.9		9999		C	95	Good	4Y1M	0	0	0				0	0		0	0	
SAN	16	M	010284	D	09/13	1722	H	24/03/12	9.8	34.7	2	NA		30,40	DF	18/10/11	HIGH	52.2		23.1		13		9.3		C	20	Poor	3Y8M	1	1	1	5	LM	5	0	0		0	0	
ANI	11	F	078959	A		153	N	22/01/14	23.6	30.3	22	B	15	50,30	PT	13/12/11	HIGH		36.8		14.6		11.2		3.4	C	20	Poor	3Y6M	0	0	0				0	0		0	0	
PRA	68	M	105015	NC		116	N	Nil				I		15	PT	###	HIGH		9999		9999		14.6		5	C	no ch	9999	3Y4M	0	0	0				0	0		0	0	
REJ	46	F	082580	D	10/12	92	N	11/09/12	15.4	29.4	1D	I		30, 60	PT	###	HIGH		32.4		11.7		15.9		2.9	C	40	Poor	3Y4M	1	1	0				0	0		0	0	
VIN	20	M	124065	NC		9999	#	11/12/12				B	3		PT	###	HIGH		40.7		15.7		11.2		###	A	85-90	Poor	3Y4M	0	1	0				1	1	IN	0	0	
RAN	20	F	084362	A		137	N	18/02/15				NA		50,70	DF	###	HIGH	47.7		17.4		15.6		9.3		C	30	Poor	3Y4M	0	0	0				0	0		0	0	
NAS	11	F	086955	D	10/14	276	N	22/10/12				I		NO L	PT	###	HIGH		34.1		10.6		13.7		2.5	A	30-35	Poor	3Y3M	0	0	0		LM	7	0	1	VS	0	0	
MOI	22	F	155351	A		77	N	08/09/15	25	31.3	14	NA		30, 40	DF	###	LOW	44		16		11.6		12.1		C	60	Poor	3Y	0	0	0				0	0		0	1	IMPF
MUC	19	M	174421	D		120	N	10/05/13				I		20	PT	###	HIGH		41		20.7		12.8		2.9	C	65-70	Poor	2Y11	1	1	0	2	LM		0	0		0	0	
SHA	18	M	191991	A		142	N	01/07/15	33.5	36.1	34	B	7	30,50	PT	###	HIGH		33.4		15.6		12.3		5.1	C	90	Good	2Y10	0	0	0				0	0		0	0	
BHA	17	F	303521	A		96	N	05/08/15	16.6	28.5	3	NA		30, 50	DF	19/11/12	IG	43.6		15.9		12.8		11.2		P	no ch	9999	2Y7M	0	0	0				0	0		0	0	
PRA	24	M	301112	A		557	H	29/09/15	21.2	35.1	22	NA		30, 50	DF	###	HIGH	46		15		14		12		AP	15-20	Poor	2Y5M	0	0	0		LM	26	0	0		0	0	
SOU	19	F	447873	A		316	H	15/06/15	28.3	33.3	7	NA		50, 30	DF	###	HIGH	41		30		14		3		C	30	Poor	1Y10	0	0	0				0	0		0	0	
SAR	19	M	470197	A		177	N	24/07/15	18.4	35.2	16	NA		50, 30	DF	###	IG	44		20		20		1.7		C	<10	Poor	1Y9M	0	0	0				0	0		0	0	
MEF	21	M	622066	A		9999	#	30/05/15	15.6	33.1	12	NA		55, 30	DF	###	HIGH	46		21		18		4		C	<50	Poor	1Y9M	0	0	0				0	0		1	0	
MOI	19	M	621311	D	07/15	70	N	23/03/15	19.8	37.2	18	NA		30	DF	###	HIGH	50		19		13		13		C	60	Poor	1Y9M	0	0	0		LM	18	0	0		1	0	
MUK	33	M	616951	A		120	N	26/09/15				B	2	50, 40	PT	###	HIGH		43		16		16		0.2	C	10	Poor	1Y8M	0	1	0				1	1	IN	0	0	
SUN	16	F	649151	A		138	N	18/02/15	25.9	27.8	1D	NA		45, 30	DF	14/11/13	HIGH	40		20		16		1.6		MP	40	Poor	1Y7M	0	0	0		LM	15	0	0		0	0	
SIV	16	M	70950	D	###	951	H	02/07/14				IA		NO L	DF	###	HIGH	50		24		13.4		8.2		ML	30-40	Poor	1Y6M	2	0	1	3	BM	8	0	1		0	0	
FOR	17	M	697797	A		54	N	04/03/15				B	9	25, 35	PT	###	HIGH		41		11		13.2		5.5	LM	0	Poor	1Y5M	0	0	0				0	0		0	0	
ROS	13	F	767765	A		9999	#	22/07/14				I		50, 15	PT	###	HIGH		35		14.5		14.5		3.5	C	60-70	Poor	1Y5M	1	0	0				0	0		0	0	
SAL	16	F	679987	D	10/14	920	H	26/09/14	-23.4	36.5	1D	IA		30	PT	###	HIGH		37		19		9.5		8	C	50	Poor	1Y5M	0	0	1	5	LM		0	1	LR	0	0	
AFS	16	F	840955	A		72	N	11/07/15	11.6	38.7	1D	I		30	PT	###	HIGH		36.4		15.3		13		3.2	C	20	Poor	1Y	2	1					1	1	IN	0	0	
HAS	17	M	834053	A		147	N	22/07/15	26.2	35.2	9	NA		30, 45	DF	###	HIGH	48.5		23		11		5.4		C	70	Poor	1Y	0	0	0		LM	10	0	0		0	0	
FAR	17	F	885220	D	05/15	67	N	25/11/14	NO PATELLA			NA		30	DF	###	HIGH	43		18		11.7		7.4		C	45-50	Poor	11M	1	1	1	3			0	1	IN	0	0	
SHA	25	M	859712	NC		160	H	03/10/14				NA		40, 20	DF	###	HIGH	41.4		18.4		12		5.8		PPX	70	Poor	10M	0	0	0				0	0		0	0	
SIR	18	F	878426	A		2180	H	31/07/15				NA		20	DF	###	HIGH	41.7		17.5		17		2.6		A	40	Poor	8M	0	0	0				0	0		0	0	
ABD	21	M	019624	A		80	N	19/09/15				NA		40	DF	###	HIGH	48		13.7		14.5		15.6		C	0	Poor	8M	0	0	0				0	0		0	0	
a	18	F	6f	A	12/99	449	H	22/02/15	0	0	0		0			3		46	0	26	0	13	0	4.1		C	70	1	2Y	0	1	0				0	0			0	

RESUT	Complications	DEG	PRE	POSTC	RT	Ht	Wdth	dpt	Flex	el
	TIBIAL COMPONENT BREAK	40,20	1	3	9999	83	70	25	100	0
	ASEPTIC LOOSENING, REVI	30,50	1	11	9999	12	85	58	110	0
MUA ON 14/10/10 A	LOCAL RECURRENCE	30	0	0	NO	85	90	70	20	0
	HAD RECURRENCE AND EX	30, 40	1	5	9999	14	10	9.8	90	0
	IMPLANT BREAK FEM, REVI	50,30	3	6	NO	120	82	47	130	0
		30,50		6	YES	88	64	62	70	30
	LUNG METS	30	3	3	NO	100	90	80	90	3
	FOLLOWUP ELSEWHERE	50	6	20	YES	100	60	50	75	0
		30	nil	nil	NO	67	60	63	75	40
19/12/2011 medial gastrocnemus flap		30	nil	1	NO	84	76	69	100	0
DEBRIDEMENT, ST	LUNG METS, AK AMPUTATIC	15	3	1	NO	220	80	60	###	##
		8	3	3	NO	90	50	50	###	50
26/12/2011 STSG	LOCAL RECURRENCE, LUNG	30,40	1	1	NO	142	100	90	90	15
		50,30	3	3	NO	72	41	50	###	##
	?DEDIFFERENTIATED CHO	15	nil	NIL	NO	130	50	57	###	##
DEBRIDEMENR AND	WASHOUT18/2/12	30, 60	3	3	YES	65	52	37	105	20
	infection 23/05/12 debridement and fla		9	0	YES	150	100	###	###	40
		50,70,	3	3	YES	150	79	69	110	25
	gangre amputation on 04/04/2(	NO LA	3	3	NO	195	54	45	###	##
		30, 40	3	3	YES	76	57	56	75	0
DEBRIDEMENR AN	LUNG METS	20	3		NO	172	59	39	###	70
	LATE INFECTION 2Y HEALEC	30,50	3	1	YES	77	60	56	90	0
		30, 50	NIL	6	YES	135	78	42	95	0
	LUNG METS	30, 50	3	3	YES	116	65	65	90	10
	MDS MPN	50, 30	3	3	YES	180	56	39	110	25
		50, 30	3	3	YES	200	63	52	75	0
MUA ON 10/03/2014		55, 30	2	4	YES	115	70	60	70	5
MUA ON 31/04/201	LUNG METS	30	3	3	YES	115	56	55	90	60
MEDIAL GASTOC F	AMPUTATION ON 04/06/2015	50, 40	3	1	NO	120	70	60	90	20
	LUNG METS	45, 30	3	3	YES	175	62	65	100	25
RESUTURED TWIC	?DIED, LOCAL RECURRENC	NO LA	1	3	FOR	130	112	112	90	10
		25, 35	2	3	YES	92	70	88	110	0
RESUTURING16/01/2015		50, 15	3	3	9999	111	62	58	0	10
AMPUTATION,24/06	DIED, LOCAL RECURRENCE	30	3	3	0	110	110	###	###	##
TWO RESUTURING	FLAP,WOUND INFECTION, A	30	4	1	9999	91	44	37	###	##
	LUNG METS	30, 45	3	3	YES	114	93	94	75	3
RESUTURING ON (	LR, AK AMPUTATION ON 03/1	30	4	6	NO	150	112	117	###	##
		40, 20	3	DONT	KNOW	135	90	82	100	10
		20	2	4	YES	11	86	70	75	0
		40	4	2	YES	116	59	67	95	3
	washout on 23/10/13	15,25	2	4	YES	230	137	###	###	##