OUTCOMES OF LIMB SALVAGE SURGERY IN PATIENTS WITH EXTREMITY OSTEOSARCOMA

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CERTIFICATE

I hereby certify that this dissertation on "**Outcomes of limb salvage surgery in patients with extremity osteosarcoma"** is a bonafide work done by **DR.G.SENTHIL KUMAR**, in the department of surgical oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai, under my guidance and supervision, to my satisfaction.

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Last but not the least, I thank all my patients for their kind co-operation in this study. May God Almighty bestow upon them good health.

CONTENTS

INTRODUCTION

Osteosarcoma is the most common malignant neoplasm of bone[1] . It occurs most often in bones around knee joint and humerus of young people. Due to rapid and aggressive nature of the disease, the traditional treatment for osteosarcoma was amputation of the affected limb. In the 1970s, two year survival rates were fifteen to twenty percent[2]. However over the past 3 decades, the prognosis for these patients has changed dramatically. The development of chemotherapy agents have revolutionised the treatment of osteosarcoma by reducing the mortality. In addition the advances in imaging and new materials have provided the surgeon broader range of operative alternatives.

AIMS AND OBJECTIVES

1. To study long term survival of patients with extremity osteosarcoma treated by limb salvage surgery
2. To identify prognostic factors influencing survival
3. To identify risk factors for local recurrence
4. To assess functional assessment of patients following limb salvage surgery

REVIEW OF LITERATURE

EPIDEMIOLOGY

Osteosarcoma is a primary malignant tumor of bone, deriving from primitive bone forming mesenchyme and characterised by production of osteoid tissue or immature bone by the malignant proliferating spindle cell stroma[3]. Only half the bone tumors in childhood are malignant, of these osteosarcoma is the most frequent, accounting for 35% of all primary sarcomas of bonw and 56% of malignant tumors in the first two decades of life[4].

The peak incidence of osteosarcoma occurs in second decade of life during the adolescent growth spurt, a feature that suggests a relationship between rapid bone growth and the development of osteosarcoma. Evidences to support this relationship are as follows. First, patients with osteosarcoma are taller than their age peers. Second, these tumors occur at an earlier age in girls than boys, corresponding to the more advanced skeletal age and earlier adolescent growth spurt of girls. Third osteosarcoma has a

predilection for the metaphyseal portions of the most rapidly growing bones in adolescents – the distal femur, proximal tibia and proximal humerus. This has lead to the speculation thatbone tumors arise from an aberration of the normal process of bone growth in length and remodelling[5].

ETIOLOGY

The etiology of osteosarcoma is unknown. A viral etiology was suggested based on evidence that bone sarcomas can be induced in select animals by viruses[6] or cell free extracts of human osteosarcoma[7].

The only environmental agent known to produce bone sarcomas in humans is ionizing radiation. Radiation is implicated in 3% of osteosarcomas[8]. The latent period between radiation exposure and development of osteosarcoma ranges from 4 to more than 40 years (median 12 to 16 years). Osteosarcoma has been reported in patients with paget disease and cases of osteosarcoma after the age of 40 years are almost exclusively associated with this premalignant condition[3]. Approximately 2% of patients with paget disease develop osteosarcoma. Histologically, osteosarcomas in patients with paget disease are similar to conventional

osteosarcoma, although multiple bone involvement is frequent and the prognosis is poor.

Other benign bone lesions are also associated with an increased risk of the development of osteosarcoma. Lesions predisposed to such malignant degeneration are solitary or multiple osteochondroma, solitary enchondroma or enchondromatosis (Oliers disease), multiple hereditary exostoses, fibrous dysplasia, chronic osteomyelitis, sites of bone infarcts and sites of metallic implants for benign conditions. Genetic syndromes associated with osteosarcoma are Rothmund-Thomson syndrome (RTS)-characterised by autosomal recessive pattern, characteristic skin rash (poikiloderma), small stature and skeletal dysplasias; Hereditary retinoblastoma and Li Fraumeni syndrome.

PATHOLOGY

The diagnosis of osteosarcoma is based on histopathologic criteria in correlation with radiologic appearance. The histologic diagnosis of osteosarcoma depends on the presence of a frankly malignant sarcomatous stroma associated with production of tumor osteoid. Because osteosarcomas are thought to arise from a stem mesenchymal cell capable of differentiating toward fibrous

tissue, cartilage or bone; osteosarcoma shares many features with chondrosarcoma and fibrosarcoma. However chondrosarcoma and fibrosarcoma are distinguished from osteosarcoma by their lack of production of osteoid, the sine qua non for the diagnosis of osteosarcoma.

Osteosarcomas are classified depending on the histological type or the location within bone as central or surface osteosarcoma and whether primary or secondary osteosarcoma. The WHO classification of osteosarcoma is as follows,

1. Classic or Conventional osteosarcoma
    a. Osteoblastic osteosarcoma
    b. Chondroblastic osteosarcoma
    c. Fibroblastic osteosarcoma
2. Telangiectatic osteosarcoma
3. Small cell osteosarcoma
4. Low grade central osteosarcoma
5. Parosteal osteosarcoma
6. Periosteal osteosarcoma

7. High grade surface osteosarcoma

8. Secondary osteosarcoma

CLINICAL PRESENTATION, NATURAL HISTORY AND PATTERN OF SPREAD

The majority of patients with osteosarcoma present with pain over the involved bone, with or without a mass. The average duration of symptoms is 3 months, although a history of 6 months or longer is not uncommon. Parosteal osteosarcomas in particular can be associated with painful symptoms of several years duration, reflecting the indolent behaviour of this tumor.

Approximately 15% to 20% of patients with osteosarcoma present with visible macrometastatic disease[9]. Majority of these metastases are found in lungs, although a small minority of patients present with bone metastases who carry an extremely grave prognosis. Involvement of lymph nodes is unusual but a poor prognostic sign.

BIOLOGY OF TUMOR GROWTH

Sarcomas form a solid lesion that grow centrifugally. In a benign lesion true capsule surrounds the tumor, which is composed

of compressed normal cells. In contrast the malignant tumor is enclosed by a pseudocapsule, consisting of compressed tumor cells. This is surrounded by a fibrovascular zone of reactive tissue with inflammatory component. The tumor cells extend through the pseudocapsule as pseudopods and can detach from the tumor and form satellite lesions in the reactive zone, the thickness of which varies with the degree of malignancy.

Skip metastases is a tumor nodule that is located within the same bone having the tumor but not in continuity with it. These develop by embolization of tumor cells within the marrow sinusoids.

EVALUATION

PLAIN RADIOGRAPH

Plain radiography is the first imaging modality when the patient presents with bone symptoms. Considering the age and the tumor characteristics depending on site, sclerotic/ lytic, margins, periosteal reaction, morphologic appearance and the matrix, a clinic-radiologic diagnosis of malignant bone tumor can be done. Chest x-ray is done as a part of staging workup.

CT/MRI OF LOCAL PART

CT and MRI are both complementary in the evaluation of bone sarcomas. Intraosseous and extraosseous extension are depicted with certainty by CT. Soft tissue extension and marrow extension, apart from skip lesions are well demonstrated by MRI.

BONE SCAN

Bone scan is done for estimating the exact tumor extension, and ruling out bony metastasis and polyostotic involvement. During limb salvage procedures, removal of bone 4cms from scintigraphic abnormality is considered as safe margin.

CT CHEST

Spiral CT chest is done to rule out lung metastasis which can occur in 10% of patients at presentation. Lung metastasis at presentation does not preclude limb salvage, when the primary tumor is suitable for salvage surgery, as discussed below.

POSITRON EMISSION TOMOGRAPHY

(^{18}f) Fluorodeoxy-D-glucose PET for bony and pulmonary evaluation is in its evolutionary phase and preliminary reports are available for staging, diagnosis, staging, assessment of response

and follow-up. FDG-PET is still investigational and early studies have shown that PET imaging is not accurate in determination of pulmonary metastasis in osteosarcoma.

All these imaging can be repeated following preoperative chemotherapy to assess the tumor response.

STAGING

The musculoskeletal tumor society (MSTS) formulated a surgical staging system for bone sarcomas. This staging system described by Enneking et al is based on GTM: grade (G), location (T) and lymph node involvement and metastases (M)[10]. The grade G is further divided into G1, low grade and G2, high grade. T denoting the site of lesion may be intra-compartmental (T1) or extra-compartmental (T2).

The surgical system developed by Enneking et al is as follows:

Stage IA (G1 T1 M0): Low-grade intracompartmental lesion, without metastasis

Stage IB (G1 T2 M0): Low-grade exrracompartmental lesion, without metastasis

Stage IIA (G2 T1 M0): High grade intracompartmental lesion, without metastasis

Stage IIB (G2 T2 M0): High grade extracompartmental lesion, without metastasis

Stage IIIA (G1 or G2 T1 M1): Any grade intracompartmental lesion, with regional nodal or distant metastasis

Stage IIIB (G1 or G2 T2 M1): Any grade extra compartmental lesion, with metastasis

AJCC AND UICC BONE TUMOR CLASSIFICATION

In 1983, the American Joint Committee on Cancer recommended a staging system for the malignant tumors of bone. This system has undergone several modifications and is now in its sixth edition(2002)[11]. A two tired grading system is used in TNM.

Primary tumor (T)

Tx Primary cannot be assessed

T0 No evidence of primary tumor

T1 Tumor 8cm or less in greatest dimension

T2 Tumor more than 8cm in greatest dimension

T3 Discontinuous tumors in the primary bone site

Regional lymph nodes (N)

Nx Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant metastasis (M)

Mx Distant metastasis cannot be assessed

M1 No distant metastasis

M1a Lung

M1b Other distant sites

Histological Grade (G)

Gx Grade cannot be assessed

G1 Well differentiated – Low grade

G2 Moderately differentiated – Low grade

G3 Poorly differentiated – High grade

G4 Undifferentiated – High grade

STAGE GROUPING

IA	T1	N0	M0	G1,2	Low grade
IB	T2	N0	M0	G1,2	Low grade
IIA	T1	N0	M0	G3,4	High grade
IIB	T2	N0	M0	G3,4	High grade
III	T3	N0	M0	Any G	
IVA	Any T	N0	M1a	Any G	
IVB	Any T	N1	AnyM	Any G	
	Any T	Any N	M1b	Any G	

TREATMENT

SURGICAL MANAGEMENT OF PRIMARY

Osteosarcomas had traditionally been treated by amputations. Recent advances in molecular medicine, the construction of better and longer lasting prosthesis and biomaterials and the use of chemotherapy have had a definitive impact on the prognosis and therapeutic approach for osteosarcoma. Nowadays ablative surgery (amputations and disarticulations) are reserved for tumors with significant

neurovascular involvement and poor distal extremity function. Additional indications for amputation include soft tissue contamination due to pathologic fracture or a poorly performed biopsy site. Following initial treatment, failed attempts at limb salvage and/or persistent local recurrence are again treated by amputation.

LIMB SALVAGE SURGERY

Campanacci and Laus proposed predetermined levels of amputation for the common presentations of osteosarcoma, emphasizing the danger of conservative surgical margins[12]. Even with this radical surgical approach, the mortality of patients before the advent of chemotherapy and more advanced imaging and surgical techniques was close to 80% at 5 years

Simon et al published the first evidence-based study supporting the benefits of limb-salvaging procedures for the treatment of bone tumors[13]. Their multicenter study, which included 227 patients with osteosarcoma of the distal end of the femur, reported the rates of local recurrence, metastasis, and survival. Three groups of patients where studied: patients in group 1 had a limb-sparing procedure, patients in group 2 had an

AKA,and in group 3,a hip disarticulation was the procedure of choice. The Kaplan-Meier curves of the patients who survived and the percentage of patients without recurrent disease showed no statistical difference among the three surgical groups after a mean length of follow-up of 5.5 years (Mantel-Cox test: *P*=.8). Limb-salvage surgery was as safe as an amputation in the management of patients with high-grade osteosarcoma.

Limb-salvage procedures can be divided into

1. Arthrodesis
2. Allograft
    a. Osteoarticular allograft
    b. Intercalary allogaft
3. Metallic prosthesis
    a. Modular prosthesis
    b. Custom-made mega prosthesis
    c. Expandable prosthesis
4. Allograft-Prosthetic composites
5. Rotation plasty

ARTHRODESIS

An arthrodesis is usually obtained using bone allografts, vascularized autografts, or both. An arthrodesis provides a stable, durable reconstruction, resistant to physical stress and activity and requiring limited postoperative follow-up. In addition, once the allograft heals, patients seldom require additional surgical procedures.

The disadvantages include the loss of knee extension with alterations in gait and function such as rising from a chair, squatting and social sitting (bus,train), an increased energy expenditure, and the additional abnormal mechanical stress to the hip and spine. With the advent of metallic prosthesis arthrodesis is seldom performed nowadays.

OSTEOARTICULAR ALLOGRAFTS

Osteoarticular allografts are one alternative for reconstruction for tumor defects of the proximal tibia, distal femur and proximal humerus. Grafts are procured according to specific guidelines and stored in a fresh frozen state at -80^{0}C until needed. They are size matched to the specific patient using radiographs of the involved bone and allograft. Allografts are immunogenic but

the immune response is reduced by the fact that they are nonvascularized and freezing reduces the antigenicity. The allograft is not resorbed but host invasion occurs primarily at the allograft-host junction and along the surface of the bone.

Osteoarticular allografts have certain advantages compared with metallic prosthesis. They provide articular surface for the adjacent bone, obviating the need to resect the articular surface and the growth plate. Allograft provides ligaments for joint reconstruction including cruciate ligaments and sites for host tendons. Once the osteosynthesis heals, it is anticipated that the longevity of the allograft is superior to metallic prosthesis because they are not subjected to loosening, particulate wear debris and mechanical breakage.

Allografts have obvious potential problems and are subject to fracture, non-union, joint instability and higher infection rate. The procedure is technically challenging and has a prolonged rehabilitation period.

INTERCALARY ALLOGRAFTS

When osteosarcomas are located in the diaphysis, the adjacent joints and metaphyses can be spared. In young patients

where a margin of bone can be obtained while preserving the proximal and distal metaphysis, an intercalary allograt can be employed to reconstruct the diaphysis. Fixation can be achieved with plates so that the growth plates can be spared; or if the epiphysis is needed for fixation, the fixation devices (screws) in the epiphysis can be removed to allow growth once the osteosynthesis has healed.

METALLIC PROSTHESIS

Endoprosthetic reconstruction is performed with the use of modular oncology prosthesis or custom made prosthesis. The modularity gives the surgeon the opportunity to restore the length of the limb in the operating room, matching the amount of bone resected. Osteosarcomas are dynamic tumors that change with time and treatment. The metallic prosthesis can be fixed to the bone with polymethylmethacrylate or a press-fit porous stem can be used instead. The joint bearing is a rotating hinge that has some freedom of movement, but it will always be more constrained than a normal knee. The disadvantages include loosening, excessive wear, material failure, and stiffness.

The custom made prosthesis is customized to individual patient. These prosthesis are cheaper when compared to the modular ones, and are made up of the same biomaterials. With the concept of neo-adjuvant chemotherapy the delay in manufacturing the prosthesis does not have any significant impact on the survival. Prosthesis failure occur due to loosening at the prosthesis-bone interface, infection and fracture. Infections are significant risk factor for endoprosthesis with rates ranging from 0% to 35%.

EXPANDABLE PROSTHESIS

A relatively novel technique of limb salvaging, especially in skeletally immature patients, is the use of an expandable prosthesis for patients with osteosarcoma The location of these tumors in the growing areas of bone commonly mandates the removal of the affected growth plate. Subsequent continued growth in the contralateral extremity results in limb-length inequality. The distal femoral growth plate produces 1.6 cm in longitudinal growth per year. From a functional standpoint, the lower extremities should be of equal length if possible. If left untreated, limb-length discrepancies can result in low back pain and even compensatory scoliosis. Gait disturbances are also commonly observed.

Custom expandable prostheses have been in use worldwide since 1976 and in the United States since 1983. The system consists of a fixed stem with a screw or a multiple plate extension mechanism . In all of the commonly used expanding mechanisms,a surgical procedure is required for the subsequent expansions.

The Phenix Growing Prosthesis (Phenix Medical, Paris, France) was designed in the early 1980s. Although this prosthesis is not frequently used at the present time, it helped spark the interest in the current models of expandable prostheses.

The Stanmore expandable prosthesis (Stanmore Implants, Stanmore Middlesex, United Kingdom) has been recently introduced to the United States with a limited Food and Drug Administration approval. When the implanted prosthesis is placed at the centre of a rotating electromagnetic field, the poles of a magnet within the implant are captured,causing it to rotate in synchrony. The external field rotates at a fixed speed, causing the implant to expand at a rate of 0.23 mm per minute (1 mm every 4 minutes). Current indication for the procedure is children who are expected to develop a limb-length discrepancy greater than 4 cm after the resection of an osteosarcoma.

ALLOGRAFT-PROSTHETIC COMPOSITES

Another alternative to limb reconstruction is to combine a standard knee or proximal humerus prosthesis with an allograft for lesions about the knee or shoulder. This offers the advantage of joint reconstruction employing a more standard arthroplasty and restoring bone stock with allograft bone. The prosthesis allows joint stability and the allograft provides attachment for tendons. At all sites the composites allow for modularity and in theory may provide a more durable reconstruction than osteoarticular allografts or metallic prosthesis.

ROTATIONPLASTY

Young children with high grade sarcomas of the knee have limited options for reconstruction following resection of the sarcoma. Limb sparing procedures have the drawbacks of activity restrictions, high complication rate, limb length inequality and complexity. An above knee amputation for a distal femoral osteosarcoma in a very young patient leaves the child with a very short lever arm to power a prosthesis and becomes shorter as the child grows.

The operation described by Borggeve and adopted for congenital defects by Van Nes has been applied to the tumor setting by Salzer. The reconstruction employs the distal leg to be rotated 160 to 180 degrees and this provides the advantage of a longer lever arm and an active “knee” joint provided by the ankle and foot.

The indications for rotationplasty include a distal femoral or a proximal tibial osteosarcoma in a skeletally immature patient or a salvage procedure for a failed distal femoral reconstruction. The advantages are the wide margin which includes the skin, adjacent knee joint and thigh muscles, the avoidance of phantom limb pain, rapid healing of the osteosynthesis site and a relatively low complication rate.

The obvious drawback is the appearance which is repulsive at some times. Interestingly the young child does not view the procedure as an amputation because the foot remains and with a good prosthesis he is able to function better than other amputees. Studies have not shown any adverse psychological outcomes. Recently the number of patients willing to undergo this procedure has diminished, many prefer to try a limb sparing procedure and reserve rotationplasty until or unless it fails.

CHEMOTHERAPY IN MANAGEMENT OF OSTEOSARCOMA

Although control of the primary tumor is reliably accomplished by surgery, data from historical studies indicate that more than 80% of patients treated only with surgery will develop metastatic disease. Microscopic subclinical metastasis is present at the time of diagnosis. Before 1970, none of the drugs tested produced responses in more than 15% of the patients. More promising results were observed in the 1970s and 1980s, in trials of doxorubicin, high-dose methotrexate, cisplatin and ifosfamide.

PREOPERATIVE CHEMOTHERAPY

The administration of neoadjuvant chemotherapy initially evolved from early attempts at limb salvage surgery at the Memorial Sloan-Kettering Cancer Centre where customized endoprosthesis were used for limb reconstruction. Because fabrication of these devices required 2 to 3 months, patients were treated with chemotherapy after biopsy while awaiting surgery[41].

The only randomized trial by Pediatric Oncology Group (POG) failed to show survival benefit for patients receiving preoperative chemotherapy when compared to patients undergoing immediate surgery[14]. There is no other randomized or

nonrandomized studies comparing neoadjuvant chemotherapy vs immediate surgery and adjuvant chemotherapy in osteosarcoma patients. Preoperative chemotherapy has become the standard owing to the fact that tumor response to chemotherapy can be predicted and has been consistently shown to be an important predictor of survival. Although several grading systems exist for assessing the histological response to preoperative chemotherapy, the general consensus is more than 90% necrosis is considered good response and these patients fair better in survival.

METASTASIS AT PRESENTATION

The presence of metastatic disease at presentation continues to be a poor prognostic factor, with most studies showing survival rates in the range of 20%. Limb salvage surgery could still be considered if an aggressive approach could be followed with resection of disease at all sites and chemotherapy. In a large analysis of COSS database that included more than 1700 patients, the 10-year survival probability was 40% for patients who were able to have all metastatic disease resected[9].

PATHOLOGICAL FRACTURE

Pathological fracture was traditionally treated by amputation. With advent of effective chemotherapy and better techniques of limb salvage surgery, pathological fracture through an osteosarcoma is no more considered a contraindication for limb salvage. Earlier study by Steadman et al who reported on nine limb salvage and eight amputations in patients with osteosarcoma induced pathologic fracture, have shown one local recurrence in limb salvage group but no difference in survival between the two groups[15]. Recent study from Lee Moffitt Cancer Institute, by Abeid and Abdelmegid, have evaluated on 31 bone tumor patients with pathological fracture of which 17 were osteosarcoma[16]. The local recurrence rate reported was 6%.

SOFT TISSUE EXTENSION

Contraindications to limb salvage surgery are major neurovascular involvement, inappropriate biopsy site, infection, immature skeletal age and extensive muscle involvement[17]. Extensive muscle involvement is considered when enbloc resection entails removal of entire tumor with surrounding normal tissue and

when enough muscle is not available to reconstruct a functional extremity[18].

Functional assessment is done following limb salvage surgery in bone and soft tissue tumors are done using either Musculoskeletal tumor society scoring system (MSTS) or the Toronto extremity salvage score (TESS). In the modified MSTS score proposed by Enneking et al[19] six factors- pain, function, emotional acceptance, supports, walking ability and gait are analyzed. Functional assessment following limb salvage surgery has been compared with amputation. Several studies have shown limb salvage surgery is associated with better functional outcome than that observed with amputation but psychological outcome for patients undergoing limb salvage surgery is not clearly superior to that of amputees.

MATERIALS AND METHODS

Three hundred and forty seven osteosarcoma patients were treated at the institute between 1990 and 2005. Of these 105 patients were treated by limb salvage surgery. Five patient's case records could not be retrieved and entire details of treatment were not available in another eight case records. Finally ninety two patients were analyzed. The case records of these patients were reviewed, follow up was updated by active and passive means.

DIAGNOSTIC METHODS

All patients suspected of bone sarcoma were evaluated with local part x-ray, CT or MRI of the affected limb. Chest x-ray, CT chest and $Tc99^{m}$ bone scintigraphy was done as part of metastatic workup. 'Jamshidi' needle biopsy was done for definitive diagnosis. For patients who had biopsy done elsewhere, the slides or paraffin blocks were reviewed.

CHEMOTHERAPY

Different chemotherapy protocols have been used in the sixteen year study period. In the initial years till 1999-2000, cyclophosphamide, adriamycin and cis-platin were used. In the

subsequent years ifosphamide, adriamycin and cis-platin were used. Three to four cycles of neo-adjuvant chemotherapy was given followed by limb salvage surgery and the remaining cycles of chemotherapy to a total dose of six. In 2003 and 2004,pre-operative intra-arterial chemotherapy was given as a part of a project. (Ratan Tata Project for borderline tumors for limb salvage)

SURGERY

Clinical assessment of response was done after each pre-operative cycles. After a minimum of three cycles, imaging for reassessment is done only for borderline tumors for limb salvage. The number of neo-adjuvant chemotherapy cycles were determined by the time taken for customizing prosthesis. All patients of limb salvage surgery underwent custom made mega prosthesis. Histopathological analysis included percentage of necrosis, and were analyzed as those above 90% necrosis and below 90% necrosis.

FOLLOW UP

All patients were followed up according to institution protocol; monthly in first year, two monthly in second year, 3

monthly in third year, semi-annually in fourth and fifth years and then annually. Clinical examination and chest x-ray is done at each visit. Further investigations were done as symptoms warranted.

MANAGEMENT OF COMPLICATIONS

Prosthesis complications were managed appropriately. Redo prosthesis was attempted in cases of fracture prosthesis, prosthesis removal was reserved for cases where prosthesis could not be replaced. Prosthesis infection were managed with removal of prosthesis or amputation. Amputation was done for patients who developed local recurrence. Patients who had lung metastases feasible for resection underwent lung metastatectomy.

FUNCTIONAL OUTCOME

Functional assessment was done using musculoskeletal tumor society scoring system[19]. Assessment was done by personal interview, postal survey and telephone interview.

Scoring system of the international society of limb salvage

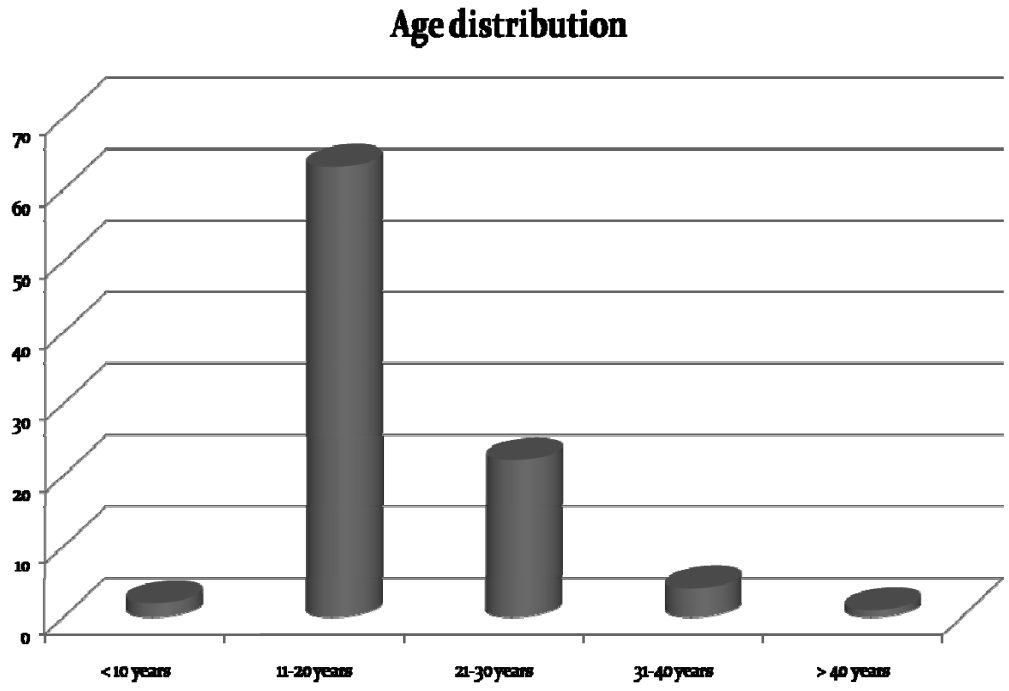
Score Points	Pain	Function	Emotional acceptance	Supports	Walking ability	Gait
5	None	No restrictions	Enthuse	None	Unlimited	Normal
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
3	Modest	Restriction in recreational activities	Satisfied	Brace	Limited	Minor cosmetic
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
1	Moderate	Partial disability	Accepts	One cane or crutch	Household	Major cosmetic, minor handicap
0	Severe	Total disability	Dislikes	Two canes or crutches	Unable to walk unaided	Major cosmetic, major handicap

STATISTICAL ANALYSIS

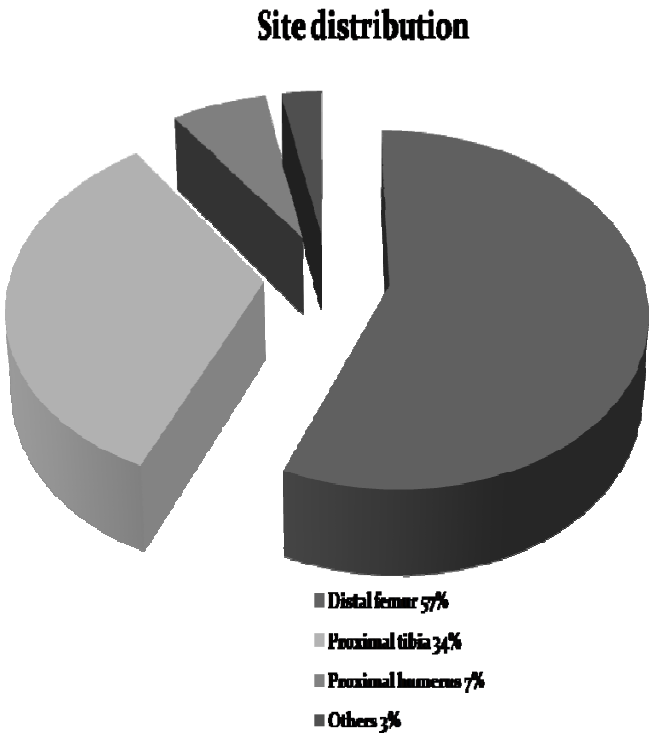
Statistical analysis was done by actuarial method, calculated using SPSS 10.0 (SPSS software Inc USA). Prognostic factors for survival and local recurrence were analyzed by Cox proportional hazards regression model.

RESULTS

Of the total 92 patients, 62 were male and 30 were female (2.1:1). The mean age of presentation was 19 years . Mean follow up period was 57 months, range 3 months to 156 months.



Osteosarcoma was located in lower extremity in 84 patients and upper extremity in 8 patients. Most common sites were distal femur in 56.5% and proximal tibia in 33%.



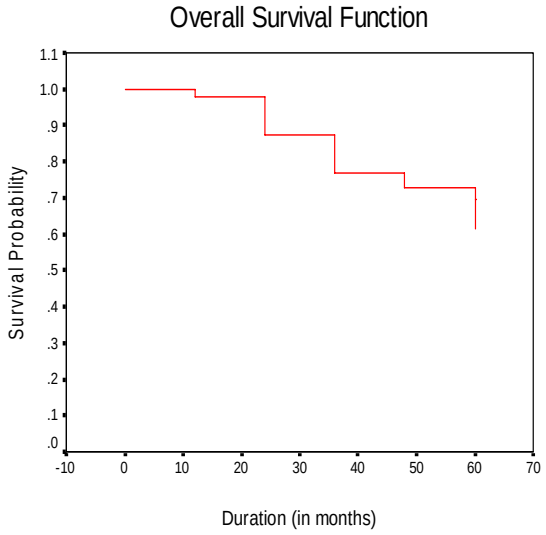
Osteosarcoma was diagnosed in 41 patients by 'Jamshidi' needle biopsy. Remaining 51 patients were diagnosed by open biopsy. Only 6.5% (n=6), of patients had a needle biopsy outside whereas 38% (n=36) of patients at this institute underwent needle biopsy. In contrast 41.3% (n=38) had an open biopsy done outside, compared to 14% (n=13) in the institute, in the same time period. Osteosarcoma can very well be diagnosed by needle biopsy, precluding the need for open biopsy.

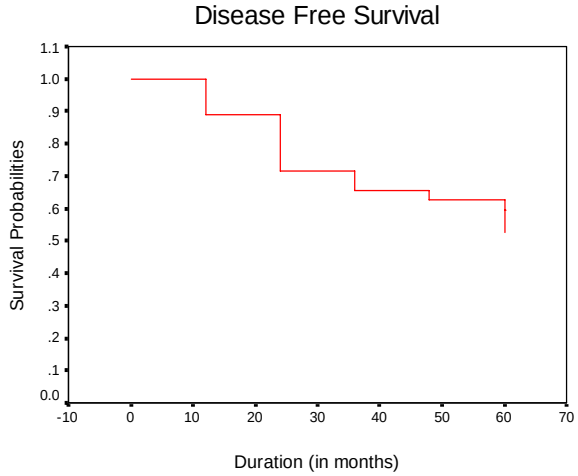
Limb salvage surgery was done using custom made mega prosthesis. Post-operative morbidity is as follows.

Morbidity	**Number of patients**
Marginal necrosis, no intervention	4
Marginal necrosis, secondary suturing	5
Marginal necrosis, excision & SSG	2
Marginal necrosis, excision & flap reconstruction	2
Foot drop	7
Ischemia leading to amputation	1
Infection resulting in amputation (within 30 days)	1

Seven patients (7.6%) had foot drop, of which two was in distal femoral tumor resection and rest were in proximal tibial tumor resection. Foot drop were temporary and resolved in four to six months.

Five year overall survival was 67.1% and disease free survival was 57.5%.





All but five patients received neo-adjuvant chemotherapy. 33 patients (39%) achieved $\geq$ 90% necrosis (Good responders). 54 patients (62%) achieved < 90% necrosis (Poor responders). Survival significantly differed in both. Five year overall survival for good responders was 88% and for poor responders was 59%

Following factors were analyzed by Cox regression analysis for survival and local recurrence.

1.Age group: $\leq$ 20 vs > 20

2.Number of preoperative chemotherapy cycles: $\leq$ 3 vs >3

3.Size of the primary tumor: $\leq$ 8cm vs > 8cm

4.Percentage of necrosis: $\geq$ 90% vs < 90%

5.Biopsy: Needle biopsy vs Open biopsy

Prognostic factors analyzed for survival

		Univariate analysis			Multivariate analysis	
Variables	Stratification	Number	Hazard ratio	P	Hazard ratio	P
Age group	≤20 > 20	65 27	HR 0.91 (0.38-2.16)	NS	HR0.68 (0.23-1.96)	NS
No: of chemo	≤ 3 > 3	65 27	HR1.78 (0.81-3.87)	NS	HR 2.03 (0.84-4.94)	NS
Size	≤ 8cm >8cm	23 69	HR1.46 (0.58-3.68)	NS	HR 1.02 (0.39-2.67)	NS
Necrosis	≥ 90% <90%	52 33	HR0.07 (0.01-0.51)	<0.005	HR 0.07 (0.01-0.51)	<0.005
Biopsy	Needle Open	41 51	HR1.36 (0.63 - 2.94)	NS	HR 1.07 (0.46-2.47)	NS

Prognostic factors analyzed for local recurrence

			Unvariate analysis		Multivariate analysis	
Variables	Stratification	Number	Hazard ratio	P	Hazard ratio	P
Age group	≤20 > 20	65 27	HR 1.28 (0.46-2.64)	NS	HR1.05 (0.33-2.34)	NS
No: of chemo	≤ 3 > 3	65 27	HR1.2 (0.97-3.66)	NS	HR 2.27 (1.09-4.74)	NS
Size	≤ 8cm >8cm	23 69	HR1.90 (0.79-4.57)	NS	HR 1.68 (0.66-4.28)	NS
Necrosis	≥ 90% <90%	52 33	HR0.09 (0.02-0.37)	=0.001	HR 0.09 (0.02-0.36)	=0.001
Biopsy	Needle Open	41 51	HR1.06 (0.55 - 2.03)	NS	HR 0.97 (0.48-1.96)	NS

Of all the factors analyzed, only response to chemotherapy was found to be a significant risk factor for both local recurrence and survival.

Twelve (13%) patients developed local recurrence. 75% of the local recurrences occured in the first year following surgery and 92% occurred within twenty-four months. Of these twelve patients, five developed distant (lung) metastases. Eight patients were treated by amputation. Remaining four were adviced supportive care in view of associated systemic metastasis. At the time of analysis, among these twelve patients, four are alive without disease, six expired and two lost to follow up.

Of these twelve patients one had pathological margin positive. 8 underwent open biopsy for tissue diagnosis. But in the final histopathology following neo-adjuvant chemotherapy none of them had tumor in biopsy scar. Majority of patients (51 patients) in this study underwent open biopsy for diagnosis. This factor was analyzed compared with needle biopsy as a risk factor for local recurrence. Though local recurrence is more in patients undergoing open biopsy, this was not statistically significant.

TYPE OF BIOPSY IN RELATION TO LOCAL RECURRENCE

	Local recurrence	No local recurrence	Total
Jamshidi needle biopsy	4 (9.8%)	37	41
Open biopsy	8 (15.7%)	43	51
		p=0.401	

Four patients had pathological fracture at presentation who received neoadjuvant chemotherapy followed by limb salvage surgery. None of these patients developed local recurrence.

In these 92 patients who underwent limb salvage surgery, a subgroup of patients were considered to have extensive soft tissue disease based on the following criterias – if more than one compartmental muscle is involved radiologically, discontinuous lesion is found intra-operatively or in the pathological examination of the specimen, or if the tumor infiltrates the surrounding muscle and extends to superficial fascia.

Based on these criterias, 7 patients had tumor confined to bone, 71 patients had tumor with minimal soft tissue extension and 14 patients had extensive soft tissue extension. In the group with bone only disease none of the patient developed local recurrence. In patients who had minimal soft tissue, 9 patients (12.7%) developed local recurrence and 16 patients (22.5%) developed distant metastasis. On the contrary approximately double the local recurrence and distant metastasis were found in the group with extensive soft tissue involvement- 3 patients (21.4%) developed local recurrence and 7 patients (50%) developed distant metastasis.

The 5 year overall and disease free survival is as follows.

Groups	Overall survival	Disease free survival
Confined to bone	85.7%	84.6%
Minimal soft tissue extension	72.3%	61.7%
Extensive soft tissue extension	49.3%	30.7%
	p=0.37	p=0.33

Local recurrence in these groups is as follows.

Groups	Local recurrence	No local recurrence	Total
Confined to bone	0	7	7
Minimal soft tissue extension	9 (12.7%)	62	71
Extensive soft tissue extension	3 (22.5%)	11	14
			p=0.382

The overall survival in patients who had amputation for osteosarcoma in our institute is 43.1% and disease free survival is 35.5%, in the same period. Patients who had extensive soft tissue disease and underwent limb salvage had survival comparable to patients who underwent amputation.

Twenty one (23%) patients developed distant metastasis. Lungs were the predominant site of metastasis. Lungs were the predominant site of metastasis (19 patients), two had soft tissue

metastasis, one had bone and one had both lung and bone metastasis. Metastatectomy was done in two patients. At the end of our study, of these twenty one patients, one patient is alive and disease free, one is alive with disease and nineteen expired

Prosthesis survival rate is 57% Prosthesis infection occurred in 11 patients(11.9%). Prosthesis fracture occurred in 17 patients(18.4%). Both were common in distal femoral prosthesis.

Prosthesis related morbidity	Number of patients
Infection (After 30 days)	11 (11.9%)
Fracture	17 (18.4%)
Displacement	2
Loosening of screws	1
Remnant bone fracture	2

Thirty revisions were done for these 92 patients. Apart from infection and fracture, the number of revisions and amputations were also high in distal femoral prosthesis reconstruction.

Site of tumor	Number of patients	Number of infection	Number of fractures	Number of revision	Number of amputations	Number of local recurrence
Distal femur	52	8	14	19	13	7
Proximal tibia	31	2	3	9	3	2
Proximal humerus	6	1	-	1	2	2
Proximal femur	1	-	-	-	-	-
Radius	1	-	-	-	-	-
Ulna	1	-	-	1	1	1
Total	92	11	17	30	19	12

Of the total of 92 patients, forty are surviving with prosthesis. Functional assessment was done using modified Musculoskeletal tumor society score (MSTS) score. The average MSTS score was 25 out of 30 (86%), revealing a good functional outcome.

DISCUSSION

Osteosarcoma is the most common primary bone malignancy in children with an overall incidence of approximately one per 100,000 per year[16]. Osteosarcoma typically presents between five and thirty years of age[20]. The predominant age at presentation in our study is in second decade of life. As reported in most series[22], males were twice commonly affected than females in our study.

Osteosarcomas can affect any bone but predominantly involves the metaphysis of long bones in appendicular skeleton (eighty percent)[21]. The most common sites affected are distal femur, proximal tibia and proximal humerus. Over half of osteosarcomas occur from the knee area[21]. Similarly majority of limb salvage surgery is feasible in tumors around knee joint. In our study limb salvage surgery was done in 89% of tumors in knee area. (Distal femur 52, proximal tibia 31, proximal humerus 6, proximal femur 1, radius 1, ulna 1)

The most common presentation had been pain and swelling. Initial work-up was x-ray of local part and chest. Further evaluation was by CT or MRI or both of the affected bone and

adjacent joint depending on individual case. CT of chest is done if x-ray chest is normal. Bone scan is done as part of local imaging and to rule out bone metastases. Prosthesis measurement is done based on bone scan extent of tumor size and scannogram of the affected limb. Patients found to be suitable for limb salvage and non-metastatic, are planned for limb salvage surgery.

Osteosarcoma was diagnosed in 41 patients by 'Jamshidi' needle biopsy. Remaining 51 patients were diagnosed by open biopsy, of which 38(74.5%) were done elsewhere before referring to our institute. Only six of forty one needle biopsies were done outside. Osteosarcoma can very well be diagnosed on needle biopsy and better be done by the surgeon / centre specialized in limb salvage surgery. The principle of biopsy cannot be overemphasized because a poorly executed biopsy can preclude limb salvage surgery[23]. In a report from M.D.Anderson cancer centre only 19% of patients referred to that institute had a properly placed biopsy and 92% of biopsies performed in the same period at that centre was needle biopsy[24].

All but five patients received neo-adjuvant chemotherapy. Two patients were diagnosed as parosteal osteosarcoma and two as low grade osteosarcoma (One patient had a preoperative biopsy

diagnosis of Giant cell tumor of bone). One patient was diagnosed as chondrosarcoma on biopsy, but following limb salvage surgery found to have chondroblastic variant of osteosarcoma and hence received adjuvant chemotherapy.

The global trend in the management of osteosarcoma is limb salvage surgery. The goal of any malignant tumor operation is to perform a complete en bloc removal of the tumor with adequate margins. The use of neoadjuvant chemotherapy with advances in imaging technique have enabled the oncologic surgeon to obtain local control rates equivalent to amputation using limb salvage surgery[25].

The survival rate of osteosarcoma patients had dramatically increased from a meagre fifteen to twenty percent in the 1970s to as high as seventy to eighty percent. The survival rates reported in recent studies compared to our study is as follows.

Journal	Author	No:of patients	Follow up years	EFS %	OS %
J Clin Oncol 2000;18:4016-4027	Bacci et al[26]	133	10	59	70
J Clin Oncol 2002;20:776-790	Bielack SS et al[9]	1702	10	48.9	59.8
The Oncologist 2004;9:422-441	Marina et al[2]	Rev article	5 10		74 71
Our study		92	13	57.5	67.1

The most extensive study is from the German-Austria-Switzerland study group, in their series of 1702 patients, the ten year overall survival rate is 59.8% and the disease free survival rate is 48.9%[9]. In our study the five year overall survival rate is 67.1% and the disease free survival rate is 57.5%, which is in comparison

with other international studies such as from Rizzoli Institute[26] and MSKCC[2].

Although there is no survival benefit, preoperative chemotherapy has become the standard practice at most centres, due to the important survival implications of biologic response to such therapy. Although different grading systems exist for response assessment to neoadjuvant chemotherapy, the general consensus is to consider greater than 90% necrosis and less than 90% necrosis as good and poor responders respectively.

In our study lesser number of patients (38%) achieved greater than 90% necrosis, and a majority (62%) were poor responders. Similar to our study the European Osteosarcoma Intergroup (EOI) have analyzed a total of 570 patients and reported 28% as good responders and 72% as poor responders[27]. Many of the patients included in this analysis did not receive high dose methotrexate which explains the reason for lesser number of patients showing good histologic response. Similarly in our study none of the patients received high dose methotrexate .

In contrast two other studies that used high dose methotrexate has shown greater response to induction

chemotherapy. The Rizzoli institute has analyzed more than 1000 patients over a 19 year period from 1983 to 2002 and reported 59% good responders and 41% as poor responders[28]. The COSS database which analyzed 1700 patients between 1980 and 1998, reported 55.6% having good response to therapy and 44.4% having poor response[9]. All three studies together suggest that good responders are expected to have a 5-year survival of approximately 75% and poor responders in the range of 45% to 55%, depending on the treatment. In our study good responders had 88% 5-year overall survival and poor responders 59%.

Response to chemotherapy has been shown to affect prognosis in many studies[9,29,30], but there are studies which report that this factor doesn't influence prognosis[26]. In our study response to chemotherapy was found to be a significant factor affecting prognosis and local recurrence.

Tumor size is another factor found to affect prognosis of patients with osteosarcoma unfavourably[9]. In our study tumors based on size more or less than 8cms did not affect prognosis. Similarly Rizzoli institute study which quantitatively evaluated tumor size, found that this factor did not affect prognosis[26]. Age at presentation particularly above forty years has shown poor

prognosis[9]. In our study we evaluated patients presenting less than or more than 20 years of age and found that this factor did not affect prognosis.

The number of chemotherapy cycles varied depending on the time taken for customizing the prosthesis. Hence this factor was analyzed if it affected the survival. Patients were analyzed depending on whether they have received three or more cycles of chemotherapy and was found not to affect the survival. Intensification of preoperative therapy to increase the number of favourable responders was studied at MSKCC, T12 protocol[29]. In this study when preoperative therapy was lengthened, histologic response loses its prognostic value and did not change the long term outcome of these patients.

Thirteen patients had suspicious nodules in lung at presentation. Two patients underwent thoracotomy and excision of the nodules, one was found to be metastatic and the other fibrotic lesion. All these patients had local tumor suitable for salvage and hence underwent limb salvage surgery. Following induction chemotherapy, re-assessment prior to surgery revealed disappearance of the nodules in five patients. Five of the thirteen patients developed lung metastases at follow up. The most

consistent prognostic factor at diagnosis is the presence of clinically detectable metastatic disease, which confers an unfavourable prognosis[9,31].

In our study local recurrence is found to be higher when compared to international studies. Of the various factors analysed only histological response to preoperative chemotherapy was found to be a significant risk factor. Though not statistically significant, open biopsy could still be considered a risk factor for local recurrence. In a study from Italy, the following factors were found to be directly related to the development of local recurrence: a) the quality of the surgical margins, b) site of the biopsy as well as complications related to the biopsy procedure, c) local response to preoperative chemotherapy[32].

The reported incidence of local recurrences in the literature are as follows.

Journal	Author	Number of patients	Local recurrence %
Acta Orthop Scand 1998;69(3):230	Bacci et al[33]	453	6
J Bone Joint Surg Am 1994;76(5):649	Rougraff BT et al[25]	73	11
Ann Oncol 1997;8:899-903	Picci P et al[32]	365	6
Cancer Control 2005;12(1):57	Ebeid W[16]	31(with pathological fracture)	6
Present study		92	13

Bacci et al[33] retrospectively evaluated 540 patients in three multicenter studies over a ten year period. The local recurrence rate

was 8% in poor responders and 3% in good responders. 84% of the 540 patients underwent limb-salvage surgery and had a local recurrence rate of 6%. Local recurrence did not correlate with patient age, gender, histologic type, site and volume, pathologic fracture incidence, chemotherapy or type of surgical procedure. In our study the rate of local recurrence was 16% in poor responders and 3% in good responders.

In general amputation is considered in patients having extensive disease where a functional limb could not be reconstructed. The local extent of tumor on disease free survival was studied by Spanier ST al at the University of Florida[42]. The tumors were classified on the basis of local extension as : E1- the tumor touches but not elevate or penetrate the periosteum; E2- the tumor elevates but does not penetrate the periosteum; E3- the tumor penetrates into, but not through the periosteum; E4- there is minimum extraperiosteal extension without invasion of another structure,such as muscle, tendon or ligament; E5- the tumor invades one additional structure (a muscle, ligament or tendon) and E6- the tumor invades two or more structures adjacent to the bone. The cumulative probabilities of disease-free survival at five years

were 79.8 ± 9.3% for Enneking stage IIB without E6 tumor and 17.6 ± 11.3% for those who had stage IIB E6 tumor.

In patients where limb salvage is feasible, there could be still be patients who portend a poor prognosis and have increased risk of local recurrence depending on the soft tissue involvement. We tried to subclassify these patients as having extensive soft tissue disease based on specific criterias. These patients are found to have increased local recurrence., distant metastasis and decreased survival, though the results are not significant. The subclassification of soft tissue extension is similar to the Spanier ST et al classification of local extension of tumor. The extensive soft tissue disease corresponds to E6 subcategory and both these studies have shown decreased disease free survival in this group. Many centres consider tumor size and volume as prognostic factors[24,43].

Considering these facts the tumors that are of large volume and have extensive soft tissue extension are likely to have poorer survival. But the observation from different institutes have shown different results. Long term outcomes from the German group, Rougraff BT et al [23] have shown no difference in the disease free or overall survival between the groups undergoing limb salvage

surgery or amputation or disarticulation. The study from Italian Rizzoli institute, Bacci et al [24] has shown improved survival for limb salvage group and patients with low tumor volume.

	Subgroups	Disease free survival	Overall survival	P value
Rougraff BT [23]	Limb salvage surgery	41%	46%	
	Above knee amputation	41%	50%	
	Hip disarticulation	46%	46%	P=0.84
Bacci [24]	Limb salvage surgery	61%		
	Amputation	46%		P NS
	Volume < 150 ml	65%		
	Volume > 150 ml	52%		P NS
Spanier [42]	Stage IIB, No E6	79.8%	82.3%	
	Stage IIB, with E6	17.6%	37.8%	
Our study	Minimal soft tissue extension	61.7%	72.3%	
	Extensive soft tissue extension	30.7%	49.3%	P=0.33

Extensive soft tissue involvement have risk of developing distant metastasis similar to patients undergoing amputation in view of large volume disease. Hence if technically feasible these patients can be considered for limb salvage surgery.

The two most common prosthesis related complications we encountered was prosthesis infection and fracture. Prosthesis infection rate is 11.9% (n=11). These were treated by prosthesis removal in five and amputation in six. Prosthesis fracture rate is 18.4% (n=17), managed by redo prosthesis in eleven, prosthesis removal in three, and two refused treatment. Both infection and fracture occurred commonly in distal femoral prosthesis (8 infections and 14 fractures).

Prosthesis infection reported in the literature ranges between 0 to 35%[35,37]. In the Indian series reported by M V Natarajan et al, periprosthetic fracture and infection were the most common complications[36]. Prosthesis fracture is high in our patients, the reason may be due to use of stainless steel prosthesis. Since 2003, titanium prosthesis are being used and fracture rate has come down.

Prosthesis failure is defined as removal of the implant for any reason. The durability of endoprosthesis is influenced by many factors, but the anticipated event-free five-year survival for proximal femur reconstructions is 90%, about 50% for distal femur and just over 50% for proximal tibia[38]. In our study the overall prosthesis survival rate is 57%, for distal femur it is 66% and

proximal tibia 70%. Henshaw et al in 1998, reported on long-term prosthetic survival analysis of 100 patients treated with modular prosthesis[38]. The survival rate for all sites was 88%, for distal femur and proximal tibia, 90% and 78% respectively. The decreased prosthesis survival in our study is due to increased infection rates, prosthesis fractures and local recurrence.

The over-all rates of revision, infection, amputation and local recurrence are 33% (thirty patients), 12% (eleven patients), 21% (nineteen patients) and 13% (twelve patients) respectively. Malawer M et al similarly has reported on prosthesis survival and clinical results with use of large segment prosthesis in 82 patients and the reported over-all rates of revision, infection, amputation and local recurrence were 15%, 13%, 11% and 6% respectively[39].

Functional assessment is done following limb salvage surgery using either Musculoskeletal tumor society scoring system (MSTS) or the Toronto extremity salvage score (TESS). In the modified MSTS score proposed by Enneking et al[19] six factors-pain, function, emotional acceptance, supports, walking ability and gait are analyzed. In our study the average score was 25 out of 30, revealing a good functional outcome. In the literature functional assessment following limb salvage surgery has been compared

with amputation. In studies by Johansen R et al[41], Rougraff BT et al[25] limb salvage surgery is associated with better functional outcome than that observed with amputation.

CONCLUSION

1. Treatment of osteosarcoma has seen a paradigm shift in the management and today limb salvage surgery is possible in a majority of patients. Survival outcomes are excellent in our study and in par with international standards.
2. Needle biopsy is the preferred method of obtaining diagnosis, preferably to be done by the centre planning the definitive treatment.
3. Tumor response to neoadjuvant chemotherapy is the most important and valid prognostic factor predicting survival.
4. Extensive soft tissue involvement and tumor necrosis following neoadjuvant chemotherapy were found to be risk factors, for the increased local recurrence, that has been observed in this study. In patients with extensive soft tissue extension, limb salvage surgery can be considered if technically feasible, although they have decreased survival similar to patients undergoing amputations. Our study has got its limitations as the results of the analysis of this group of patients are not statistically significant and due to lesser number of patients. The influence of this subgroup of patients undergoing limb salvage surgery,

on local recurrence and survival needs to be validated in a prospective study involving more number of patients.

5. Functional outcome after limb salvage surgery is excellent in our patients.

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