The Clinical Profile of Children with Osteosarcoma
and
Outcome of Children Treated for Osteosarcoma on Two protocols
and
Quality of Life among those who had Amputation versus Limb Sparing Surgery

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF MD BRANCH VII (PEDIATRICS) EXAMINATION OF THE DR. M.G.R. MEDICAL UNIVERSITY, TAMIL NADU, CHENNAI TO BE HELD IN MARCH 2013.

CERTIFICATION

This is to certify that the dissertation titled " The clinical profile and outcome of children treated for osteosarcoma on two protocols and quality of life among those who had amputation versus limb sparing surgery " is a bonafide original work done by Dr David SuvarnaRajuParimi under my guidance during his academic term March 2011-February 2013 in the Paediatric Department of Christian Medical College, Vellore in partial fulfillment of the requirement for the MD - Paediatrics Examination of The Tamil Nadu Dr M G R Medical University, Chennai to be conducted in March 2013.

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- To my family, without their support and understanding, I could not have completed this work.
- All credit to God Almighty.

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INTRODUCTION

INTRODUCTION

Osteosarcoma is the most common primary malignant bone tumor with an incidence of 400 cases/year (US) and 5 year survival rate of 63%.Bimodal age distribution is seen in Osteosarcoma with >60% presenting in the first 2 decades of life and about 10% in >60years. The mean age of presentation in males is 18 years compared to 17 years in females. Males: Females ratio is 1.6:1 [1, 2]. The exact cause of osteosarcoma is unknown, even though rapid bone growth during puberty, environmental factors and genetic predisposition has been implicated; the vast majority apparently arises spontaneously.

Osteosarcoma arises from the metaphysis of long bones most cases. Most common site of osteosarcoma is around the knee joint; distal femoral in 44% and proximal tibia in 17%. Third common site is proximal humerus. Other rarer sites are axial skeleton and craniofacial bones[1]. Clinical features are pain, limp and swelling. Diagnosis is from clinical history, radiographic evidence and histological examination. Bone scan and CT/MRI help in assessing the extent of the tumour.

Accurate diagnosis of osteosarcoma is from:

- Clinical history
- Radiographic evidence
- Histological examination

- Extention of local involvement is known from:
  - Bone scan
  - CT
  - MRI

Clinical features of Osteosarcoma are:

- Sudden onset of symptoms
- Pain
- Swelling - Fusiform eccentric configuration.
- Painful mass appears near end of long bone.
  - Skin over it is stretched,
  - Shiny with dilated veins and
  - Increased local temperature,
  - Consistency soft to firm/hard.
  - Restriction of joint movements,
  - Limp,
  - Pathologically fracture

Classification of osteosarcoma:

- Primary/idiopathic
  - Conventional
  - Telangiectatic
  - Small cell
  - Fibrohistiocytic
  - Low-grade intramedullary
  - Multicentric
- Secondary
  - Pagets disease
  - Radiation associated with benign preexisting conditions
  - Radiation induced
  - Assocaited conditions

  Juxtacortical
- Parosteal
- Periosteal
- High-grade surface
- Dediffrentiated parosteal

Histological features of osteosarcoma are:

- Absolute criteria for diagnosis of this lesion are sarcomatous stroma and direct formation of tumour osteoid and bone by the malignant connective tissue
    - Fibroblastic (fibrosarcomatous)
    - Chondroblastic (chondrosarcomatous)
    - Osteoblastic
    - Telangiectatic
    - Small cell variety

Before 1970, the only mode of treatment was amputation with a survival rate of 15-20%. Adjuvant chemotherapy was started in 1970 and neoadjuvant chemotherapy was started in the late 70s. With chemotherapy and surgery, the 5 year survival for non-metastatic extremity osteosarcoma is currently 65-75 %.[3] Current approach is to treat patients with neoadjuvant chemotherapy to treat micrometastatic disease and to facilitate limb sparing surgery. Various combinations of cisplatin, doxorubicin, high dose methotrexate and ifosfamide are currently used [4].

Neo-adjuvant chemotherapy offers the unique opportunity to evaluate the response to chemotherapy histologically on the resected specimen. Most investigators have agreed that > 90% tumour necrosis is considered good response to pre-op chemotherapy in Osteosarcoma.[5- 11] The degree of histological response of the primary tumour was closely related to the risk of systemic metastatic recurrence [7, 12] Response to pre-op chemotherapy was confirmed as the most important prognostic factor in osteosarcoma[13]. Post-operative treatment modifications in poor responders have failed to show significant change in outcome. [9]

The goal of surgical treatment is to safely remove the tumour yet preserve as much extremity function as possible. Depending on the anatomical location of the

tumour this can be achieved by ablative techniques such as amputation, disarticulation or by limb salvage procedures. [14, 15]

Quality of life in osteosarcoma survivors have assessed using various scoring systems such as MSTS(musculoskeletal tumour society), Toronto Extremity Salvage Scale (TESS) scores, Functional Mobility Assessment (FMA).[16] Traditionally, physicians have believed that limb-salvage surgery has functional and cosmetic advantages over amputation, yet the literature is equivocal. Robert et al performed a study on 57 adolescents treated for extremity osteosarcoma, (33 limb salvage and 24 amputation) on various aspects of quality of life, body image, self-esteem, and social support and found that participants with more functional lower limbs had better quality of life than did those with less functional lower limbs regardless of whether they underwent amputation or limb-salvage surgery [17].

This study is undertaken to look at clinical profile of children with osteosarcoma, treatment refusal and abandonment of treatment in this group. In our unit, children are treated on either a two drug (Cisplatin + Doxorubicin) or a three drug (Cisplatin + Doxorubicin + high dose methotrexate) protocol, based on the financial status. We will compare the outcome of children treated on these two protocols in terms of age at presentation, localized or metastatic disease, response to pre-op chemotherapy and overall survival. We will also look at treatment refusal and abandonment in this study population. We have devised a simple scoring system assessing functional ability of our patients in their day-to-day life. This has been pretested in 6 patients for ease of administration for direct interview or telephone interview. We will compare the quality

of life of survivors who had limb salvage vs amputation surgery using this scoring system.

LITERATURE REVIEW

EPIDEMIOLOGY

Osteosarcoma is the 8th commonest malignant tumour of childhood representing about 2.4% of all malignancies in this age group[1] and is the most common malignant bone tumor seen in both children and adolescents (19% of all bone tumours)[18]. Overall incidence is about 5 per million in children less than 19 years[18]. Osteosarcoma has a bimodal age distribution with the first peak seen during the adolescent growth spurt[19]. The second peak occurs after 60 years of age.

The incidence of osteosarcoma is higher in males than in females, occurring at a rate of 5.4 per million persons per year in males vs. 4.0 per million in females [18].

ETIOLOGY

The exact etiology of osteosarcoma is still unknown however; epidemiologic, environmental and genetic factors have been studied.

Incidence of osteosarcoma is the highest during the adolescent growth spurt suggesting a close relationship[18]. Ottaviani suggests that rapidly proliferating cells may be more susceptible to oncogenic agents and mitotic errors[18].

The environmental factor that is definitely known to predispose to osteosarcoma is exposure to radiation[18]. Exposure to alkylating agents may also be associated with osteosarcoma[18].

Several genetic factors have been found to predispose to osteosarcoma. Hereditary retinoblastoma which is associated with RB1 gene[18] and Li-Fraumeni syndrome is associated with p53 gene[20].

CLINICAL PRESENTATION

Osteosarcoma is a highly aggressive tumor which usually involves the long bones and often metastasizes to the lungs[18]. Tumors are thought to originate from the metaphysis of long bones in most cases and are primary mesenchymal tumors that are characterized histologically by the production of osteoid by malignant cells[18].

Most common site of osteosarcoma is around the knee joint; distal femoral in 44% and proximal tibia in 17%. Third common site is proximal humerus. Other rarer sites are axial skeleton and craniofacial bones [1.18,19,21].

Symptoms include pain, swelling and a limp with duration of symptoms ranging from 1-3months [1,20,22].

60-80% of the children have localized disease at presentation and around 20-40% of them have metastatic disease[18,22,23].

HISTOLOGY

Osteosarcoma is defined by the presence of malignant mesenchymal cells which produce osteoid. High-grade osteosarcoma,is the most frequent subtype and accounts for 80–

90% of all osteosarcomas. Other subtypes are osteoblastic, chondroblastic, and fibroblastic. Other high-grade types are telangiectasic, small cell osteosarcoma, and high grade surface osteosarcoma. Low-grade central osteosarcoma and paraosteal osteosarcoma are low-grade malignancies, while periosteal osteosarcoma is an intermediate-grade[22].

TREATMENT

Before 1970, the most common mode of treatment was amputation. Despite good local control, most patients developed metastasis within a short time and succumbed to their disease. The 2 year overall survival was 15-20% and 5 year disease free survival rate was 12%[18].

Adjuvant chemotherapy was started in 1970[1] with dramatic improvement in outcome. Doxorubicin and methotrexate were among the first drugs to be used successfully[18]. Cisplatin and ifosphamide were subsequently added. The goal of adjuvant chemotherapy was to eradicate the micro metastasis which is present at the time of diagnosis. It was found that combination of different chemotherapeutic agents yielded better results as compared to single drug regimes. This improved the disease free survival upto 70%[1].

Neo-adjuvant chemotherapy was started in the late 70s[1]. This was used to treat micro metastatic disease and to facilitate limb sparing surgery[18,19]. Neo-adjuvant chemotherapy offers the unique opportunity to evaluate the response to chemotherapy histologically on the resected specimen. Most investigators have agreed that > 90% tumour necrosis is considered good response to pre-op chemotherapy in Osteosarcoma[1,18,19,21]. The degree of histological response of the primary tumor was closely related to the risk of systemic

metastatic recurrence[6,18] . Response to pre-op chemotherapy was confirmed as the most important prognostic factor in osteosarcoma[18]. Post-operative treatment modifications in poor responders have failed to show significant change in outcome[18].

With chemotherapy and surgery, the 5 year survival for non-metastatic extremity osteosarcoma is currently 65-75 %[1]**.**

CHEMOTHERAPEUTIC AGENTS AND REGIMENS USED IN OSTEOSARCOMA

At present, high dose methotrexate, doxorubicin, cisplatin and ifosfamide are considered the most efficacious in osteosarcoma and are used in various combinations.

Methotrexate is an antifolate drug which blocks the action of dihydrofolatereductase. It was one of the first drugs found to be efficacious in osteosarcoma[18,19]. High dose methotrexate requires good supportive care including hydration, alkalization of urine and folinic acid rescue. Inspite of this some patients will experience severe toxicity. The development of acute renal failure is the potentially life threatening complication. Methotrexate is primarily cleared by the kidney and renal dysfunction will delay the clearance, increasing the other toxic effects of the drug[18].

Doxorubicin is an anthracycline which was first used in osteosarcoma in early 1070s[18]. This drug continues to be included in current treatment regimes. Anthracycline therapy can be associated with both early and late cardiotoxicity. Severe cardiomyopathy has been reported during long term follow up of children who have been treated with doxorubicin.[18]

Cisplatin was also found to be efficacious in the treatment of osteosarcomas[18] and is used in multiagent regimens in the treatment of osteosarcoma. Cisplatin therapy requires supportive care with hyperhydration and the major toxic effects include ototoxicity and nephrotoxicity.

Ifosphamide has proven activity against osteosarcoma and has been included in many chemotherapy regimens.[18] Supportive measures decrease the incidence of haemorrhagicuropathy. Ifosfamide is also associated with significant CNS toxicity.

The above 4 agents are currently used in various combinations however; the best combination is still under debate.

Bramwell et al[24] from European osteosarcoma intergroup, compared doxorubicin(DOX) and cisplatin(CDDP) with doxorubicin, cisplatin and the additional high dose methotrexate(HD MTX) and found that disease free survival(DFS) was 57% vs 41% for CDDP/DOX as compared to CDDP/DOX/HD MTX. The overall survival was 64% Vs 50% which was not significant. They concluded that the results with CDDP/DOX were comparable to CDDP/DOX/HD MTX. Souhami et al also found 44% event free survival (EFS) with CDDP/DOX[25].

Addition of high dose methotrexate of 8-12gm/m2 to the above regimen has shown to improve 5 year event free survival by another 10-15%[26].

Table 1: Results of selected osteosarcoma protocols for localized extremity osteosarcoma.

S.No	Protocol	Patients	Preoperative chemotherapy	Response	Postoperative chemothearpy	Event-free	References
1	COSS-80	116	MTX-HD, DOX,DDP	Any	MTX-HD, DOX,DDP	68% at 2.5 y	Winkler 1984
2	COSS-82	59	MTX-HD, DOX,DDP	Good	MTX-HD, DOX,DDP	68% at 5 y	Winkler 1988
3	SSG T-10	97	MTX-HD	Good	MTX-HD, BCD	54% at 5 y	SAETER 1991
4	EOI-80831	99	DOX,DDP	Any		57% at 5y	Bramwell 1992
		99	MTX-HD, DOX,DDP	Any		41% at 5 y	Bramwell 1992
5	EOI-80861	199	DOX,DDP	Any	DOX,DDP	44% at 5 y	Souhami 1997(49)
6	IOR/OS-2	164	MTX-HD, DOX,DDP	Good	MTX-HD, DOX,DDP	59% at 10y	Bacci 2000
				Poor	MTX-HD, DOX,DDP, IFOS,ETO		
7	EOI-8629-4690	250	DOX,DDP	Any	DOX,DDP	41% at 3y	Lewis 2003
		254	DOX,DDP+ G-CSF	Any	DOX,DDP+ G-CSF	46% at 3Y	
8	SSG-VIII	113	MTX-HD, DOX,DDP	Good	MTX-HD, DOX,DDP	63% at 5Y	Smeland 2003
9	INT 0133	172	MTX-HD, DOX,DDP	Any	MTX-HD, DOX,DDP	71% at 3y	Meyers 2005

In a meta analysis of 19 studies where neoadjuvant chemotherapy was given ,the mean 5-year event free survival (EFS) was 48% for 2- drug regimens and 58% for 3 drug regimens, with a 5- year overall survival (OAS) of 62% and 70%, respectively. This analysis further showed that 4 drug regimens including methotrexate plus adriamycin plus cisplatin plus ifosfamide (MAP(Ifo)) had significant better outcome (EFS: HR=0.701 (95% confidence interval [95% CI]: 0.615-0.799); OAS: HR=0.792 (95% CI: 0.677-0.926) than 2-drug regimens, but there was no significant difference between MAP

and MAPIfo or plus etoposide[4].Currently Combination of cisplatin, doxorubicin and high dose methotrexate, given pre and postoperatively, is considered standard treatment for localized high grade osteosarcoma.

LIMB SALVAGE SURGERY

Before chemotherapy was used, osteosarcomas were treated with ablative surgery alone. This had a poor outcome as majority of patients developed metastasis and the five-year overall survival (OS) was less than 20%[27].

Chemotherapy alone does not even come close to controlling the primary tumor. Surgery therefore, cannot be avoided if cure is to be achieved.

The most important risk factor for local failure is inadequate surgical margins. With the introduction of neo-adjuvant chemotherapy, surgery became easier as the pre treated tumors were better demarcated against the surrounding tissues[28] this allowed more limb salvage procedures.

A good tumor response also contributes to the safety of surgery. Several groups have found local failure rates which were lower for good as opposed to poor responders to preoperative chemotherapy. [29]

Response and margins interact, and the local failure rate becomes excessive if inadequate margins and poor response come together. Limb-salvage surgery may be associated with

increased local failure rates in poor responders, implying that margins are sometimes not as wide as assumed during surgery[30, 31].

The goal of surgical treatment is, therefore, to safely remove the tumour yet preserve as much extremity function as possible. Over the past 3 decades surgical techniques have improved and led to newer types of reconstructive surgeries with use of prosthesis and in the past two decades, there has been a major shift away from amputations towards limb salvage surgery.

QUALITY OF LIFE AMONG SURVIVIORS (COMPARING LIMB SALVAGE vs AMPUTATION)

Improvement in the chemotherapeutic regimes and availability of reliable reconstruction options in the treatment of osteosarcoma has resulted in improved mortality and morbidity. This makes quality of life after treatment completion an important consideration.

WHO defines Quality of Life as "individuals'perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". This definition highlights the multiple components that contribute to "quality of life" which according to Nagarajan[31] , would include physical functioning, disease/treatment related symptoms, psychological functioning and social functioning.

Literature on quality of life in survivors of osteosarcoma is varied in terms of aims and assessment tools. Various scoring systems such as MSTS(musculoskeletal tumour

society), Toronto Extremity Salvage Scale (TESS) scores, Functional Mobility Assessment (FMA) have been used.[16] Traditionally, physicians have believed that limb-salvage surgery has functional and cosmetic advantages over amputation, yet the literature is equivocal. Robert et al performed a study on 57 adolescents treated for extremity osteosarcoma, (33 limb salvage and 24 amputation) on various aspects of quality of life, body image, self-esteem, and social support and found that participants with more functional lower limbs had better quality of life than did those with less functional lower limbs regardless of whether they underwent amputation or limb-salvage surgery [32].

Studies done by Mathew R et al[2], Rougraff et al[3] and Renard et al[4] reported that functional outcome and patient satisfaction appear to be at least as good, and probably better after skeletal reconstruction than after amputation. They also reported that limb sparing surgery is associated with additional surgical procedures and complications which are three times more common than amputation group. In another study Otis et al[5] reported that prosthetic reconstruction provides superior function whereas, the patients studied by Harris et al[6] functioned similarly.

Other studies have also shown that although limb salvage surgery seems to have better outcome in terms of function[789], there was a higher rate of complications 89 and there

was no significant difference in the two groups when patients' perception of quality of life was compared. [10]

No studies were found to compare these two groups in the Indian scenario.

AIMS AND OBJECTIVES

i) To study the clinical profile of children with osteosarcoma.

ii) Outcome of children treated for osteosarcoma on two chemotherapy protocols

iii) To look at treatment refusal and abandonment in the study population

iv) To compare the quality of life in children with osteosarcoma who had amputation versus limb sparing surgery**.**

METHODOLOGY

METHODOLOGY

Children and adolescents upto 18 years of age with a diagnosis of osteosarcoma, who attended Paediatric Hematology- Oncology division of Department of Pediatrics, Christian Medical College, Vellore from 2004 till March 2012 were included in this study. Their demographic data, symptoms and signs, investigations such as biopsy reports, imaging and bone scans were collected from the hospital clinical record system.

Treatment details were obtained from the data base in the department. The follow up information was also collected from the hospital clinical records. Quality of life of those who have completed treatment and on follow up was done using an indigenously prepared and pretested questionnaire.

Diagnosis of Osteosarcoma was confirmed in all patients from the clinical history, radiological findings and histopathological examination. Children were then divided into those with high grade osteosarcoma and others. Those with high grade osteosarcoma were treated on one of the two treatment protocols based on their financial status. Children without any financial constraints received a three drug regimen (MAP) using Cisplatin 100mg/m2/day on day-1 + Doxorubicin 25mg/m2/day x 1-3 days + Methotrexate 8-12gm/m2/day on days 21 and 29.

In those with limited finance methotrexate was omitted(CD). Response to treatment was assessed at surgery by percentage of tumour necrosis for those who received neoadjuvant chemotherapy. Adjuvant chemotherapy was then planned based on patient affordability as well as response to treatment. Those children who have completed treatment were

followed up regularly for recurrence of disease, orthopedic intervention and complications of treatment as well as for quality of life.

For the purpose of this study, the following information was collected from all children diagnosed to have osteosarcoma (Appendix-1): demographic data, age and sex distribution of patients, localized vs metastatic disease at diagnosis, joints involved at presentation, histological types of osteosarcoma. Those with high grade osteosarcoma were divided into CD or MAP group based on the pre-operative chemotherapy received and further analyzed for response to treatment, type of surgery, completion of treatment, abandonment, relapse as well as survival.

The study was approved by the Institution Review Board. Both the proformas – Data collection as well as QOL questionnaire were filled up after obtaining consent/Assent. Both children and parents were provided with information sheets regarding proforma/questionnaire. The information sheet with consent and assent forms were provided in English as well as local languages.

Quality of life of the survivors was analyzed with a pretested questionnaire in 6 patients (3 direct and 3 by telephonic interview.) Questionnaire comprised of simple questions related to activities of daily living in the community. (Appendix -2) Quality of life was compared among survivors who had amputation versus limb sparing surgery. Children were also asked to rate them against their peers for day to day activities of life. This depicts their perception of their quality of life.

Statistical methods- used software SPSS 16, Basic frequency distribution, Chi square test, t-test and survival analysis.

RESULTS

RESULTS

SECTION I : CLINICAL PROFILE OF OSTEOSARCOMA STUDY POPULATION

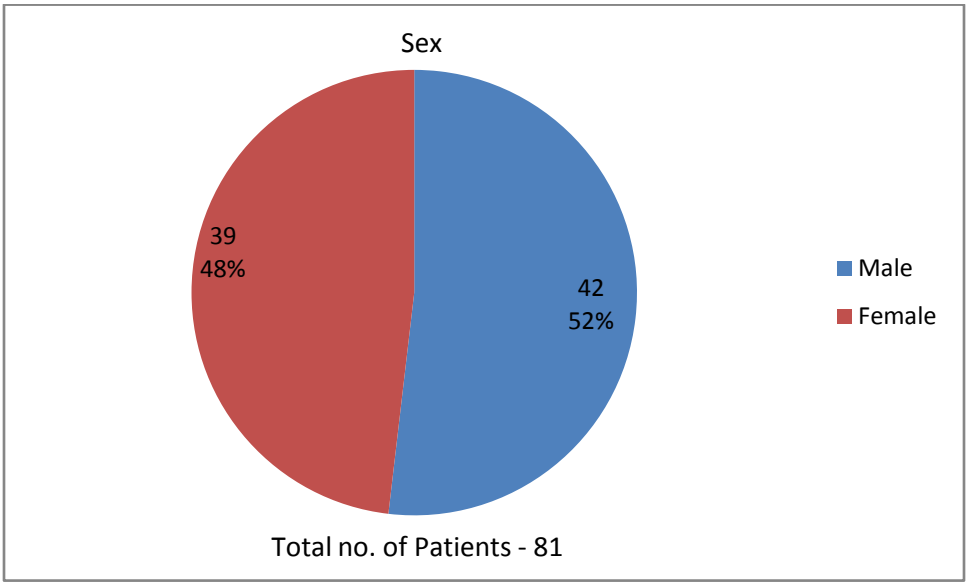
Medical Records of 81 children with osteosarcoma, who were seen in Paediatric Hematology-Oncology outpatient clinic at Christian Medical College Vellore during the study period 2004 to 2012 March, were analyzed. The clinical profiles of these children were studied.

Table 1: Age and sex distribution

Age	Male	Female	Total
<5 years	2 (5%)	2 (5%)	4 (5%)
6-10 years	13(30%)	10(27.5%)	23 (28 %)
>10 years	27(65%)	27 (67.5%)	54 (67%)
Total	**42**	**39**	**81**

The age and sex distribution of the study population is shown in Table-1. The mean age at presentation was 11.4 years, with a range of 3 to 17 years. There were four children less than 5 years of age at diagnosis, their primary tumours were in the distal femur(2) , proximal tibia(1) and proximal humerus(1). 67% of children were adolescents at diagnosis.

Figure 1:Sex distribution



Male to Female ratio in this study population was 1:1.07.

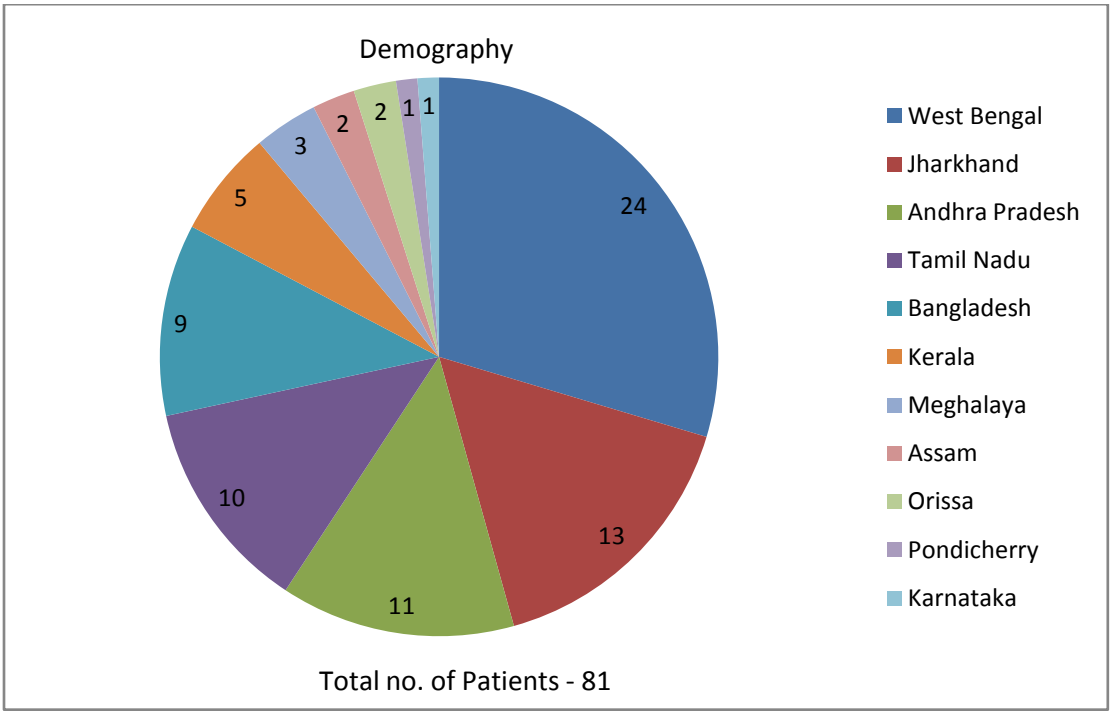


Figure 2: Demographic distribution

Table 2: Geographic distribution of patients

Place	**Number**	**Percentage**
West Bengal	24	29.6%
Jharkhand	13	16%
Andhra Pradesh	11	13%
Tamil Nadu	10	12.3%
Bangladesh	9	11.1%
Kerala	5	6.1%
Meghalaya	3	3.7%
Assam	2	2.4%
Orissa	2	2.4%
Pondicherry	1	1.2%
Karnataka	1	1.2%
Total	**81**	**100%**

Table 3: Duration of symptoms

Duration	**Number**	**Percentage**
<2 months	40	49 %
2-4 months	22	27 %
>4 months	19	24 %
Total	**81**	**100%**

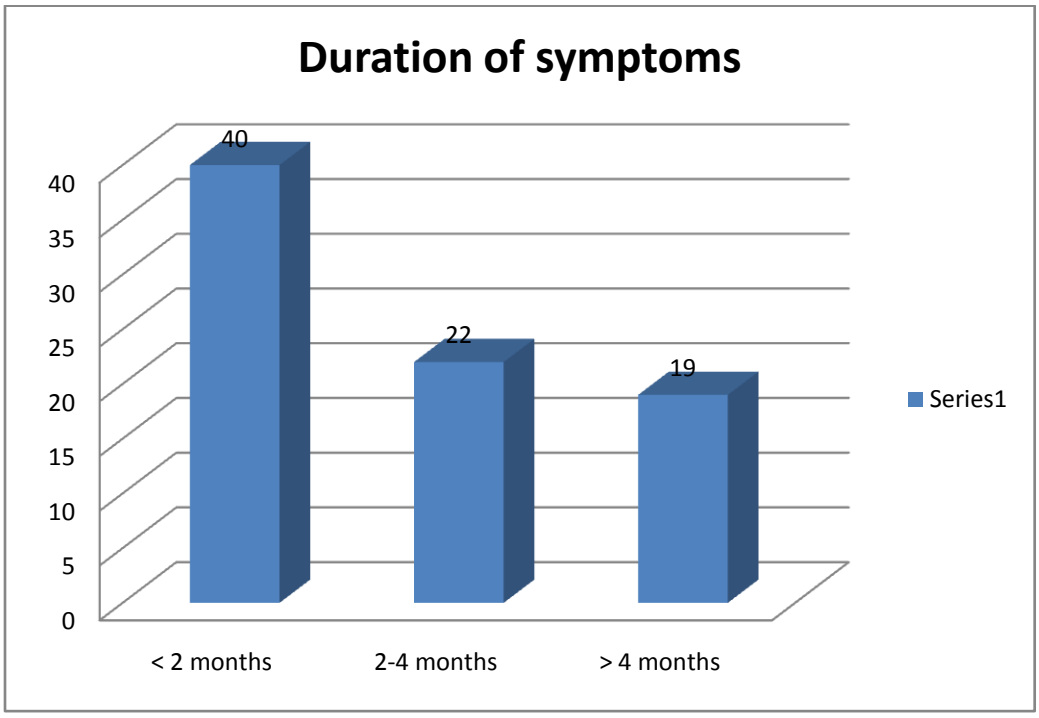


Figure 3:Duration of symptoms

The duration of symptoms before diagnosis was established varied from 0.25-18months with a mean duration of 3.31 months**.**75%of children presented within 4 months of onset of symptoms.

Table-4A:Presenting symptom vs duration of symptoms

Presenting symptom	<2 months	2-4months	>4months	Total
Pain & Swelling	27	11	11	49
Pain & swelling with fever	3	3	2	8
Swelling alone	5	4	0	9
Pain alone	1	1	2	4
Path. fracture with swelling	1	0	2	3
Path. Fracture with pain & swelling	3	1	1	5
Pain, swelling &fungating ulcer	0	1	0	1
Weakness of lower limbs	0	0	1	1
Weakness of lower limbs with pain	0	0	1	1
Total	**40**	**21**	**20**	**81**

Table 4B: Age at diagnosis vs duration of symptoms

Age group	</=2months	2-4months	>4months	Total
</=10years	15	8	4	27
> 10years	25	14	15	54
Total	**40**	**22**	**19**	**81**

The above tables show duration of symptoms vs presenting symptom and age at diagnosis in our patients. Pain and swelling of the limb was the most common symptom. It was interesting to note that 10%of children had pathological fracture at presentation; all of them were >10years of age, nine had localized disease and five of them had biopsies done elsewhere prior to coming to CMC. Two children had vertebral disease and presented with weakness of lower limbs and another child presented with a fungating ulcer in the arm. There was no significant difference between presenting symptom and duration or age at diagnosis in this group

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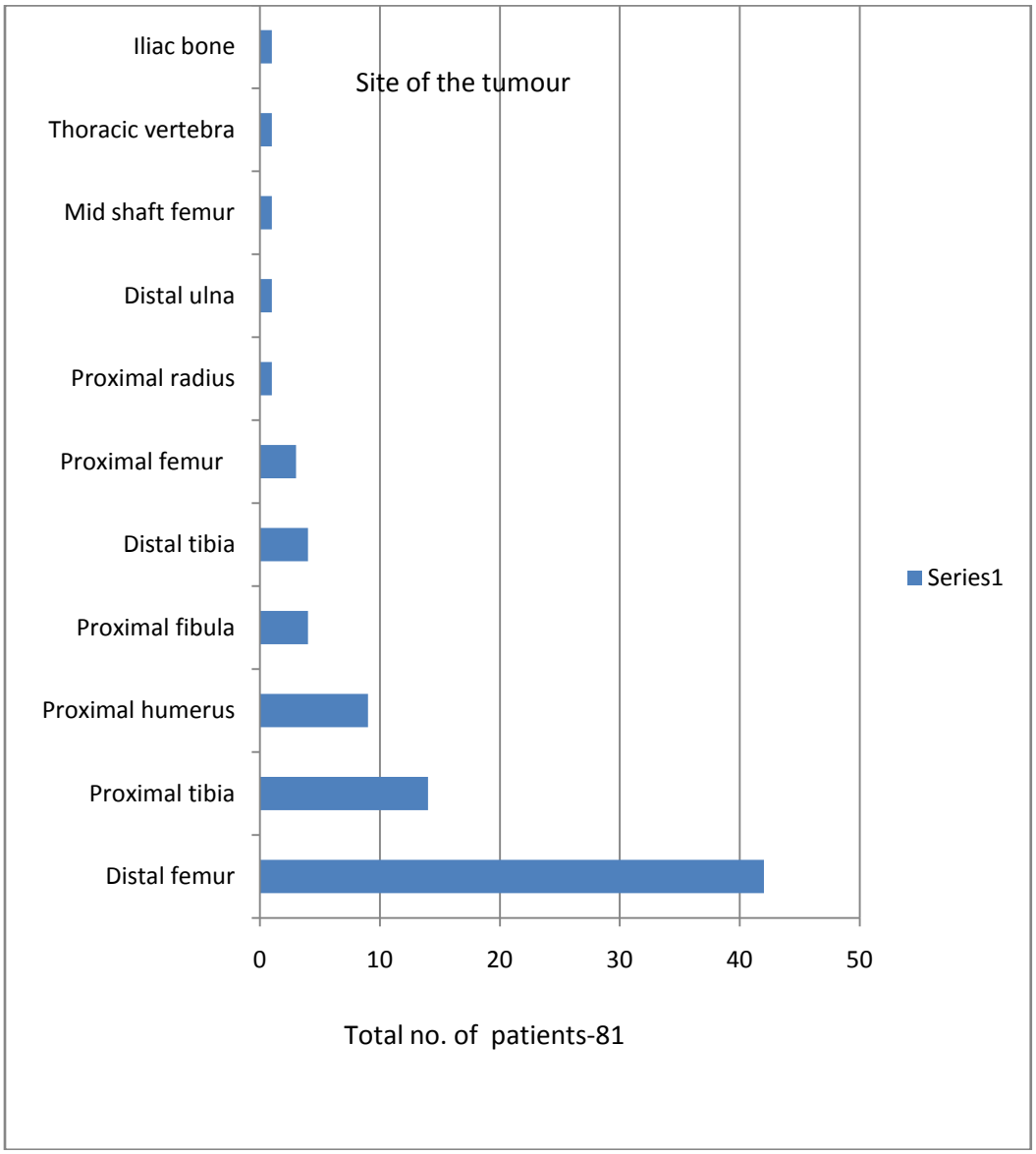
Figure 4: Site of primary tumour



The most common site of the tumour was in the distal femur 52% (42/81) followed by 17.2% (14/81) each in proximal tibia and proximal humerus. 75% (61/81) of the children had thetumour around the knee joint.

Table 5: Biopsy report

Biopsy report	Number
High grade	71
Intermediate Grade	3
Low grade	7
Total	**81**

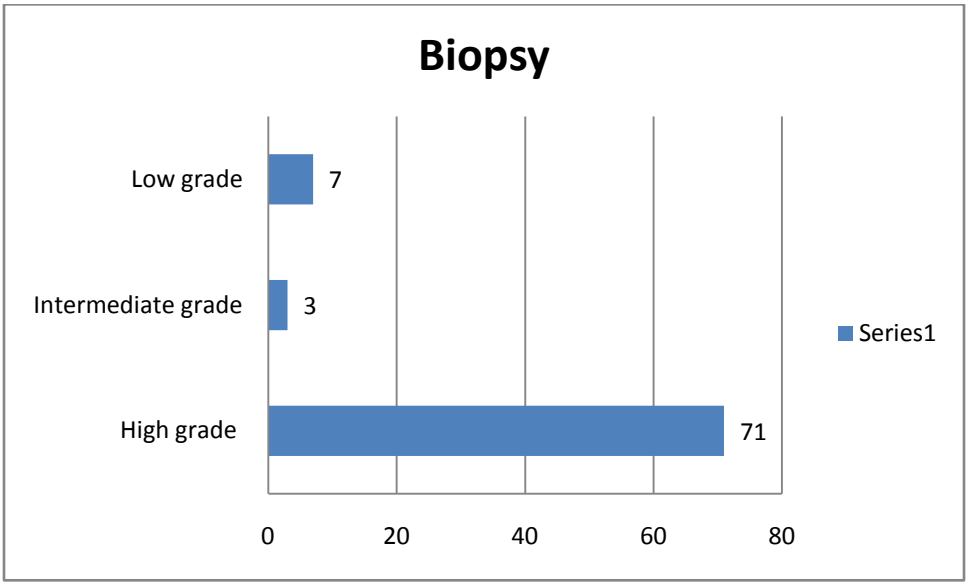


Figure 5: Biopsy report

Diagnosis of osteosarcoma was established based on histopathological examination. The tumour was divided into high, intermediate or low grade based on standard criteria. 71/81 children had high grade osteosarcoma.17/81 children had biopsies done elsewhere and diagnosis was made before coming to CMC; these biopsies were reviewed here and diagnosis of osteosarcoma was confirmed.

Table 6: Detailed Biopsy report

Biopsy report	Number
High grade	
Osteosarcoma (CAN WE CLUB THIS WITH THE HIGH GRADE?)	7
High grade spindle cell osteosarcoma	3
High grade osteosarcoma with telangiectatic change	1
Poorly differentiated osteosarcoma	2
High grade osteosarcoma	58
Intermediate Grade	
Intermediate grade osteosarcoma	3
Low grade	
Low grade spindle cell osteosarcoma	1
Low grade osteosarcoma	3
Low grade chondroblasatic osteosarcoma	2
Chondroblastic osteosarcoma	1
Total	81

Majority of children had high grade disease.

Table 7: Stage of disease at diagnosis.

Disease	**Number**	**Percentage**
Localized	67	83%
Metastatic	14	17%
Total	**81**	**100%**

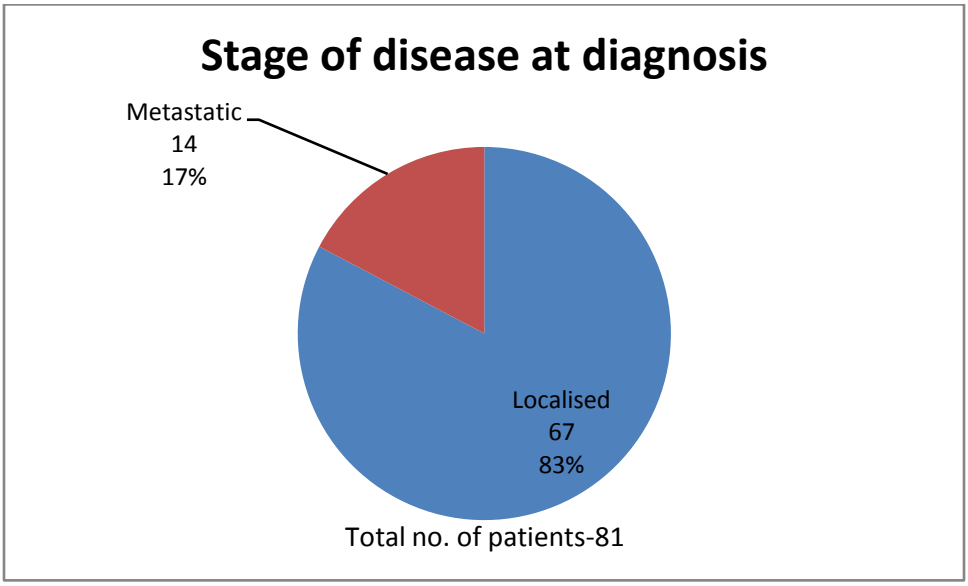


Figure 6: Stage of disease at diagnosis

Based on radio-imaging and nuclear scan, the tumour was divided into localized or metastatic disease at diagnosis. 83% of children in this group had localized disease at diagnosis.

Table 8: Site of tumourVs metastatic disease

Site	**Localized**	**Metastatic**	**Total Number**
Distal femur	33	8	41
Proximal humerus	6	3	9
Proximal tibia	13	2	15
Thoracic vertebra	1	1	2
Proximal fibula	5	0	5
Distal tibia	3	1	4
Proximal femur	2	0	1
Proximal radius	1	0	1
Distal ulna	1	0	1
Mid shaft femur	1	0	1
Iliac bone	1	0	1
Total	67	14	81

Knee joint was the most common site of tumour in localized disease as well as in those who presented with metastatic disease. Sites of metastasis were bone (8), lungs (5) and both(1).There was no significant difference in duration of symptoms between localized or metastatic disease.

Table 9: Treatment options chosen by those completed treatment

Treatment options at diagnosis	**Number**
Opted for treatment	77
Opted against treatment	nil
Transferred to another centre	2
Palliative treatment	2

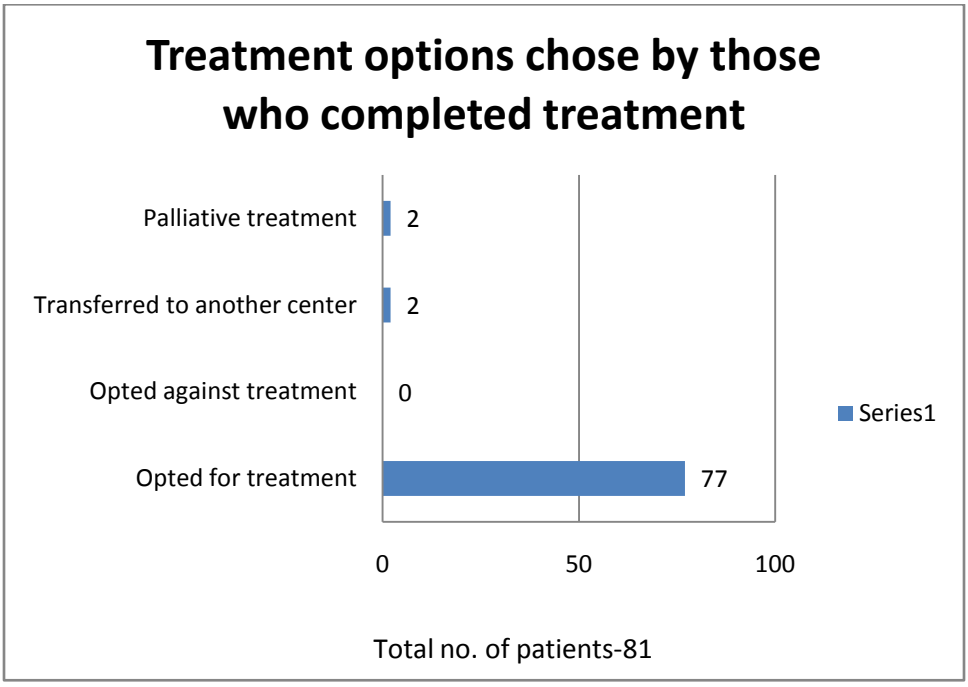


Figure 7: Treatment options

After establishing the diagnosis, various treatment options were discussed with the family based on the type of tumour, extend of the primary leasion, localised vs. metastatic disease. None of our patients opted against some form of treatment.

Table 10:Outcome of all the cases included in this study at the time of analysis

Completed treatment , in first CR (alive & disease free)	30
Completed treatment, in second CR (relapsed, alive and disease free)	5
Completed treatment , relpased and died	10
Completed treatmet, died of other causes	1
Completed treatment, lost to follow up	3
Sent home on Palliation	2
Transferred to other centres	2
Abandoned treatment	16
Died while on treatment	3
On treatment	9
Total	81

CR- complete remission

48/72 (66%)children completed treatment. Excluding the 9 children who are currently on treatment, the overall survival in our group is 35/72 (48%) and event free survival is 30/72(41%). The abandonment rate was 22% (16/72(22%).

Table 11: **Details of 12 patients who are not included in the analysis. With their Age, site, biopsy, localized/metastatic, treatment received and outcome.**

	Age	**Site**	**Biopsy**	**Localised /Metastatic disease**	**Rx.received**	**Outcome**
1	13	Distal femur	High grade OS	Localised	Outside 3cycles (details not known), here CDx3, Surgery(LSS), MAPx8, Recurrence, Surgery (Amputation)	Lost to follow up
2	13	Distal femur	Osteosarcoma	Localised	Outside 6cycles of cyclophosphamide, cisplatin & etoposide, Surgery (LSS), IFOS+ETO x 2.	Lost to follow up after that
3	10	Proximal humerus	Possible osteosarcoma	Localised	Outside one course of vincristine, cyclophosphamide & doxorubicin, here MAPx2, Surgery (LSS), MAPx4	Alive and disease free
4	15	Distal femur	Poorly differentiated osteosarcoma	Localised	Outside 2cycles of chemo (details not known), here Surgery (amputation), IFOS+ETO x 4	Lost follow up after that
5	6	Proximal tibia	High grade OS with telangiectatic changes	Localised	Amputation, MAP x 6	Alive and disease free
6	10	Distal tibia	High grade OS	Metastatic	Surgery (amputation), CDx2	Refused treatment, came back with extensive

						mets and died
7	13	Distal tibia	High grade OS	Localised	Surgery (amputation), CDx5.	Lost to follow up after that
8	10	Distal ulna	High grade telangiectatic OS	Localised	Surgery (amputation), CDx6,MAPx1,	Relapsed with pulm. Mets, Surgery (thoracotomy excision), IFOS+ETO x3. Now alive and well
9	6	Distal femur	High grade OS	Localised	Surgery (amputation) done, went back to local hospital (transferred) for continuation further chemotherapy.	Lost to follow up after that
10	15	T4 vertebra	Low grade OS	Localised	CD was planned to take in local hospital (transferred) and come for further assessment, Lost to follow up with us, but seen in PMR where he had spine decompression.	Lost to follow up with us but is alive with paraplegia
11	14	Distal femur	High grade OS	Metastatic	Refused treatment, wanted palliation so sent home on oral etoposide	Lost to follow up after that
12	14	Distal femur	High grade OS	Metastatic	Refused treatment, wanted palliation so sent home on oral morphine and paracetamol	Lost to follow up after that

SECTION II:

OUTCOME OF PATIENTS TREATED ON 2 DIFFERENT PRE-OP CHEOTHERAPY PROTOCOLS -CISPLATIN AND DOXORUBICIN(CD) Vs CISPLATIN, DOXORUBICIN AND METHOTREXATE(MAP)

In this section we plan to compare two chemotherapy protocols used in our unit for children with high grade osteo sarcoma.51 children with high grade osteosarcmawho were treated on one or the other protocols (CD or MAP) were included in further analysis. Those who are currently on treatment was also excluded.

Table 12: Treatment Groups

Group	Chemo. Drugs	Number
1	MAP	30
2	CD	21
Total		**51**

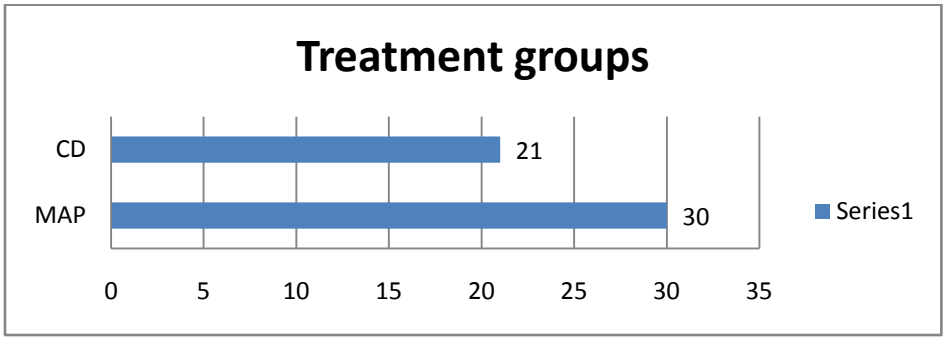
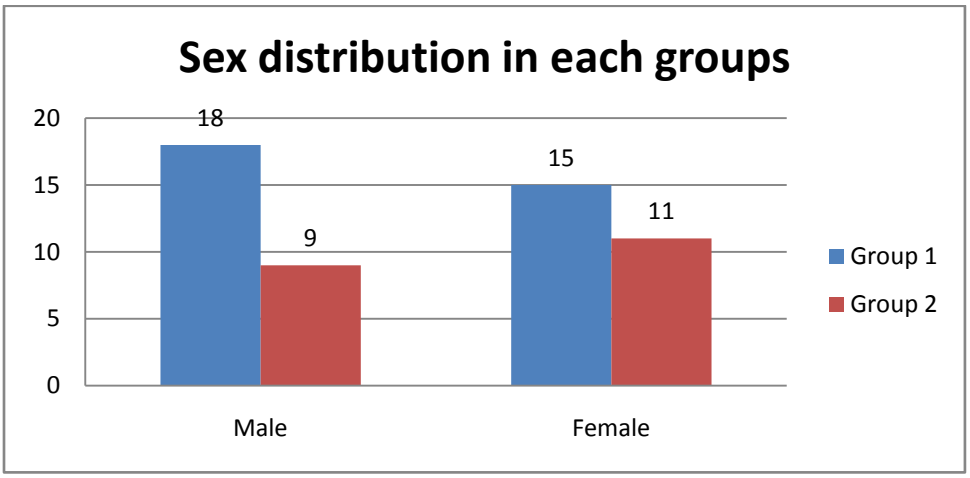


Figure 8:Treatment groups

Figure 9: Sex distribution in each groups



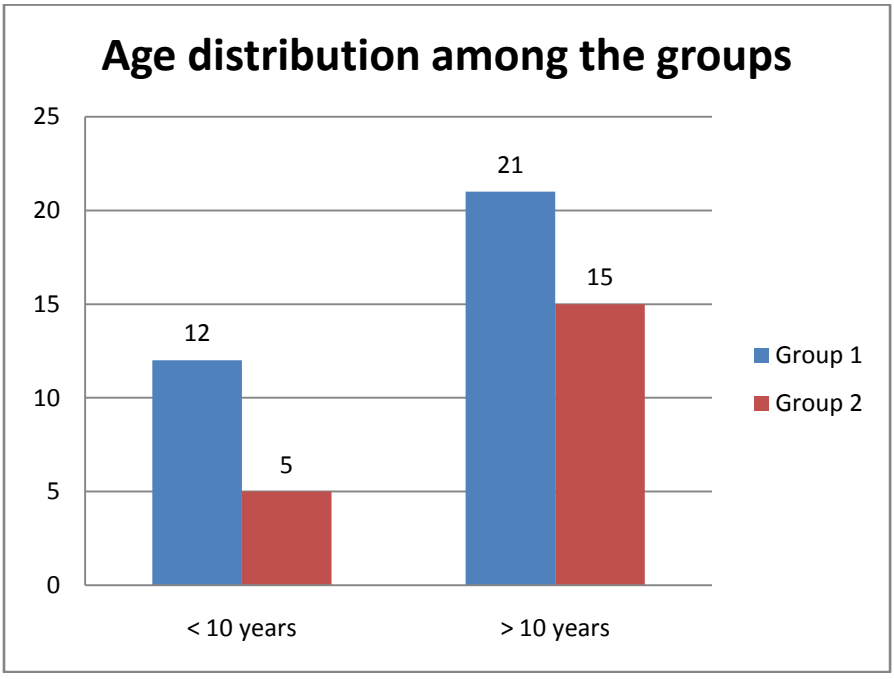


Figure 10: Age distribution among the groups

Figure 11:Duration of symptoms in each group

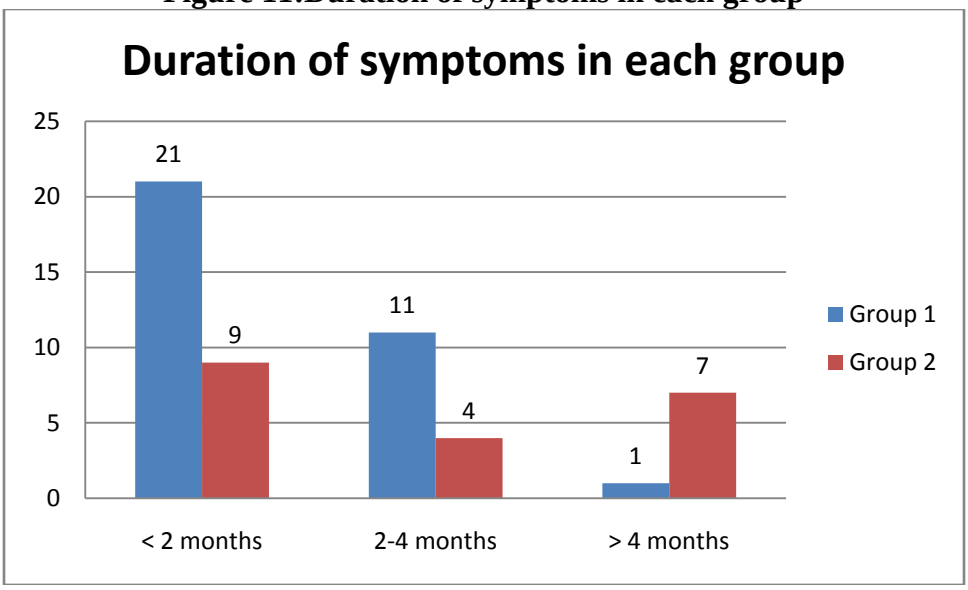
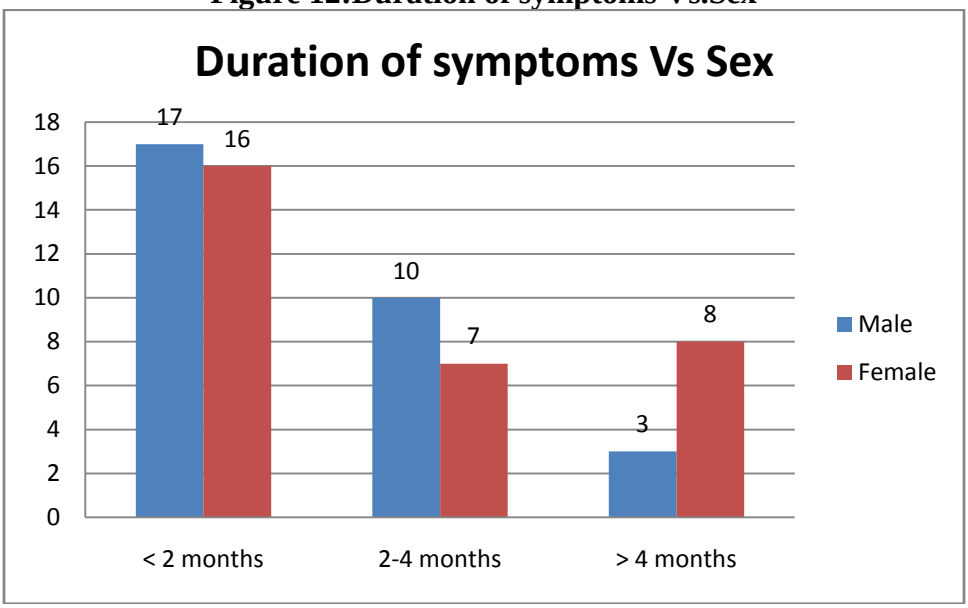


Figure 12:Duration of symptoms Vs.Sex



In almost half of them symptoms present within 2 months duration

Figure 13:Duration of symptoms Vs. Age groups

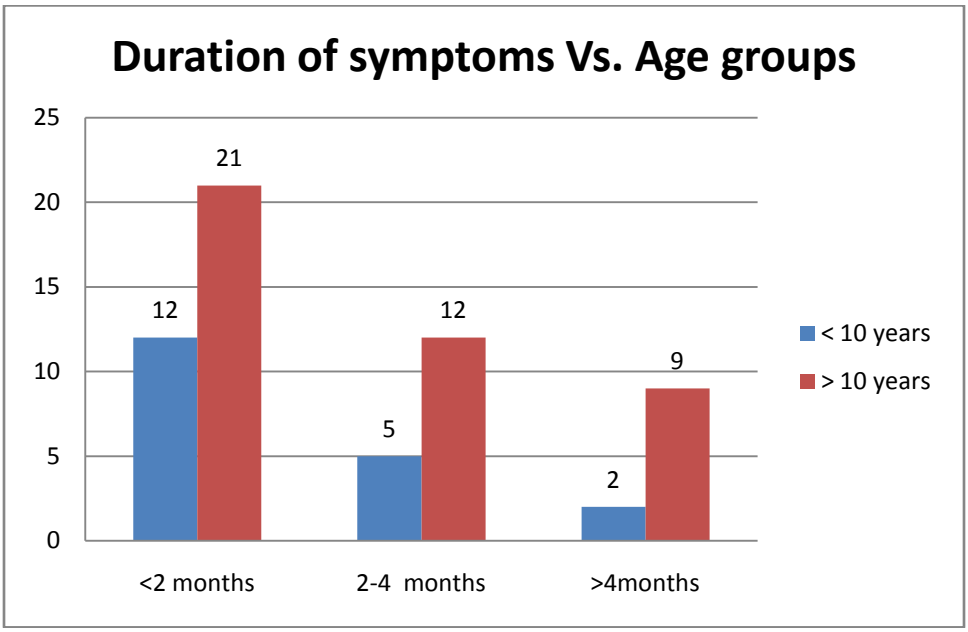
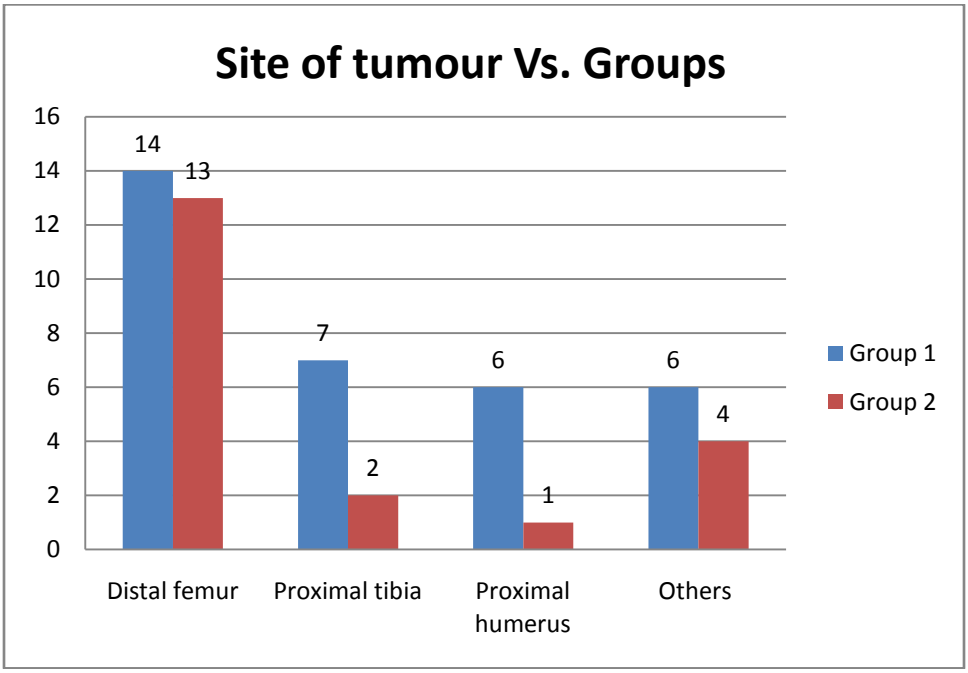


Figure 14: Site of tumour Vs. Groups



Distal femur is the most common tumour site

Figure 15: Site of tumour Vs.Sex

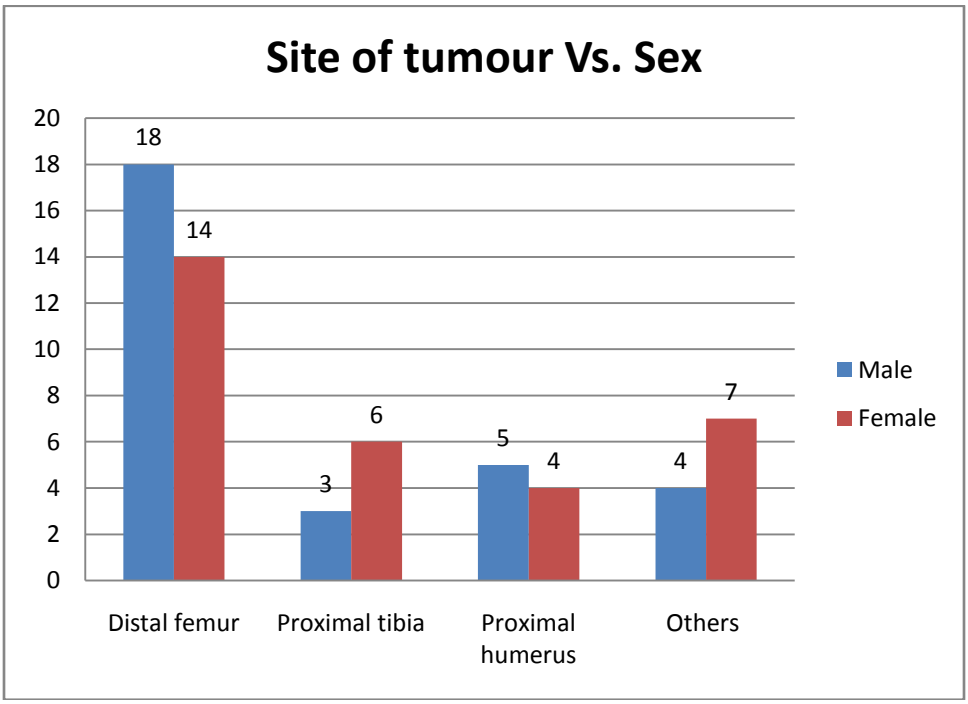


Figure 16: Site of tumour Vs. Age groups

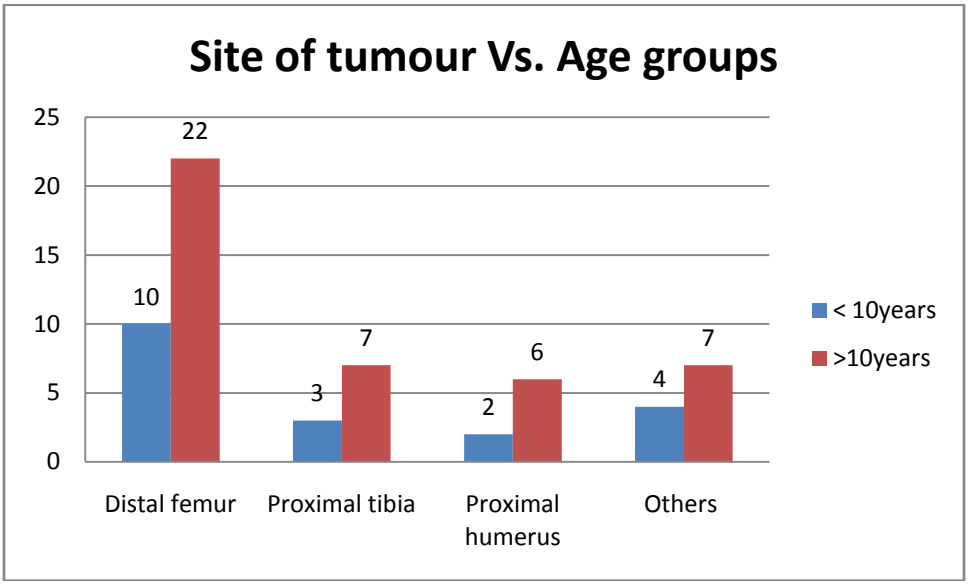


Table 13: Response to pre-op chemotherapy

	CD	**MAP**
Good response (>90% necrosis)	6 (40%)	12 (50%)
Poor response (<90% necrosis)	9 (60%)	12 (50%)
Total Available	15	24

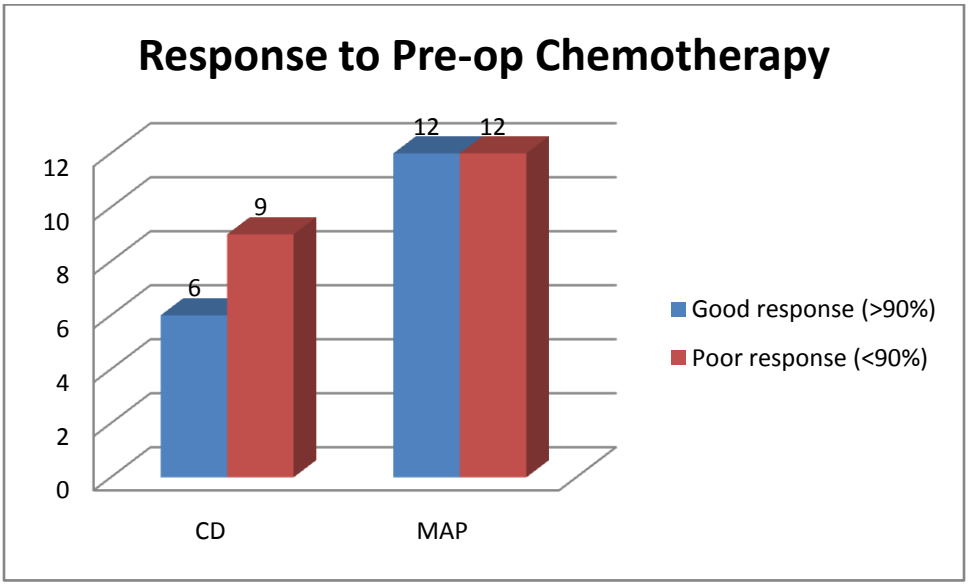


Figure 17: Response to Pre-op chemotherapy

The response to pre-op chemotherapy was assessed based on percentage necrosis seen on biopsy at the time of excision of tumour. 15/21 in CD group and 24/30 had tumour necrosis documented in the biopsy report. More than 90% necrosis was considered good response. 50% in the MAP group and 40% in CD group had good response to pre-op

chemotherapy. There is no statistically significant difference between the two groups. (p=0.54)

Table 14: SURGERY

	CD	MAP
Amputation	12	10
Limb salvage	6	18
Total	18	28

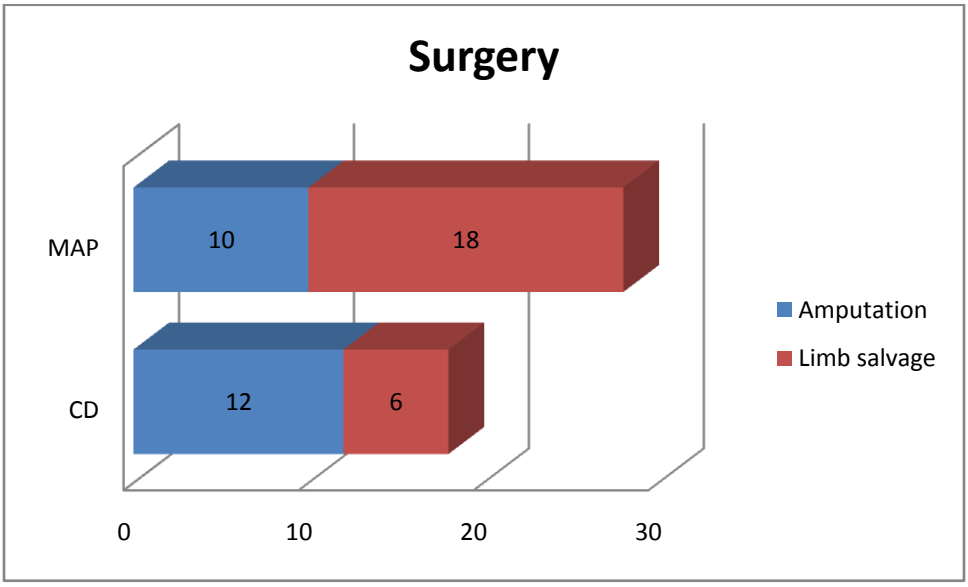


Figure 18: Surgery

In CD group 2 children abandoned treatment before surgery and 1 died during while on treatment, hence only 18 underwent surgery. Similarly in MAP group 2 children abandoned treatment before surgery and only 28 underwent surgery. 66% of children in CD group had amputation compared to 35% in MAP group. This difference was statistically significant (p=0.04). The cost of limb salvage surgery was much higher than

that of amputation hence many of those belonged to poorer socio-economic strata opted for amputation.

Table no.15: Type of amputation

Type of Amputation	Number	Percentage
Above knee amputation	12	50%
Hip disarticulation	6	25%
Forequarter amp.	2	8%
Above elbow amp.	2	8%
Below knee amp.	1	4%
Shoulder disarticulation	1	4%

Total	**24**	**100%**

Among those who has had amputation, 12 of them 50% under went above knee amputation, reason being some of them with extracompartmental disease definitely needed amputation and the other reason is because of financial constraints who would have benefitted with limb sparing surgery. Lack of finance most of them went for amputation

TREATMENT COMPLETION:

Table 16: Treatment completion

	CD	**MAP**
Completed treatment	12	23
Abandoned	8	3
Died during treatment	1	4
Total	21	30

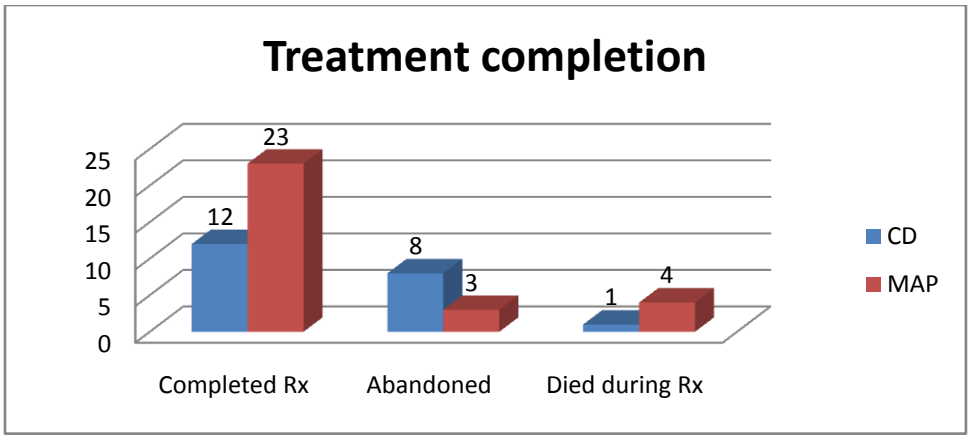


Figure 19: Treatment completion

At the time of analysis 23/30 in the MAP group and 12/21 in the CD group have completed treatment. In the CD group 3children abandoned treatment before surgery and 5 after surgery and in MAP group 2 abandoned treatment before surgery and 1 after surgeryAbandonment rate was higher in the CD group 38%, compared to 10% in the MAP group. This was probably because children from low socio-economic strata received CD. One each from both groups died of sepsis while on treatment and 3 in MAP group died of progressive disease.

OUTCOME OF THOSE COMPLETED TREATMENT

Table 17:Outcome at the time of analysis

	CD (12)	**MAP (23)**
Alive and well	**9**	**16**
Lost to follow up	1	2
Died	2	5

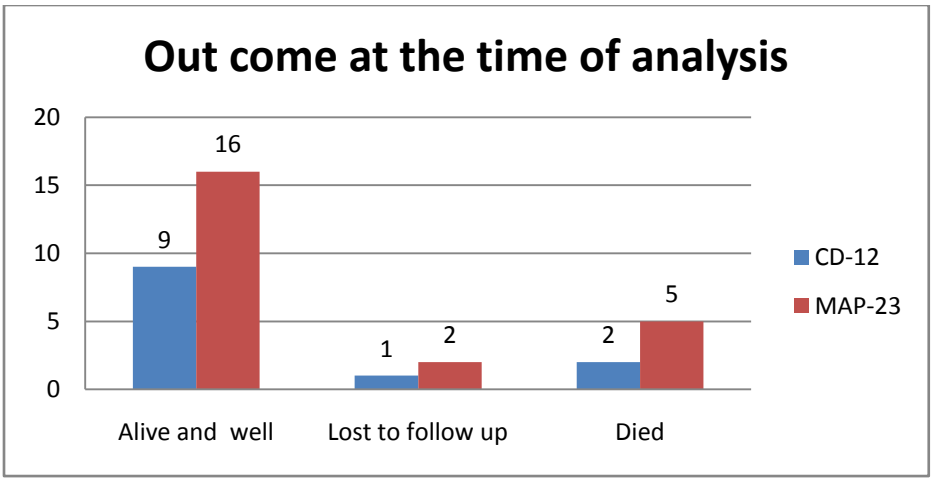


Table 20: Outcome at the time of analysis

Mean follow up in the CD group was 19 months (1-59 months) and in the MAP group was 28 months (2-72months).Two childrenin the CD group and 5 in the MAP group relapsed. All those who relapsed, but one in the MAP group, died of disease. One child in the MAP group died 6 weeks after completion of treatment due to an unrelated illness. In CD group 9/2 are alive and disease free, compared to 16/23 in the MAP group at the time of this analysis.

Table 18:Outcome vs tumour response

	CD-Alive	CD-Relapsed	MAP- Alive	MAP relapsed
>90%	4/6	2/6	9/12	3/12
<90%	8/9	1/9	9/12	3/12

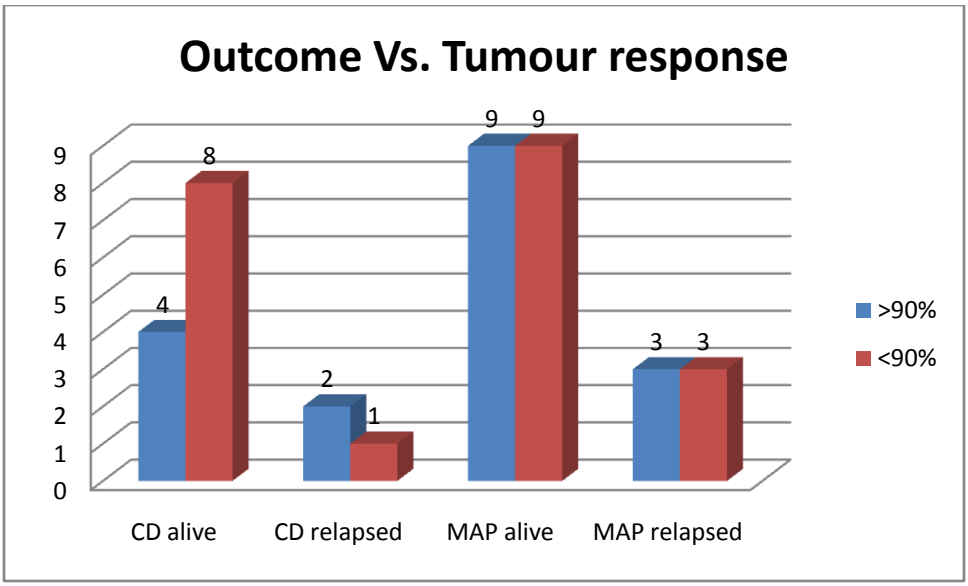


Figure 21: Outcome Vs Tumour response

Among those with tumour necrosis recorded in their biopsy reports, overall 18 children had good response to pre-op chemotherapy and 21 had poor response. 13/18 with good response and 17/21 with poor response are alive and well. There was no significant difference between these two groups or the type of pre-op chemotherapy they received.

Table 19:Outcome of CD group those who have completed treatment:

S.no	Sex	Disease	Neoad. Rx	Surgery	Adj. Rx	Necrosis	Relapse	Adverse events	Status
1	F	Localised	CDx3	Amputation	IEx6	<90%			Alive
2	F	Localised	CDx3	LSS	IEx4	<90%		SNHL	Alive
3	F	Localised	CDx2	Amputation	CDx 4	>90%		Stump overgrowth,revised	Alive
4	M	Localised	CDx2	Amputation	CDx 4	>95%	Relapsed (Pulm Mets)IEx6	SNHL	Died
5	F	Locali	CDx4	LSS	IEx4	<90%			Aliv

		sed							e
6	F	Localised	CDx2	Amputation	CDx4	>90%			Aband (A)
7	F	Localised	CDx2	Amputation	CDx4	>90%			Alive
8	M	Localised	CDx3	LSS	MAPx3	<90%		Cracked prosthesis, revised	Alive
9	M	Localised	CDx2	LSS	CDx4	>90%			Alive
10	M	Localised	CDx2	Amputation	CDx3	<90%			Died
11	M	Localised	CDx2	Amputation	CDx4	>90%		SNHL	Alive
12	F	Localised	CDx2	Amputation	CDx4	<90%			Alive
13	F	Localised	CDx3	Amputation	IEx6	<90%			Alive
14	F	Localised	CDx3	LSS	IEx4	<90%		SNHL	Alive
15	M	Localised	CDx2	LSS	CDx4	<90%			Alive

Table 20:Outcome of MAP group those who have completed treatment:

S.no	Sex	Disease	Neoad. Rx	Surgery	Adj.Rx	Necrosis	Relapse	Ad.events	Status
1	F	Metastatic	MAPx2	LSS	MAPx4	>90%			Alive
2	F	Localised	MAPx1	Amputation	CDx4	<90%		SNHL	Alive
3	F	Localised	MAPx3	LSS	IEx4	<90%		Dislocated prosthesis, revised	Alive
4	M	Localised	MAPx2	LSS	MAPx4	<90%	Relapsed(Path. fracture)		Alive

							IEx2		
5	F	Localised	MAPx2	LSS	MAPx4	>90%		Non union graft, revised	Alive
6	M	Localised	MAPx2	Amputation	MAPx4	<90%	Relapsed (Bone mets)		Died
7	F	Localised	MAPx2	LSS	MAPx4	>90%	Relapsed (H'gic Pl.effusion) MAP		Died
8	M	Localised	MAPx2	LSS	MAPx4	>90%		SNHL, Non union graft, revised	Alive
9	F	Localised	MAPx2	LSS	MAPx4	>90%	Relapsed, (IE) AKAmp, Sent on palliation		Died
10	F	Localised	MAPx2	LSS	MAPx4	>90%		SNHL, Prosthesis lengthening done	Alive
11	M	Locaslied	MAPx2	LSS	MAPx4	<90%			Alive
12	F	Localised	MAPx3	LSS	IEx5	<90%			Aband
13	M	Metastatic	MAPx3	LSS	IEx4	<90%	Relapsed (Pulm.mets) Sent on palliation		Alive
14	F	Localised	MAPx2	LSS	MAPx4	>90%		Liver failure after 1 month of completion of Rx	Died

15	M	Metastatic	MAPx2	Amputation	MAPx4	<90%	Ralapsed, Pulm.mets(IE)		Died
16	M	Localised	MAPx2	Amputation	MAPx4	>90%			Alive
17	F	Localised	MAPx2	LSS	MAPx4	>90%			Alive
18	F	Localised	MAPx2	LSS	MAPx4	>90%			Alive
19	M	Localised	MAPx3	LSS	IEx3	<90%			Alive
20	M	Localised	MAPx2	LSS	MAPx4	>90%			Alive
21	M	Metastatic	MAPx2	Amputation	MAPx4	<90%			Alive
22	F	Localised	MAPx2	LSS	MAPx4	>90%			Alive
23	M	Localised	MAPx2	Amputation	MAPx4	<90%			Alive
24	F	Localised	MAPx2	LSS	MAPx4	<90			Alive

Table 21 : **Among those who had fractures**:

S.no	Age at presentation	Duration of symptoms	Site of tumour	Disease	Biopsy done	Opted for Rx.	Rx. Group	Outcome

1	13 years	1 month	Dist.Femur	Localised	Outside	Yes	CD	Lost follow up
2	11 years	0.25month	Dist.Femur	Localised	Outside	Yes	MAP	Alive
3	14 years	3 months	Prox.Humerus	Metastatic	Outside	Yes	MAP	Abandoned
4	14 years	1 month	Dist.Femur	Localised	Here	Yes	CD	Abandoned
5	10 years	6 months	Dist.Femur	Localised	Outside	Yes	CD	Alive
6	11 years	12 months	Prox.Humerus	Localised	Here	Yes	CD	Abandoned
7	12 years	0.5 month	Dist.Femur	Localised	Here	Yes	CD	Alive
8	15 years	6 months	Dist.Femur	Localised	Outside	Yes	IFOS +ETO	Alive

III: QUALITY OF LIFE:

For quality of assessment, all those who have completed treatment and alive were contacted; 33/35children responded. The mean duration of follow up in the responders was 3 years with a range of 6 months to 8 years. The scoring system was devised based on day to day activities of life such as eating, dressing, bathing, ambulation as well as their social life.

Table22 A: QOL score

Score	Number of children
0-7	0
8-13	0
14-20	6
21-27	27
Total	**33**

Table 22 B: QOL score

:

Score (marks out of 27)	Number
15	1
17	1
18	1
19	2
20	1
21	3
22	5
23	5
24	7
25	2
26	3
27	2

The mean score was 21.5 with a range of 15-27.

Table 23: QOL score vs. site of tumour:

Site of tumour	Score 1-7	Score 8-13	Score 14-20	Score 21-27	Total
Lower limb	0	0	4	23	27

Upper limb	0	0	0	4	4
Axial skeleton	0	0	2	0	2
Total	**0**	**0**	**6**	**27**	**33**

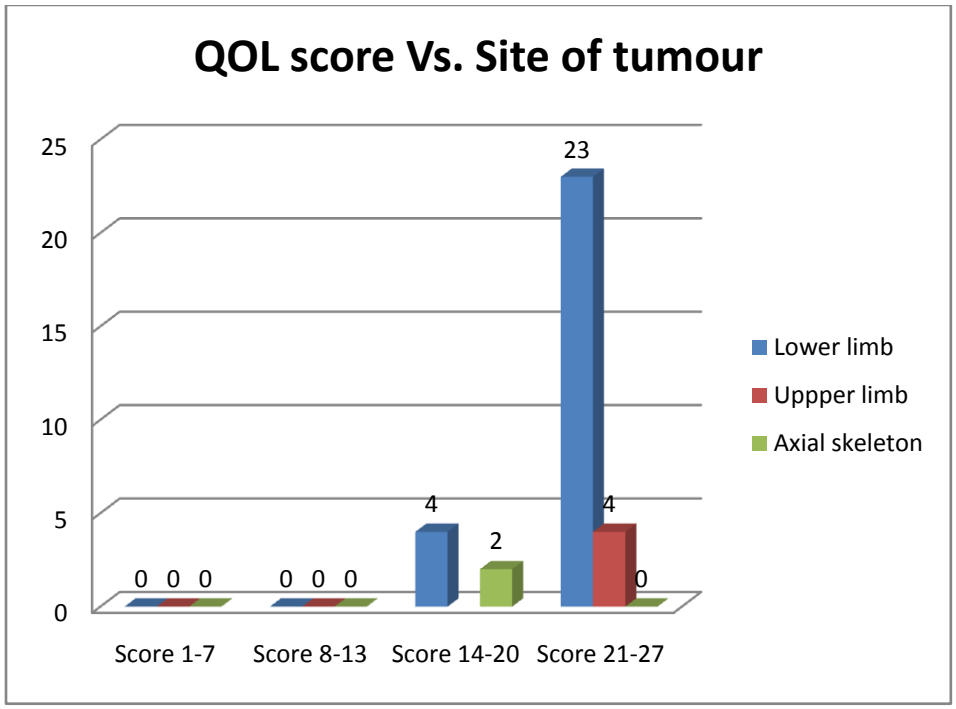


Figure 22: QOL score Vs site of tumour

Table 24: Type of surgery vs. QOL

Surgery	Score 1-7	Score 8-13	Score 14-20	Score 21-27	Total
LSS	**0**	**0**	**0**	**16**	**16**
Amputation	**0**	**0**	**4**	**10**	**14**
Total	**0**	**0**	**4**	**26**	**31**

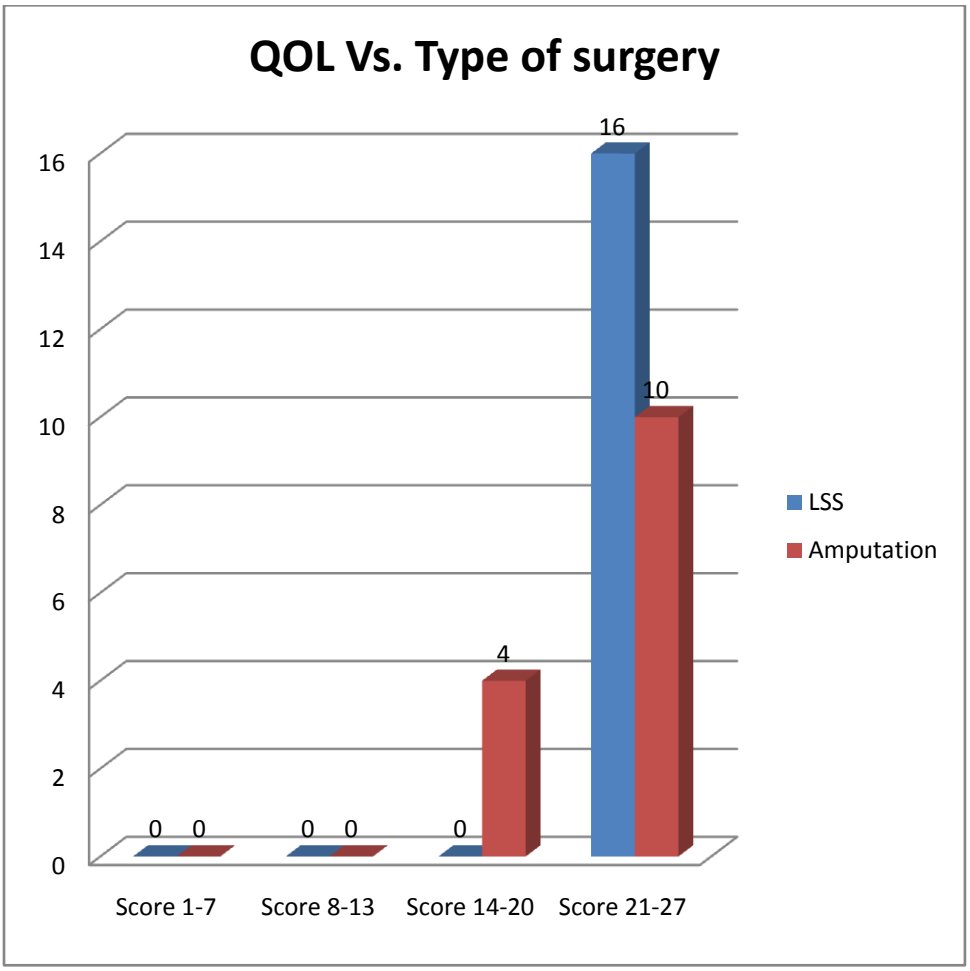


Figure 23:QOL Vs Type of surgery

Table 25: Age at diagnosis Vs. QOL

Age	Score 1-7	Score 8-13	Score 14-20	Score 21-27	Total
<10years			2	9	11
>10 years			4	18	22
Total			6	27	33

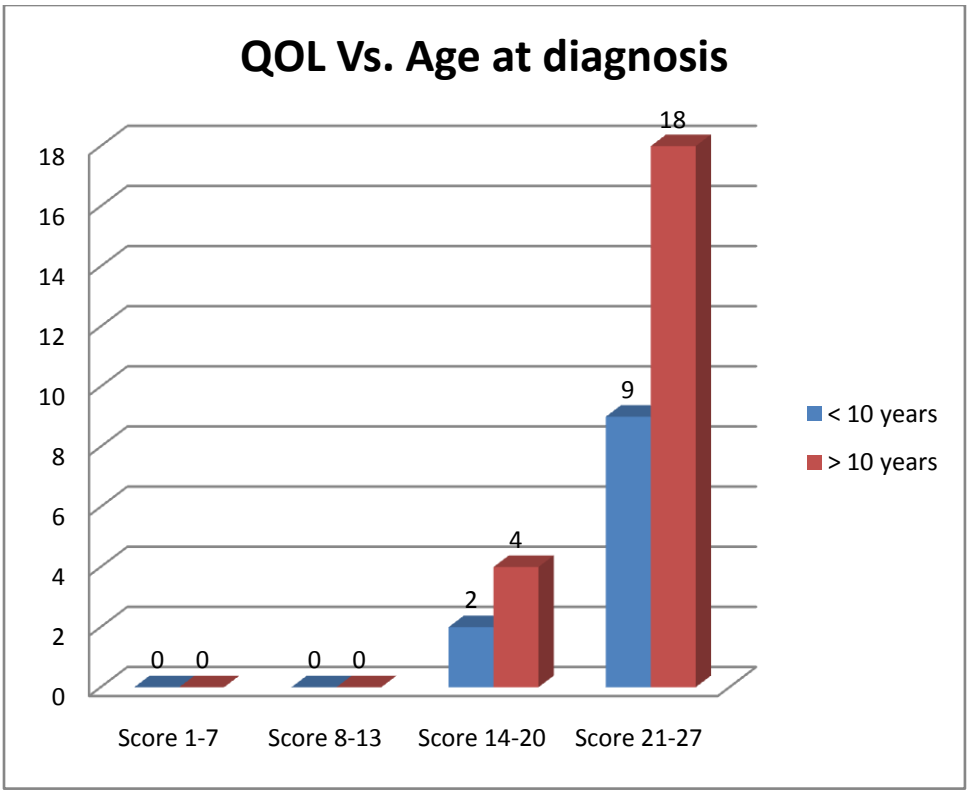


Figure 24: QOL Vs Age a diagnosis

In tables 22-25 we assessed quality of life score in those completed treatment. 6/33(18%) scored 14-20 and the rest 21-27. While looking at the site of tumour, both children with axial skeleton tumour scored 14-20 compared to other sites. When we compared the type of surgery and QOL, all those who had limb salvage surgery rated themselves to be having a good quality of life.

Table 26: Patients' perception of their QOL compared to peers

Score	Number
Upto 25%	3
26-50%	6
51-75%	22
76-100%	2
Total	**33**

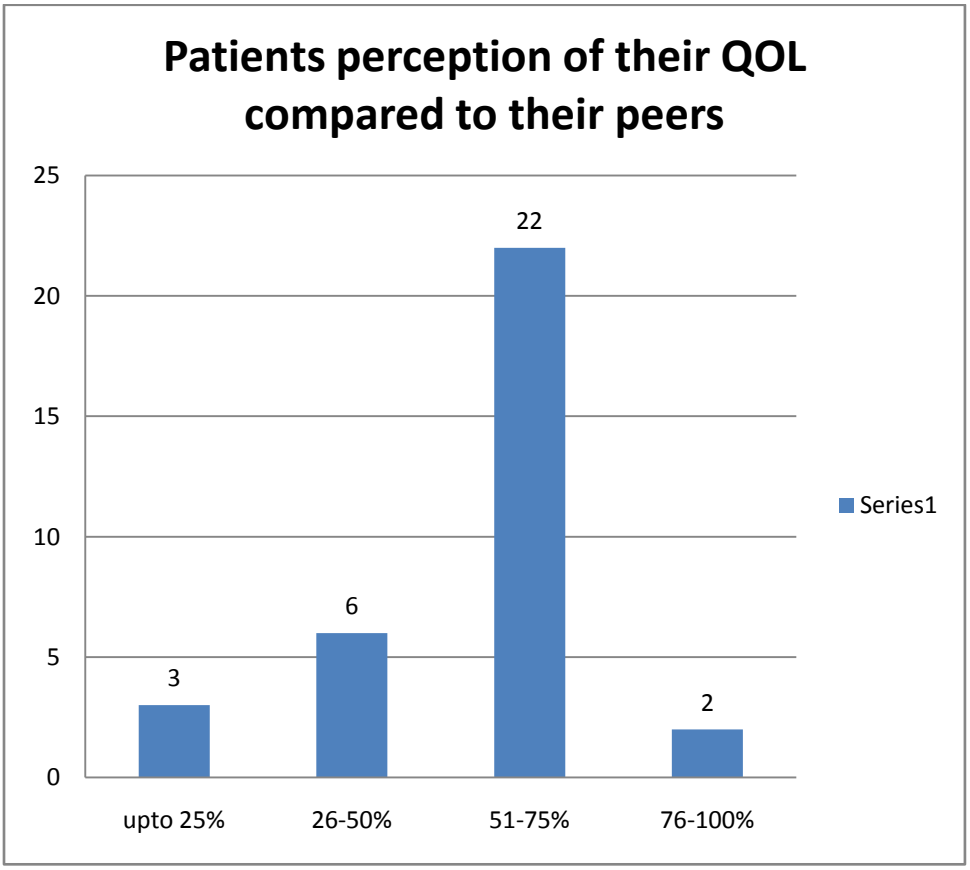
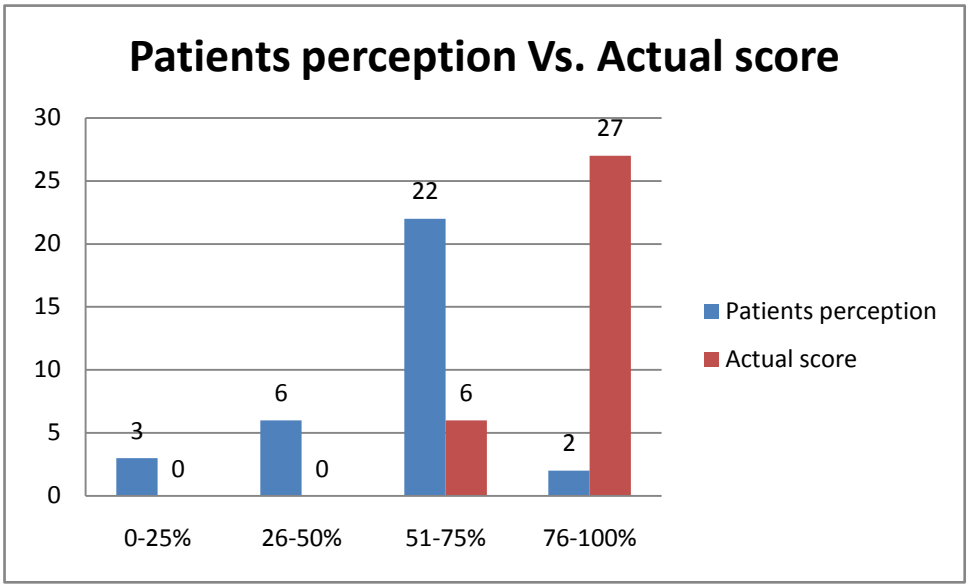


Figure 25:Patients perception, compared to peers

Table 27 Patients perception of QOL vs QOL score

Score	0-25%	26-50%	51-75%	76-100%
Patients perception	3	6	22	2
Actual score	0	0	6	27

Figure 26: Patients perception of QOL vs. QOL score.



It was interesting to note that even though while using the scoring system, all patients scored >50%, while their perception of abilities compared to peers seemed much less. 3/33 rated them to have only up to25% of ability compared to their peers, 6/33 with 26-50%. In the QOL scoring27/33 rated themselves to be more than 75%, in their perception majority (22/33) rated themselves between 51-75%. However this difference was not statistically significant. ($p>0.05$)

DISCUSSION

DISCUSSION

CLINICAL PROFILE

In this descriptive study we first looked at the clinical profile of all children with osteosarcoma registered in our unit from 2004. A total of 81 children were recruited for the study. The male: female ratio is 1.025, which is similar to a study from Ethiopia[34]. Other studies from around the world showed a slightly male preponderance[1] with males being affected with osteosarcoma 1.5 to 3 times more than the female population.

The age at presentation ranged from 3-17 years with an average of 11.5years.This was similar to other reports[5,6]. 52 (72%) were more than 10 years old at presentation and 23 (28%) were aged less than or equal to 10 years. Among the less than 10 year group, a small number (5%) were less than 5 years old at diagnosis.

The geographic profile of our patients showed that children travel long distances to attend a specialized centre for treatment.72/81 were from India and 9/81 were from Bangladesh. 62% of children belonged to various states of eastern part of our country such as West Bengal, Jharkhand, Meghalaya, Assam & Orissa. Similar geographic distribution is seen among all children attending our unit with various other malignancies also. This directly depicts dearth of specialists and centres with adequate facility in our country. Travelling long distances to fetch treatment increases the indirect cost of treatment such as boarding, lodging as well as loss of job for parents. This may also contribute to abandonment of treatment, and poor survival in children with cancer.

The duration of symptoms varied from 0.25-12months with a mean duration of 2.7 months. It was less than 2months in almost half (49%) of the patients, 2-4months in 27% and more than 4months in 24% of the patients. In a study done by Yang JY et al[35] from Hong Kong reported the median duration of initial symptoms as 30 (range, 0-360) days. Wu Set al[11]from China reported that the mean duration of symptoms as 4weeks with a range of 1-14weeks.

The most common presenting symptom was swelling followed by pain. 66% (54/81) of them presented with both swelling and pain. About 10 % of our children had pathological fracture at diagnosis. Similar presenting symptoms were reported by other authors also; in a study done by Staals EL et al[22] the most common symptoms were swelling and pain 92% and 67% of the cases respectively. Yang JYet al[35] from Hong Kong reported the swelling (76%) and pain (90%) were the most common presenting complaints.

The most common site of tumour was found to be the distal end of femur 52% (42/81), followed by proximal end of tibia in 17% (14/81) and then proximal end of humerus in 11% (9/81). Knee jointtumours accounted for 74% in our population. Several other authors also reported similar distribution of tumours. Muthupheiet al[23] in African population, Yang JY, et al[35] from HongKong, Rech' et al[36] from Brazil as well as Ottaviani G et al[18] reported similar sites of occurrence of osteosarcoma like our group.

The diagnosis of osteosarcoma was confirmed by biopsy. Of the 81 patients 21% of them (17/81) had biopsy done outside and the rest 79% of them (64/81) are new cases and had biopsy done in our hospital. Of all 81 patients, 71had high grade osteosarcoma, 3had intermediate grade 7 of them with low grade osteosarcoma.

At presentation 83% (67/81) of the children with osteosarcoma had localized disease where as 17% (14/81) had metastatic disease.Among those with metastatic disease 5 had metastasis in lungs, 8 had metastasis to other bones and 1 has disease in both lungs and bone. Among those patients with metastastic disease 42% (6/14) of them had duration of symptoms $\leq$2months. Among those patients with metastatic disease 77.7% (7/9) belonged to MAP protocol whereas 22.8% (2/9) belonged to Cisplatin +Doxorubicin group (Table 16). In a study done by Yang JYet al[35] from Hong Kong reported 76% had localized disease and 24% of patients had metastatic disease at presentation. In an another study done by RechA'et al[36] from Brazil reported 38% of the patients had metastatic disease at presentation and 62% had localized disease. Bacci G et al[15] from their study reported 83% (891/1071) had localized disease at presentation whereas 17% (180/1071) had metastatic disease.

Excluding the 9 children who were on treatment at the time of analysis, 48/72 (66%)children completed treatment.The overall survival in our group is 35/72 (48%) and event free survival is 30/72(41%). The abandonment rate was 16/72(22%).

COMPARISON OF TWO CHEMPTHERAPY PROTOCOLS

We compared two pre-operative chemotherapy protocols currently used in our centre for high grade osteosarcoma for toxicity and efficacy. In each group, one child each died of septicemia while on treatment. Since by default poorer children received Cispatin+ Doxorubicin, abandonment of treatment was higher in this group comapred to MAP group.

Of those who underwent surgery, 55% (37/67) of them underwent Limb sparing surgery and 45% (30/67) of them underwent amputation.94% with localized disease underwent limb sparing surgery whereas only 6% with metastatic disease had LSS. 66% of children in CD group had amputation compared to 35% in MAP group. This difference was statistically significant (p=0.04). The cost of limb salvage surgery was much higher than that of amputation hence many of those belonged to poorer socio-economic strata opted for amputation. **Rech Aet al**[36] from Brazil reported that 52% had an amputation and 34% received limb sparing surgery in their series. **Bacci G et al**[15] from their study reported that 71% of the 126 operated patients had limb salvage procedures compared to 26%who had amputations and three patients had a rotation plasty (3%). **Rhonda S et al**[32] from their study of 57 patients participated 33(57%) who underwent limb-salvage surgery and 24 (43%) who underwent amputation.

The response to pre-op chemotherapy was assessed based on percentage necrosis seen on biopsy at the time of excision of tumour. 15/21 in CD group and 24/30 had tumour necrosis documented in the biopsy report. More than 90% necrosis was considered good response. 50% in the MAP group and 40% in CD group had good response to pre-op chemotherapy. There is no statistically significant difference between the two groups. (p=0.54)

Several authors have compared good histpathological response to pre-op chemotherapy with survival. A response of >90% was observed in 36% of patients treated with CD and 50% of MAP was reported by **Ian J. Lewis et al**[37] reported from their study that good

histologic response (>90% tumor necrosis).**Provisor AJet al**[10] in their study reported that two hundred six patients had their tumors assessed for histologic response: 28% displayed a good histologic response to preoperative chemotherapy. In our series overall 46% of 39children who had tumor necrosis recorded had good response. 13/18 with good response and 17/21 with poor response are alive and well. There was no significant difference between these two groups or the type of pre-op chemotherapy they received.

At the time of analysis 23/30 in the MAP group and 12/21 in the CD group have completed treatment. Abandonment rate was higher in the CD group 38%, compared to 10% in the MAP group. This was probably because children from low socio-economic strata received CD. Mean follow up in the CD group was 19 months (1-59 months) and in the MAP group was 28 months (2-72months). Two children in the CD group and 5 in the MAP group relapsed. All those who relapsed, but one in the MAP group, died of disease. One child in the MAP group died 6 weeks after completion of treatment due to an unrelated illness. In CD group 9/12 are alive and disease free, compared to 16/23 in the MAP group at the time of this analysis.

In summary both CD and MAP were well tolerated, treatment related mortality was acceptible. Histological response to pre-op chemotherapy was similar in both groups. Though it seem that overall survival is better in the CD group, compared to MAP group, it is probably because more children were treated in MAP and they had much longer followup period.

QUALITY OF LIFE:

It was believed that limb-salvage surgery has functional and cosmetic advantages over amputation, yet the literature is equivocal.Many authors reported thatThe function of Lower limb was a significant predictor of quality of life ($p< 0.001$), whereas the type of surgery did not impact this relationship (Robert RS et al[17]) Studies done by Mathew R et al[14], Rougraff et al[38] and Renard et al[39] reported that functional outcome and patient satisfaction appear to be at least as good, and probably better after skeletal reconstruction than after amputation. They also reported that limb sparing surgery is associated with additional surgical procedures and complications which are three times more common than amputation group. In another study **Otis et al[39]** reported that prosthetic reconstruction provides superior function whereas, the patients studied by **Harris et al[40]** functioned similarly.

We analyzed quality of life using a questionnaire prepared by us, which is relevant to our culture and social life. It was interesting to note that while assessing ability to perform day-to-day activities 81% of children rated themselves as having 76-100% and 19% rated between 51-75%. While looking at the site of tumour, both children with axial skeleton tumour scored 14-20 compared to other sites. All children with LSS rated themselves between 76-100% QOL. However there was no significant difference in QOL between, site of tumour or type of surgery

It was interesting to note that even though while using the scoring system, all patients scored >50%, their perception of abilities compared to peers seemed much less. 3/33 rated them to have only up to 25% of ability compared to their peers, 6/33 with 26-50%. In the QOL scoring 27/33 rated themselves to be more than 75%, in their perception majority (22/33) rated themselves between 51-75%. Even though this difference was not statistically significant ($p>0.05$), this probably depicts their limitations due to altered body image.

Overall, quality of life in children completed treatment for osteosarcoma seem good, both in their perception as well as by objective testing using a QOL questionnaire

SUMMARY

SUMMARY

- 81 children, 42 boys and 39 girls with osteosarcoma were studied. The mean age at presentation was 11.4 years, with a range of 3 to 17 years. 54/81 were more than 10 years of age and 4 were less than 5 years of age at diagnosis.
- Pain and swelling was the most common symptom. The common sites were distal end of femur followed by proximal end of tibia and proximal end of humerus. There was no significant difference between presenting symptom and duration or age at diagnosis in this group. 71/81 had high grade osteosarcoma. 67/81 children had localized disease at diagnosis. The incidence of pathological fracture was ----
- 77/81 children opted for curative treatment at diagnosis. Excluding the 9 children who are currently on treatment,48/72 (66%)children completed treatment, of these 30 are in 1st CR and 5 in second CR. The overall survival in our group is 35/72 (48%) and event free survival is 30/72(41%) at a mean follow up period of 3 years with a range of 6 months to 8 years. The abandonment rate in this group was 22% (16/72)
- 51 children with high grade osteosarcoma were further studied to compare the efficacy of two chemotherapy protocols used, namely cispatin+ Doxorubicin vscisplatin+ doxorubicin+ methotrexate. Children received one or the other protocols based on their financial status.Response to pre-op chemotherapy was assessed using tumout necrosis on the excised tissue; 50% in the MAP group and 40% in CD group had good response(>90% necrosis) to pre-op chemotherapy. There is no statistically significant difference between the two groups. (p=0.54)

- 66% of children in CD group had amputation compared to 35% in MAP group. This difference was statistically significant (p=0.04). The cost of limb salvage surgery was much higher than that of amputation hence many of those belonged to poorer socio-economic strata opted for amputation.

- 12/21 in the CD group and 23/30 in the MAP group have completed treatment. Abandonment rate was higher in the CD group 38%, compared to 10% in the MAP group. This was probably because children from low socio-economic strata received CD. One each from both groups died of sepsis while on treatment and 3 in MAP group died of progressive disease.

- Mean follow up in the CD group was 19 months (1-59 months) and in the MAP group was 28 months (2-72months). 9/10 in CD group are alive and disease free, compared to 10/15 in the MAP group. Longer follow up is required to comapre the two groups.

- An indigenously prepared and pre-tested scoring system was used to assess quality of life in survivors. A score of up to 7 was considered 25%, 8-13 as 50%, 14-20 as 75% and 21-27 as 100% QOL. 33/35 survivors responded. 6/33(18%) scored 14-20 and the rest 21-27. When we compared the type of surgery and QOL, all those who had limb salvage surgery rated themselves to be having a good quality of life with a score of more than 21.

- It was interesting to note that even though while using the scoring system, all patients scored >50%, while their perception of abilities compared to peers seemed much less. 3/33 rated them to have only up to 25% of ability compared to their peers, 6/33 with 26-50%. In the QOL scoring 27/33 rated themselves to be more than 75%, in their perception majority (22/33) rated themselves between 51-75%. Even though this difference was not statistically significant ($p>0.05$), this probably depicts their issues with body image.

LIMITATIONS

LIMITATIONS:

- Sample size of children in this study was small.
- Children were divided into treatment groups based on their financial status rather than by proper randomization. Rate of abandonment was higher in the CD group. The results of comparison between the two groups will have to be interpreted with caution.
- Follow up period of those completed ranged from 19- 28 months only. There were very few patients who had completed 5 years post treatment to be labeled as cancer survivors.

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BIBLIOGRAPHY

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ANNEXURE

Contents:

ANNEXURE 1

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

August 13, 2012

Dr. David Suvarna Raju Parimi
PG Registrar
Department of Paediatrics
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
Clinical profile and outcome of children with osteosarcoma treated on two protocols and quality of life among those who had amputation versus limb sparing surgery.
Dr. David Suvarna Raju Parimi, PG Registrar, Paediatrics, Dr. Leni G Mathew, Dr. Rikki R John, Paediatrics, Dr. Vrisha Madhuri, Paediatric Orthopaedics, Dr. Gautham Shah, Pathology, Dr. Sridhar Gibikote, Radiology.

Ref: IRB Min. No. 7859 dated 04.06.2012

Dear Dr. David,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled" Clinical profile and outcome of children with osteosarcoma treated on two protocols and quality of life among those who had amputation versus limb sparing surgery" on June 4, 2012.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Data Collection Sheet
3. Patient Information Sheet and Informed Consent Form (English, Hindi and Telugu)
4. Questionnaire
5. Cvs of Drs. David Suvarna Raju Parimi, Leni G Mathew, Rikki R John.
6. A CD containing documents 1- 5

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
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Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Ethics & Research Committee members were present at the meeting held on 4th June 2012, Monday by 1.30 PM in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. B.J.Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	External
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External
Mr. Sampath	BSc, BL	Advocate	External
Mrs. Ellen Ebenezer Benjamin	M.Sc. (Nursing), Ph.D.	Deputy Nursing Superintendent, CMC.	Internal
Dr. Vathsala Sadan	M.Sc, Ph.D	Addl. Deputy Dean, College of Nursing, CMC.	Internal
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	Internal
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	Internal
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal
Dr. Srinivas Babu	MSc, Ph.D.	Sr. Scientist, Neurological Sciences, CMC.	Internal
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerlogy & Leprosy, CMC.	Internal
Dr. Anil Kuruvilla	MBBS, MD, DCH	Professor, Neonatology, CMC.	Internal
Dr. Bobby John	MBBS, MD, DM, PhD, MAMS	Professor, Cardiology, CMC.	Internal
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC.	Internal

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

Dr. Sujith Chandy	MBBS, MD	Professor, Pharmacology & Clinical Pharmacology, CMC.	Internal
Dr. Denny Fleming	BSc (Hons), PhD	Honorary Professor, Clinical Pharmac CMC.	Internal

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

CC: Dr. Leni G. Mathew, Professor, Department of Paediatrics, CMC

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

ANNEXURE 2

Christian Medical College, Vellore

Participant Information sheet and Consent form

Thesis: ‘’Clinical profile and outcome of children treated for Osteosarcoma on two protocols and quality of life among those who had amputation versus Limb sparing surgery’’

Invitation

You are invited to participate in this study – **’’**Clinical profile and outcome of children treated for Osteosarcoma on two protocols and quality of life among those who had amputation versus Limb sparing surgery’’. The study is being conducted by Dr.David Suvarna Raju Parimi, PG registrar in the Department of Paediatrics, under the guidance of Dr.Leni Mathew (Professor and Head of the Department of Paediatric Oncology and Paediatrics unit-I) and Dr.Rikki John (Research Officer, Department of Paediatrics. This study is part of academics of The Tamil Nadu Dr.MGR Medical University, Chennai.

We would like to take 10 minutes of your time and ask you to fill/answer this questionnaire. We are trying to assess the quality of life of children who have been treated for osteosarcoma. We would like to know if there is any change we could make in our treatment which would mean a better life after treatment for children who will be diagnosed with this problem in the future.

We will also need your permission to look into your medical records to note the type of treatment you have received. Your identity will not be disclosed. Only the researchers named above will have access to your details and results that will be held securely at Christian Medical College, Vellore. Any results of this study that may be published will be done without any names and with care not to disclose your identity.

Participation in this study is voluntary. Whatever you decide, it will not affect the treatment you receive now or in future. It will not affect your relationship with the hospital staff caring for you.

If you wish to not to answer any question once you have started, you can just leave it empty/ say you don’t want to answer without giving any further reason.

All it will take is 10 minutes of your time and it may benefit lots of children who like you will require treatment for osteosarcoma in the future, just as you benefitted from similar research programmes that children with the same disease participated in before you.

You will however have to give your consent either verbally (for telephonic interviews) or by signing in the consent form attached with this.

ANNEXURE 3
CHRISTIAN MEDICAL COLLEGE, VELLORE
CONSENT FORM

(To be used in conjunction with a participation information sheet)

''Clinical profile and outcome of children treated for Osteosarcoma on two protocols and quality of life among those who had amputation versus Limb sparing surgery''

1. I ……Son/Daughter of ……, agree to participate in the study described above by completing the said questionnaire.
2. I agree to the researchers going through my medical records for information about my treatment.
3. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.
4. I understand that if I have any questions relating to my participation in this research, I may contact Dr David on telephone 07708077038, who will be happy to answer them.
5. Complaints may be directed to the Research Office at phone number 0416 228 4294

Signature of the participant Name of the participant Date

Signature of participants parent Name of participants parent Date

Signature of witness Name of the witness Date

Signature of the Investigator Name of the Investigator Date

ANNEXURE 4
CHRISTIAN MEDICAL COLLEGE, VELLORE
OSTEOSARCOMA IN CHILDREN-Data collection sheet

Serial number:
Name:
Hospital number:
Date of birth:
Sex:
Place:
Age at diagnosis
Presenting complaints: 1.Swelling 2.Pain 3.Fever 4.Weight loss 5.others
Duration of symptoms:
Co-morbid features:
Weight:
Height:
Site of tumour
Status of the patient: new case/ Biopsy done elsewhere/ partially treated

Investigations	Diagnosis	Pre-op	End of Rx	Follow-up
CBC				
Creatinine				
LDH				
Chest X-ray				
CT-Chest				
MRI-Limb				
Bone scan				
ECHO				
Audiogram				
Biopsy				

Diagnosis: Localised/ metastatic disease

Pre-op treatment: yes/no, drugs (CDDP/DOX vs PAM)and no of courses

Surgery:
Limb salvage/ amputation
Details
Reason for choice of surgery
Biopsy report
% necrosis of tumour

Post op Rx: drugs(CDDP/DOX, PAM, Ifos/Etop, others and courses

Treatment completed: yes/no
If no: refused Rx/ abandoned Rx/Died while on Rx
If abandoned, when: pre-op/immediate post op

If died while on Rx: cause of death

End of treatment Assessment

Follow up: duration in months

Status of the patient: alive and disease free/ alive , on relapse Rx / died

Cause of death: disease/ infection/ others

Relpase: yes/No

If yes, when
site of relapse
Rx of Relapse
Outcome

Quality of life:

ANNEXURE 5

Quality of life after completion of treatment

1. Are you able to eat your meals by yourself? 1) need full support, 2) some assistance, 3) yes
2. Are you able to put on your dress by yourself? 1) need full support2) some assistance ,3) yes,
3. Are you able to take bath by yourself? 1)No, 2)yes with some assistance, 3) yes by myself
4. Has your family made any modifications in your house after your treatment

   -To help you walk in the house – 1) yes, 2) No
   -To help you use the toilet and bath- 1) Yes, 2) No
5. Are you able to walk? 1)No, 2) yes, with some support, 3) Yes with no support

   What kind of support do you use? _____
   If unable to walk- state reason_____
6. Are you able to climb stairs? 1) No 2)Yes with some difficulty 3) Yes with no support

   If no, state reason_____
7. Mode of transport
   a. Before you had this disease 1)Auto rickshaw, 2)Town bus, 3) private car, 4)others
   b. After completion of treatment1)Auto rickshaw, 2)Town bus, 3) private car, 4)others

   Any change? 1) Yes, 2) No
   Reason for change_____
8. Have you been attending school /College after your treatment? 1) No, 2)Yes

   If yes, details _____
   If no, why_____
9. Do you go out with your friends? 1)No, 2)Yes

10. Do you play any games/sports? 1)No, 2)Yes
    a. If yes. what games, how often_____
11. Compared to your friends , you would rate your ability to do the above activities as

    1) 25%, 2) 50%, 3)75%, 4) Same as them.

Quality of life of the survivors was analyzed with a pretested Questionnaire in 6 patients (3 direct and 3 by telephonic interview). Both the groups did not show any difference, so it was decided that it was acceptable to go by telephonic interview. Questionnaire comprised of simple questions related to activities of daily living in the community. Quality of life was compared among survivors who had amputation versus limb sparing surgery. In the initial part of the questionnaire, children were asked about the activities of daily living tasks (eating, dressing, bathing, walking, going to school, playing, etc). Each of these activities has points scored according to their capability. In the later part of the questionnaire children were also asked to rate them against their peers for day to day activities of life. This depicts their perception of their quality of life.

ANNEXURE 6

The Clinical Profile of Children with Osteosarcoma and Outcome of Children Treated for Osteosarcoma on Two protocols and Quality of Life among those who had Amputation versus Limb Sparing Surgery

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF MD BRANCH VII (PEDIATRICS) EXAMINATION OF THE DR. M.G.R. MEDICAL UNIVERSITY, TAMIL NADU, CHENNAI TO BE HELD IN MARCH 2013.

FORMAT

TITLE OF THE ABSTRACT :The clinical profile and outcome of osteosarcoma treated on two protocols and quality of life among those who has had amputation versus limb sparing surgery.

DEPARTMENT :Paediatrics
NAME OF THE CANDIDATE :David Suvarna Raju Parimi
DEGREE AND SUBJECT :MD (Paediatrics)
NAME OF THE GUIDE :Dr.Leni Grace Mathew

OBJECTIVES: Describe the objectives of your study (maximum 30 words)

To study the clinical profile of children with osteosarcoma and outcome of children treated for osteosarcoma on two chemotherapy protocols. To look at treatment refusal and abandonment in the study population. To compare the quality of life in children with osteosarcoma who had amputation versus limb sparing surgery.

METHODS: Explain the clinical and statistical methods used (maximum 100 words)

Variables:
outcomes: Survival based on age at diagnosis, localised vs metastatic disease, high grade vs low or intermediate grade tumours, extremity vs axial skeleton tumours as well as chemotherapy used in these patients.

predictors: Treatment complications, deformities,

potential confounders: Socioeconomic factors- Poorer patients received CDDP+DOX

Data Sources/measurement: Data sources are taken from Medical records of all these patients with Osteosarcoma. And also from the details from Chemotherapy records.

Bias: No bias.

Sample size: all children with osteosarcoma registered under pediatric Hemato-Oncology will be included in the study.

Statistical methods:
The data will be analysed using SPSS package 16.0 version. Tests of significance to be used are Chi-square tests, paired sample tests and Wilcoxon signed ranked tests.

RESULTS: Summarize the findings and conclusions of your study (maximum 90 words)

Study included 81 children. Male: Female ratio 1.07. Mean age at presentation was 11.4 years. Pain with swelling was most common symptom. Most common site was distal femur. 66% children completed treatment. Overall survival is 48% and event free survival is 41%. Abandonment rate was 22%.

50% in MAP group and 40% in CD group had good response to pre-op chemotherapy. 66% of children in CD group had amputation compared to 35% in MAP group. 57% in CD group and 76% in MAP group completed treatment. Abandonment rate was higher in CD group 38%, compared to 10% in MAP group.

For quality of life 33/35 survivors responded. All those who had limb salvage surgery rated themselves to be having a good QOL.