CLINOCOPATHOLOGIC FEATURES, TREATMENT PATTERN AND OVERALL SURVIVAL OF PATIENTS WITH OSTEOSARCOMA TREATED AT RADIOTHERAPY CENTER OF TIKUR ANBESSA SPECIALIZED HOSPITAL, ETHIOPIA: CROSS-SECTIONAL STUDY

BY: Dr. YasinWorku, 4th year clinical oncology resident, Addis Ababa University

THESIS FOR SPECIALITY CERTIFICATE IN CLINICAL ONCOLOGYADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES SCHOOL OF MEDICINE DEPARTMENT OF CLINICAL ONCOLOGY

ADDIS ABABA, ETHIOPIA

MARCH, 2021

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ABSTRACT

Background: Primary malignant tumors of bone are extremely rare neoplasms accounting for <0.2% of all cancers, although the true incidence is difficult to determine due to the rarity of those tumors. Bones Sarcomas occur throughout the musculoskeletal system. Osteosarcoma is the most common malignant bone tumor. Osteosarcomas are more common in the appendicular skeleton. Most patients with osteosarcoma have an advanced disease at presentation and the survival is generally poor in low income countries despite the 5-year survival rate of about 80% in the developed countries.

Objective: The objective of this study is to describe the clinical features, treatment pattern, and two year overall survival of patients with osteosarcoma admitted at TikurAnbessa Specialized Hospital oncology ward.

Methodology: A cross-sectional study design was used and all patients with a diagnosis of osteosarcoma admitted to oncology ward were included. A descriptive analysis and frequency were used to analyze mean, median, standard deviation and range. Kaplan Meier was used to analyze the survival pattern of patients. Bivariate and multivariate Cox regression was used to analyze association between dependent and independent variables. Multicolinearity test was done on independent variables found to have association with the outcome variable (VIF>10). STATA software version 16.0 was used for statistical analysis.

Result: From 80 patients included in our study, the age ranged between 11 and 58 years with a median age of 19.5 years. Ostoesarcoma peaks between 15-19 years of age. From all patients, 93.75% came after 3 months of the onset of symptoms. Thirty-four patients (42.5%) had documented distant metastasis at presentation. Of all patients with extremity tumors that had surgery, 43 patients (95.5%) had an amputation. Seventy-one patients received chemotherapy, 37 patients (52.11%) received a palliative intent, 18 patients (25.35%) got adjuvant intent, and 16 patients (22.4%) neoadjuvant intent. The median overall survival of osteosarcoma was 20.8 ± 2.96 months (95% CI, 14-50-33.63) and 2-year overall survival was 45%.

Conclusion/recommendation: Most patients are delayed at presentation and have an advanced disease. Patients with osteosarcoma were under-investigated and received suboptimal care. Patients with osteosarcoma had low median and two-year overall survival. Overall survival was found to be significantly associated with curative surgery (p=0.001), distant metastasis at presentation (p=0.004) and not taking chemotherapy (p=0.05) on bivariate Cox regression but the intent of chemotherapy was the only significantly associated factor for overall survival (p=0.005) on multivariate Cox regression.

Key words: osteosarcoma, clinical features, treatment pattern, TASH, Ethiopia

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Table 1: ACROMYMS AND ABBREVIATIONS

AAU	Addis Ababa University
ACS	American Cancer Society
ALP	Alkaline Phosphatase
ASIR	Age-Standardized Incidence Rate
BCD	bleomycin, cyclophosphamide, and dactinomycin
CDF	Continuous Disease-Free
CIR	Crude Incidence Rate
CO-60	Cobalt-60
COSS	Cooperative Osteosarcoma Study Group
CPL	Cisplatin
CT	Computed Tomography
DFS	Disease Free-Survival
DMS	Distant Metastasis Free Survival
Dx	Diagnosis
FNA	Fine Needle Aspiration
Gm	Gram
Gy	Gray
IV	Intravenous
LDH	Lactate Dehydrogenase
LINAC	Linear Accelerator
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
MRN	Medical Registration Number
MTX	Methotrexate
OS	Overall Survival
POG	Pediatric Oncology Group
RT	Radiotherapy
SD	Standard Deviation
TASH	TikurAnbesa Specialized Hospital
UKCCSG	United Kingdom Children's Cancer Study Group
Vs.	Versus
HMIS	Health Management Information System
U/L	Units per Liter

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1 INTRODUCTION

1.1 Background

Primary malignant tumors of bone are extremely rare neoplasms accounting for <0.2% of all cancers, although the true incidence is difficult to determine due to the rarity of those tumors (1). Osteosarcoma, chondrosarcoma, and Ewing sarcoma are the most common primary bone tumors comprising about 35%, 30%, and 16% of cases respectively. There is slight male predilection, with a ratio of 1.2:1

An epidemiological study conducted in Sweden between 1971 and 1984 investigated possible changes in typical features of 227 conventional osteosarcomas. The mean annual incidence was 2.1 per million. The male to female ratio was 1.6:1 and remained unchanged over the study period as did the location and distribution of tumors. The only change over the study period was an increase in the age of patients beyond the classic peak age range of 10-29 years (2).

In the United States, the incidence of osteosarcoma considered to be higher in males than females occurring at a rate of 5.4 per million persons per year in males vs.4 per million per year in females with the highest incidence in blacks which is 6.8 per million persons per year and Hispanics 6.5 per million per year than in whites which are 4.6 per million per year (3).

It has bimodal age distribution with a peak incidence in early adolescence and another smaller peak in adults older than age 65 years of age. The first peak is in the 10-14 years old age group, coinciding with the pubertal growth spurt. This suggests a close relationship between adolescent growth spurt and osteosarcoma (4).Osteosarcoma develops in 10 % of patients after the age of 60 years. This group composes the second peak of the bi-modal distribution curve. In those older patients, the anatomic regions of presentation differ substantially from the sites of classic osteosarcoma.

Data on the prevalence of osteosarcoma in low-income countries is limited. An estimate of population-based registry data report in Ethiopia in 2015 showed the crude incidence rate(CIR) and age-standardized incidence rates (ASIR) of bone and cartilage tumors of 0.6 and 1.0 per 100,000 population in men respectively and CIR and ASIR of 1.0 and 1.3 per 100,000 population in women respectively .The same report for pediatric cancers revealed 271 cases of bone and cartilage cancers among a total of 3,707 pediatrics cancers with a CIR of 0.7 per 100,000 population (5) .

The etiology of bone sarcomas is not known with certainty (6)-(7). There are genetic and environmental factors associated with osteosarcoma. Germ line mutation in the TP53 gene places patients with L-Fraumeni syndrome at risk for the development of osteosarcoma (8).

Germ line mutation in the RB1 gene is associated with an increased risk for osteosarcoma in patients with bilateral retinoblastoma (9).

Environmental factors are also known to be involved in the genesis of bone sarcomas. Ionizing radiation; either therapeutic or inadvertent is thought to be responsible for approximately 3% of bone sarcomas (10)-(11). Independent of radiation exposure treatment with alkalizing agents are known to increase osteosarcoma risk (12).

Some benign bone diseases predispose patients to develop osteosarcoma. It is estimated that 0.3% of patients with Paget's disease of bone will develop osteosarcoma most often at an advanced age (13- 14) .

Bone sarcomas occur throughout the musculoskeletal system .Osteosarcomas are more common in the appendicular skeleton with the most frequent sites being in the distal femur (32%), proximal tibia (15%), proximal humorous (8%), and proximal femur (5%) (15).This distribution corresponds to the relative activity of the epiphyseal plates in the growing skeleton. Lesions of classic osteosarcoma in adolescent age groups arise in the knee region in 50% of cases but these sites account for 15% of osteosarcoma cases in older patients. Moreover osteosarcomas in older populations characteristically present in regions that have had previous RT, underlying Paget's disease of bone, fibrous dysplasia, or some other abnormality. In many ways the older group can be thought of as having "secondary" osteosarcoma (4).

Bone sarcomas were the third leading cause of cancer death in young individuals, but recently they are estimated to cause as few as 197 deaths per 100,000 cases in those younger than 20 years of age in 2015 (16).This remarkable low rate of mortality is attributable to the adoption of the multi-disciplinary team /MDT management approach and implementation of potent chemotherapy drugs and sophisticated surgery. This resulted in 5-year relative survival rates of children up to 14 years of age increased from 50% in 1978 to 78% in 2008 (17). Optimal management of osteosarcoma consists of multi-agent chemotherapy and local control measures including amputation or limb-sparing surgery. Before the development of limb-sparing procedures amputation was the standard surgical method used for the curative treatment of osteosarcoma. Now amputation is generally reserved for primary unresectable tumors. Over the past several years the role of limb-sparing procedures has increased dramatically. As a result of refinement in neoadjuvant chemotherapy , bioengineering and imaging techniques, it is estimated as many as 80% of patients with osteosarcoma will eventually be candidates for limb-sparing surgery (18) .Before the introduction of adjuvant chemotherapy fatal metastatic disease developed in more than 80% of patients with osteosarcoma (19).Trials of single-agent chemotherapy began in the 1960s and early 1970s and established the role of chemotherapy in the management of osteosarcoma in nonrandomized manner. Response to single-agent high dose methotrexate/MTX or doxorubicin occurred in 20-40% of patients with metastatic disease ((19)-(20). Since then different combinations of platinum compounds, doxorubicin, and high dose

MTX have found the basis of standard chemotherapy regimens that leads to cure in 50 to 75% of patients with non-metastatic disease.

For primary lesions in unresectable sites control with conventional photon radiotherapy is limited. With proton beam therapy 60% local control was achieved for patients with axial skeletal tumors.

1.2 Statement of the problem

Ethiopia is home to a growing population of more than 110 million people and is expected to become the ninth most populous country in the world by 2050 (21). The burden of cancer is growing in parallel to the population growth. Despite an increment in cancer burden the attention given by government and policy makers is low (22). The inadequate attention of governmental organizations, policy makers, and nongovernmental organizations could be due to a low level of awareness on the scale of the burden of disease in the country. To know the exact burden of cancer is hardly possible due to the unavailability of population-based cancer registry data for the whole country. A retrospective cross- sectional study of 12 years of data at theTikurAnbesa Specialized Hospital/ TASHradiotherapy center conducted from 1998-2010 showed sarcomas (both soft tissue and bone) accounts for about 5% of all cancers (23). But this is a single institution- based study that didn't show the true national incidence and prevalence of the disease burden. Estimates of cancer incidence in Ethiopia in 2015 using population -based registry data showed cancers of bone and cartilage accounted for 7% of all pediatrics cancers (5).

Most patients used to appear at an advanced stage. Patients are delayed at presentation. There is no established MDT to discuss the management and care of patients with osteosarcoma at TASH Patients in the western world with a diagnosis of osteosarcoma and localized disease are managed with limp-sparing surgery in more than 80% of the cases (18) .

1.3 Significance of the study

Literature is hardly available in low-income countries on the clinical features, treatment pattern and survival outcome of patients with osteosarcoma. To my knowledge, there is no published literature on osteosarcoma in Ethiopia. The purpose of this study is to describe the clinical presentation, treatment patterns received by patients and to determine the overall survival of osteosarcoma at TASH, and compare it with similar studies done in developed and resource-limited countries. The findings of this study will give input data for individuals who are interested in further research on osteosarcoma.

2 LITERATURE REVIEW

2.1 Clinical presentation, histopathology, and staging

Most patients with osteosarcoma present with localized pain in the affected bone. There may be associated soft tissue swelling or associated palpable mass. Some patients come with pathologic fractures associated with the disease. Although most patients have a micrometastatic disease at presentation, only 10-20% of patients present with clinically evident macrometastasis. The lung is the most common site of metastatic disease followed by the bone (24). The symptoms are often missed initially because other causes of joint pain are much more common than osteosarcoma. It is not unusual for the symptoms to date back to 6 months before the documentation of the tumor. Data on the clinical presentation of osteosarcoma in developing countries are limited. A retrospective study on a South African tertiary hospital in 61 patients treated for osteosarcoma showed that the majority of patients (58 patients, 95.1%) presented with a painful swollen limb and 3 patients (4.9%) presented with pathologic fractures. The tibia was the most common site of involvement for 30 cases (49.2%), with the femur and humerus which accounted for 19 cases (31.1%) and 12 cases (19.7%) respectively. The majority of patients (41 patients, 67.2%) were at Enneking stage 2B, (4 patients, 6.6%) were at stage 2A, and (16 patients, 26.2%) presented with metastatic disease (stage3). An average of 4.5 months was elapsed before patients were seen at the tumor unit. In most cases the delay was due to limited access to MRI (25).

A plain x-ray of the affected bone classically demonstrates the destruction of normal trabecular bone with lytic or sclerotic lesions or both lytic and sclerotic lesions at the same time, osteoid formation under the periosteum which is called Codman's triangle and variable association of soft tissue mass. MRI of the affected bone is important to fully delineate the extent of the lesion, evaluate any soft tissue component and evaluate the involvement of neurovascular structures. The entire affected bone should be imaged to evaluate the presence of skip metastasis. Skip metastasis is well recognized in osteosarcoma but occurs less frequently with less than 5% incidence (26) .

Biopsy of the tumor should be performed to confirm the diagnosis and to differentiate it from other bone lesions. The biopsy should be performed at a center with expertise in bone tumors and should be carried out by or in conjunction with an orthopedic surgeon who will be performing future definitive surgery to not jeopardize subsequent treatment, particularly a limb preserving procedure. Osteosarcoma is broadly classified in to three histologic subtypes (intramedullary, surface and extraskeletal) (28). High-grade intramedullary osteosarcoma is the classic or conventional form comprising nearly 80% of osteosarcomas. It is a spindle cell neoplasm that produces osteoid or immature bone (28). When found in the long bones the epicenter of conventional osteosarcoma lesions tends to be in the metaphysis with diaphyseal extension. Low- grade intramedullary osteosarcoma comprises less than 2% of all osteosarcomas and the

most common sites are similar to that of conventional osteosarcoma (29). Parosteal and periosteal osteosarcomas are juxtacortical or surface variants. Parosteal osteosarcomas are low-grade tumors accounting for up to 5% of osteosarcomas whose most common site is the posterior distal femur. This variant tends to metastasize later than the conventional form (29). Transformation of the lo- grade lesion to high -grade conventional form is reported in 24-43% of cases(30)-(31) . Periosteal osteosarcomas are intermediate- grade lesions most often involving the femur followed by the tibia (29) . High- grade surface osteosarcomas are very rare accounting for 10% of all juxtacortical osteosarcomas (32)-(33). Classic osteosarcoma develops in females slightly earlier than males and there appears to be no race predilection (34). Although the common histologic presentations of malignant cells produce osteoid would suggest a homogeneous group of tumors the morphologic appearance can vary considerably ranging from classic osteoblastic osteosarcoma (45%) through fibroblastic (9%), chondroblastic (25%), anaplastic (17%), telangiectatic , low grade central , and other osteosarcomas (2%) (35).

A review of data at one of the Egyptian pediatric cancer hospitals revealed the following histological types of osteosarcoma. Osteoblastic osteosarcoma was the most common histologic subtype accounting for 40% of cases and chondroblastic ,fibroblastic, and telangiectatic subtypes accounted for 18%, 12% ,and 9% respectively (36) .

Elevated serum alkaline phosphatase/ALP and lactate dehydrogenase/LDH have been identified as prognostic indicator in patients with osteosarcoma. In a cohort of 1421 patients with osteosarcoma of extremities, Bacci et al. reported significantly higher serum LDH levels in patients with metastatic disease at presentation than in patients with localized disease (36.6% vs. 18.8%; $p < 0.0001$ (37).The 5-year disease- free survival/DFS correlated with serum LDH levels (39.5% for patients with high LDH levels and 60% for those with normal levels). In another retrospective analysis of 789 patients with osteosarcoma of the extremity, Bacci et al. reported serum ALP level was significant prognostic factor of event-free survival/ EFS in patients with osteosarcoma of the extremity , the 5-year EFS rate was 24% for patients with serum ALP value of more than 4 times higher than the normal value and 46% for patients with high values below this limit ($p<0.001$) (38). In a review of 57 patients with localized osteosarcoma of the extremities treated at the children's cancer hospital in Egypt, serum ALP level was predictive of EFS, and the significantly better prognosis was found in patients in normal values than in patients with elevated values (3 year EFS was 86.9% and 33.9% in patients with normal and elevated ALP respectively; $p<0.001$) (36)

Systemic staging should include a CT scan of the chest and radionuclide bone scan to evaluate lung and bone metastasis respectively. Positron emission tomography (PET) scan can be used as an alternative for systemic staging but may have less sensitivity than CT and bone scan. PET scan has also been used to assess response to preoperative chemotherapy (27) .

There are two staging systems commonly used for osteosarcoma. The musculoskeletal tumor society (MSTS) staging system is a surgical staging system stratifying tumors by grade and subdividing based on local extent (39). The other staging system is the tumor , node , metastasis (TNM) with principles set by the American joint committee on cancer (40). Staging correlates directly with prognosis.

2.2 Management and outcome of treatment of osteosarcoma

The management and care of osteosarcoma need the involvement of multidisciplinary teams involving orthopedic surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, and physiotherapists.

The mainstay of treatment of localized osteosarcoma is surgery. Surgical management of osteosarcoma should involve a complete enbloc resection of the tumor. The extent and functional implications of surgery have dramatically evolved with an emphasis on more conservative, limb-sparing resections with the maintenance of functions rather than amputation. Neoadjuvant chemotherapy has played an important role in this evolution. For extremity lesions, limb preservation is preferred and can be accomplished in the majority of cases. Retrospective studies have shown equivalent results of limb-sparing surgery and amputation as long as adequate margin can be achieved (41) . Contraindications to limb-sparing surgery include major nerve or vascular encasement, the presence of large biopsy-related hematoma, and pathologic fracture. Some data suggests that pathologic fracture does not increase the risk of local recurrence after limb-sparing surgery as previously believed (41). Reconstructive options include the use of allograft, endoprosthesis, and rotationoplasty. Axial tumors even though there are much less common they have a particular challenge because achieving a complete surgical resection can be difficult. As a result those sites have a worse prognosis compared to the extremity tumors.

The survival of patients with malignant bone sarcomas has improved dramatically over the past 30 years largely as a result of the use of effective chemotherapy. In the absence of chemotherapy 80-90 % of patients will subsequently develop distant metastasis despite achieving local tumor control, and died of their disease. It was subsequently demonstrated that subclinical metastatic disease was present at the time of diagnosis in the majority of patients and that chemotherapy can successfully eradicate those deposits if initiated at the time when disease burden is low (42).The benefit of chemotherapy is best illustrated by a systematic review of literature which showed that long-term survival after local tumor control without chemotherapy was only 16% (43). In contrast the addition of systemic chemotherapy with three or more drugs provided a 5-year survival rate of 70%.Therefore chemotherapy plays an important role for all patients with intermediate and high-grade tumors. Historically there was a controversy about the role of chemotherapy in the management of patients with high-grade oseosarcoma. Level one evidence for the benefit of chemotherapy in the management of high grade osteosarcoma was established by two randomized trials which were done in 1980s.

Eilber et al. reported on 59 patients with nonmetastatic osteosarcoma randomized to surgery followed by observation vs. adjuvant chemotherapy. Disease-free survival/DFS at 2 years was 55% with chemotherapy and 20% with observation ($p<0.01$). Overall survival/OS was also superior at 2 years which were 80% vs.48% with and without adjuvant chemotherapy respectively ($p<0.01$) (44).

Link et al. reported similar results in a group of 36 patients with nonmetastatic high-grade osteosarcoma randomized to observation vs. adjuvant chemotherapy after primary surgery. Disease-free survival at 2 years was 66% with adjuvant chemotherapy and 17% with observation($p<0.001$)(45) .

In the MIOS study patients with newly diagnosed localized extremity high- grade osteosarcoma was randomized after complete surgical resection to adjuvant chemotherapy or observation. Chemotherapy consists of 45 weeks of combination therapy including bleomycin, cyclophosphamide, and dactinomycin/BCD cycles, high dose methotrexate/MTX cycles targeted to achieve 1,000 μM peak concentration, and cisplatin-doxorubicin cycles. Thirty-six eligible patients were randomized. Of 18 patients randomized to adjuvant chemotherapy, 6 patients (33.3%) developed local recurrence. Of 18 patients randomized to observation 15 patients (83.3%) experienced recurrence and 2 of the 3 patients in this group who did not experience recurrence didn't accept the outcome of the randomization and were treated with adjuvant chemotherapy. Two-year actuarial relapse -free survival/ RFS in the observation group was 17± 9% as compared to 66±13 % in the adjuvant chemotherapy group. These results confirmed the significant impact of chemotherapy on outcomes of high-grade osteosarcoma and this trial established a new standard of care for this disease (45). The positive finding from the MIOS trial led to some subsequent trials designed to determine the optimal timing and type of chemotherapy. One trial compared adjuvant from neoadjuvant chemotherapy.

In the POG-8651 trial, patients with newly diagnosed localized resectable high-grade osteosarcoma were randomized at study entry to undergo immediate surgical resection followed by 42 weeks of adjuvant chemotherapy or to receive 10 weeks of neoadjuvant chemotherapy followed by surgery and then 32 weeks of adjuvant chemotherapy. Apart from the timing of surgical resection all patients received 42 weeks of the same chemotherapy regimen as that of the MIOS trial. A total of 100 patients were randomized. Twenty-eight patients among 45 patients (62.2%) in the presurgical chemotherapy group were disease- free, 8 patients (17.7%) developed distant relapses, one of whom also had local recurrence (the only patient in the entire study) after 12 years of follow up. Among 55 patients treated with immediate surgery 39 patients (70.9%) remain disease-free and 15 patients (27.2%) developed distant relapses. Three patients with distant relapses developed pulmonary relapses after resection of primary tumors but before the start of chemotherapy. Five-year event free- survival/EFS ± SE was 69% ± 8% for patients assigned to the immediate surgery group and 61% ± 8% for patients assigned to the presurgical chemotherapy group (one- sided log- rank, $p=0.8$).The projected 5- year survival ± SE is 79%

± 7% for patients assigned to the immediate surgery and 76% ± 7% for patients assigned to theprechemotherapy group (one-sided log-rank, p=0.6). Among patients assigned to presurgical chemotherapy, 50% had limb-sparing surgery while 55% had limb-sparing surgery in those assigned to immediate surgery. Overall survival, EFS and rates of limb salvage surgery were similar between the two arms of the trial demonstrating the timing of surgical resection didn't impact outcomes. With those results, the use of neoadjuvant chemotherapy has become wide spread because this approach allows more time for surgical planning and allows one to assess the extent of tumor necrosis in response to chemotherapy (46).

Two older trials sought to clarify the role and optimal dosing of MTX in patients with newly diagnosed localized osteosarcoma.

In an Italian trial, patients were randomized to receive MTX 200 mg/m2-regimen I (moderate dose) or 2 gm/m2 regimen II (high dose) as a component of multi-agent adjuvant chemotherapy. Among 106 evaluable patients randomized in to high vs. moderate-dose of MTX, 55 % (31/46) were continuously disease- free and 50% (25/50) were disease-free in the moderate- dose MTX and high -dose MTX respectively. The difference was not statistically significant. Outcomes were equivalent between the two groups (47).

The UKCCSG conducted a similar trial, although the dose of MTX under investigation was 690 mg/m2 or 7.5gm/m2. Patients were randomized to high dose MTX containing regimen-MTX 7500mg/m2 every 6 weeks X 12 starting 3 weeks after surgery vs. moderate dose MTX 690mg/m2 every 6 weeks X 12 starting 3 weeks after surgery, both treatment arms received adriamycin 30mg/m2 at the time of surgery and 30mg/m2 X 3 every 6 weeks to 570 mg/m2 starting 6 weeks after surgery,vincristine 2 mg/m2 and folinic acid 12mg/m2 every 6 hours X 7 IV was given for both groups. Only the presence of tumor necrosis was found to be independently prognostic after multiple adjustments (p=0.03), increased DFS was associated with the presence of necrosis. No effect associated with treatment was detected after adjustment for prognostic factors. Median survival after treatment failure from all patients experiencing treatment failure was approximately 12 months. Treatment before failure was not prognostic of subsequent survival (p>0.5). The outcome was again equivalent between the two groups suggesting that either MTX dose does not contribute to disease control in osteosarcoma or that lower dose MTX is adequate for the efficacy of this agent (48).

A series of trials from the German/Australian/Swiss Cooperative osteosarcoma study group (COSS) has clarified the use of cisplatin and doxorubicin in osteosarcoma.

In the COSS-80 trial, all patients received doxorubicin and MTX and then randomized to either cisplatin or BCD. After 10 weeks of chemotherapy patients in the two groups were randomized for the second time to receive or not to receive interferon. Methotrexate 12gm/m2, adriamycin 45mg/m2 X 2, cisplatin 120mg/m2, bleomycin 12mg/m2, cyclophosphamide 600mg/m2, and

dactinomycin 0.45mg/m2 were used. Definitive surgery was done 9-18 weeks after the start of chemotherapy. One hundred sixteen patients with primary nonmetastaticresectable classic/central osteosarcoma were included in the analysis. The analysis of the randomized subgroups revealed no difference in the expected 30 months continuous disease free/CDF rates between the BCD and CPL arm (76% versus 73%) and not also between in patients who received interferon in addition to chemotherapy vs. the control group without interferon (77% vs. 73%). Resected tumors from 57 patients treated preoperatively were available for pathohistologic analysis of tumor response. Thirty- eight resected specimens (67%) showed ≥50% tumor cell destruction. The 30 months expected CDF rate of those patients is significantly superior to that of 19 (33%) patients whose tumors showed <50% tumor cell destruction (87% vs. 49%) CDF rates, ($p<0.005$). To examine the possible adverse influence of delayed surgery, the outcome of patients after primary amputation, and after preoperative chemotherapy was compared and no significant difference in CDF rates has been observed. After preoperative chemotherapy 61 patients (55%) of 116 patients had resections of their primary tumor instead of amputation (48).

In the COSS-82 trial patients were randomized to receive BCD and MTX or doxorubicin, cisplatin, MTX. Patients with primary classical/central osteosarcoma of the extremities and free of detectable metastasis whose age is ≤40 years is included. Patients with a good histologic response at the time of surgery continued to receive the same chemotherapy, whereas patients with a poor histologic response received different salvage regimens. A total of 125 patients were randomized. Patients randomized to BCD arm with no doxorubicin or cisplatin in the neoadjuvant setting had significantly inferior metastatic free survival/MFS even though those patients with the poor histological response received cisplatin and doxorubicin in the adjuvant setting (49). Findings from those two trials highlighted the importance of early doxorubicin treatment in osteosarcoma.

The European osteosarcoma intergroup completed a randomized trial to assess the role of high dose MTX in patients with newly diagnosed localized extremity osteosarcoma. Patients were randomized at study entry to chemotherapy with 6 cycles of doxorubicin-cisplatin or the same regimen and high dose MTX given 10 days before each cycle of doxorubicin and cisplatin. Surgical resections were planned at the same time in both arms of the trials such that patients receiving doxorubicin and cisplatin had time to receive 3 cycles and patients receiving with MTX had time to receive 2 cycle of chemotherapy before surgery. Ninety- nine patients were randomized in each arm of the trial. Disease- free survival was superior for patients who received doxorubicin and cisplatin which was (57%) at 5 years compared to 41% in patients randomized to receive also MTX). Because all patients received the same planned cumulative dose of doxorubicin and cisplatin, those results highlighted the importance of dose intensity of those agents in the treatment of osteosarcoma. Moreover those results called into question the role of MTX (50)

The European osteosarcoma intergroup conducted another randomized trial comparing 6 cycles of doxorubicin and cisplatin to a chemotherapy regimen similar to that used in the MIOS trial. Patients with newly diagnosed localized resectable osteosarcoma were eligible and 391 eligible patients were randomized .The proportion of patients with good histologic response to neoadjuvant chemotherapy was similar between the randomized groups. Although the preoperative histopathological response was a major prognostic indicator for survival, no treatment difference was found in good or poor responders. Progression- free survival and overall survival estimates were nearly identical between the randomized groups. Based on those findings the group concluded that a shorter regimen with doxorubicin and cisplatin is preferable to the more complicated and longer regimen used in the MIOS trial. Those results called into question the role of the BCD regimen used in the MIOS trial which has now largely abandoned (51).

This group conducted a subsequent trial evaluating interval compression to dose intensify the doxorubicin and cisplatin regimen. Patients with newly diagnosed localized osteosarcoma were randomized to receive 6 cycles of doxorubicin-cisplatin administered either every 3 or 2 weeks. Surgical resection occurred after 2 cycles in every 3 weeks regimen and after 3 cycles in every 2-week regimen. A total of 497 eligible patients were randomized. Patients in every 2-week arm had a higher likelihood of achieving a good histologic response although they had also received an additional cycle of neoadjuvant chemotherapy. Progression -free survival and OS were similar between groups indicating that dose intensification by interval compression didn't improve outcome in this setting (52) .

Metastatic disease is mainly hematogeneous spread to the lungs and bone followed by involvement of the kidney, liver and brain. Regional lymph nodes are involved in less than 10% of cases. Metastatic disease at presentation does not preclude long- term DFS when the disease is sensitive to chemotherapy and all sites of the disease can be surgically resected (53)-(54). Aggressive surgical treatment of lung metastasis can yield a DFS rate from 17%- 40% (55)-(56). Generally favorable prognostic indicators include metastasis later than 1 year from the original diagnosis, unilateral disease, presence of fewer than five nodules, and completeness of resection. Early lung metastasis, unresectable bilateral disease, hilar, nodal, or pleural-based lesions have a poor prognosis. The combination of etoposide with cyclophosphamide or ifosfamide has been evaluated in clinical trials. In phase II trial of the French society of pediatric oncology, high dose ifosfamide and etoposide resulted in a response rate of 48% in patients in relapsed or refractory osteosarcoma (57). In another phase II trial cyclophosphamide and etoposide resulted in a 19% response rate and a 35% rate of stable disease in patients with relapsed high- risk osteosarcoma. Progression- free survival at 4 months was 42% (58). Single- agent gemicitabine and combination regimens such as docetaxel and gemicitabine , cyclophosphamide and topotecan or ifosfamide, carboplatin, and etoposide have also been effective in the treatment of patients with relapsed or refractory osteosarcoma (59)-(60).

The main stay of therapy for osteosarcoma has historically omitted radiation because osteosarcomas were thought to be radio resistant (61) . However, surgery and chemotherapy lead to suboptimal local control in challenging disease sites like the spine and pelvis. Relatively lower doses of 30 to 56 gray/Gy for spine osteosarcomas and 56 to 68 Gy for pelvic disease yielded very disappointing local control rates of less than 20% in few patients who were irradiated in the cooperative osteosarcoma study group (62)-(63). However, when higher radiation doses were used better local rates are achieved for unresectable or marginally resectable tumors. Dose of 60 Gy, in 2.5 to 3 Gy once-daily fractions or 1.25 to 1.5 twice daily fractions resulted in local control of 60% in patients with unresectable osteosarcoma (64) . The role of particle RT for the treatment of unresectable or incompletely resected disease is promising.

Kamada et al. reported a local control rate of >70% in patients with unresected osteosarcoma treated with carbon ions (65). Ciernik et al. report on the Massachusetts general hospital experience of 55 patients treated with a mean dose of 68.4 Gy (SD,5.4 Gy) for whom 58.2% (range 11-100%) of the dose delivered using protons. The 5- year local control rate was 72% and 5-years OS was 67%. Grade 3 to 4 late toxicities were seen in 30.1% of patients and two patients died of treatment -related second malignancies (66). Thus with careful planning and respect for radiation tolerance of adjacent normal structures, RT can contribute to favorable clinical outcomes in patients with unresectable or marginally resectable osteosarcoma.

Analysis of prognostic factors in 333 chine's patients with high-grade osteosarcoma treated by multidisciplinary combined therapy was retrospectively analyzed in nonmetastatic or primarily metastatic high-grade sarcoma of the extremities or trunk to see the correlation between survival and age, sex, site, histological type, clinical-stage, ALP level, preoperative chemotherapy or not, response to preoperative chemotherapy, preoperative chemotherapy cycles and manner of surgery. The median survival time was 52 months for 333 patients. Univariate analyses revealed that sex, ALP level, preoperative chemotherapy and number of cycles of preoperative chemotherapy may influence the prognosis of high -grade osteosarcoma of extremities or trunk. Multivariate analysis revealed female sex, normal ALP level, preoperative chemotherapy with good response ,and ≥ 4 cycles of postoperative chemotherapy correlated with better outcome (67).

Retrospective study of 61 patients treated for osteosarcoma at Charlotte Maxeke Johannesburg Academic Hospital, a tertiary hospital in South Africa in 46 cases (75.4%) in whom surgery was undertaken to achieve wide local resection margins. Of those 46 patients, 13 patients (28.3%) had limb salvage procedure and 33 patients (71.7%) had amputations, 4 patients (6.6%) refused any form of treatment and discharged from the hospital and the rest 11 patients (18%) received palliative care only without amputation due to late presentation and those included two patients who received radiotherapy/RT. Fifty- five patients (90.2%) received chemotherapy. Of those, 52 patients (94.5%) had neoadjuvant and post adjuvant chemotherapy and 3 patients (5.5%) post

adjuvant chemotherapy only. One year survival rate was 62.7% (95% CI;49.1-73.9) and 5 year survival was 38.1% (95% CI;24.6-51.4) P=0.009 (25).

A retrospective review of data in 37 patients has conducted at the pediatric hematology/oncology department Ain Shams University, Cairo, Egypt. This retrospective data included 15 patients with osteosarcoma. Nine out of thirteen patients (69.2%) were treated with regimen A (protocol CCG 7921), 2 patients (15.4%) were shifted to regimen B (Protocol CCG 7921) with the addition of ifosfamide due to disease progression and 2 patients refused treatment. Most patients had tumor necrosis <90% (83.3%) and only 2 patients had tumor necrosis >90% (16.7%). Limb salvage was the most common surgical local control modalities (59.26%) and 2 patients underwent amputations (7.4%). One of them had an amputation due to aggressive behavior of the tumor and the other patient had an amputation due to osteomyelitis after a limb salvage operation. One year, 2 years, and 3 years OS rates were 93.3%, 40%, and 13.3% respectively. one year, two years, and three years EFS were 80%, 40%, 13.3% respectively (68).

3 OBJECTIVES

3.1 General objectives:

To describe clinical features, treatment pattern and find out the two years overall survival of patients with osteosarcoma at TASH

3.2 Specific objectives:

-To describe the clinical features of osteosarcoma at TASH

-To describe the treatment pattern of osteosarcoma at TASH

-To find out the two years overall survival of patients with osteosarcoma at TASH

4 METHODS AND MATERIALS

4.1 Study setting:

This study was conducted at TASHRT center, Addis Ababa, Ethiopia. It is a referral hospital accepting patients from all over the country. The hospital gives undergraduate training, specialty certificate training, and fellowship training programs in addition to patient treatment service. The radiotherapy center was established in 1998 with two CO-60 teletherapy machines. In 2015 one high dose rate CO-60 brachytherapy machine was added which provides radiotherapy for cervical cancer and endometrial cancer patients. Quite recently one LINAC machine with a CT simulator was installed and started 3D- conformal RT. The center is the only radiotherapy center in the country with a population number of 110 million+. The radiotherapy center has 7 consultant clinical oncologists, 3 medical physicists, 6 radiotherapist, and 40 clinical oncology residents.

4.2 Study design

A cross-sectional study was conducted from March 2014 to March 2020

4.3 Sources of data

Ward admission HMIS log book data were reviewed and patients with a diagnosis of osteosarcoma were reviewed for the study, and all patients who fulfilled the inclusion criteria were selected for data collection. For survival analysis phone calls were made through phone numbers that were registered in patient charts.

4.4 Source population

All patients with a diagnosis of osteosarcoma and admitted to the TASH oncology ward were the source population of this study.

4.5 Study population

Those are histologically proven osteosarcoma cases admitted at oncology ward of the TASHduring the study period.

4.6 Inclusion and Exclusion Criteria

4.6.1 Inclusion criteria

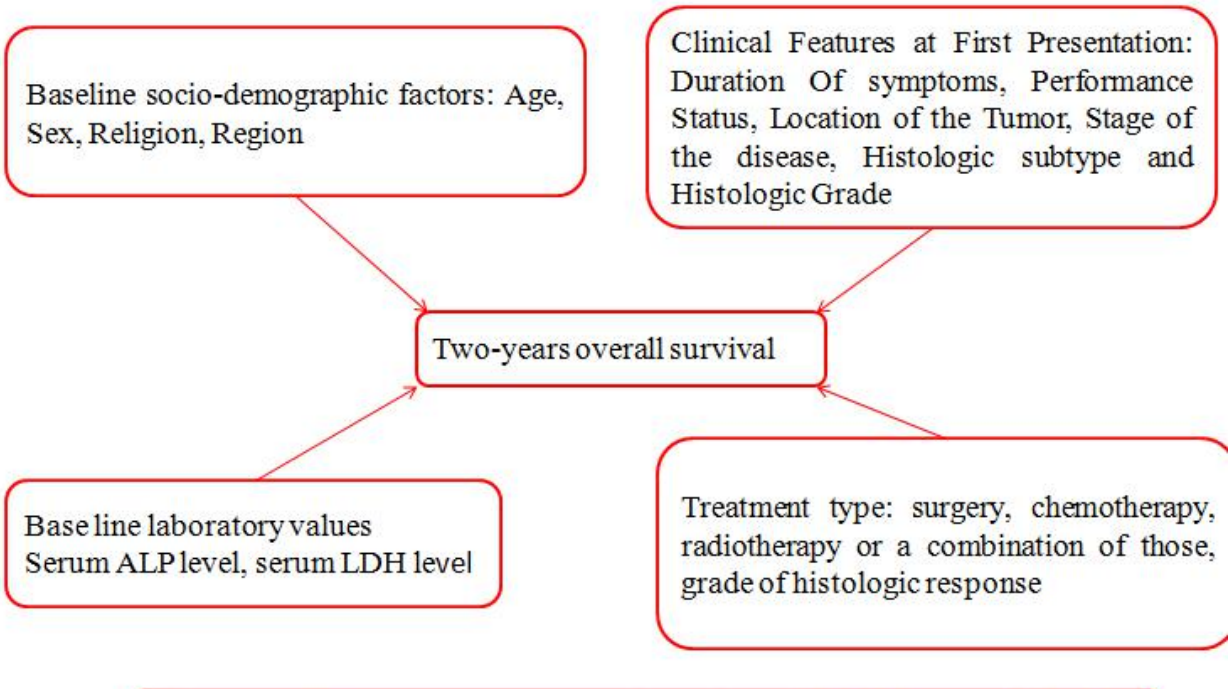
-all patients with tissue diagnosis of osteosarcoma

4.6.2 Exclusion criteria

-patient charts with missing data (socio-demography, treatment history)

- Patient charts with uncertain diagnosis of osteosarcoma

4.7 Study variables



Conceptual framework showing the relationship between independent variables and dependent variable (2-years overall survival)

4.8 Sample size

All patients with a diagnosis of osteosarcoma admitted to TASH oncology ward from March 2014 to March 2020 were included in this study.

4.9 Data collection tool and procedures

Data abstraction format which contains important variables for the research problem was prepared by the investigator. Data were collected by two oncology residents working at the radiotherapy center. A brief training was given for the data collectors on the significance of the study, how to take complete data and explained the meaning of words included on the data abstraction tool. Pretesting of data extraction format was given by the principal investigator before the actual study on 10% of charts that were not included in the study. An appropriate modification was made based on pretest results. Continuous follow -up and support on how to collect relevant data were given to the data collectors by the principal investigator before the start of data collection, and ongoing supervision and assistance were given to check for the completeness of data.

4.10 Data processing and monitoring

The collected data were entered into excel, cleaned and analyzed using STATA version 16.0. Basic descriptive analyses like frequency, mean, and median were used. Bivariate Cox regression and multivariate Cox regressions were done for survival analysis. Kaplan Meier curve is used to show survival estimates. Test of association level of significance set at 5%.

4.11 Ethical consideration

Ethical clearance was obtained from the ethical review board of TASH. The study was approved by the clinical oncology department and the ethical review board of the hospital and data collection started .Verbal consent was taken from patients and patients' history confidentiality is protected.

Dissemination of result

The findings of this study were submitted to the clinical oncology department. Some copies of the research papers will be submitted to AAU CHS, policy makers and concerned governmental institutions. Publication in local and international journals will be considered after peer review.

4.12 Operational definitions

Tissue diagnosis: is the diagnosis of a lesion based on a tissue sample taken from a biopsy or a surgical specimen

Histologic subtype: is a specific variant of the osteosarcoma type

Histologic grade: is a description of the tumor behavior based on how the abnormal cancer cells and tissue look like under a microscope and it determines how fast the cancer cells grow and spread

Histologic grading of tumor response: microscopic assessment of the degree of cancer cell kills after chemotherapy for patients who received neoadjuvant chemotherapy

Group Stage: is the aggregate extent of the disease based on the extent of the primary tumor, the status of regional lymph node the presence of distant metastasis and histologic grade.

Functional status: is a physiologic reserve and determinant of how a patient is likely to cope with the physiologic stresses imposed by cancer developed by the eastern cooperative oncology group

The pattern of treatment: is the type of treatment given like surgery, chemotherapy, radiotherapy or the combination of those treatment types

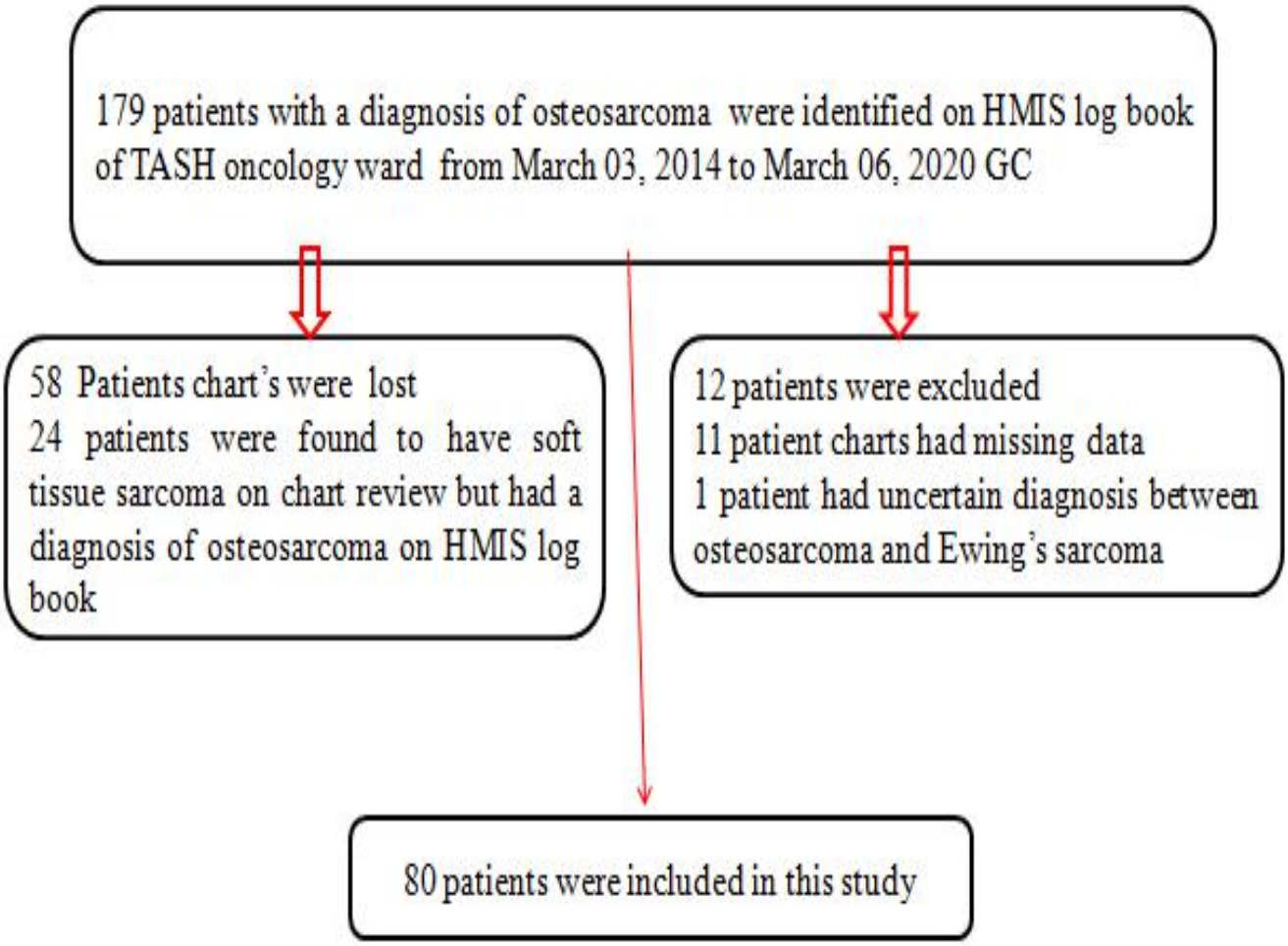
Amputation/Disarticulation: is a surgical procedure that removes a part of a limb or the whole limb

Limb-sparing surgery: removing the tumor without removing the limb where the tumor is found

Adjuvant chemotherapy: systemic chemotherapy given after excision of the tumor

Neoadjuvant chemotherapy: is systemic chemotherapy given before excision of the tumor

5 RESULTS


179 patients with a diagnosis of osteosarcoma were identified on HMIS log book of TASH oncology ward from March 03, 2014 to March 06, 2020 GC
58 Patients chart's were lost
24 patients were found to have soft tissue sarcoma on chart review but had a diagnosis of osteosarcoma on HMIS log book
12 patients were excluded
11 patient charts had missing data
1 patient had uncertain diagnosis between osteosarcoma and Ewing's sarcoma
80 patients were included in this study

5.1 Socio-demographic data of patients with osteosarcoma at TASH

Table 3: Socio-demographic data and co morbidity of patients with osteosarcoma at TASH

Variable	Category	Frequency	Percentage
Sex	Male	49	61.25%
	Female	31	38.75%
Age	10-14	7	8.75%
	15-19	33	41.25%
	20-24	14	17.50%
	25-29	12	15%
	≥ 30	14	17.50%
Religion	Orthodox	43	53.75%
	Muslim	23	28.75%
	Protestant	13	16.25%
	Jehovah's Witness	1	1.25%
Region	Oromia	36	45%
	Amhara	16	20%
	SNNR	9	11.25%
	Tigray	4	5%
	Addis Ababa	15	18.75%
Performance Status	ECOG-I	53	66.25%
	ECOG-II	19	23.75%
	ECOG-III	8	10%
Co-morbidity	No	77	96.25%
	Yes (DVT)	3	3.75%

5.2 Clinical presentation and histopathology of patients with osteosarcoma at TASH

Table 4: Clinical presentation and stage of patients with osteosarcoma at TASH

Variable	Category	Frequency	Percent
Patient complaints at presentation	Swelling	48	60%
	Swelling and pain	29	36.25%
	Pathologic fracture	3	3.75%
Duration of symptoms	<3mo	5	6.25%
	3-6mo	48	60%
	>6mo	27	33.75%
Body site of the primary tumor	Extremity	65	81.25%
	No extremity	15	18.75%
Extremity sub -site of the primary tumor	Distal femur	36	55.38%
	Proximal tibia	19	29.23%
	Distal tibia	3	4.62%
	Proximal femur	2	3.08%
	Proximal humerus	5	7.69%
Nonextremity sub-site	Mandible	5	33.33%
	Maxilla	3	20%
	Other	7	46.67%
Imaging of the primary site	MRI	29	36.25%
	CT	12	15%
	X-ray	1	1.25%
	No	38	47.50%
Epicenter of the primary tumor for extremity sites	Metaphysis	9	13.85%
	meta-diaphysis	6	9.23%
	Diaphysis	5	7.69%
	Epiphysis	1	1.54%
	Unknown	44	67.69%
Maximum diameter of primary tumor (in cm)	≤8cm	14	17.50%
	>8cm	55	68.75%
	missing	11	13.75%
Skip lesion for extremity sites	Yes	2	3.08%
	No	25	38.46%
	Unknown	38	58.46%
Lymph node involvement	Yes	6	7.50%
	No	74	92.50%

Tissue diagnosis made by	Biopsy	77	96.25%
	FNA	3	3.75%
Histologic sub-type	Conventional osteosarcoma	20	25%
	conventional osteoblastic osteosarcoma	14	17.50%
	Osteosarcoma ,NOS	15	18.75%
	conventional chondroblastic osteosarcoma	7	8.75%
	conventional fibroblastic osteosarcoma	4	5%
	Osteoblastoma like osteosarcoma	3	3.75%
	conventional mixed osteoblastic&chondroblastic osteosarcoma	2	2.50%
	Osteogenic sarcoma, NOS	10	12.50%
	Giant cell rich osteosarcoma	2	2.50%
	Parosteal osteosarcoma	1	1.25%
	Small cell osteosarcoma	1	1.25%
	Telangiectatic osteosarcoma	1	1.25%
Histologic grade	High grade	71	88.75%
	Intermediate grade	1	1.25%
	Low grade	1	1.25%
	No report	7	8.75%
Metastasis at presentation	Yes	34	42.50%
	No	46	57.50%
Metastatic site at presentation	lung only	29	85.29%
	Lung & other organ	3	8.82%
	Liver	1	2.94%
	Vertebral bone	1	2.94%

Table 5: Cross Tabulation of Stage for Extremity & Non-extremity Sites

	TNM Stage						
Extremity Vs. Non-Extremity	I	IIA	IIB	III	IVA	IVB	Total
Extremity	0	7	26	0	23	9	65
Non-extremity	2	2	8	1	1	1	15
Total	2	9	34	1	24	10	80

5.3 Baseline laboratory parameters of patients with osteosarcoma at TASH

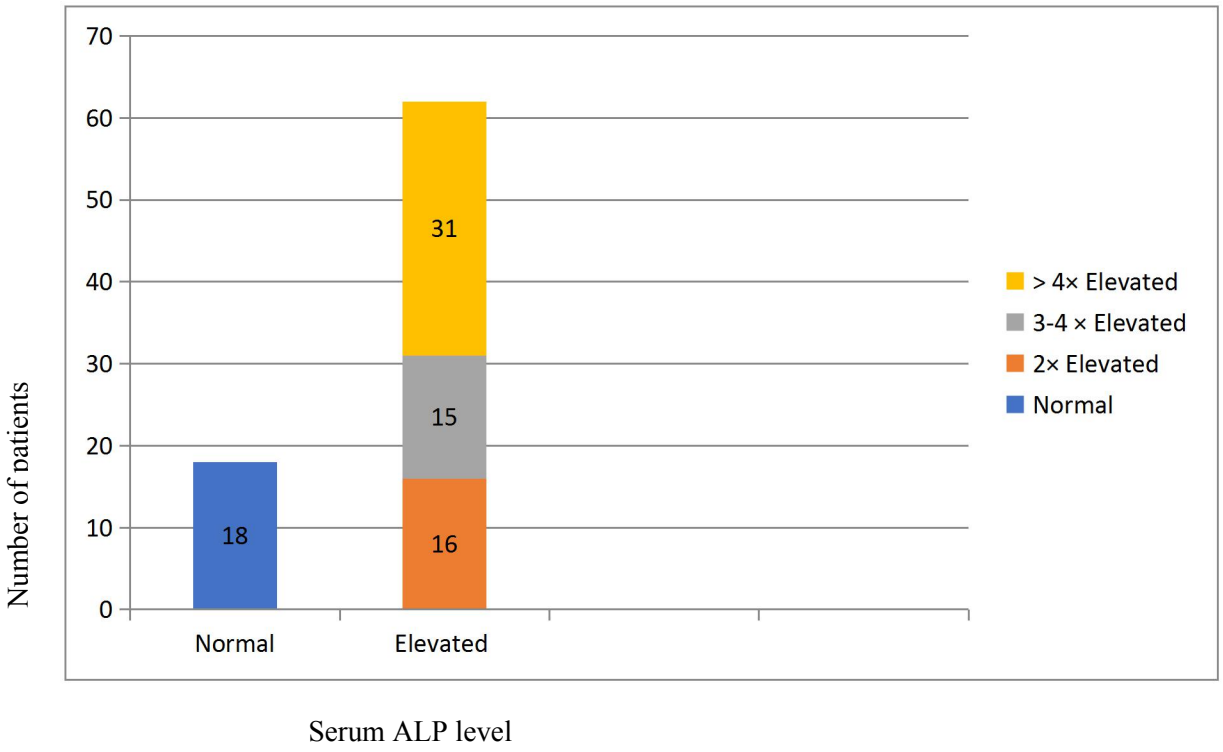


Figure 1: Base line alkaline phosphatase level of patients with osteosarcoma at TASH

The minimum and the maximum ALP levels were 84 u/l and 4430 u/l respectively with a mean of 690.89 ± 725.42. The minimum value of LDH was 169 u/l and the maximum LDH value 1347 u/l with a mean value of 575.44 ± 422.39 (See figure 1 & 2)

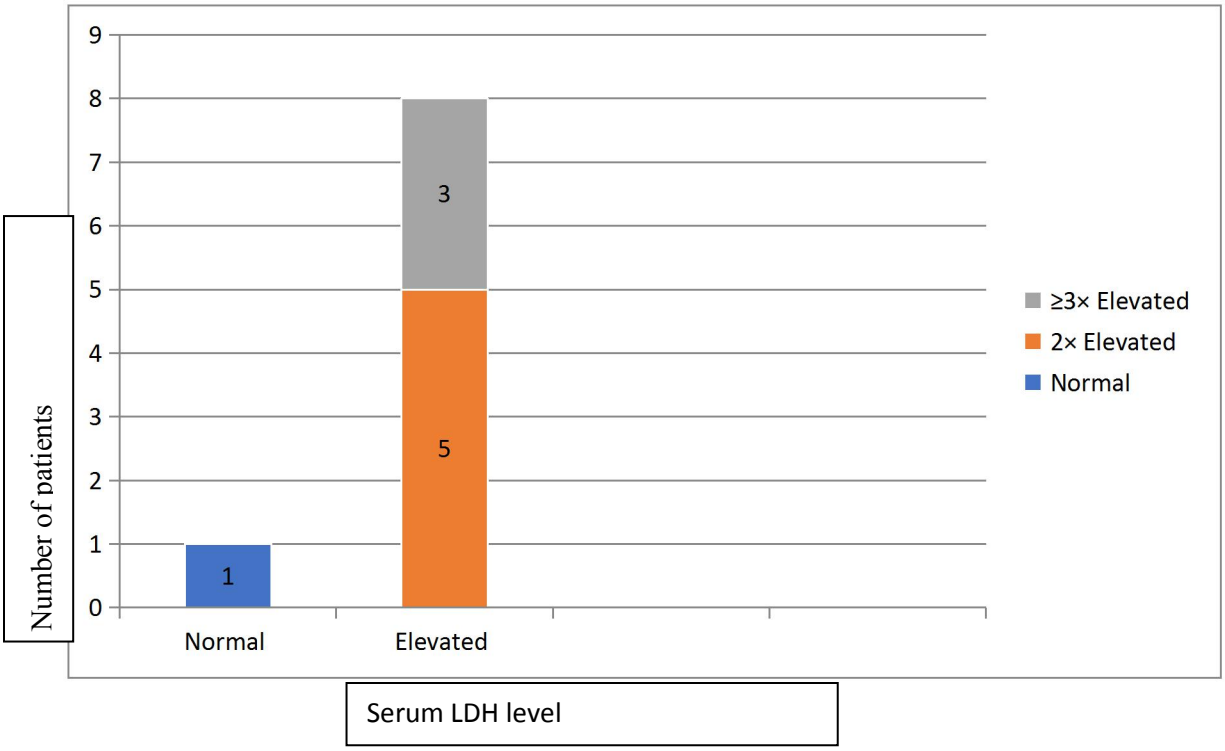


Figure 2: Baseline Lactate Dehydrogenase Level of patients with osteosarcoma at TASH

5.4 Management of patients with osteosarcoma at TASH

Table 6: Treatment pattern of patients with osteosarcoma at TASH

Variable	Category	Frequency	Percent
type of surgery	Palliative AKA	14	28%
	Palliative hip disarticulation	6	12%
	Palliative knee disarticulation	1	2%
	Palliative shoulder disarticulation	2	4%
	Curative AKA	13	26%
	Curative hip disarticulation	7	14%
	Excision & reconstruction	7	14%
1st line chemotherapy	Doxorubicin +cisplatin	68	95.77%
	VAC	3	4.23%
Intent of chemotherapy	Palliative	37	52.11%
	Adjuvant	18	25.35%
	Neoadjuvant	16	22.54%
Radiotherapy	Yes	9	11.25%
	No	71	88.75%

Of all patients, 50 patients (62.5%) had surgery. From all patients who had surgery 45 patients (90%) were from tumors of extremity sites. Of all extremity sites that underwent surgery 43

patients (95.55%) had amputation or disarticulation, 23 patients (51.11%) had surgery for palliation. Of all patients who had a tumor on nonextremity sites 4 patients (80%) had surgery for curative intent (See table5)

Table 7: The minimum and maximum dose of cisplatin and doxorubicin and number of cycles received by patients with osteosarcoma at TASH (refer Annex- III for details)

Variable	Observations	Mean	Std. Dev.	Min	Max
Dose of Cisplatin	68	59.57	10.27	40	100
Dose of Doxorubicin	71	68.71	10.01	45	90
Number of Cycles	71	4.98	1.89	1	6

Table 8: Treatment gap between chemotherapy and surgery, clinical and histologic grade of response and surgical margin status of patients with osteosarcoma at TASH

Variables	Category	Frequency	Percentage
Time gap between neoadjuvant chemotherapy and surgery	13weeks	1	14.29%
	14weeks	1	14.29%
	20 weeks	2	28.57%
	22 weeks	2	28.57%
	24 weeks	1	14.29%
Clinical response after neoadjuvant chemotherapy	Discontinue treatment	5	29.41%
	New lung metastasis	3	17.65%
	Stable disease	8	47.06%
	No imaging	1	5.88%
Histologic grading of tumor response	Fair response(60%necrosis)	2	28.57%
	No report	1	14.29%
	Biopsy not sent	4	57.14%
Surgical margin	free	4	36.36%
	involved	3	27.27%
	no report	4	36.36%
Time gap between surgery and adjuvant chemotherapy	≤6weeks	9	52.94%
	7-12 weeks	5	29.41%
	13-18weeks	1	5.88%
	>18weeks	2	11.76%

5.5 Survival of Patients with Osteosarcoma at TASH

The minimum and the maximum follow-up time from the diagnosis to the last follow up date ranges from 0.4 months to 48.56 months respectively with a mean follow-up time of 12.12 ± 9.68 months.

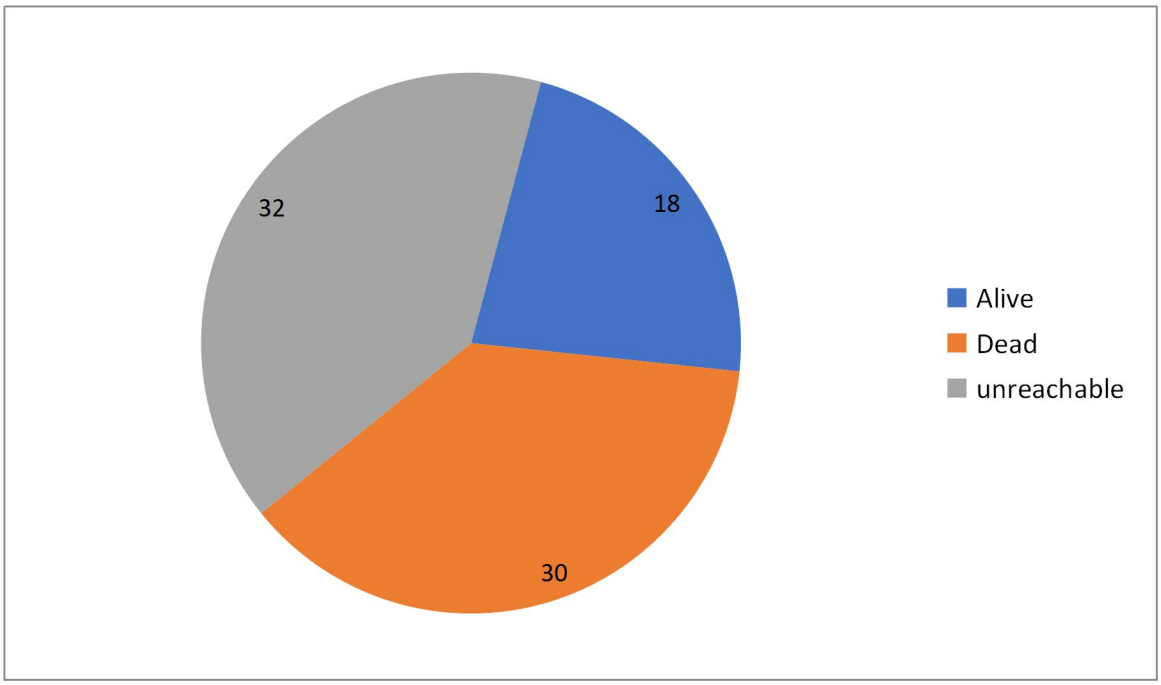


Figure 3: Outcome of patients with osteosarcoma at TASH

One year and two-years overall survival rates were 73% and 45% respectively with a median survival of 20.8 ± 2.96 months (95% CI, 14-50-33.63) (look Annex-IV)

Table 9: Survival time in years of patients with osteosarcoma at TASH

Interval in Years		Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
0	1	80	17	34	73.02%	0.06	0.60	0.82
1	2	29	9	11	45.05%	0.08	0.29	0.60
2	3	9	3	4	25.74%	0.10	0.10	0.45
3	4	2	1	1	8.58%	0.10	0.00	0.39

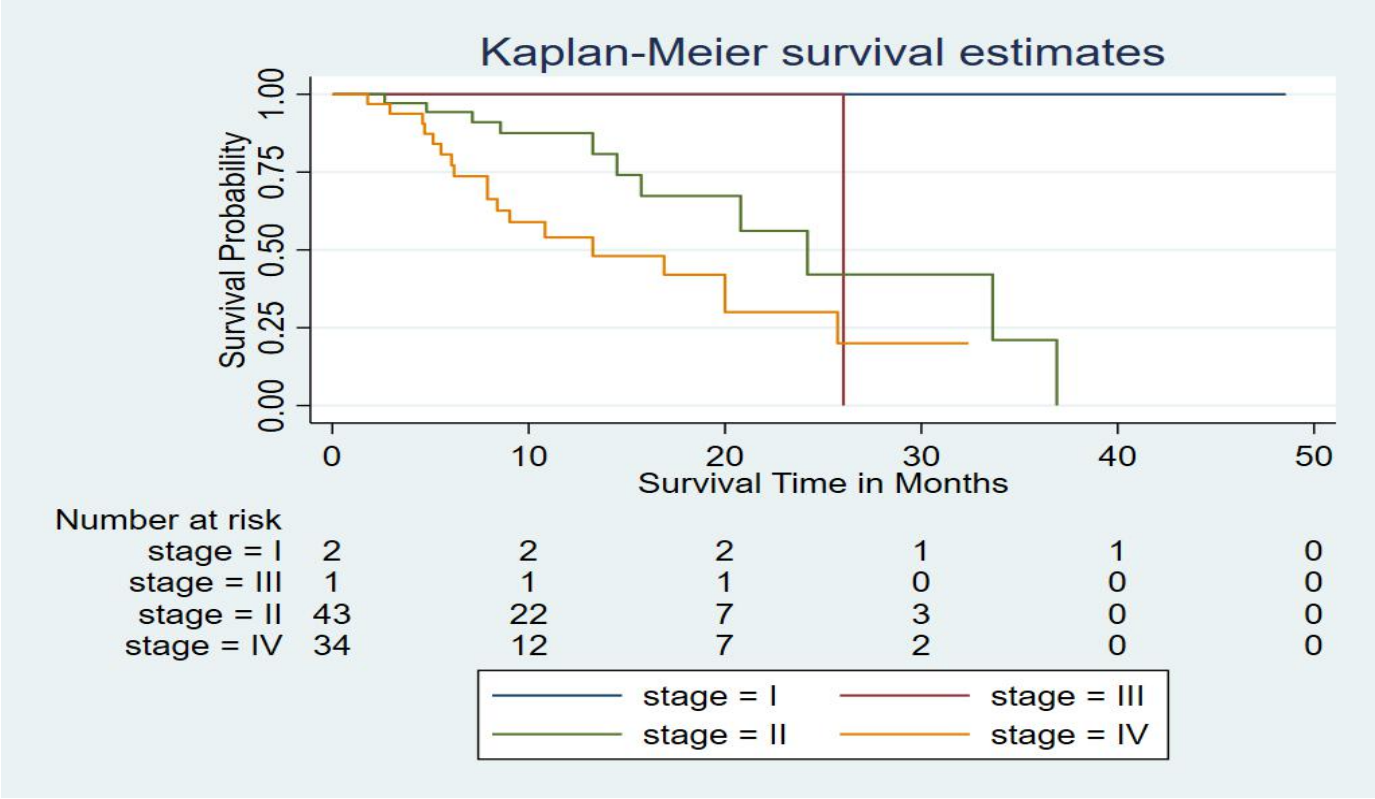


Figure 4: Kaplan Meier survival estimates of patients with osteosarcoma at TASH based on the stage

Table 10: Bivariate Cox regression of patients at TASH (Dependent variable is survival time in months)

_t	Haz. Ratio	Std. Err.	Z	P>z	[95% Conf. Interval]	
Duration of Symptom	1.113638	0.2888911	0.41	0.678	0.6697799	1.851637
ALP Elevation	1.052073	0.0346643	1.54	0.123	0.9862796	1.122256
Stage	1.0528	0.0187385	2.89	0.004	1.016706	1.090175
Stage						
IIA	1.49e	1.78e	19.69	0	1.45e	1.54e
IIB	6.70e	7.36e	20.6	0	7.78e	5.77e
IVA	1.49e	1.59e	22.02	0	1.85e	1.20e
IVB	6.84e	7.63e	22.37	0	7.69e	6.09e
Types of Surgery						
Curative Intent	0.0773173	0.0585408	3.38	0.001	0.0175303	0.3410077
Palliative Intent	0.8125327	0.3267961	0.52	0.606	0.3693962	1.787267
No Chemo	2.938753	1.616522	1.96	0.05	0.9998665	8.637425
Neoadjuvant	10.9394	12.35297	2.12	0.034	1.196191	100.0428
Palliative	12.85057	13.20777	2.48	0.013	1.714197	96.33501
Number of Cycles	0.8118731	0.0937347	-1.81	0.071	0.6474597	1.018037
Dose of Cisplatin	1.000911	0.0228781	0.04	0.968	0.9570605	1.046771
Dose of Doxorubucin	1.017652	0.0253106	0.7	0.482	0.9692335	1.068488
time gap between surgery and adjuvant chemotherapy	1.192059	0.1699822	1.23	0.218	0.9014054	1.576432

Table 11: Multivariate Cox Regression of patients with osteosarcoma in TASH (Survival time in Months)

_t						
	Haz. Ratio	Std. Err.	Z	P>z	[95% Conf. Interval]	
Type of Surgery	0.6260622	0.1783245	-1.64	0.1	0.3582329	1.094132
Intent of Chemotherapy	3.455261	1.532958	2.79	0.005	1.44823	8.243737
Dose of Doxorubucin	0.9812714	0.0304595	-0.61	0.542	0.9233517	1.042824
Dose of Cisplatin	1.000291	0.0227969	0.01	0.99	0.9565933	1.045985
Number of cycles	0.8181246	0.1023045	-1.61	0.108	0.640293	1.045346

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6 DISCUSSION

6.1 Socio-demography

Our study showed that males were 1.58 times more affected by osteosarcoma than females, which is similar to studies done in Sweden and the USA. An epidemiological study of osteosarcoma in Sweden showed a male to female ratio of 1.6 to 1 (2). A similar epidemiological study done in the USA showed a male to female ratio of 1.35 to 1 (3). The reason for the higher prevalence of osteosarcoma in males compared to females in our study and the Swedish as well as the American study is not clear. The peak age of osteosarcoma in our study occurred between 15-19 years of age while 14 patients (17.5%) were aged 30 and above. Even though the peak age prevalence of osteosarcoma was consistent with the peak age in most literatures, significant number of patients in this study were above the age of 30. A clinicopathologic analysis of 117 patients by Huvos AG.et al showed 10% of osteosarcoma cases occurred above the age of 60 years (4).

6.2 Clinical Presentation, Staging, and Histopathology

The most common site of osteosarcoma in our study was the distal femur which accounted for 36 patients (55.38%) followed by proximal tibia which accounted for 19 patients (29.23%). About 85% of osteosarcomas occurred around the knee joint in our study. A study done by Sim FH ; et al. showed distal femur was involved in 32%, proximal tibia in 15%, proximal humerus in 8%, and proximal femur in 5% of all cases (15). A retrospective study in South Africa in 61 patients with osteosarcoma showed the tibia was affected in 30 patients (49.2%) followed by femur in 19 patients (31.1%) and humerus was affected in 12 patients (19.7%) (25). About 47% of osteosarcoma cases occurred around the knee joint according to Sim FH, et al study which was lower than our study but the South African study showed that about 80.3 % of osteosarcoma cases occurred around the knee joint which was more or less similar to the findings of this study. Seventy- seven patients (96.25%) presented with swelling and pain and 3 patients (3.75%) had pathologic fracture in our study which was very similar to a study done in South Africa which showed 95.1% of patients came with painful swollen limb and 4.9% came with pathologic fracture (25). Forty-eight (60%) of patients in this study came within 3-6 months of the onset of symptoms, while 27 (33.75%) of patients came after 6 months and 5 (6.25%) patients came within 3 months with a mean duration of symptoms of 7.8 ± 9.1 months, while it took an average of 4.5 months for the South African study (25). Compared to the South African study patients in our study were delayed at presentation. The reason for the delayed presentation was not identified, but the reasons for delay might be due to patients' poor health- seeking behavior or delayed referral system at the primary health institutions where patients were usually seen before they came to TASH. Thirty- four patients (42.5%) had documented distant metastasis at the presentation of our study. The lung was the most commonly affected organ by metastasis in 29 patients (85.29%). In general 32 (94.11 %) patients had lung or lung and other organ metastasis. Bone accounted only for one patient as a metastatic site. A study done by Kumar; et al. showed that 10-20% of patients presented with metastasis , the lung being the most common site of metastasis followed by bone (24). A retrospective study in South Africa in 61 patients showed that 16 (26.2%) patients had distant metastasis at presentation (25). Our study revealed a higher prevalence of distant metastasis compared to the study done by Kumar et al. and the

South African study; the reasons might be most patients in our study were delayed at presentation which leads to metastasis at the patient's arrival to TASH.
In our study 62patients (77.50%) had conventional osteosarcoma which was the predominant histologic subtype, and from patients who had conventional osteosarcoma 14 (17.5%) patients had osteoblastic conventional osteosarcoma subtype ,7 (8.75%) patients had chondroblastic conventional osteosarcoma subtype, 5% of patients had fibroblastic conventional osteosarcoma subtype ,2.5% had mixed chondroblastic and osteoblastic conventional osteosarcoma subtype. Fifteen patients (18.75%), 10 (12.5%) patients, and 6.25 % had osteosarcoma, NOS, osteogenic sarcoma, NOS and other rare types respectively. A study done by Huvos AG. showed that classic conventional osteosarcoma was the predominant subtype accounted for 45% of all cases while chondroblastic subtype accounted for about 25%, fibroblastic subtype 9% and other rare histologies (anaplastic,telangiectatic, low-grade central) combined accounts about 2% of all cases (35). A study done in South Africa showed conventional osteosarcoma was the predominant subtype accounted for 93.4% of all cases , while chondroblastic osteosarcoma , osteoblastic osteosarcoma, fibroblastic conventional osteosarcoma accounted for 15.8%, 38.6%, 8.8% respectively. Not specified variants account for 33.3% (25). A retrospective study in Egypt revealed osteoblastic osteosarcoma in 40% of cases, chondroblastic, fibroblastic, and telangiectatic subtypes accounted for 18%, 12%, and 9% respectively (36). There was a high difference between the conventional osteosarcoma sub-type between our study and a study done in South African patients, which were 77.50% and 93.4% respectively, but not specified subtypes were closer in prevalence which was 31.25% and 31% respectively. The prevalence of classic osteosarcoma in Egyptian patients was about 79% which was similar to our study and the study a study done by Huvos AG which was 79%. The difference in rates on the conventional oateosarcoma sub-type on the above studies was not clear, but inconsistent reporting of subtypes by pathologists might affect the results.

6.3 Baseline Laboratory

In our study all patients had base line serum ALP levels measured. Of all patients, 18 patients (22.5%) had normal ALP level and the rest had elevated ALP levels. From all patients who had elevated values 16 patients (25.8%) had twice elevation, 15 patients (24.2%) had 2-4 times elevation and 31 patients (50%) had elevation more than four times. A retrospective study by Bacci, et al in 789 patients with osteosarcoma of the extremity showed that 492 patients (69.2%) had normal ALP while 291 patients (44.7%) had elevated ALP levels. This retrospective study showed that serum ALP level was a significant prognostic factor of EFS. Five-year EFS was 24% in patients with ALP 4 times elevated from the normal value and 46% in patients who had elevated ALP level below 4 times from the normal limit ($p<0.001$) (38). But our study didn't show any association between serum ALP levels and disease stage or survival time ($p=0.123$). The reason for the lack of association between ALP levels and survival was not clear, but the inclusion of both extremity and nonextremity sites together in our study could change the result compared to the study done by Bacci et al. which only included patients with extremity sub-sites of osteosarcoma.

6.4 Treatment Pattern of Osteosarcoma

In our study from all patients, 50 patients (62.5%) had surgery. Of 65 patients with extremity osteosarcoma, 45 patients (69.2%) had surgery. From all extremity sites that had surgery, only 2 patients (4%) had limb- sparing surgery and the rest 43 patients (96%) had either an amputation

or limb disarticulation. From all patients from extremity sites that had surgery 23 patients (51%) had a palliative amputation and 20 patients (44.5%) had curative limb amputation. A study by Choong PF, Sim FH on bone tumors showed that 80% of patients with osteosarcoma had limb-sparing surgery (18). A retrospective study of 61 South African patients showed that 46 patients (75.4%) had surgery, from those patients who had surgery 13 patients (28.3%) had limb- sparing procedure and 33 patients (71.7%) had an amputation (25). A retrospective study of 28 patients with osteosarcoma in Egypt had shown that limb- sparing procedure was done in 59.26 % of patients and 7.4% had an amputation (68). The rate of limb- sparing surgery in our study was very small compared to a study done by ChoongPF,Sim FH as well as the African studies which were done in South Africa and Egypt. The reason for the high rate of amputation and disarticulation in our study might be multifactorial, but lack of a multidisciplinary approach in treatment and care of osteosarcoma, lack of optimal training in the surgical management of osteosarcoma and poor infrastructure might play a big role.

In our study 71 patients (88.75%) of all patients received 1st line chemotherapy which contained cisplatin and doxorubicin. Three patients (4.2%) received VAC. Of all patients who received chemotherapy about half of the patients received as palliative intent and the rest as neoadjuvant and adjuvant intent. The minimum and the maximum number of chemotherapy cycles were 1 and 6 respectively with the mean cycles of 4.98 ± 1.89. The minimum doxorubicin dose was 45 mg/m2 and the maximum dose of 90mg/m2 with a mean dose of 68.71 ± 10.1 and the minimum and maximum dose of cisplatin were 40mg/m2 and 100mg/m2 respectively with a mean dose of 59.57 ± 10.27 which are significantly lower than used by western clinical trials and standard guideline recommendations.

6.5 Survival of Patients with Osteosarcoma

The median overall survival in our study was 20.8±2.96 months (95% CI, 14-50-33.63) with one year, two years, survival rates of 73.02%, 45.05% respectively.

Overall survival was found to be significantly associated with curative surgery (p=0.001), distant metastasis at presentation (p=0.004) and not taking chemotherapy (p=0.05) on bivariate Cox regression but the intent of chemotherapy was the only significantly associated factor with overall survival (p=0.005) on multivariate Cox regression.

In our study patients who had curative amputation had better survival (HR, 0.077; 95% CI, 0.017-0.341; p=0.001). About 92% of deaths from osteosarcoma were prevented by having curative surgery. Patients who didn't receive chemotherapy had worse survival (HR, 2.938; 95% CI, 0.999-8.637; p=0.05). Patients who didn't receive chemotherapy were about 2.9 fold likely to die compared to patients who received chemotherapy. Advanced stage at presentation was predictive of inferior overall survival (HR, 1.053; 95 CI, 1.017-1.090; p=0.004). Those patients who received neoadjuvant chemotherapy (HR, 10.939; 95% CI, 1.196- 100.043; p=0.034) or palliative chemotherapy (HR, 12.850; 95% CI, 1.714-96.335; p=0.013) had significantly inferior survival compared to those patients who received adjuvant chemotherapy.

A prospective study by Eilber et al. showed a two- year overall survival of 80 % (p<0.01), while a similar prospective study by Link et al showed a two -year DFS of 66% (p<0.001) (44)-(45). A prospective study by MIOS showed that a 2-year actuarial relapse- free survival of 66 ± 13%, while a prospective study by POG showed a 5-year survival of 76 ± 7% (45)-(46). A South African retrospective study of patients with osteosarcoma had shown a one- year survival of 62.7% (95% ,CI,49.1-73.9) and five- year survival of 38.1% (95% CI, 24.6-51.4), p=0.009 (25) . A retrospective study on osteosarcoma at Aims Shams university in Cairo showed one- year,

two- year, and three- year survival of 90.3%, 40%, 13.3% respectively (68). Our study had shown an inferior survival rate compared to studies underwent in western countries as well as studies done in Africa (South Africa and Egypt). The difference in survival between the western countries and our study might be related to the difference in study design in which the studies by Eilber et al, Link et al, and POG were randomized controlled trials only for tumors of the extremity sites with a high dose of neoadjuvant and adjuvant chemotherapy while our study was a retrospective study which contained both extremity and nonextremity sites together with high number of patients with metastatic disease at initial presentation which resulted difficult to compare. The overall survival of patients in our study was also inferior compared to the South African patients. The reason might be the high number of South African patients who received neoadjuvant and adjuvant treatment in 93% compared to 47% of patients who received adjuvant or neoadjuvant treatment in this study. Our study also included a significant number of patients who didn't complete the standard number of cycles of chemotherapy and significant numbers of patients were lost from follow up which may affect the quality of the results.

7 CONCLUSION AND RECOMMENDATION

7.1 Conclusion

The peak age of osteosarcoma occurs between 15-24 years of age. Males are 1.58 times more affected by osteosarcoma than females. The majority of osteosarcoma occurs around the knee joint. Patients are delayed at presentation and about 42.5% of patients had metastasis on presentation. The lung was the commonest site of metastasis. Conventional high-grade osteosarcoma was the predominant histologic subtype. Limb -sparing surgery practiced very little. The options of chemotherapy are according to the standard recommendation but the dose is lower.

The median overall survival of osteosarcoma is 20.8 ± 2.96 months. Patients who had curative surgery had the best- estimated survival. Being stage IV disease at presentation and not taking chemotherapy are associated with poor overall survival. Taking adjuvant chemotherapy is associated with better survival compared to neoadjuvant or palliative chemotherapy.

7.2 Recommendation

Since patients are delayed, and very high number of patients have metastasis at presentation. The cause of the delay should be investigated. Osteosarcoma treatment and care should be expanded so that patients could get treatment at the nearest health facility. By doing that patients will receive curative surgery and survival will be improved. Patients with osteosarcoma at TASH were under- investigated compared to the standard recommendation. Standard investigations should be done at the base line to know the exact extent of the disease. In our study, almost all patients with osteosarcoma had an amputated limb and this has to be improved with the establishment of a dedicated tumor board and adoption of the current standard of care. Patients with advanced disease at presentation and those patients who didn't receive chemotherapy as well as patients who received palliative surgery had worse survival, so awareness on osteosarcoma should be given to motivate patients to come early and to receive standard of care treatment.

Literature is very limited in low-income countries on osteosarcoma and we recommend generating high quality data with future prospective studies.

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9 ANNEXES

Annex-I: English version of patient information sheet

This patient information collection sheet was intended to determine the clinical features, treatment pattern, and overall survival of osteosarcoma at TASH, Addis Ababa, Ethiopia. The study was conducted through reviewing secondary data. The study will give some evidence and information for individuals or organizations that need further investigation and the result of this study will provide basic information on the clinical status, pathology, and overall survival of osteosarcoma. Information which is necessary for the study was taken from patient charts and final interview. The individual patients were not subjected to any harm as far as the confidentiality is kept. No personal identifiers were used on the data collection tool.

Date of review: 02/15/2021-03/15/2021

Date of interview/phone call: 02/15/2021-03/15/2021

Name of reviewer: Dr.Eyoel Negash Signature _____.

Dr. YasinWorku Signature_____.

Total number of records reviewed: 179

Result: (A) complete: 80 (B) incomplete: 11 (C) excluded: 83

Action taken for incomplete data: excluded from the study

Name of supervisor: Dr.YasinWorku Signature_____.

Principal investigator address +251930587413

Annex-II: Assurance of the investigator

I, undersigned clinical oncology resident agreed to accept responsibility for the scientific, ethical , and technical conduct of the research project and provision of required progress reports as per terms and conditions of the research and publication office of Addis Ababa university.

Name of investigator: Dr. Yasin Worku (final year clinical oncology resident)

Signature _____Date: 03/12/2021

Approval of primary advisors

Advisors Name: Dr.Aynalem Abreha (MD, Internist, Clinical Oncologist)

Signature_____ Date: 03/12/2021

Dr.Edom Seife (MD, Clinical Oncologist)

Signature _____Date: 03/12/2021

Table 12: Annex-III: dose frequency of doxorubicin and cisplatin

Dose of Doxorubicin	Freq.	Percent
45	1	1.41
50	6	8.45
52	1	1.41
55	2	2.82
60	15	21.13
70	3	4.23
75	38	53.52
77.7	1	1.41
78	1	1.41
80	1	1.41
86	1	1.41
90	1	1.41
Dose of Cisplatin		
40	1	1.47
50	16	23.53
55	3	4.41
57	1	1.47
60	39	57.35
63.8	1	1.47
65	1	1.47
75	2	2.94
80	1	1.47
90	1	1.47
100	2	2.94

Table 13: Annex- IV: life table of patients with osteosarcoma at TASH

Interval in Months	Beginning Total	Deaths	Lost	Survival	Error	[95% Conf. Int.]	
0 1	80	0	2	1	0	.	.
1 2	78	1	5	0.9868	0.0132	0.9097	0.9981
2 3	72	2	3	0.9588	0.0233	0.8775	0.9865
4 5	67	3	1	0.9155	0.033	0.8214	0.9612
5 6	63	2	4	0.8855	0.0382	0.7838	0.9411
6 7	57	2	3	0.8536	0.0429	0.7444	0.9186
7 8	52	3	1	0.8039	0.0491	0.6853	0.8815
8 9	48	2	3	0.7693	0.0527	0.6455	0.8546
9 10	43	1	5	0.7503	0.0547	0.6234	0.8398
10 11	37	1	3	0.7292	0.0571	0.5983	0.8235
11 12	33	0	4	0.7292	0.0571	0.5983	0.8235
12 13	29	0	4	0.7292	0.0571	0.5983	0.8235
13 14	25	2	0	0.6708	0.0658	0.5241	0.7814
14 15	23	1	0	0.6417	0.0691	0.4897	0.759
15 16	22	1	0	0.6125	0.0718	0.4568	0.7359
16 17	21	1	0	0.5833	0.0741	0.4251	0.7121
17 18	20	0	2	0.5833	0.0741	0.4251	0.7121
18 19	18	0	1	0.5833	0.0741	0.4251	0.7121
20 21	17	3	1	0.4773	0.0821	0.3113	0.6257
21 22	13	0	1	0.4773	0.0821	0.3113	0.6257
22 23	12	0	1	0.4773	0.0821	0.3113	0.6257
23 24	11	0	1	0.4773	0.0821	0.3113	0.6257
24 25	10	1	0	0.4295	0.0867	0.2594	0.5891
25 26	9	1	0	0.3818	0.0892	0.2124	0.5497
26 27	8	1	0	0.3341	0.0899	0.1697	0.5079
28 29	7	0	1	0.3341	0.0899	0.1697	0.5079
31 32	6	0	1	0.3341	0.0899	0.1697	0.5079
32 33	5	0	2	0.3341	0.0899	0.1697	0.5079
33 34	3	1	0	0.2227	0.1089	0.0582	0.4523
36 37	2	1	0	0.1114	0.0957	0.0088	0.3611
48 49	1	0	1	0.1114	0.0957	0.0088	0.3611

Table 14: Annex -V: American Joint Committee on Cancer TNM Staging System for Bone

<table>
<tr><td>T (primary tumor)</td><td>N (regional lymph node involvement)</td><td>M (distant metastasis)</td><td>G (histologic grade)</td><td colspan="2">prognostic groups</td></tr>
<tr><td rowspan="2">Tx:primary tumor cannot be assessed</td><td rowspan="2">Nx:regional lymph nodes cannot be assessed</td><td rowspan="2">M0:no distant metastasis</td><td rowspan="2">Gx: grade cannot be assessed</td><td colspan="2">IA=T1N0M0G1,Gx</td></tr>
<tr><td colspan="2">IB=T2/T3N0M0G1,Gx</td></tr>
<tr><td rowspan="2">T1: ≤ 8cm in greatest dimension</td><td rowspan="2">N0:no regional lymph node involvement</td><td rowspan="2">M1a:lung</td><td rowspan="2">G1:well differentiated (low grade)</td><td colspan="2">IIA=T1N0M0G2,G3</td></tr>
<tr><td colspan="2">IIB=T2N0M0G2,G3</td></tr>
<tr><td>T1:>8cm in greatest dimension</td><td>N1:regional lymph node involvement</td><td>M1b:bone or other distant sites</td><td>G2: moderately differentiated (high grade)</td><td colspan="2">III=T3N0M0G2,G3</td></tr>
<tr><td rowspan="3">T3:discontinuous tumor in primary site</td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3">G3: poorly differentiated (high grade)</td><td colspan="2">IVA=anyTNoM1a any G</td></tr>
<tr><td rowspan="2">IVB=</td><td>anyT,N1 any M , any G</td></tr>
<tr><td>any T, any N, M1b, any G</td></tr>
</table>

Table 15: Annex- VI: Data Extraction Tools

SN	Variable	Category
1.	MRN	…..…….
2.	Phone Number	…..……
3.	Sex	1)Male 2)Female
4.	Age (in years)	……
5.	Religion	1)Orthodox 3)Muslim 5)Other (specify) 2)Protestant 4)Catholic
6.	Region	……..
7.	Co- morbid illness	1)HIV 2)DM 3)HTN 4)ASTHMA 5)Others (specify)
8.	Patient complaints	1) Pain (duration)…… 2) Swelling (duration)…… 3) Fracture (duration)…… 4) Fever (duration)……. 5) Weight loss (duration)…… 6)Other (specify)
9.	Site	1)Extremity 2)Non-extremity
10.	For extremity sites	1)Proximal humerus 2)Distal humerus 6)Distal femur 3)Radius 7)Proximal tibia 4)Ulna 8)Distal tibia 5)Proximal femur 9)Fibula

		10. Carpal bones/Phalanges 11. Tarsal Bones
11.	For non-extremity sites	1)Mandible 4)Ribs 7)Clavicle 2)Maxilla 5)Vertebral Bone 8)Scapula 3)Pelvis Bone (Specify) 6)Skull Bone
12.	MRI/CT of the primary site	Epicenter of the tumor(extremity tumors) 1)Metaphysic 2)Diaphysis 3)Epiphysis 4)Missing
13.	Size of the primary lesion (in cm)	1) ≤ 8cm 2) >8cm 3) Skip lesion
14.	Regional LN involvement on clinical examination or imaging	1)Yes 2)No
15.	Biopsy date (……)	1)FNA 2) Biopsy
16.	Histologic subtype	1)High grade intramedullary conventional osteosarcoma 2)Surface high grade osteosarcoma 7)Fibroblastic 3)Intramedullary low grade osteosarcoma 8)Telangiectatic 4)Parosteal9)Clear cell 5)Periosteal 10)Other (specify) 6)Chondroblastic
17.	Histologic grade	1)Gx-cannot be assessed 2)G1-well differentiated-low grade

		3)G2-moderately differentiated-low grade 4)G3-poorly differentiated-high grade 5)G4-undifferentiated-high grade
18.	Metastasis site at presentation (if any)	1)Lung 2)Bone 5)Brain 3)Liver 4)Bone Marrow 6)Other(Specify)
19.	Baseline laboratory	1)LDH level 2)ALP level
20.	Group Stage	1)IA 2)IB 3)IIA 4)IIB 5)III 6)IVA 7)IVB
21.	Type of Surgery (Date//)	1)Amputation –radical -palliative 2)Limb-sparing surgery 3)Other(specify)
22.	Chemotherapy – (date of initiation)…	**Adjuvant/Neoadjuvant** 1) Regimen with dose…… 2) Number of cycles…… 3) Date of end cycle chemotherapy……. 3) Time between the last cycle of chemotherapy and surgery in weeks (for those who received neoadjuvant chemotherapy)… **Palliative** 1) Regimen with dose…… 2) Number of cycles……
23.	Time gap between surgery and	…….

	adjuvant chemotherapy in weeks	
24.	RT (Date//)	1)Yes 2)No
25.	Clinical response after neoadjuvant chemotherapy(based on RECIST criteria)	1)Complete response 2)Partial response 3)Stable disease 4)Progressive disease 5)Can't be assessed (information missing)
26.	Histological grading of the tumor response(for those who received neoadjuvant chemotherapy)	1)Total response-no viable tumor 2)Good response-90-99% tumor necrosis 3)Fair response-60-89% tumor necrosis 4)Poor response <60% tumor necrosis
27.	Surgical Margin (for those who received definitive surgery)	1)Negative(R0 resection) 2)Involved microscopic margin(R1 resection) 3)Involved gross and microscopic margin(R2 resection) 4)Unknown margin
28.	Last follow up (date……) Condition	1)No Evidence Of The Disease 2)Stable Disease 3)Progressive Disease- 3.1) Primary Site 3.2)New Metastatic Site(specify) 4)Lost From Follow Up
29.	Time gap in months between diagnosis and last follow up date	….……

30.	Final Outcome	1)Alive 2)Died 3) Unknown
31.	If died date of death (month/date/year)	_____.