Osteosarcoma outcomes in Johannesburg: A retrospective multicentre review

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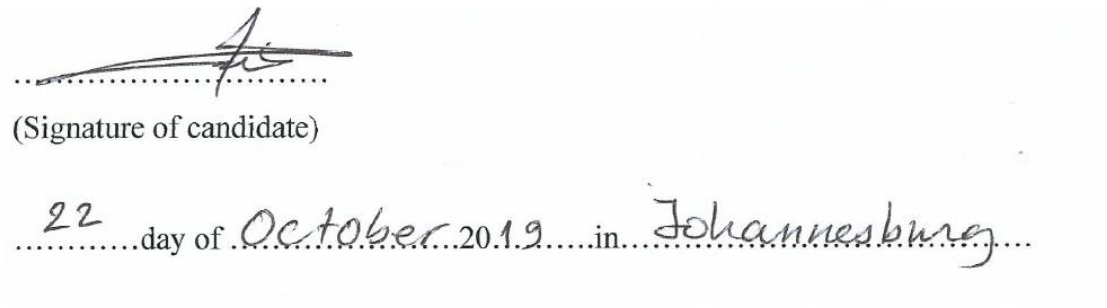
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine

Johannesburg, 2019

Declaration

I Dr Ali Nasar declare that this Research Report is my own work. It is being submitted for the Degree of Master of Medicine in the branch of Orthopaedic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

22 day of October 2019 in Johannesburg

Dedication

I dedicate my research report to my family. A special feeling of gratitude goes to my loving parents, Mohammed and Masoudah whose words of encouragement and push for tenacity ring in my ears. My wife Manal who supported me throughout my journey with this research report. I devote this piece of work to my 3 days old son Mohammed. I dedicate this work and give special appreciation to my brothers and sisters for being there for me throughout the entire study program. I dedicate my work to my beloved country Libya.

Presentations arising from research project

Nasar A, Geel JA, Ngcana TVZ, Eyal KC, Linda Z, Kyte R, Ramguthy Y, Lisenda L, Lukhele M, Wainwright RD, Firth GB. Osteosarcoma outcomes in Johannesburg: A 26-year multicentre review. Oral Presentation held at the COMOC Congress, Cape Town International Conference Centre on the 11th – 15th April 2016, Cape Town, South Africa.

Abstract

There is limited literature on the topic of paediatric osteosarcoma in South Africa, in particular status at presentation to tertiary hospital and five-year survival rates. The objective of this study was to evaluate the clinical outcomes of children younger than 18 years of age with osteosarcoma at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH) and Wits Donald Gordon Medical Centre (WDGMC), tertiary hospitals in Johannesburg, South Africa, and compare these with similar studies in the developing world. This was a retrospective study of 102 children treated at CMJAH, CHBAH and WDGMC between 1985 and 2015. Records of children with osteosarcoma kept at the three hospitals were reviewed to assess them at the time of presentation and the five-year survival rates following treatment. An average of 113.7 days (74.2 SD) elapsed before patients presented to hospitals for medical care after the onset of symptoms. Conventional osteosarcoma constituted just over 92.2% of the cases. Most patients (n = 52, 51%) were at Enneking stage III, 39 (38.2%) were at stage IIB, 10 (9.8%) were at stage IIA, and none presented at stage 1A or stage IB. Of all the patients, 17 (16.7%) underwent limb salvage surgery (LSS), 33 (32.4%) had amputations, nine (8.9%) had disarticulation of either the hip or shoulder, 11 (10.8%) declined surgery and were referred for palliative treatment and 18 (17.7%) were not fit for surgery and received palliative care only. The treatment given in eleven patients (10.8%) was not recorded. The five-year overall survival rate was 42%. There were no significant differences ($p > 0.05$) in the mean survival time between males and females. After surgery, the five-year survival rate was higher ($p < 0.05$) in males (~42%) compared with females (~30%). The children that had limb salvage surgery (LSS) had a significantly higher ($p < 0.05$) five-year overall survival are (76% vs 44%) than those children that had their limbs amputated. More than 51% of patients in this cohort from three hospitals in Johannesburg presented for medical attention at tertiary hospitals after the disease had metastasized. The five-year survival rates from this cohort are better than those published in other developing countries but significantly lower than those in the developed world. This study highlights the need for ongoing education of the general public about the dangers of delayed medical attention. Urgency is required, to facilitate rapid tertiary referral, expedite management and potentially improve outcomes.

Acknowledgements

This research report has been undertaken in partial fulfilment of the Degree of Master of Medicine in Orthopaedic Surgery. I wish to acknowledge certain institution and individuals for their input towards the formulation of this research report. I would like to thank my family with sincere gratitude for their unconditional support. My sincere thanks also go to my sponsors. I want to thank the Libyan government specifically University of Zawia for sponsoring my studies as well as my living expenses.

I am also grateful to the colleagues who participated in this study.

Firstly, I wish to humbly acknowledge with sincere gratitude, my supervisor Dr GB. Firth for his advice and guidance during the writing of this report.

It is his persistent criticism that brought hope and confidence in me, even at the most depressing moments. He was truly a source of inspiration. Dr. GB. Firth's support has certainly made studying at Wits an enhancing and developmental experience. Although the views and opinions conveyed in the report remain my own, my ability to enlist with the debates and discussions remain the responsibility of my supervisor and the other lecturers in Wits school of health science.

Secondly, the continuous support of Prof MT. Ramokgopa, the head of department of Orthopaedic surgery, during the final months of compiling this report are worth noting.

Lastly, special thanks go to Dr M. Jingo: Scientific input and proof reading. I thank you so much.

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Nomenclature

ALP	–	Alkaline Phosphatase
CHBAH	–	Chris Hani Baragwanath Academic Hospital
CMJAH	–	Charlotte Maxeke Johannesburg Academic Hospital
HIC	–	High Income Country
LDH	–	Lactate Dehydrogenase
LSS	–	Limb Salvage Surgery
LIC	–	Low Income Country
MIC	–	Middle Income Country
MRI	–	Magnetic Resonance Imaging
OPD	–	Out Patient Department
OS	–	Osteosarcoma
TNM	–	Tumour, Lymph Node, Metastasis
WDGMC	–	Wits Donald Gordon Medical Centre
Vs	-	versus

CHAPTER 1

1 Introduction and literature review

1.1 Background

There is sparse literature on paediatric osteosarcoma in South Africa (SA) and the available data reflects dismal survival rates. There is limited available information on the status of the children below the age of 18 years at the presentation to tertiary hospitals as well as the five-year survival overall rates. Most of the studies conducted in SA have focused on the mixed samples that included both adults and children and as such there is no information specifically on the outcomes of paediatric osteosarcoma. In addition, all the existing studies from South Africa have small patient numbers, potentially limiting relevance[1–4].

Research conducted in most low-income (LIC) and middle-income countries MIC) has attributed low survival rates to factors such as smoking, absence of awareness of the significance of early screening, stigma associated with cancer and limited financial resources that prevent many people from seeking preventive health services and/or care. In SA, the same reasons have also been noted as contributing to the poor five-year survival rates in several different cancers. There are enormous discrepancies in survival rates between low-income and middle-income countries. The estimated case mortalities for the different cancers (e.g. breast, cervical, testicular cancer, and acute lymphoblastic leukaemia in children), are 75% in LIC, 72% in low-middle income incomes countries, 64% in middle-high income countries, and 46% in high income countries[5].

In this study we aimed to assess the status of the children at presentation and outcome of patients over a thirty-year period. The present study intended to document the incidence based on year of diagnosis, age at presentation, duration of symptoms, sex, site of metastases, level of amputation, site of mass, serum ALP, serum LDH and histologic types were examined. And determine the five-year survival rates of patients and assess the numerous variables to present additional knowledge in concern of the characteristics of osteosarcoma in children from this population.

1.2 Literature review

1.2.1 Epidemiology

Osteosarcoma (OS) is the commonest primary cancerous bone tumour with 3.4 new cases per million people diagnosed every year worldwide[6]. OS has a bimodal distribution by age with a main peak in adolescence and a smaller peak among the elderly between the six and seventh decade of life[6]. The annual frequency among children and adolescents seems to be relatively constant around the world[6], and most rates range from 3 - 5 per million men population and 2 - 4 per million in women[6]. The incidence of OS may depend on ethnicity[7].

Osteosarcoma is an uncommon malignant bone neoplasm, account for 0.2% of all malignancies. Even though rare, it is the third most common malignant tumour in adolescence. In HIC, five-year survival rates of patients with osteosarcoma in excess of 60% are well documented and limb salvage is considered standard-of-care. In a study conducted in Norway between 2010 and 2014, in the age group of 1 - 14 years of age, the bone cancers currently constituted about 4% of all childhood cancers among males and 3% among females, with a cumulative risk of 0.1% of developing bone cancer by the age of 75[8]. The sparse South African literature reflects dismal survival rates[2–4].

Osteosarcoma is an uncommon cancer that characterise histologically by the production of osteoid that are associated with malignant mesenchymal cells[9]. Despite its scarcity, it has been recorded as the third most frequent malignant tumour in adolescence after lymphomas and brain tumours[10,11] and an annual incidence of 5.6 cases per million children of 15 years old or younger[10,11]. Osteosarcomas account for 0.2% of all malignancies[11]. Osteosarcoma is however rare under five-years of age[12] but peak incidences are noted in the children of 10 to 20 years of age[13]. It arises occasionally, with few cases related to known hereditary errors in cell cycle division control mechanism. The majority of cases, approximately 70%, demonstrate a chromosomal irregularity, comprising either mutations in tumour-suppressor genes or in DNA helicases[14]. According to the WHO's histologic taxonomy of bone tumours, osteosarcoma can be divided into three distinct types - Central/medullary is one type. Osteosarcoma is actually divided into Primary and Secondary. Primary is divided into

Central/medullary, Surface/peripheral, intra-cortical, extra-osseous and multifocal – each with subgroups[15].

1.2.2 Central

a. Conventional osteosarcoma

Conventional osteosarcoma is the most frequent type of osteosarcoma and account for 80% of all OS cases mostly affecting adolescents. Conventional osteosarcoma has three variants that are the *osteoblastic, chondroblastic,* and *fibroblastic subtypes* noticed by the principal characteristic of the cells. The clinical consequences among the three mentioned variations are similar[15]. OS is usually high grade and arises from the intramedullary cavity. When observing the X - Rays for osteosarcoma, it can be seen as either being osteolytic, osteoblastic, or both patterns. The majority of OSs (80%) arise from the metaphyseal area of the long bones, nevertheless OS has been reported to originate from the diaphysis of long bones or from the axial skeleton[16].

b. Telangiectatic osteosarcoma

Telangiectatic osteosarcoma (TOS) constitutes on average about 4% of all osteosarcoma cases[17]. Histologically, it is identified by enlarged blood-filled cavities. High-grade sarcomatous cells on the septae and border illustrate the presence of TOS. On the radiographs, TOS is metaphyseal lesion, characterise physically with bone loss and a wide area of transition. Moth-eaten or permeative obliteration is noteable[18].

c. Small-cell osteosarcoma

The small-cell osteosarcoma (SOS) contributes on average between one to two percent of all osteosarcoma cases. The histological characteristic of SOS demonstrate small cells that have circular hypochromatic nuclei with minimal nuclear polymorphism which is similar to Ewing's sarcoma[19]. Even though the formation of osteoid by tumour cells proves osteosarcoma, this is not a nature character of Ewing's sarcoma[20]. A destructive action with lytic zones and sclerosis is noted on the radiographs[19].

1.2.3 Surface

a. Parosteal osteosarcoma

Parosteal osteosarcoma (PAOS) is a low-grade osteosarcoma which derives from the bone periosteum. PAOS accounts for about 4 - 6% of osteosarcoma and usually arise from the posterior surface of the distal femur but can originate in the proximal end of the humerus and proximal metaphysis of the tibia[21]. Radiological examination shows compactly ossified and lobulated masses, however the medullary canal is spared[22]. On the histological examination, PAOS shows spate of bone trabeculae which display a great side-by-side alignment, comparable to what could be identified in a periosteal new bone reaction[20].

b. Periosteal osteosarcoma

Periosteal OS (PIOS) has a medium element which is mostly cartilaginous in composition and rare compared to the parosteal OS. PIOS arises between the cortex and the cambium sheet of the periosteum, and as such a periosteal reaction is typically noticeable on radiographs[23]. Histologically, PIOS appears as an intermediate-grade tumour, enclosing a cartilaginous medium with zones of calcification[20].

c. High-grade surface osteosarcoma

High-grade surface OS (HGSOS) accounts for less than 1% of the entire cases of osteosarcoma[17] and appears as a high-grade histological appearance surface lesion[24]. The local expansion is enhanced in HGSOS compared to PAOS. The HGSOS carry similar malignant potentiality as the conventional subtype, and to certain extent localised invasion of the bone cortex and the endosteum is observed[20]. On the radiographs, HGSOS reveals a surface lesion with partial mineralisation, and the tumour that spreads to adjoining soft tissues[25].

1.2.4 Diagnosis

The characteristic symptoms at first clinical presentation are a history of localised bone pain followed by a palpable mass (or swelling) and limitations of joint movement[26]. The first symptoms are normally associated with a recent traumatic event, and this is the major reason the patients' attention is drawn to the body part affected by injury[26]. The disease might also present with a pathological fracture, either spontaneously or after a minor trauma[27].

There is divergent histologic differentiation in osteosarcoma that necessitates that a triple diagnostic approach be implemented in all suspected osteosarcoma cases. Definitive diagnosis requires histological examination of suspected tumour material, preferably by open biopsy[28] and then magnetic resonance imaging (MRI) and X-Rays[29]. Both X-Rays in two planes and MRI are normally conducted prior to a biopsy to determine the tumour's intramedullary and soft tissue extension and its relationship to vessels and nerves[29]. Patients with radiological findings suggesting the presence of osteosarcoma must be referred to a tertiary hospital prior to taking a biopsy, as a wrong diagnostic procedure can permanently compromise any chance for limb-salvage or even a cure[28]. The area evaluated by MRI should comprise the entire affected bone, including the neighbouring joint in order not to miss skip lesions[30], that is, intramedullary tumour foci without direct connection to the primary tumour. To exclude metastatic disease at the time of diagnosis, staging should include chest X-rays, Computed Tomography (CT) scanning of at least the thorax and a radionuclide bone scan[29]. In addition, F-18 FDG3 PET/CT has been shown to be a useful method in evaluating bone tumours during initial staging and for monitoring therapeutic response[31].

When a bone lesion is suspected and as a plan for surgery and further management a standard radiographic protocol is adopted, that involves obtaining a minimum of standard orthogonal X-ray planes of the entire bone and the neighbouring joint. The radiographs display an unclear lesion originating from the metaphyseal area of the bone, with osteoblastic and/or osteolytic zones, periosteal reaction, and a soft tissue mass[32].

1.2.5 Staging

The Musculoskeletal Tumour Society staging scheme, also recognised as the Enneking staging system is the staging classification used in OS[33] (see Table 1.1). This system based on either the tumour is low grade (I) or high grade (II), either the tumour is intra or extra-compartmental (A or B), and either there is metastatic disease or not(III)[33]. Stage IA means a low-grade tumour which is intra-compartmental, IB represents a low-grade tumour that is extra-compartmental, stage IIA is when there is intra-compartmental high-grade tumour, and IIB means an extra-compartmental high-grade tumour. If there is any metastasis, the tumour is classified as stage III category[33]. Most frequently, osteosarcoma patients are diagnosed at stage IIB[34].

Table 1.1: Enneking Stages

Stage	Site	Grade	Metastasis
1A	Intercompartmental	Low	No
1B	Extracompartmental	Low	No
IIA	Intercompartmental	High	No
IIB	Extracompartmental	High	No
III	Any	Any	Regional or Distant

1.2.6 Pathogenesis

1.2.6.1 Metastases

The most frequent site of metastases in children with osteosarcoma is in the lungs with bone being the second most common site[16]. However, these patients with lung metastases are managed with the same treatment approaches as the cases with localised tumour[35]. Therefore, removal of pulmonary metastases remains an essential and effective adjunct to multiagent chemotherapy[35]. Surgical resection is considered an option if all lung nodules can be removed and the remaining amount of pulmonary tissue can adequately maintain pulmonary function[36]. Repeated metastasis excisions are acceptable for patients with resectable lung metastases[37]. The impact of surgery for other locations of metastases is not well established, but surgical resection appears to be the treatment of choice if a complete removal of all lesions is feasible[38,39].

1.2.6.2 Five-year survival rates

The five-year survival rate in many countries has increased in the last 30 years from 10% to 70%[40]. Pakos *et al.*[11] reported a five-year overall survival of 52% among the 2 680 patients that were included in an international multicentre study. Damron[41] *et al*. reviewed 8 104 osteosarcoma patients in the USA National Cancer Data Base, and found a five-year survival rate of 53.9% which remained relatively constant over an 18 year period (1985 to 2003). In contrast the five-year survival rate has been very low in the few studies conducted in South African children with the five-year overall survival ranging from 7.5% to 50%[3,4,42].

1.2.7 Treatment

1.2.7.1 Current therapeutic strategies – LSS and Amputation

The current management of OS includes neoadjuvant and adjuvant chemotherapy, and surgery[43]. The difference between neoadjuvant and adjuvant chemotherapy is that neoadjuvant chemotherapy refers to treatment given as the initial step to decrease the tumour size before embarking on the main treatment, normally which is surgery while adjuvant chemotherapy is additional cancer treatment that is given after the initial treatment to decrease the risk of a recurrence of the tumour.

a. Surgical treatment

Limb salvage and amputation are the two surgical options currently used to completely resect the disease through wide excision of the tumour[44].

b. Limb salvage

Limb salvage surgical techniques are known to offer a safe system of treatment for 85 – 90% of patients with osteosarcoma in HIC[45]. Resection and reconstruction are the two fundamental steps of limb salvage. Resection is critical in the eradication of the disease and includes surgical removal of the site and tracts of the previous biopsy with a minimum of two cm margin. The main vessels in the surgical field need to be recognised first then ligated when necessary. Before surgery, the radiological examination, for instance, CT and bone

scan, ought to be utilised to decide on the required amount of bone to be removed and should be about six to seven centimetre distal to the lesion to establish clear margins[46]. Tumour resection surgery in skeletally immature patients may result in the destruction of the physis which might lead to growth disturbances. Previously, the situation of the tumour in the physis was a contraindication for LSS and an indication to amputate. Nowadays, the management involves wide resection of the affected bone and reconstruction with expandable growth endoprostheses and allograft endoprosthetic composites[47]. Resections around joints are difficult, and joint contamination precludes LSS, necessitating an amputation. Reconstruction is the next step in limb salvage. Of note that non-weight-bearing bones, for example the clavicle or proximal fibula, do not necessitate reconstruction, because resecting these bones alone does not have effect on the functionality[48]. When reconstruction is utilised in weight-bearing bones, it can be either an endoprosthetic replacement or biological reconstruction.

A number of studies argue that LSS provides a better daily functioning compared to amputation and has superior survival rates post surgery[49]. A new surgical treatment incorporates osteointegration implants to the treatment of the amputees to increase functionality. Rotationplasty comprises of resection of the distal femur, then turning the distal part by 180° as consequence the ankle joint is converted into a ‘‘knee’’ joint[50], with the gastrocnemius and soleus plantar flexors becoming ‘‘knee’’ extensors[50]. Rotationplasty has demonstrated satisfying functional and rehabilitative outcome, specifically in children and active adults[50]. However, in rare circumstances in some patients it causes psychological problems and there is a risk of the reconstruction derotating[51].

c. Amputation

The amputation was once regarded as a classic surgical treatment of osteosarcoma, but it is now restricted to the non-resectable tumours with soft tissue and neuromuscular contamination not amenable to limb salvage surgery.

1.2.7.2 Comparison of Limb Salvage Surgery and Amputation

The functional results and the quality of life for patients who had Limb Salvage Surgery (LSS) *versus* amputation does not differ in a number of international studies[52] in terms of psychosocial outcomes or of achievements in marriage and employment[40]. Cancer survivors

are at high risk of psychological and behavioural problems, for which they need long term, follow up[53]. In comparison to the healthy population, the survival group complained of severe physical and functional impairment[54]. Patients with LSS had higher local recurrence rates than the amputees in a study by Gaston[55].

Previous studies documented slightly higher recurrence rates with LSS than amputation, nevertheless the overall survival rate of patients who had disease recurrences was comparable[56]. Other studies have shown that survival rates are greater with LSS in comparison to amputation. In 2001, Ferrari *et al*. reported an eight-year-survival rate of 62% patients that underwent LSS, in contrast to 43% who opted for limb amputation[57]. Endoprosthetic replacement in tumour surgery led to better quality of life. Lang *et al*. conducted a retrospective study to analyse the sporting capabilities in 27 patients presented with osteosarcoma who had LSS in form of modular endoprostheses[58]. Their study reported that, in the five years after the surgery, the same number of patients who had previously participated in sports played sports after being operated on. They inferred that patients might again attain significant achievement of performance in sports after a modular endoprosthesis, and the likelihood to accomplish that was dependent on the activity before the surgery rather than the procedure and implant itself[58]. The majority of patients from recent studies prefer limb salvage surgery for treatment of malignant sarcomas[59].

1.2.7.3 Non-surgical treatment

Non-surgical treatment that has been developed over time to treat osteosarcoma includes chemotherapy and radiation.

1.2.7.3.1 Chemotherapy

Before chemotherapy was introduced in the 1970's for treating osteosarcoma, survival rates were dismal. Neither chemotherapy nor surgery alone can effectively treat osteosarcoma; as such a combination of them is usually required[60]. The typical treatment of osteosarcoma includes neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy. The neoadjuvant chemotherapy, was presented in 1978[61], and can lead to tumour necrosis in the primary tumour, facilitate surgical resection, and destroy micrometastases[62].

Adjuvant chemotherapy regime must be chosen according to the extent of tumour necrosis resulted from neoadjuvant chemotherapy. The combination chemotherapy regime used in patients in this study consisted of methotrexate (cumulative dose 96 mg/m^2), doxorubicin (350 mg/m^2), cisplatin (360 mg/m^2) and ifosfamide (5400 mg/m^2). The four chemotherapy agents (with mode of action) which included in almost all therapy protocols are methotrexate with leucovorin rescue, cisplatin, doxorubicin, and ifosfamide and are listed in the Table 1.2 below.

Table 1.2: The chemotherapy drugs and their mode of action[62]

Agent	**Mechanism of action**
Doxorubicin	Doxorubicin intercalates at point of uncoiling of the DNA double helix and inhibits the synthesis of DNA and RNA
Cisplatin	Cisplatin binding to tumour DNA, inhibits the DNA synthesis via the DNA crosslinks
Methotrexate	Methotrexate is a folate antimetabolite and inhibits the synthesis of purine and thymidylic acid by binding dihydrofolate reductase
Isosfamide	Isosfamide causes crosslinking of DNA strands which inhibits the synthesis of DNA and protein.

The present typical regime for multi-agent chemotherapy (MAP) compose of cisplatin, doxorubicin and high-dose methotrexate (MTX) with leucovorin-rescue, ±ifosfamide[29] (see Table above), that provides nearly 70% overall survival for patients with primary osteosarcoma[63]. Undeniably, doxorubicin and methotrexate have been successful used as chemotherapy drugs in patients with localised osteosarcoma[64]. Furthermore, adding cisplatin and ifosfamide to doxorubicin and MTX promoted the clinical outcomes of OS treatment[65]. A meta-analysis validated that multi-agent protocols comprising of MAP ± ifosfamide have superior outcomes than two-drug protocols, when there was no significant difference between MAP and MAP with ifosfamide[66]. By comparison, other chemotherapy drugs for instance bleomycin, vincristine, and dactinomycin were noted to be ineffective[67].

1.2.7.3.2 Radiation

Radiotherapy has a questionable role in the treatment of OS because of its doubtful efficacy and linked risk of infection. Radiation has been popularised in Japan where it is being used as a complement to low-cost reconstructive modality. A 2013 study retrospectively evaluated 101 patients with sarcomas (37 of whom had OS) following the treatment with extracorporeal irradiation (ECI) and none of osteosarcoma patients presented with recurrence. The ECI includes En bloc excision of the lesion, treatment of each resected bone fragment with 50 Gy radiation, and final replantation of the bone. Hong *et al*. started promoting ECI as an inexpensive treatment efficient at preventing disease recurrence and carried a low risk of infection[68].

1.2.8 Prognosis and prognostic factors

The prognostic factors for high-grade OS are well known[35], and the most commonly cited ones are mentioned below [41, 765, 76, 77, 78, 79, 80]:

(a) Age,
(b) Sex.
(c) Tumour sites and
(d) Surgical resection margin.

1.3 Study Aim and Objectives

The aim of the study was to assess the status of the children at presentation and outcome of patients over a thirty-year period and to document the incidence based on age at presentation, duration of symptoms, sex, site of metastases, level of amputation, site of mass, serum ALP, serum LDH and histologic types.

The objectives of this study are:

- To identify the overall five-years survival rate as well as the five-year survival rate for patients who had amputation and those who had limb salvage surgery (LSS).
- To estimate the overall recurrence rate as well as the recurrence rate for patients who had amputation and those who had LSS.
- To document the level of amputation vs LSS.

CHAPTER 2

2 Methodology

2.1 Research Questions

1. What is the five-year survival rate for children in the clinics presenting with OS?
2. What is the recurrence rate of OS in this population (children below 18 years)?
3. What level of amputation was performed in the children who had amputation?

2.2 Research Design

This was a retrospective cohort study using secondary data from medical records and follow up care in outpatient clinic or home visit treated in Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Wits Donald Gordon Medical Centre (WDGMC), from 1985 to 2015. There are two state hospitals (CHBAH and CMJAH) and one private hospital (WDGMC), in an urban setting and all being referral hospitals with multidisciplinary teams.

2.3 Materials and Methods

Records of the patients who fell within the duration of symptoms were measured in months. Duration of symptoms or time to presentation was gathered and calculated from the history which was taken from the patient, patient's parents or the care giver that was documented in each patient's file. Types of patient management procedures were divided into operative (LSS or amputation or both), chemotherapy only, and declined treatment. Local recurrence was detected by physical, radiologic, and histopathology examinations. Metastasis was detected by chest X-ray, computed tomography (CT) scan, and/or bone scintigraphy. Osteosarcoma patients who did not complete the profile data and the follow up of their condition were excluded.

2.4 Sample

2.4.1 Inclusion criterion

1. All patients diagnosed with osteosarcoma below the age of 18 years, from January 1985 to December 2015 at CHBAH, CMJAH and WDGMC.

2.4.2 Exclusion criteria

1. Patients with markedly incomplete or missing data
2. Patients older than 18 years on the date of presentation

2.5 Data Collection

Files of children diagnosed with osteosarcoma between January 1985 to December 2015 were retrospectively reviewed and analysed for age at presentation, sex, presenting complaint, duration of symptoms, site of mass, histological type of tumour, tumour stage, type of treatment and duration of survival at last follow-up. For each patient, the following factors were analysed in relation to survival: sex, age, time to presentation, Enneking classification at presentation, levels of alkaline phosphatase (ALP) and lactate dehydrogenase (LDH), type of surgery and level of amputation. We evaluated the presence of local recurrence, metastasis and survival after treatment.

2.6 Data Analysis

Relevant medical data for the 102 children were obtained from medical records, using a defined protocol, and captured in a database (Excel 2013, Windows software) and then imported into Statistical Program for Social Sciences (SPSS) (SPSS) (IBM SPSS Statistics for Windows, Version 23.0., IBM Corporation Armonk, NY, USA) which was used for statistical analysis. Descriptive analysis was performed using means, medians and percentages. The simple frequencies of all the studied variables were computed. The accumulated survival chances were determined using the Kaplan-Meier technique. Multivariate analysis was performed using the logistic regression technique, with the Cox proportional hazards model. Statistical significance was defined as $p < 0.05$. The results are presented as mean plus the 95% Confidence Interval (CI).

CHAPTER 3

3 Results

There were 102 children (55 females and 47 males) under the age of 18 years diagnosed with osteosarcomas in the three hospitals CHBAH, CMJAH and WDGMC between 1985 and 2015 that were included in the study (see Table 3.1).

Table 3.1: Characteristics of osteosarcoma in children below the age of 18 years, diagnosed with osteosarcoma from January 1985 to December 2015 at CHBAH, CMJAH and WDGMC

Variable	Frequency (n)	Deaths	Survival	Unknown
Cases of osteosarcoma	102	54 (52.9%)	28 (27.5%)	20 (19.6%)
Sex				
Female	55 (53.9%)	31 (56.4%)	14 (25.5%)	10 (18.2%)
Male	47 (46.1%)	23 (48.9%)	14 (29.8%)	10 (21.3%)

The mean age of the children at diagnosis was 147.8 months ± 38.9 SD (median 156 months). The diagnosis was confirmed by histology in all cases.

3.1 Time to presentation

The mean duration of symptoms at presentation was 113.7 days (74.2 SD) with a median of 90 days (95% CI: 60 to 150). Females presented with symptoms at a much earlier age ($p < 0.001$) of 106.5 ± 63.2 months (95% CI: 132.4 to 152.4) with males presenting at 122.3 ± 83.4 months (95% CI: 143.1 to 166.0).

3.2 ALP and LDH

ALP and LDH were determined in 82 cases. ALP was high in 72/82 cases (87.8%) and LDH was high in 58/82 cases (70.7%). Only 1/82 cases (1.2%) had normal ALP and 4/82 cases (4.9%) had normal LDH. ALP levels were not documented in 9/82 (11.0%) and LDH was not documented in the 20/82 (24.4%) of cases respectively.

Table 3.2 below shows the distribution of cases across the different Enneking stages. Most cases presented in stage IIB (38.2%) and III (51%) and only 9.8% of the cases presented to the hospital at earlier stages (IIA) and none of the children presented at stage I.

Table 3.2: Prevalence of osteosarcoma in children below the age of 18 years according to the Enneking stage at presentation

Enneking classification	Frequency (n)	Percent (%)
1A	0	0
1B	0	0
IIA	10	9.8
IIB	39	38.2
III	52	51.0
Undocumented	1	1.0
TOTAL	**102**	**100**

Conventional osteosarcoma was the most common histological diagnosis and was found in 94/102 children (92.2%); these were histologically subdivided into 74 osteoblastic (72.5%), 16 chondroblastic (15.7%), four fibroblastic (3.9%). Non-conventional osteosarcoma (telangiectatic) constituted 6/102 cases (5.9%), and two surface osteosarcoma cases (one parosteal (1.0%) and one periosteal (1.0%)) were recorded.

At presentation, 52 out of 102 (51.0%) patients had tumours that had metastasised (see Table 3.3). Pulmonary metastases were most common (42/52, 80.89%) while 5/52 (9.6%) had concurrent bony metastases and 5/52 (9.6%) had both bone and lung metastases. Forty-nine

children (48.0%) had localised osteosarcoma. The presence of metastases was not known in one child.

Table 3.3: Proportion of children with tumours that had metastases

Metastases	Frequency (n)	Percent (%)
Lungs	42	41.2
Bones	5	4.9
Lungs/Bones	5	4.9
Localised	49	48.0
Undocumented	1	1.0
Total	**102**	**100.0**

Of those that had lung metastases (n = 42), 26 had amputations; four had LSS while 10 either declined surgery or had none (palliative treatment). The treatment of five patients was not documented.

3.3 Common sites

Figure 3.1 shows the distribution of cases. Most cases (84/102 – 82.3%) were reported in the lower limb with cases in the upper limb accounting for only 17/102 cases (16. 7%). The site of one case (1.0%) was not documented. In the lower limb, the metaphyseal location was the most common anatomic site with 41/102 (40.2%) cases being reported in the distal femur, 3/102 (2.9%) in proximal femur, 34/102 (33.3%) cases reported in the tibia and 6/102 (5.9%) cases had OS in both the proximal tibia and distal femur. All the upper limb OS cases, 17/102 (16.7%), were reported in the humerus.

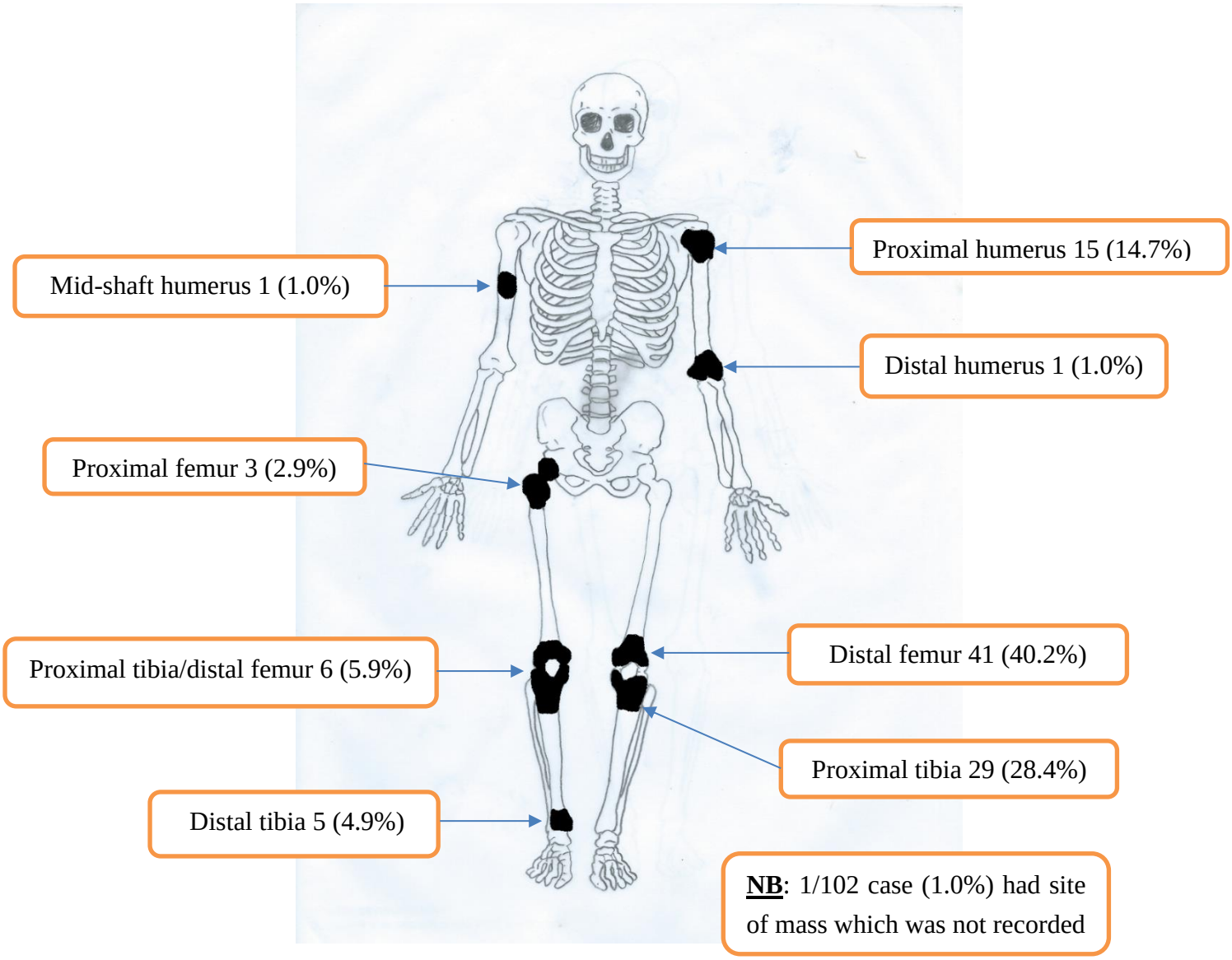

Figure 3.1: Percentage distribution of cases on the proximal and distal parts of the long bones among the 102 children in the study

Table 3.4 shows the proportion of children whose limbs were amputated at different positions. Amputation above the knee was the most common procedure with 30 cases (29.41%) followed by limb salvage surgery in 17 cases (16.7%). 23.6% (n = 13) of the children who had limb amputation ended up being palliated while 11.8% (n = 2) of the children who underwent LSS were eventually palliated.

Table 3.4: Proportion of the level of amputation amongst the children that were included in the study

Level of amputation	**Frequency (n)**	**Percent (%)**
Above elbow amputation	1	1.0
Above knee amputation	30	29.4
Below knee amputation	2	2.0
Disarticulation hip	7	6.9
Disarticulation shoulder	2	2.0
Limb salvage surgery	17	16. 7
Palliative therapy	18	17.7
Declined surgery, palliative therapy	11	10.8
Treatment abandonment	3	2.9
Undocumented	11	10.8
Total	**102**	**100.00**

3.4 Relapse

Table 3.5 shows the proportion of children that received different procedures and the numbers/frequencies that either became palliated or relapsed by means of either local recurrence or metastasis after a period of complete remission. There was no statistically significant ($p > 0.05$) higher chance of relapse in the children that were amputated compared to those who had limb salvage surgery.

Table 3.5: Frequency and percentages of type of surgery carried out on the children and the proportion that relapsed

	Type of surgery performed				
	Amputation	LSS	unknown	None	Total
Number	42 (41.2)	17 (16.7%)	11(10.8%)	32 (31.4%)	102 (100.0%)
Relapsed	**10 (23.8%)**	**3 (17.6%)**			**13 (22.1%)**

3.5 Overall survival

The survival rate was calculated on a smaller number of records as 34 records were excluded owing to insufficient data (no actual dates when deaths occurred were recorded). As such only 68 patients were used in the calculations (see Figure 3.2). Five-year survival rate was defined as the number of patients with osteosarcoma who were living five-years after diagnosis.

Figure 3.2 shows the survival rates for the 68 cases. The five-year overall survival rate for all the children with osteosarcomas in the three hospitals was 42% (n = 29) (95% CI 47 to 69) and 10-year survival for the entire group was 40% (n = 27) (95% CI: 10-148).

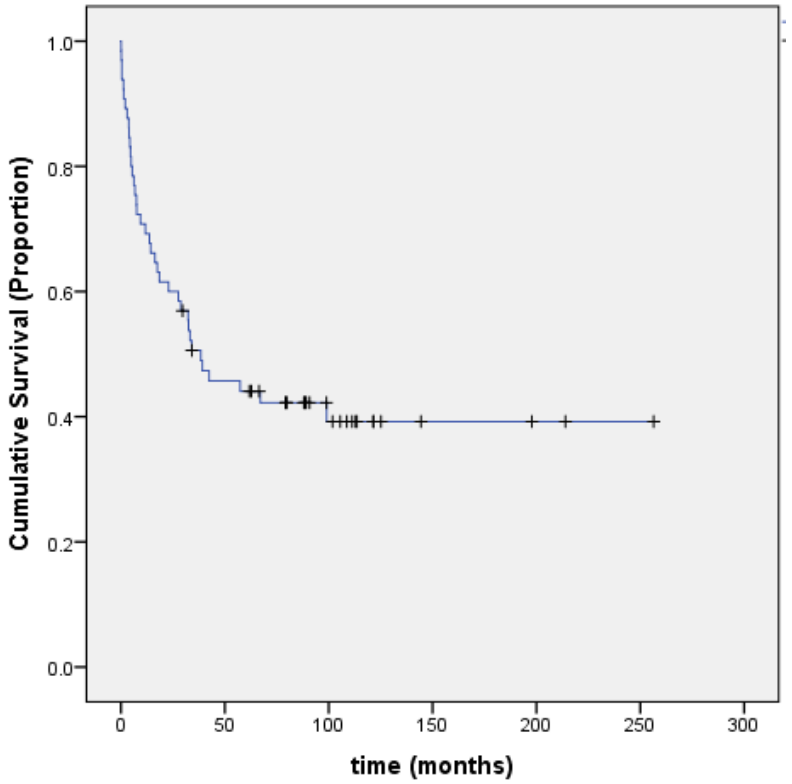

Figure 3.2: Kaplan-Meier plot showing the overall survival of the 68 patients that had complete records for multicentre osteosarcoma study

In this report, the mean and median were both used because the data was skewed. The median overall survival was 33 months (95% CI 19 to 48).

There was a statistically significant difference ($p < 0.001$) between those that had surgery and those that did not have surgery in terms of overall survival. Patients who underwent surgery had a higher median survival time of 67 months while those that did not have surgery had a median of two months (95% CI: 0 to 5.3). The subgroup analysis showed that survival for patients who had limb salvage surgery (LSS) was higher than in the patients that had amputations which was (74% vs 44%) as shown in the Figure 3.3. Most of the patients that opted for LSS fell in stage II (13 patients) and III (4 patients).

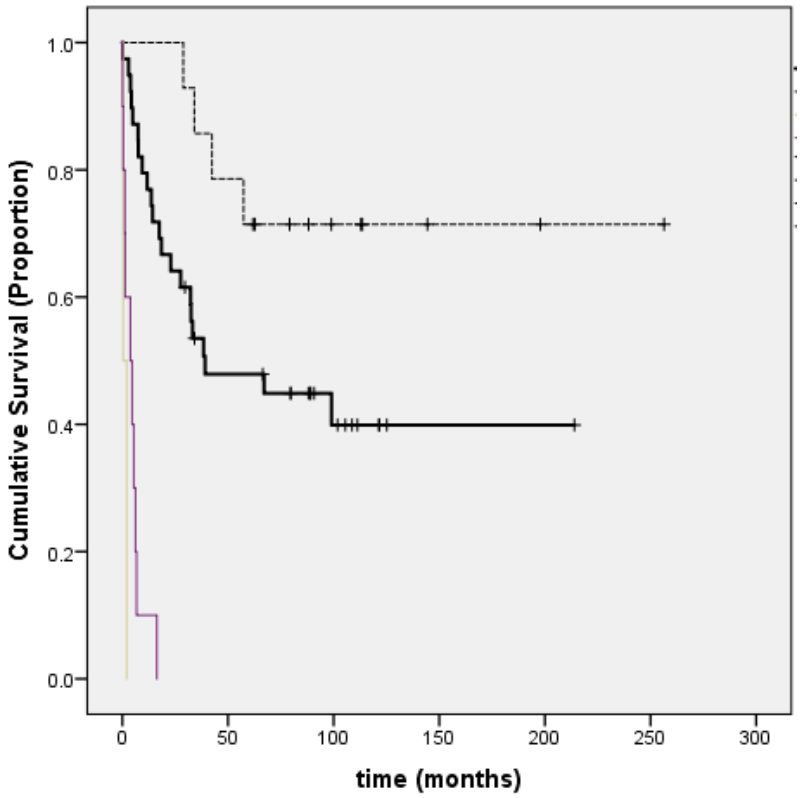

Figure 3.3: Kaplan-Meier plot survival of the children that received two types of surgery showing the higher overall survival in the LSS patients (dotted line) compared with patients who had an amputation (unbroken line). [**KEY**: LSS (dotted line); Amputation (unbroken line); Unknown (vertical line); None (purple line)]

There was a statistically significant difference ($p < 0.001$) in survival between the methods used whether it was limb amputation or limb salvage. Limb salvage surgery resulted in a higher mean survival time of 195 months (95% CI: 144 to 246) compared to the children that had amputations having a mean survival time of 101 months (95% CI: 71 to 132). The children who did not receive surgery had the shortest survival time of between 2 - 4 months.

3.6 Sex

Sex-associated differences revealed that there were no statistically significant differences between female and male children in them developing osteosarcoma although more female children (53.9%) had osteosarcoma compared to male children (46.1%). There was no statistically significant difference ($p > 0.615$) in survival between the female and male

patients. The females had a median of 33 months (95% CI: 0 to 77) while males had a median of 34 months (95% CI: 22 to 46). The five-year survival rate was higher ($p < 0.05$) in males (~42%) than in females (~30%) post-surgery (see Figure 3.4)

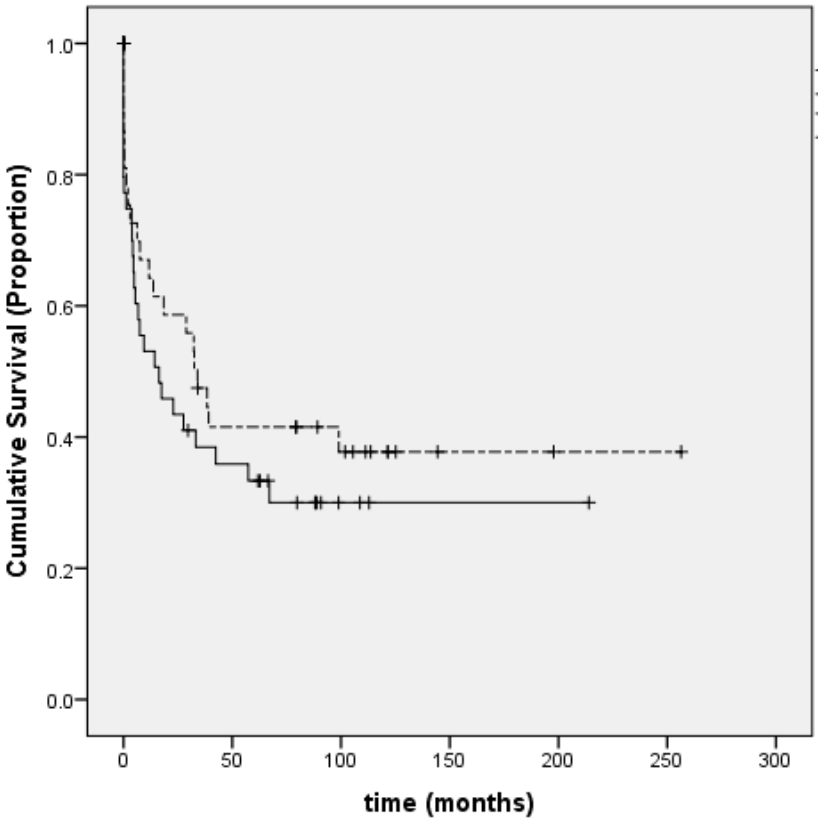

Figure 3.4: Kaplan-Meier plot showing the overall survival of the 68 patients that had complete records for multicentre osteosarcoma study. [**KEY**: Female (solid line); Male (dotted line)]

3.7 Site of metastases

There was a statistically significant difference ($p < 0.001$) in the survival time of the children that had metastases either in the lungs, bones or both lungs and bones compared to those that did not. Children who did not have metastases (n = 49) had a longer mean survival time of 181 months (95% CI: 137 to 225) while those that had lung metastases (n = 42) had a mean survival time of 40 months (95% CI: 21 to 58); those with bone metastases (n = 5) had a mean of 12 months (95% CI: 0 to 27) and those that had both bone and lung metastases (n =

5) had the lowest mean survival time of two months (95% CI: 1 to 4). Those with no metastases detected had a higher five-year survival rate of 76%; those with lung metastases had a five-year survival rate of 16%, while those with bone metastases had a median survival time of 3.8 months (95% CI: 0.0 – 15.2) and those with both lung and bone metastases had a median survival time of 1.3 months (95% CI: 0.0 – 3.3) (see Figure 3.5).

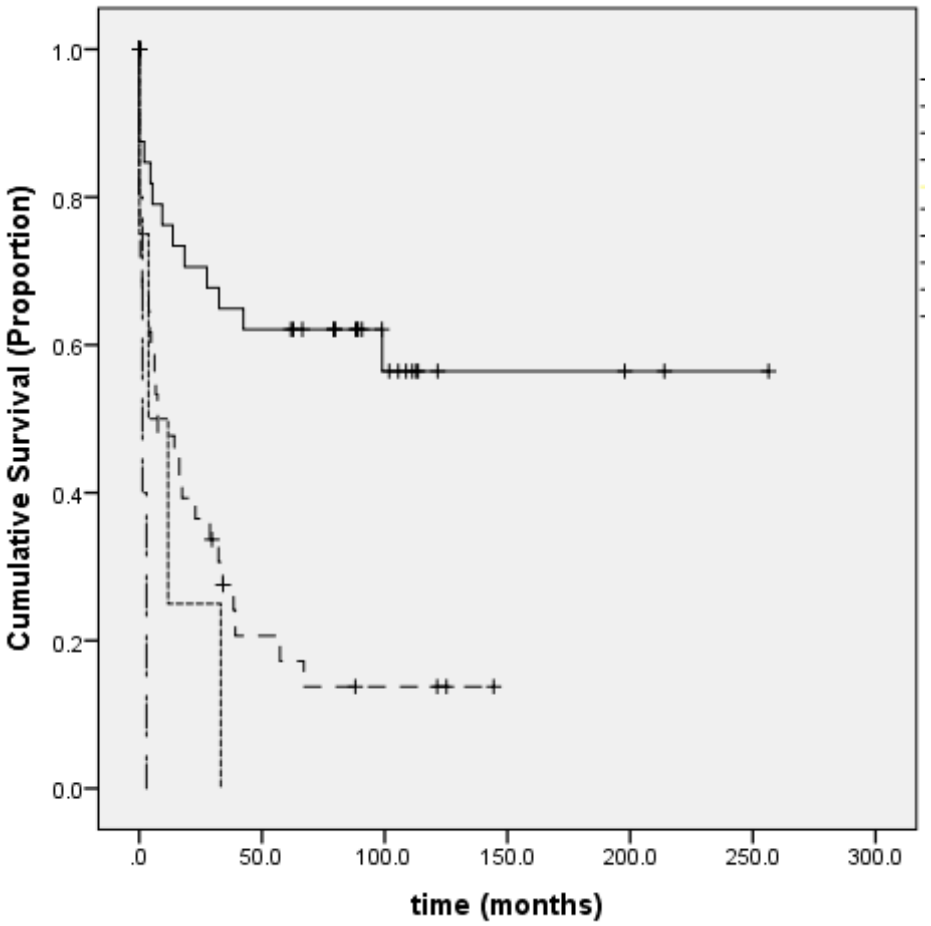

Figure 3.5: Kaplan-Meier plot showing the overall survival of the 68 patients that had complete records for multicentre osteosarcoma study (**KEY**: lungs (broken line); Bones (dotted line); Lungs/Bones (vertical line); None (solid line); Undocumented (yellow line)

3.8 Histology

There were no statistically significant differences ($p > 0.05$) in the survival of the patients between the histology types. Figure 3.6 below shows the survival curves for children with

different osteosarcoma types. The five-year survival rate was highest in children who were diagnosed with telengiectatic (n = 2) followed by those with chondroblastic (n = 4) and lastly those with osteoblastic (below 40%) osteosarcoma (see Appendix A).

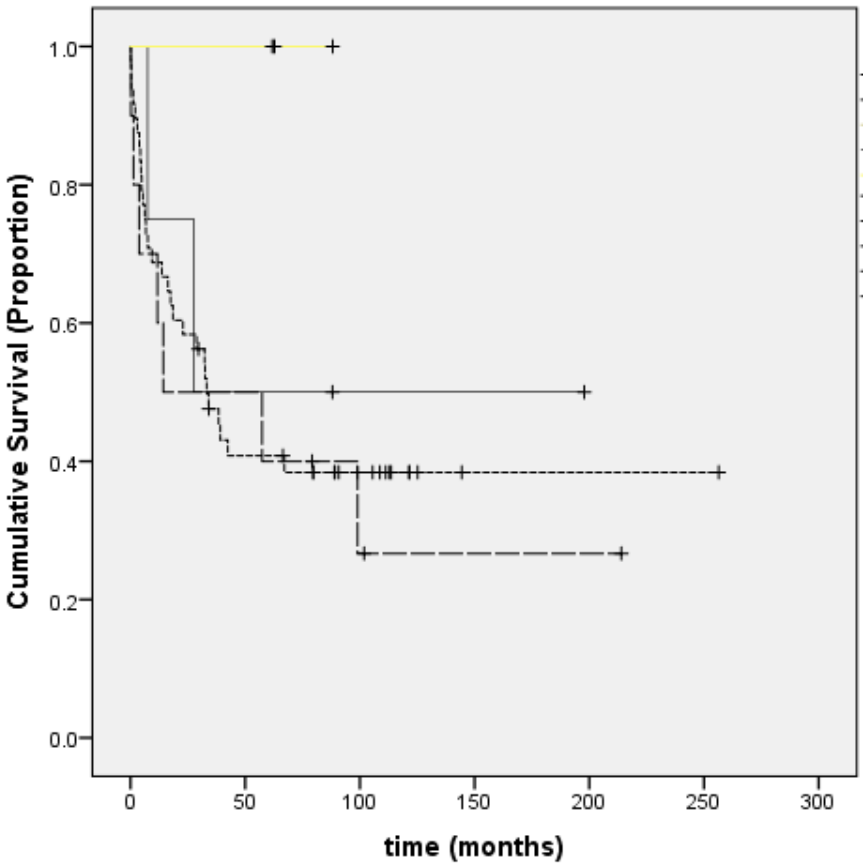

Figure 3.6: Kaplan-Meier plot showing the overall survival of the 68 patients that had complete records for multicentre osteosarcoma study. [**KEY**: Osteoblastic (dotted line); Chondroblastic (broken line); Fibroblastic (green line); Telangiectatic (solid line); Periosteal (yellow line)]

3.9 ALP

There was only one child that had normal ALP as such there were no enough number for comparison with the children with high ALP. The children that had raised ALP had a five-year survival rate of 38% and those whose ALP levels were undocumented had a five-year survival rate of 20%. Of note that 46.3% of the patients who had raised serum ALP at initial presentation had clinically detectable metastatic disease at presentation.

3.10 LDH

The Log Rank (Mantel-Cox) comparison showed there was a statistically significant difference (*p = 0.003*) in the five-year survival time of the children that that had raised LDH levels compared to those that had normal LDH levels (see Figure 3.7). The children that had normal LDH had a five-year survival rate of 100% and the those with raised LDH had a five-year survival rate of 40% and those whose LDH levels where undocumented had a five-year survival rate of 16%. It has been also noted that 39.0% of the patients who had raised LDH at initial presentation had clinically detectable metastatic disease at presentation

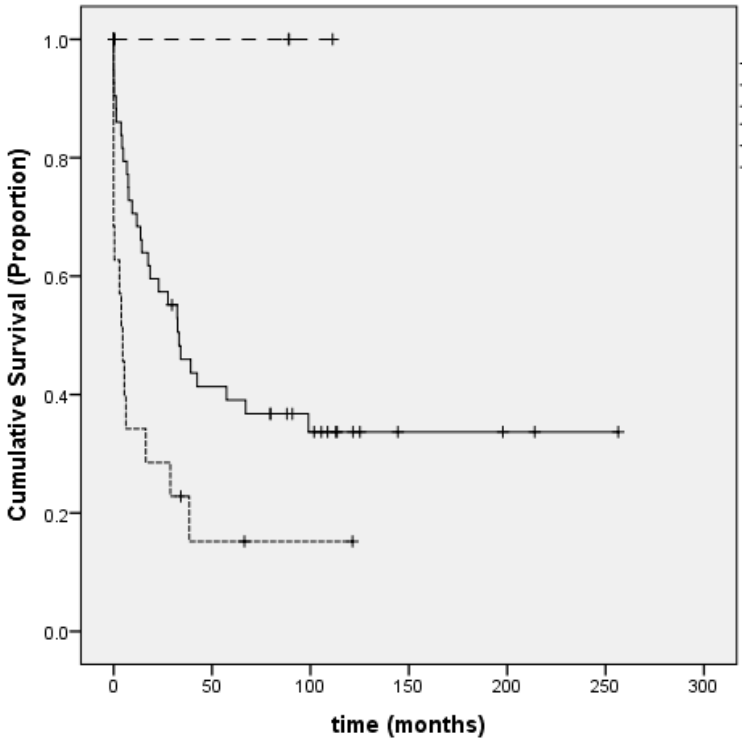

Figure 3.7: Kaplan-Meier plot showing the overall survival of the children with high serum LDH levels compared to those with normal levels. [**KEY**: Raised LDH (solid line); Normal LDH (broken line); Undocumented levels of LDH (dotted line)]

3.11 Enneking Classification

There was a statistically significant difference ($p < 0.001$) in the survival time of the children that presented at the different stages of the osteosarcomas. Children who presented at Stage IIA had a longer mean survival time of 224 months (95% CI: 164 to 283), those in Stage IIB had a mean survival time of 112 months (95% CI: 77 to 148); those in Stage III had a mean survival time of 53 months (95% CI: 25 to 82); while those children who presented at the hospitals and whose Enneking classification was not known had the shortest mean survival time of three months (95% CI: 0 to 5). Figure 3.9 shows the survival of patients who presented at different stages according to Enneking classification. The five-year survival rate was highest in children who presented in stage IIA (86%) followed by those in Stage IIB (55%) and least in those children who presented at Stage III (15%) (see Figure 3.8).

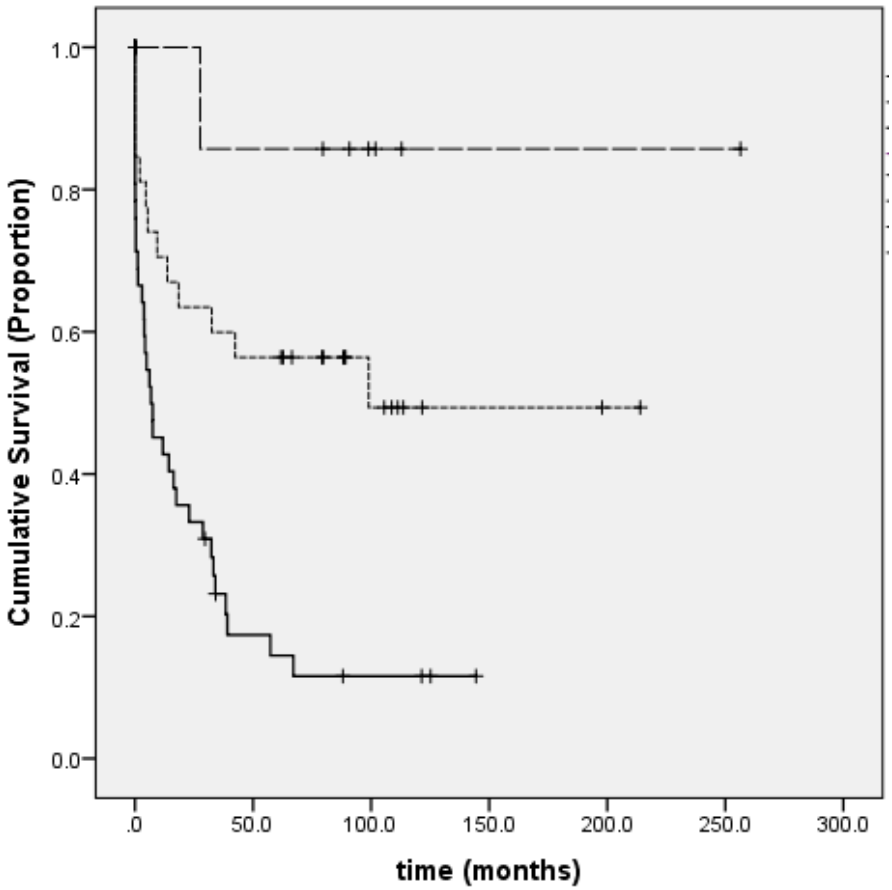

Figure 3.8: Kaplan-Meier plot showing the overall survival of the children who presented in the different Enneking Stages at presentation at the hospitals. [KEY: IIA (broken line); IIB (dotted line); III (solid line)]

3.12 Cox Regression Model

Multivariate Cox regression analysis was done in order to determine which variables were contributory to survival. The results of the multivariate Cox regression analysis are indicated in Table 3.6. In the univariate analysis, factors with significant differences included, sex, age at diagnosis, duration of symptoms, site of mass, surgery, surgery type and stage ($p < 0.05$). About six models were used, each time adding a factor at each iteration to determine which combination of factors contributed to survival of the patients. Some factors when analysed did not have an effect on the survival in Model 1 but did in Model 2 (Table 3.6). Sex, age at diagnosis, duration of symptoms and surgery were included in Model 1 of the multivariate Cox regression analysis ($p < 0.05$). In Model 2 of the multivariate Cox regression analysis, independent risk factors included sex, age at diagnosis, duration of symptoms, site of mass, surgery, surgery type and stage ($p < 0.05$).

Table 3.6: Model 2 covariates

							95,0% CI for Exp(B)	
	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Age at presentation	**0.012**	**0.006**	**5.084**	**1**	**0.024**	**1.013**	**1.002**	**1.024**
Sex	**1.040**	**0.371**	**7.871**	**1**	**0.005**	**2.830**	**1.368**	**5.853**
Duration of symptoms	**0.006**	**0.003**	**3.915**	**1**	**0.048**	**1.006**	**1.000**	**1.012**
ALP	-0.047	0.371	0.016	1	0.900	0.955	0.461	1.977
LDH	0.387	0.270	2.056	1	0.152	1.473	0.867	2.502
Site of mass	**-0.119**	**0.054**	**4.798**	**1**	**0.028**	**0.888**	**0.799**	**0.988**
Level of amputation	0.039	0.070	0.309	1	0.578	1.040	0.906	1.194
Surgery	**1.982**	**0.911**	**4.730**	**1**	**0.030**	**7.254**	**1.216**	**43.259**
Surgery Type	-0.205	0.308	0.442	1	0.506	0.815	0.446	1.490
Enneking Classification	**0.778**	**0.306**	**6.479**	**1**	**0.011**	**2.178**	**1.196**	**3.965**

Table 3.6 shows that the age at presentation, increased as the prognosis got worse. Sex was statistically significant with the males having a slightly higher survival rate than the females. Duration of symptoms was also significant. Proximal site of the mass had a worse prognosis. Surgery was statistically significant with a huge CI (95%: 1.216 – 43.259). LSS was better

than amputation because of the better Enneking stages reserved for LSS. Those patients in the Enneking stage III had an increased chance of dying leading to the lowest survival rate compared to all patients in the lower Enneking stages.

CHAPTER 4

1 Discussion

According to analysis of the previous literature this study is the largest to be conducted on the African continent. It was conducted at three academic hospitals under the University of the Witwatersrand in the Greater Johannesburg region. No major significant differences were found between the level of amputation, type of surgery implemented, histological differences in the tumours, ALP and LDH on the overall outcome of the children. Children who had limb salvage surgery had a higher five-year survival rate compared to children undergoing amputation, but this was not significant when assessing overall survival. A retrospective study was performed to assess the status of the children at presentation and the outcome of the children following treatment over a minimum five-year period.

Studies conducted in SA have reviewed smaller cohorts of patients and included both children and adults[1,3] and as such their results had limited applicability to the paediatric community. Our study is different to these two studies in that it only included children aged 18 years and younger and is the largest study conducted so far in the country and on the African continent. In SA, Lisenda *et al*.[1] conducted an OS study at CMJAH using 61 patients whose ages ranged from 7 to 48 years. Ferreira and Marais[3] reviewed 11 patients with OS in a study from KwaZulu Natal Province in older patients (aged: 30 to 60 years) and focused on the relationship between HIV and OS. In another study[69] Marais *et al*. noted that 16 of 24 patients (67%) presented late to tertiary hospitals when the tumours had already metastasised. The current study included 102 children aged 18 years and younger and is currently the largest study conducted so far in the country and on the continent.

4.1 Time to Presentation

In the current study there was a prolonged time to presentation from the onset of symptoms. Patients with no metastases presented to tertiary hospitals after 114 days (74 SD), those with lung metastases presented after 107 days (59 SD), bone metastases presented after 96 days (54 SD), lung and bones metastases at 97 days (117 SD), and those with unknown status

presented after 165 days (111 SD). The patients with no metastases presented later for medical attention most likely due to less aggressive tumours. In two SA studies, Lisenda *et al*.[1] recorded a 4.5 month delay while Ferreira and Marais[3] recorded a median of 4 month delay before presentation to a tertiary hospital which were all longer than the times recorded in this study with a median of 3 month (from the onset of the symptoms to the diagnosis) maybe because the other SA studies included adult patient who presumably seek medical advice later than would the caregiver of a sick less active child. The delays in presenting to the hospitals may be attributed to the misdiagnosis by the doctors who had attended to the patients initially in the rural areas and also the system delays in referring patients to the tertiary hospitals[70]. The misdiagnosis could be due to the fact that, histologically, osteosarcomas resemble numerous kinds of benign lesions[71], for instance, aneurysmal bone cysts and osteoblastoma. Failure to diagnose osteosarcoma early inevitably results in suboptimal treatment and/or treatment delay[70]. According to Shipley, delays in seeking help in the low-income country setting may be attributed to factors such as parents first seeking help from traditional healers, lack of resources to move and pay for help in modern health facilities or simply being in the rural areas without access to facilities till the situation deteriorated or from neighbouring countries where the health system is not conducive to rapid diagnosis of osteosarcoma. The duration of symptoms has implications on the treatment and recovery of the patient.

4.2 ALP and LDH

To try and determine the predictive value of the biomarkers (ALP and LDH) and presence of metastases at presentation, analysis of serum for the levels of ALP and LDH was conducted. It is generally accepted that the LDH and ALP have a diagnostic value. The LDH is well-known to be a predictor of general cancer and its predictive role has been proved in numerous malignancies such as osteosarcoma[72] and Ewing's sarcoma[73]. Only two studies by Marais *et al*.[74] and Marais and Ferreira[69] measured ALP and LDH, while most of the studies[1,3,4,75] conducted in South Africa did not report on ALP and LDH levels. The current study showed that as the ALP level increased the survival rate decreased. The results of the current study also suggest that as LDH increased the survival decreased. This finding is the same as the current understanding that these two had a predictive value for survival with osteosarcoma. In contrast, other authors have found that serum ALP did not have prognostic value in terms of

disease outcome[76]. In the current study, 46.3% of the patients who had raised serum ALP and 39.0% of the patients who had raised LDH at initial presentation had clinically detectable metastatic disease at presentation compared to the rates of between 10 and 20% recorded in Turkey and United Sates of America [77,78] using both ALP and LDH. Petrilli *et al*. recorded rates of about 20.8% in Brazil[79]. The lower rates reported in the developed world and Brazil indicated that patients sought medical attention much earlier than here in SA. However, the current results were lower than the 49-66% reported in the two studies here in SA[3,4]. The variations in these studies are perhaps due to delay in diagnosis and advanced disease at the time of diagnosis, and possibly the first cause of mortality among these patients, and considered one of the significant prognostic factors of this disease[79]. In the current study, there were 69.5% children (n = 57) who had both ALP and LDH raised.

4.3 Common sites of osteosarcoma

Previous studies have shown that osteosarcoma had a high predilection for the area surrounding the knee joint[80]. In the current study we recorded 76 cases (74.5%) that involved the knee – either distal femur (n = 41 cases) or proximal tibia (n = 29 cases) plus cases that involved both the distal femur/proximal tibia (n = 6 cases) (see Figure 3.1). With regard to the anatomical region most affected by these tumours, the literature shows that the femur is the most frequent site, followed by the tibia and humerus[81]. In the present study, we also found that these sites were the most affected locations. This trend is similar to what was reported in other studies conducted in South Africa[74,82]. A study conducted in South Korea, also noted that the distal femur was the most frequently affected site in children and adolescents[83] and this observation agrees with the observation in the current study.

4.4 Sex

Sex-associated differences revealed that female patients had a higher incidence rate of osteosarcoma compared with male patients. Similar results have been reported in previous studies by Lisenda *et al*.[1], Mirabello *et al*.[84] and Homa *et al*.[85] but contrary to the results reported by Nie and Peng[86].

4.5 Metastases

Among children with metastasis, children that were diagnosed with lung metastases had the longest duration of survival while patients diagnosed with other bone metastases had the longest duration of symptoms in those with metastases. Pulmonary metastases were identified in forty-two patients (41.2%). Lung metastases were the most common and with the bone and both lung/bone metastases occurring in almost similar proportions. This finding is similar that reported by Ferreira and Marais[3]. Eight of whom progressed to death after on average 13 months (18 SD). Six children were still alive with pulmonary disease between 29 and 144 months after the diagnosis. In a previous study patients that had lung metastases at diagnosis lived on average between 9 and 16 months[81] which was shorter than what was recorded in the current study. All children with bone metastases died within 12 months (15 SD) of diagnosis while those diagnosed with both pulmonary and bony metastases died within two months (1.2 SD) of diagnosis. The patients with localised tumours died within 181 months (30 SD) of diagnosis while those whose metastases status was unknown died within six months (12 SD).

4.6 Histology

In most studies[87,57] the most common histological type of osteosarcoma is the osteoblastic type. In the present study osteoblastic osteosarcoma constituted about 72.5% of the cases and the other types made up 27.5%. Numerous studies conducted in SA[1,3,75] also noted a higher proportion for osteoblastic osteosarcoma compared to the other types. In a study done in Brazil, Rech *et al*.[87], made a diagnosis of osteoblastic subtype in the majority (65%) of their patients.

4.7 Enneking stages

Most patients with osteosarcoma have stage IIB disease on presentation.[88] This is similar to the finding by Lisenda *et al.*[1], who noted that most of the patients in their study population were in Stage IIB followed by those in Stage III. The finding of this study is contrary to the findings of Lisenda *et al*. where 51% of the children were in Stage III and those children in Stage IIB constituting 38.2%. In the current study, most cases presented to the hospital for attention very late could be due to delays emanating from the misdiagnoses and faults within

the healthcare system and this increased the risk of distant metastases. The reasons for late presentation to hospitals could also be the referral systems in place, or patients are staying further away in the rural areas and could not have access to medical health care. Barriers to accessing medical care may discourage individuals from seeking medical attention unless symptoms are severe. In some cases, patients might be misdiagnosed or there may have been system delays in referring patients to the tertiary hospitals[70]. In the current study, patients in Enneking stage III lived the shortest time (mean of 42 months) followed by those in Enneking stage IIB (mean of 103 months) and those in Enneking stage IIA lived the longest (mean of 224 months). Those in Enneking stage III are already in a compromised situation due metastasis to lungs and bones.

4.8 LSS vs Amputation

The international literature shows numerous accounts of improved survival rates of patients that have received LSS compared with amputation[89,90]. Li *et al.*[89], observed that the five-year overall survival rate in LSS group was 58% and 49.8% in the group that was amputated. The finding in our study also concurs with this observation (76% - LSS vs 46% - amputation). However, it is difficult to have a direct comparison of these numerous studies because they focused on different variables and the sample sizes varied – some studies did not have the Enneking Classification of patients, had mixed populations of children and adults[82], had the HIV status of some patients[75] and ages ranged from two up to 82 years[91]. One study conducted in China, reported a lower five-year survival rate for patients who underwent limb-salvage surgery than the patients that received amputation[91], contradicting the major finding in most studies. Several authors have demonstrated that there is no difference in terms of survival between patients who have amputation and those who have limb salvage[92,93]. Limb Salvage Surgery (LSS) has emerged as a viable option for patients with osteosarcoma with the increased long-term survival rates of 60 to 80%, especially in children with Enneking stage IIB.[80,94] Despite these improvements, and although the indications for limb salvage surgery have greatly expanded, it is still unclear whether limb salvage affects osteosarcoma outcomes.[95] In the current study, 41.2% of the cases (n = 42) had amputations while LSS was performed in (n = 17) (16.7%) of the cases. This resulted in an improved five-year survival rate of about 76% in those children that had limb salvage surgery and the survival rate was 44% among those children that had amputation. The improved survival rate in children

following LSS is in keeping with findings in the literature. A study in India reported an improved five-year overall survival rate of patients treated with LSS was 58.6% compared to 49.8% for those treated with amputation[96]. Ayerza *et al.*[95] reported an improved survival rates of 67% and Ferrari *et al.*[45] reported an increased long-term survival rates of 60 to 80%[80,94] following LSS. The survival rates for LSS reported in the current study was higher than that reported by Ayerza *et al.* (36-67%) but within the range of the values reported by Tan *et al.*[80] (61.8%) and Aksnes *et al.*[94](78%). Patients who underwent limb salvage surgery had a higher five-year survival rate in comparison to those that had their limb amputated. Patients who had limb sparing surgery had a more favourable long-term outcome when compared to patients who had amputations. This might be attributed to the fact that patients who went for LSS had the disease in its early stages whereas, many amputations in the current study were done as palliative procedures when patients presented at late presentation with distant metastases.

There was a higher rate of relapse among patients who had amputation 41% (n = 23), in comparison to the LLS group where the relapse rate was 35.3% (n = 6). This is because most of the amputated group had metastases by the time of presentation and they were not the right candidates for LSS. In addition, the aggressive nature of some tumours as well as those that might have developed resistance to the chemotherapy. According to Takeuchi *et al.*, patients with recurrence have poor long-term prognosis[97].

4.9 Survival rates

In the current study, the five-year overall survival rate was 42%. The finding in this present study was slightly lower than the five-year survival rate of 45% reported in Argentina with a survival rate for those patients with localised disease being 52% and those with the tumour that had metastasised being 22%[98]. In the current study 46 of the 49 patients with localised disease had a five-year survival rate of 100% while the 42 patients who presented with metastases (lungs) had a five-year survival rate of 80%. Petrilli *et al.*[79], reported an overall five-year survival rate of 49%, which was lower than the rate recorded in the present study. In the current study, 11 patients (10.8%) declined surgery on presentation and opted for palliative care which affected the overall five-year survival rate. In another South African study, Muthupei *et al.*[42] recorded a five-year survival rate of 7.5% in 66 patients treated at Ga-Rankuwa Hospital. In a study which included some patients from the current study,

Lisenda *et al.* reported an overall five-year survival rate of 38.1%[1], which is lower than what was reported in the current study. Those that had limb salvage surgery had a significantly higher five-year survival rate than those who elected for amputation. The higher amputation rate (41.3%) than the LSS option (16.7%) in the current study shows a higher percentage of patients presented with locally aggressive disease which was not amenable to LSS.

4.10 Cox regression analysis

Age of presentation, sex of patient, duration of symptoms, site of tumour mass, type of surgery, and Enneking stage were significant predictors of overall survival. The systematic analysis of the present study may provide useful information for guiding clinical work. Female patients below 18 years of age had a higher incidence rate of osteosarcoma than males, suggesting the requirement for an early screening of this aforementioned high-risk population for osteosarcoma. Sex, age at diagnosis, duration of symptoms, site of mass, surgery, surgery type and Enneking stage were demonstrated in the present study to be independent risk factors in the multivariate Cox regression analysis. A study by Nie and Peng[86] noted that the year of diagnosis, sex, Enneking stage, tumour site, surgery were significant but they had other factors that were beyond the scope of the study. This makes it difficult to compare the two studies though some of the factors were similar.

4.11 Limitations

Some of the details on the case records were incomplete and did not capture the actual date of death of the children and this reduced the number of children used in the final analysis of the survival rates. Other children that received chemotherapy died shortly after treatment started due to poor response to chemotherapy thereby lowering the survival rates. There was selection bias in that patients with metastases did not undergo local excision surgery. Only those with metastases were recommended for amputation and not all of these patients underwent this surgery due to refusal by families or patients being too sick.

4.1 Recommendations

The aim of this research report is to contribute to the understanding of the factors that paediatric patients with osteosarcoma present with to hospitals and as well as determining the overall five-year survival rate within the children aged below 18 years of age.

i. The huge difference in the overall five-year survival rate between those children that had LSS and those that had limb amputation indicates that LSS should be supported as the method of choice if the Enneking stage makes it possible, highlighting the poor prognosis associated with distant metastases on diagnosis.

ii. Delays in seeking help from tertiary health facilities also shows that the health professionals and the Department of Health have to intensify efforts in spreading the message on advising the parents on what to do in instances of unexplained limb/joint swelling. Literature on osteosarcoma has to be made available to parents at all clinics and highlights the need to strengthen oncology health educational campaigns among communities in both urban and rural settings.

iii. Educating general practitioners and doctors working in the peripheral hospitals on osteosarcoma and creating an effective referral system between health facilities should be studied further.

iv. A South African Musculoskeletal oncology registry to gather more systematic structured data on all patients with different kinds of paediatric malignancies should be created. This is another area for future research and one which has been promoted by the South African Orthopaedic Association.

CHAPTER 5

2 Conclusion

More than 75% of children presented late (average 113 ± 74 days) after onset of symptoms for medical attention at tertiary hospitals. By this time many children (n = 52, 51%) had distant metastases thereby reducing their chances of survival. Those who received LSS had a higher five-year survival rate than those who had an amputation, this can be attributed to the fact that 76.5% (n = 13) of the LSS patients presented with Enneking stage II and only 23.5% (n = 4) were in Enneking stage III. The five-year survival rates in the current study are better than those in other South African/developing countries but still lower than those in the developed world. This study highlights the need for ongoing education of the general public regarding the dangers of delayed medical attention to improve the outcomes of osteosarcoma as a matter of urgency, to facilitate rapid tertiary referral and expedite management.

3 References

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4 Appendices

4.1 Chemotherapy Protocol used in the Gauteng Hospitals among the patients that were included in the study

PROTOCOL

TREATMENT FOR METASTATIC OSTEOGENIC SARCOMA

PRE-OPERATIVE	WEEK 0 :	Ifosfamide 1800mg/m² x 5d + Mesna 600mg/m² x 6 Adriamycin 25mg/m² x 3 d
	WEEK 3 :	Methotrexate 12g/m² + Leucovorin
	WEEK 4 :	Methotrexate 12g/m² + Leucovorin LFT dependant
*		
	WEEK 5-7 :	Operation with Histology to determine degree of necrosis
**	WEEK 8 OR 9 :	Adriamycin x 3 days Cisplatinum 120mg/m² (ECHO)
	WEEK 12 :	Ifosfamide and Adriamycin (SAME AS WEEK 0)
	WEEK 15 :	Methotrexate
	WEEK 16 :	Methotrexate
	WEEK 17 :	Cisplatinum and Adriamycin
	WEEK 20 :	Methotrexate
	WEEK 21 :	Methotrexate
	WEEK 22 :	Ifosfamide
	WEEK 25 :	Methotrexate
	WEEK 26 :	Methotrexate
	WEEK 27 :	Cisplatinum

* Give Week 8 or 9 prior to surgery in non metastatic disease

** Adriamycin dependent on response to treatment and cardiac function

4.2 Ethics Clearance Certificate

R14/49 Dr Ali Mohammed Omar Nasar

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161110

NAME: (Principal Investigator)	Dr Ali Mohammed Omar Nasar
DEPARTMENT:	Orthopaedic Surgery Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital Wits Donald Gordon Medical Centre
PROJECT TITLE:	Osteosarcoma Outcomes in Johannesburg. A Retrospective Multicentre Review
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr GB Firth
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 03/02/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

4.3 Data Collection Sheet

.....	12	11	10	9	8	7	6	5	4	3	2	1	Patient Number
													Name
													Surname
													Date of birth
													Date of Diagnosis
													Age at presentation
													Sex
													Duration of Presentation
													Histology
													ALP
													LDH
													Sit of Mass
													Sit of Metastasis
													Enneking Stage
													Surgery
													Type of Surgery
													Relapse
													Palliation
													Date of Death
													Survival time in days
													Survival time in Months
													Level of Amputation