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Retrospective Review of children with osteogenic sarcoma from 1990 to 2010 at a tertiary hospital in Johannesburg

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

Of

Masters in Medicine (MMed)

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DECLARATION

I, Thandeka Vuyiswa Zamansundu Ngcana, declare that this research report is my own work. It is being submitted for the degree of Masters in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……..

Signature of candidate

…… day of…… ……

DEDICATION

I dedicate this paper to my parents, Mvula Ngcana and Nomasonto Ngcana, my sisters, Mbali and Nandipha Ngcana. My daughter Lwandle and my Partner for the unwavering support.

In memory of my grandmother, Thakane Thusi, for believing in me.

PUBLICATION AND PRESENTATION

- Poster presentation: Poor prognostic features and metastatic disease at presentation contribute to low survival rates of children with osteogenic sarcoma in Johannesburg. 47th Annual congress of The International Society of Paediatric Oncology. 8-11 October 2015
- Wits Paediatric Fund research day September 2015: Oral presentation
- Wits Research day 2016: Poster presentation
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List of Abbreviations

OS	osteosarcoma
BMI	Body mass index
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CI	Confidence interval
IQR	interquartile ranges
LDH	lactate dehydrogenase
ALP	alkaline phosphatase
HIV	Human Immunodeficiency Virus
IU/L.	International units per litre
LFS	Li-Fraumeni syndrome

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The CMJAH Paediatric oncology unit staff and patients

ABSTRACT

BACKGROUND

Survival rates of South African children with osteosarcoma (OS) are known to be poor but prognostic factors have not been elucidated in an African setting.

AIM AND SETTING

To determine the overall survival rate and prognostic factors in children with OS at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

METHODS

A retrospective review was conducted of children with OS from 1990 to 2010. Descriptive statistics, Kaplan-Meier survival analysis and Cox logistic regression were performed.

RESULTS

55 files were available for analysis. The median symptom duration was 90 days. The median age was 12.1years. The majority had poor prognostic features: 47 (85%) had masses larger than 8cm diameter, all patients had high alkaline phosphatase and 46 (83.6%) had elevated lactate dehydrogenase (LDH). Histology included osteoblastic (37/55) and chondroblastic OS (9/55). Forty-three (78.2%) patients had low BMI at presentation. Forty-one patients were treated with ifosfamide, doxorubicin, methotrexate and cisplatinum and one patient was on a hybrid protocol. Thirteen (25%) did not receive chemotherapy and four patients declined surgery. The five-year survival rate of those treated with curative intent was 42%. Causes of death included progression of disease (22/42) and treatment complications (5/42). On univariate analysis site of primary tumour (p = 0.044), LDH (p = 0.011) and stage (p = 0.0001) impacted on survival, while on multivariate analysis confirmed only stage (p=0.0001) and unknown LDH level (p= 0.011) as significant.

CONCLUSION

Advanced disease at presentation, which is a modifiable factor, was common and impacted negatively on overall survival.

Introduction

Primary bone tumours represent the third most frequent group of malignancies in adolescents and young adults, after leukaemia and lymphomas [1,2,3,4,5] Osteosarcoma (OS) is the most common bone malignancy in adolescents. This tumour is more common in black than in white patients, and has a higher incidence in males [3].

Survival rates of osteosarcoma in high income countries range from 60 to 80% [2, 3,4]. Successful treatment requires a combination of multi-agent chemotherapy and complete surgical excision of the tumour. This data originates from studies done in well-resourced centres [3] and there is a paucity of data from low and middle income settings. Current survival rates reported from South Africa range from 7.5% in a study done in Ga-rankuwa [6] to 30% in Bloemfontein [7].

This poor survival rate is postulated to be due to advanced disease at presentation, among other factors, which may be related to delays in diagnosis [,4,5,6]. In South Africa, patients with osteosarcoma may present rather later than in well-resourced countries. Due to several reasons, among them suboptimal access to health care, these patients may seek medical attention only when a large mass has ulcerated or is constantly oozing fluid and requires medical attention [2] .

In studies from high income countries factors shown to have prognostic significance include sex, site of primary tumour, size of tumour, levels of non-specific tumour markers lactate dehydrogenase and alkaline phosphatase. In addition, presence of pulmonary and/or bone metastases, extent of necrosis after pre-operative chemotherapy and histological subtype affect outcome [2,4,11,12,13].

The patients who survive face devastating effects from the treatment, as most aggressive chemotherapy protocols are associated with severe, often long-term side effects, such as hearing impairment, cardiotoxicity and infertility [3, 15]. In high income countries amputation has become a rarity in the treatment of this disease [3], while in South Africa this modality is still standard of care[6, 8].

Numerous studies have addressed the issue of delay in diagnosis and whether this contributes to poorer outcomes in children with cancer [11, 12,13,14]. However, all these studies originate in high income countries, and this issue has not been satisfactorily addressed in an African setting. This study aims, in part, to contribute to this small but growing body of knowledge.

Aims and objectives

The aim of the study was to characterise the demographics and tumour characteristics of a paediatric population with osteosarcoma in Johannesburg and to determine modifiable and non-modifiable prognostic factors. Five-year survival rate and causes of death were described.

Research methods and design

The study is a retrospective folder review of paediatric patients with OS treated at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between 1 January 1990 and 31 December 2010. The Paediatric Oncology Unit at CMJAH is a tertiary referral centre in an urban area accepting patients from a wide drainage area in Gauteng, other areas of South Africa as well as neighbouring African states. All children with histological confirmed OS under the age of 18 during the study period were included. Folders with substantially incomplete records were excluded. This included patients for whom no records existed, those whose histology results were unavailable and those who completed treatment in other centres.

Descriptive statistical methods were used to characterise demographics (age, sex, ethnicity and Human Immunodeficiency Virus [HIV] infection), duration of symptoms and nutritional status at presentation. A body mass index (BMI) <18 was used as a marker for the 'under-nutrition' indicator [12]. The duration of presenting symptoms was recorded according to history given by the primary caregiver noted in the folders. This was determined from the date of first presentation with disease-specific symptoms to the first date seen in the paediatric oncology unit or orthopaedic unit at CMJAH.

Enneking stage I and II tumours were defined as localised disease while stage III tumours were classified as metastatic disease [1].

Table 1: The Enneking staging system for skeletal malignancies

Stage	Tumour grade	Tumour size
IA	Low	<8cm
IB	Low	>8cm
IIA	High	<8cm
IIB	High	>8cm
III	Any tumour grade skip metastases	

All histological specimens were reviewed to determine extent of post chemotherapy necrosis. Ninety five percent (95%) tumour necrosis post chemotherapy was regarded as favourable response to chemotherapy [1,4,10]. Serum Alkaline phosphatase level was used as a marker of disease. A cut off level for different ages was used. ALP> 1.5 of normal was regarded as significantly high. (Normal ranges: Age two to 10 years 420IU/L. For the ages 10 to 11years 560 IU/L; 12 to 15 years male: 495IU/L; 12 to 13 years female: 420IU/L and 14 to 15 years female: 230IU/L (see Table below). Reference ranges for LDH in this population was 140 IU/L to 280IU/L.

Table 2: Normal Alkaline phosphatase ranges for sex and age

Age in years	Range
2 -10	420 IU/L
10-11	560 IU/L
12-15 MALES	495 IU/L
12-13 FEMALES	420 IU/L
14-15 FEMALES	230 IU/L

Means with standard deviations were employed for normally distributed data and medians with interquartile ranges (IQR) for non-parametric data were calculated. Five-year actuarial survival was calculated using the Kaplan-Meier method. Prognostic factors were determined with Cox regression analysis and a p value of <0.05 was considered statistically significant. Multivariate logistic regression analysis of variables associated with mortality using Cox proportional hazard model was also performed. Ethical approval was obtained from the University of Witwatersrand Human Research Ethics Committee for the study (Ethics Number: M170492).

Results

Over the 20 year period a total of 1941 patients were diagnosed with malignancies, 65 (3.3%) of whom had osteosarcoma. Ten files were excluded from the study as records were substantially incomplete, thus 55 files were available for evaluation.

Patient characteristics

Twenty-seven (49%) patients were male and twenty-eight (51%) were female. The median age at presentation was 12.1 years (IQR: 9.75 years to 14 years). The youngest patient was 2.8 years old. A minority of patients (12/55, 22%) were of healthy weight while most children (43/55, 78%) were underweight at presentation, with a BMI <18. It was not documented whether these patients were underweight due to cachexia or malnutrition. Forty patients had documented HIV negative results. Fifteen were unknown prior to 1994 as there was no routine HIV treatment programme at CMJAH.

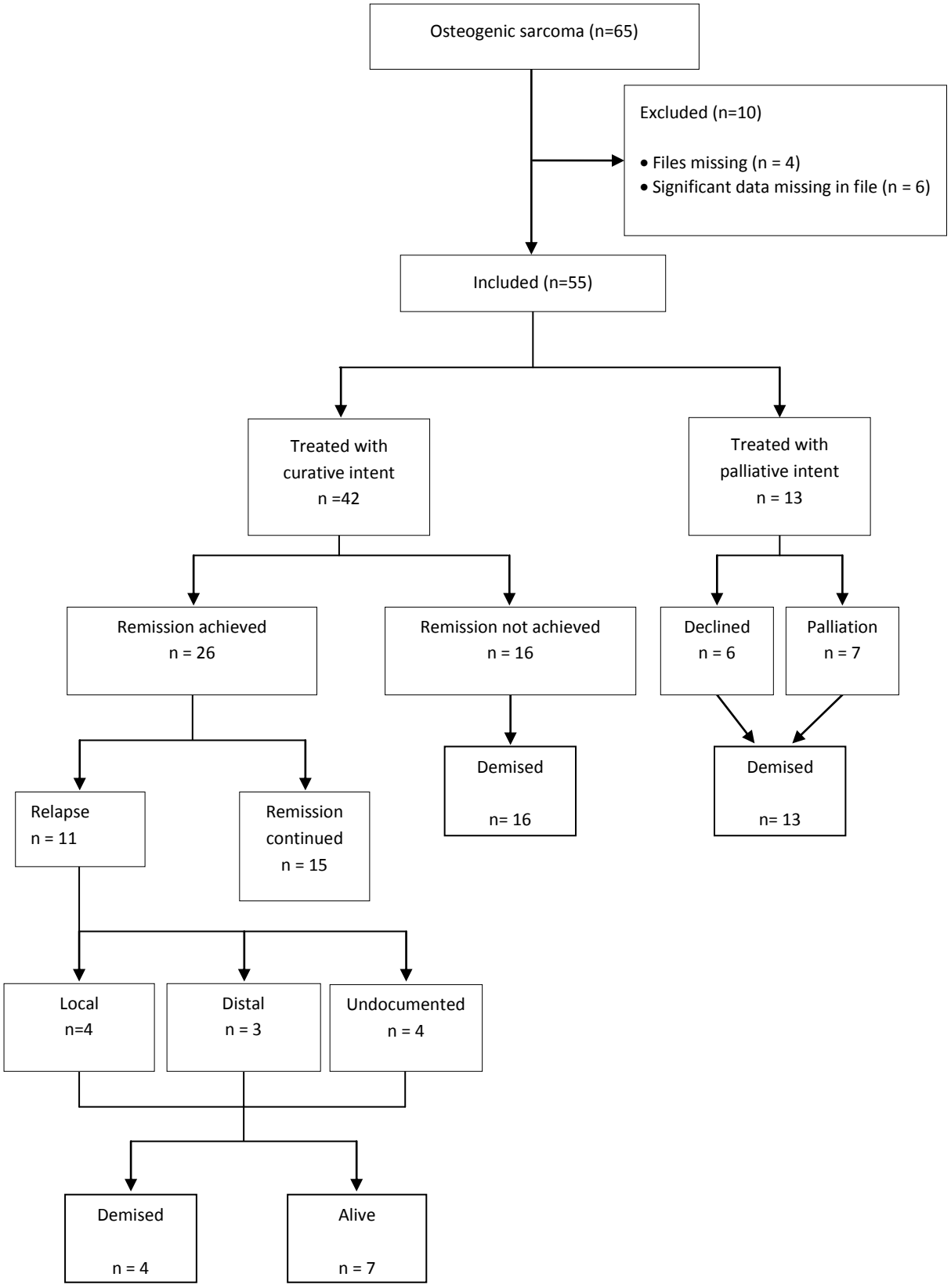

FIGURE1: Population diagnosed with osteosarcoma at CMJAH

Table 3: Characteristics of children with osteosarcoma at CMJAH

Variable	Number of patients n =55	Percentage
DEMOGRAPHICS		
Sex		
Male	27	49
Female	28	51
HIV		
Negative	40	72.7
Positive	0	0
Unknown	15	27.3
Race		
Black	40	72.7
White	8	14.6
Mixed ancestry	6	10.9
Asian	1	1.8
Body mass index (BMI)		
BMI>18	12	21.8
BMI<18	43	78.2

The median duration of disease-specific symptoms was 90 days (IQR: 60 to 120 days) with the longest recorded duration of 180 days. One patient had Li-Fraumeni syndrome (LFS) known to predispose to the development of osteosarcoma. Forty-one patients were treated on combination chemotherapy consisting of methotrexate (cumulative dose 96mg/m^2), doxorubicin (350mg/m^2), cisplatin (360mg/m^2) and ifosfamide (5400mg/m^2). The patient with LFS was treated on a hybrid protocol as she had previously been treated for multiple malignancies. Thirteen patients did not receive any curative therapy: six patients declined treatment for reasons such as fear of mutilation and cultural barriers to amputation and seven patients presented with advanced disease and were palliated. Twenty-nine patients (52.7%) presented with localised disease while 26 (47.3%) presented with metastatic disease. Two patients in the study had palliative amputations. Of the forty-two who had curative surgery, thirty-five patients had amputations and seven underwent limb salvage procedures. (See table 4)

Response to treatment

Forty-two patients were treated with curative intent. Twenty-six of the 42 who received chemotherapy had more than 95% necrosis documented in response to treatment, and were deemed to be in remission (see table 4).

Four (9.5%) patients developed dilated cardiomyopathy secondary to the use of doxorubicin. These four patients, treated in the 1990's all received doses higher ranging between 375mg/m^2 and 530mg/m^2. Further toxicities were not analysed in this series.

Sites of relapse included local in four patients, distal in three patients and undocumented in four patients.

Table 4: Tumour characteristics

Variable	Number of patients	Percentage
Treatment		
Chemotherapy	42	76.3
***No Chemotherapy**	13	23.6
Palliation	*7*	*53.8*
Declined	*6*	*46.2*
Response to chemotherapy n=42		
>95 %	26	61.9
< 95%	16	38.1
Surgery n=55		
Yes	42	76.3
No	13	23.6
Type of surgery		
Amputation	35	83.3
Limb salvage	7	16.7

**Reasons for not receiving chemotherapy: Treatment declined and for palliation from the onset*

Outcome

The five-year overall survival (OS) for all patients was 30.3 % while the overall survival for patients treated with curative intent to treat was 42%. The median follow up time was 1.3 years (IQR: 0.4 to 3.5).

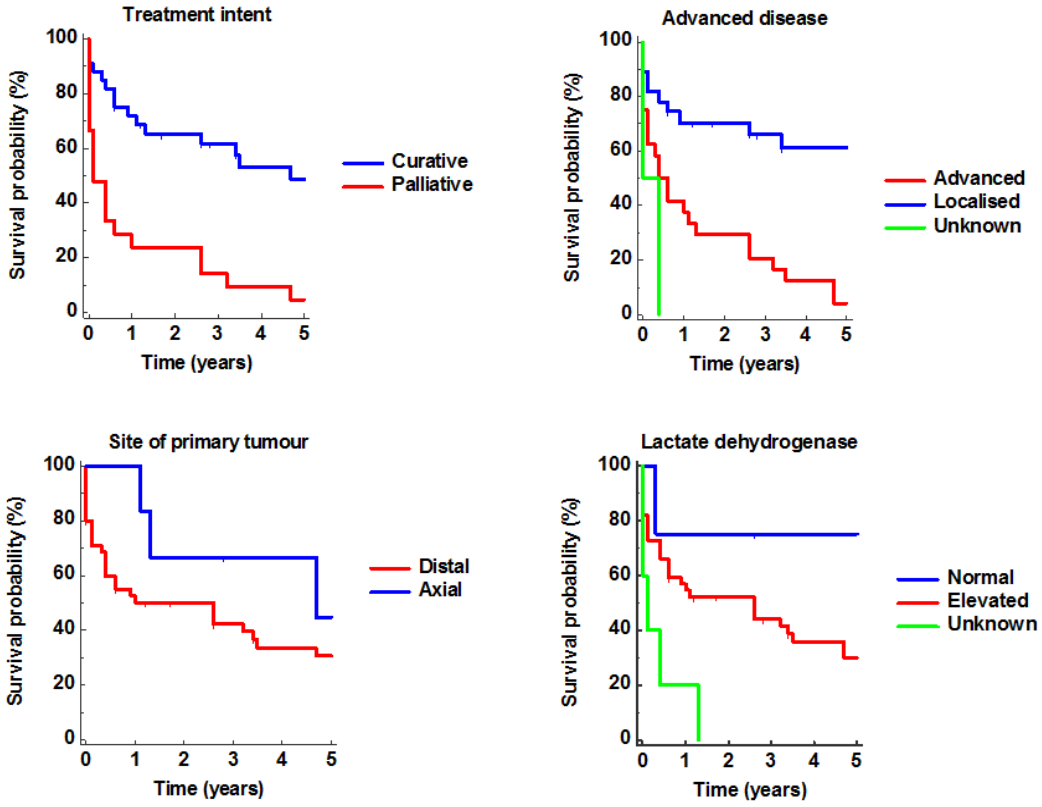

Figure 2: Kaplan-Meier survival analysis of factors shown to have prognostic significance on univariate analysis

As shown in Figure 2, site of primary tumour (p = 0.044) advanced stage at presentation (p = 0.0001) and unknown LDH (p = 0.01) were shown on univariate analysis to confer prognostic significance. In the multivariate analysis site of tumour was not confirmed as a significant prognosticator (p =0.123) but unknown LDH levels were demonstrated to have significance.

TABLE 5. Risk factor analysis of children and adolescents with osteogenic sarcoma at CMJAH

Variables	5 year overall survival (%)	Hazard ratio	95% CI Lower	95% CI Upper	*p* value Logrank
Sex					
Male	34.8	Ref			0.265
Female	25.5	1.411	0.736	2.706	
Ethnicity					
African	29.9	Ref			0.423
Other	30.5	0.737	0.358	1.521	
Body mass index (BMI)					
BMI<18	24.3	1.793	0.858	3.746	0.165
BMI>18	40.9	Ref			
Site of Tumour					
Axial	44.4	2.032	0.842	4.908	0.044
Appendicular	30.5	Ref			
Duration of symptoms					
< Median	22.2	Ref	0.350	1.749	0.499
>Median	32.9	0.783			
Histological subtype					
Osteoblastic	30.3	1.077	0.452	2.567	0.749
Chondroblastic	37.5	Ref			
Telangiectatic	30	0.986	0.260	3.746	
Stage of tumour					
Localised	61.0	Ref			**0.0001**
Metastatic	41.0	3.879	1.971	7.633	
Site of metastases					
Pleuropulmonary	6.7	Ref			0.762
Skeletal	0	1.102	0.401	3.033	
Combination	0	0.759	0.179	3.214	
Size of primary tumour					
< 8 cm	15.6	1.209	0.475	3.077	0.655
> 8 cm	32.6	Ref			
Alkaline phosphatase					
Normal	N/A	N/A	N/A	N/A	N/A
Elevated	30.3				
Lactate dehydrogenase					
Normal	75.0	Ref			
Elevated	29.9	2.855	0.631	12.914	**0.011**
Unknown	0	10.329	1.727	61.789	
Response to chemotherapy					
>95% necrosis	52.0	Ref			0.440
<95% necrosis	23.6	1.361	0.598	3.098	

Ref denotes the reference value against which other values were compared. CI: confidence interval.

Causes of death

In the cohort of 55 patients, 24 patients died of disease progression while five died from relapsed disease. Seven of the 42 patients given chemotherapy died secondary to neutropaenic sepsis. One patient developed a right ventricular thrombus and one died secondary to doxorubicin-related dilated cardiomyopathy. The treatment-related mortality was thus 21. 4%.

DISCUSSION

This single centre, 20-year study showed that the 5-year survival rate of children with osteosarcoma was lower than anticipated, but higher than in similar South African series [(5)]. The median duration of presenting symptoms was 90 days, a large proportion of patients (38.2%) presented with advanced disease and the majority had a body mass index less than 18, a possible surrogate marker for under nutrition. All our patients presented malnourished. This could be due to cachexia due to disease progression or other socio-economic factors. In addition, most patients presented with elevated LDH and ALP, possibly reflecting the large size of the tumours.

It is notable that the four patients who received doses of doxorubicin > 350mg/m^2 developed cardiomyopathy secondary to doxorubicin toxicity. The safe dose of doxorubicin is now considered to be < 350mg/m^2. We do not comment on other acute toxicities as the data in a retrospective study such as this is incomplete.

Univariate analysis of prognostic factors demonstrated that site of primary tumour, advanced disease and elevated LDH were significant. The finding that high LDH levels at presentation were associated with inferior outcomes is consistent with published literature, which suggests that LDH is an effective biomarker of prognosis. However, multivariate analysis confirmed only unknown LDH results and advanced stage as significant prognosticators. Patients who

did not have LDH levels recorded presented *in extremis*, and demised before blood tests were taken.

It was not possible to assess whether an elevated alkaline phosphatase (ALP) level was associated with poorer outcomes as all patients presented with high ALP levels and there was thus no comparison group. Interestingly, delay in diagnosis and poor nutritional status were not shown to affect outcome adversely, as in other studies [16, 17]. Many referral centres cover a large drainage area, including surrounding African countries and to get to a specialised unit most of our patients have been seen at primary health care clinics then referred to different level hospital before being sent to the referral or treating centre. Patients may experience barriers to accessing quality health care despite post-apartheid health policies designed to increase access to health care [1, 3, 5]. These barriers may include financial shortage, and time constraints especially for people employed in the informal sector [15,16].

The five-year survival rate of those treated with curative intent of only 42% can be considered to be low. The survival rate of 30.3% for the entire cohort, while higher than those in other South African series [5], still leaves a lot of room for improvement. Five year survival rates in high income countries range from 60-70% [1, 5], dropping to approximately 20% for those patients with metastatic disease. [5, 6, 7, 9]. The discrepancy may in part be explained by the limited capacity to perform specialised surgery such as excision of multiple metastases in South Africa [1, 2, 6]. The fact that seven patients did not receive the indicated curative treatment due to cultural impediments indubitably contributed to the low survival rate [13, 14].

Parameters such as size of tumour and histological subtype, shown to have prognostic value in larger studies [3, 7], were not shown in this series to be significant, most likely due to the small numbers. As osteosarcoma is a rare condition, the number of patients included in this study is small.

Treatment-related mortality was 21.4% in this cohort and if this modifiable factor can be addressed, it might contribute positively to our five-year survival rate.

Limitations

As this was a retrospective review, data collection relied on adequacy and completeness of the clinical notes and data filed on the clinic database. Folders with substantially incomplete data represented a relatively large proportion of the study number (15.4%). Duration of symptoms was retrospectively calculated based on history of symptoms stated in the folder and may thus be inaccurate.

Nutritional assessment was suboptimal in this series and was based merely on BMI which is an incomplete indicator of nutrition especially in the paediatric population.

Normal or healthy weight status is based on BMI between the 5th and 85th percentile on the CDC growth chart. It is difficult to provide healthy weight ranges for children and teens because the interpretation of BMI depends on weight, height, age, and sex. The average BMI is somewhere between 16 and 17 as of 2010, depending on age and gender, but the range of what is healthy is broader than this.

Despite the small numbers, this is currently the largest group of paediatric patients with osteosarcoma reported in South Africa and indeed one of the largest in Africa. This is the only study that has attempted to determine the prognostic factors.

Conclusion

Osteosarcoma, while rare, is the most common bone tumour in children and adolescents and has poor survival rates. Children in South Africa who presented with advanced disease or unknown LDH levels have higher mortality rates and the five-year overall survival rate was low.

Clinicians who are aware of the early warning signs of childhood cancer may detect osteosarcoma when these tumours have not yet metastasised, facilitating early intervention. This may contribute to a rise in the survival rate and a decrease in the rate of radical amputations.

Although nutritional status and duration of presenting symptoms were not shown to have significant prognostic implications in this small series, these modifiable factors may prove to have relevance in a much larger sample.

As treatment-related mortality is responsible for more than 20% of deaths in our series, protocol review should be considered.

A prospective, multi-centre study, conducted on children in low and middle income settings, including both the private and the public sectors, is required to determine definitively whether modifiable factors such as nutrition, treatment related mortality and diagnostic lag time affect prognosis.

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Declaration

I declare that I have no financial or personal relationships that may have inappropriately influenced me in writing the article.

Author contribution

JAG and TVZN conceptualised the study

TVZN performed data capturing.

JAG and KCE performed statistical analysis.

JEP approved the manuscript.

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