Prognostic factors for overall survival of conventional osteosarcoma of the appendicular skeleton

a single-centre experience in South Africa with minimum three-year follow-up

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Aims
The aim of this study is to determine the predictors of overall survival (OS) and predictive factors of poor prognosis of conventional high-grade osteosarcoma of the limbs in a single-centre in South Africa.

Methods
We performed a retrospective cross-sectional analysis to identify the prognostic factors that predict the OS of patients with histologically confirmed high-grade conventional osteosarcoma of the limbs over ten years. We employed the Cox proportional regression model and the Kaplan-Meier method for statistical analysis.

Results
This study comprised 77 patients at a three-year minimum follow-up. The predictors of poor OS were: the median age of ≤ 19 years (hazard ratio (HR) 0.96; 95% confidence interval (CI) 0.92 to 0.99; $p = 0.021$); median duration of symptoms ≥ five months (HR 0.91; 95% CI 0.83 to 0.99; $p < 0.037$); metastasis at diagnosis (i.e. Enneking stage III) (HR 3.33; 95% CI 1.81 to 6.00; $p < 0.001$); increased alkaline phosphatase (HR 3.28; 95% CI 1.33 to 8.11; $p < 0.010$); palliative treatment (HR 7.27; 95% CI 2.69 to 19.70); $p < 0.001$); and amputation (HR 3.71; 95% CI 1.12 to 12.25; $p < 0.032$). In contrast, definitive surgery (HR 0.11; 95% CI 0.03 to 0.38; $p < 0.001$) and curative treatment (HR 0.18; 95% CI 0.10 to 0.33; $p < 0.001$) were a protective factor. The Kaplan-Meier median survival time was 24 months, with OS of 57.1% at the three years. The projected five-year event-free survival was 10.3% and OS of 29.8% (HR 0.76; 95% CI 0.52 to 1.12; $p = 0.128$).

Conclusion
In this series of high-grade conventional osteosarcoma of the appendicular skeleton from South Africa, 58.4% (n = 45) had detectable metastases at presentation; hence, an impoverished OS of five years was 29.8%. Large-scale future research is needed to validate our results.

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Take home message

- In low- and middle-income countries, such as South Africa, a large proportion of patients with conventional osteosarcoma present with metastasis at 58.4%. Hence, the Kaplan-Meier median survival time was 24 months, with overall survival (OS) of 57.1% at a three-year follow-up. The projected five-year event-free survival was 10.3%, and OS was 29.8%.
- A curative treatment strategy and definitive surgery reduced mortality risk by 89%. Amid the advanced disease burden, amputation was almost four times more likely to succumb.
- Other factors associated with a poor prognosis were age ≤ 19 years, duration of symptoms ≥ five months, elevated serum alkaline phosphatase, and palliative treatment strategy.

Introduction

Osteosarcomas are a group of primary malignant mesenchymal cancers of bone characterized by the formation of an osteoid matrix, with predilection in childhood and young adults.[1] Central high-grade conventional osteosarcoma (COS) is the most common subtype, comprising 90% of all osteosarcoma variants.[1,2] Osteosarcoma is the most frequently diagnosed primary bone cancer in low- or middle-income countries (LMIC) settings,[3,4] in keeping with the developed world.[4-7] In LMICs, osteosarcoma accounts for 73% of all primary bone tumours when excluding haematological malignancies,[3,4] compared to the high-income countries (HICs), where it accounts for 28%, 34%, and 60% in the USA, UK, and China, respectively.[4–7]

Currently, the treatment of COS typically involves neoadjuvant chemotherapy, wide surgical resection of all sites, and adjuvant chemotherapy.[8-11] Despite this aggressive strategy, the five-year overall survival (OS) of non-metastatic COS has plateaued at 60% to 70% in HICs.[8-11] The survival outcomes reported globally are yet to be replicated in LMICs.[8-15] The five-year survival COS remains extremely impoverished in LMIC settings, well below 50%.[12-15] Socio-economic factors and healthcare system inequalities are the main contributing factors.[12-16]

Numerous poor prognostic factors for survival have been identified globally, including older age, male sex, large tumours, non-extremity osteosarcoma, proximal osteosarcoma, poor chemotherapy response, no surgical treatment, and amputation.[17] Surgical resection of all sites and response to chemotherapy are the most important prognostic factors to improve OS.[8,17] However, there is limited data about prognosis from LMIC and Africa in particular.[12-15] Previous studies have identified the advanced stage of disease at presentation, high tumour burden, and metastatic disease at presentation as adverse prognostic factors.[12-15]

This study aimed to determine the OS and predictive factors of poor prognosis of central high-grade conventional osteosarcoma of the limbs within a single centre in the Republic of South Africa (RSA) with a minimum three-year follow-up.

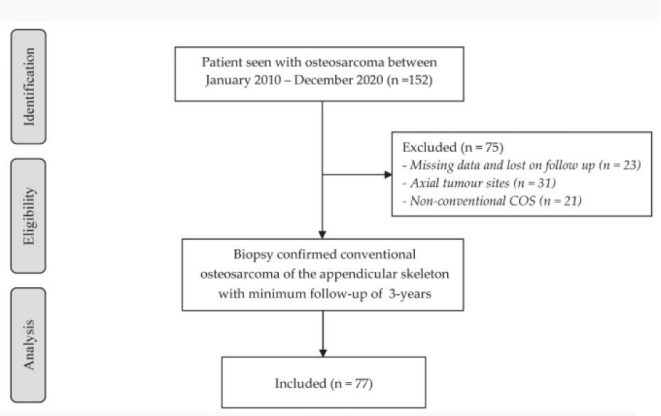


Fig. 1
STROBE flowchart of patients with high-grade central conventional osteosarcoma of the appendicular skeleton selected for inclusion.

Methods

Patients' data and research design

This is a retrospective review from a single institution (University of KwaZulu-Natal, Durban, South Africa) from our electronic database over a ten-year period at a three-year minimal follow-up. After institutional ethical review board approval (BREC/00002737/2021), patients and/or caregivers, where applicable, consented. We identified 152 osteosarcoma patients from January 2010 to December 2020. We included all patients with biopsy-histological confirmed central high-grade conventional osteosarcomas of the appendicular skeleton. Patients were excluded if they had missing data (n = 23; 30.7%), or had tumours involving the skull, spine, chest, and pelvis (n = 31; 41.3%), surface osteosarcomas (n = 11; 14.7%), and secondary osteosarcomas (n = 10; 13.3%). The remaining 77 patients were included in the analysis (Figure 1).

The following variables were assimilated: age, sex, duration of symptoms in months, days from presentation to diagnosis, tumour location (site), presence of pathological fracture, Enneking classification,[18] metastasis at diagnosis, metastatic site, serum alkaline phosphatase (ALP), lactic dehydrogenase (LDH), serum albumin, histological subtype, the treatment strategy employed (being either curative with surgery, or palliative for unresectable tumours), definitive surgery performed, and adjuvant chemotherapy used. Tumour volume was assessed using MRI and measured using a previously defined formula for an ellipsoidal mass (width × height × diameter × 0.52).[19]

Outcome measure

The outcome measure was to determine the OS and factors predictive of poor prognosis in high-grade conventional osteosarcoma of the appendicular skeleton.

Statistical analysis

Descriptive statistics and survival analysis were carried out with R v. 3.6.3 (R Project for Statistical Computing, Austria). The continuous variables were summarized by means and standard deviations (SDs). Categorial variables were summarized as counts and percentage frequencies with associations tested using a chi-squared test or Fisher's exact

Table I. Patient factors associated with overall survival of the central high-grade conventional osteosarcomas of the appendicular skeleton in South African patients.

Patient-related factors	Univariate analysis				Multivariate analysis			
Three-year survival	**Overall (n = 77)**	**Alive (n = 33)**	**Died (n = 44)**	**p-value**	**HR (95% CI), adjusted**	**p-value**	**HR (95% CI), stepwise**	**p-value**
Age, yrs, n (range); median (IQR)	77 (4.0 to 61.0); 19.0 (14.0 to 27.0)	33 (8.0 to 61.0); 19.0 (15.0 to 27.0)	44 (4.0 to 52.0); 19.0 (14.0 to 25.0)	0.636	0.96 (0.92 to 1.01)	0.106	0.96 (0.92 to 0.99)	< 0.021*
Sex, female: male, n (%)	39 (50.6): 38 (49.4)	15 (45.5): 18 (54.5)	24 (54.5): 20 (45.5)	0.43	0.71 (0.28 to 1.83)	0.479	N/A	N/A
Duration of symptoms, mnths, n (range); median (IQR)	77 (0 to 73.0); 5.0 (3.0 to 7.0)	33 (0 to 18.0); 5.0 (3.0 to 6.0)	44 (0 to 73.0); 4.5 (3.0 to 7.3)	0.491	0.92 (0.82 to 1.02)	0.101	0.91 (0.83 to 0.99)	< 0.037*
Presentation to diagnosis, days, n (range); median (IQR)	77 (0 to 527); 12.0 (7.0 to 15.0)	33 (0 to 90.0); 10.0 (10.0 to 20.0)	44 (0 to 527); 12.0 (7.0 to 15.0)		1.01 (1.00 to 1.02)	0.16	1.01 (1.00 to 1.02)	0.092
Serum albumin group, normal: decreased, n (%)	24 (72.7): 9 (27.3)	23 (53.5): 20 (46.5)	47 (61.8): 29 (38.2)	0.087	N/A	N/A	N/A	N/A

*Statistical significance.
CI, confidence interval; HR, hazard ratio; N/A, not applicable.

test. A univariate Cox proportional hazards regression model was performed to assess the OS and covariates of interest (dependent with one explanatory variable). In some cases, Cox models could not be fit because of the lack of events in one or more categories or missing datasets; in those instances, variables were dropped for the regression, leaving us with 63 regressed observations. Furthermore, the Fisher's exact test was used to assess whether the proportions of events were the same between groups. Subsequently, the multivariate Cox proportional hazard regression model (adjusted with all explanatory variables) was conducted, followed by a repeated stepwise multivariate Cox proportional hazard regression model for most essential variables with differences considered statistically significant at $p < 0.05$. The Kaplan-Meier curves were employed to test patients' survival rates in different groups. The starting point was time from diagnosis to time to event (death). Posthoc sample size calculations were undertaked using Stata v. 18 (StataCorp, USA). The posthoc analysis estimated that the available n = 77 and α err prob = 0.05, β err prob = 0.2 could detect medium effect sizes (δ) of at least 1.7908 about 80% of the time.

Results

Patient-related factors

The median patient age was 19 years (interquartile range (IQR) 14.0 to 27.0; range 8.00 to 61.0), with an almost equal distribution between males and females (49.4% vs 50.6%) (Table I). Age and sex were not significantly associated with the three-year OS (p = 0.636, Fisher's exact test) and (p = 0.430, Fisher's exact test), respectively. However, in the multivariate Cox regression, increasing age emerged as a significant predictor, reducing the likelihood of mortality by 4% (hazard ratio (HR) 0.96; 95% CI 0.92 to 0.99; p < 0.021) at three-year follow-up (Figure 2A). Serum albumin (Alb) was normal in 47 patients (61.8%) and decreased in 29 (38.2%). However, albumin was not a predictor of three-year OS (p = 0.087). The medians for the duration of symptoms and days from presentation to diagnosis were five months (IQR 3 to 7; range 0.00 to 73.0) and 12 days (IQR 7 to 15; range 0 to 527), both of which were not significantly associated with three-year OS (p = 0.816 and p = 0.586), respectively. However, the duration of symptoms of < five months was a significant predictor of three-year OS, reducing the likelihood of mortality by 9% (HR 0.91; 95% CI 0.83 to 0.99; p < 0.037) (Figure 2B).

Tumour-related factors

Around the knee was the predominantly affected site, especially the distal femur (n = 34; 44.2%) and proximal tibia (n = 19; 24.7%) (Table II). Additional tumour sites were the proximal humerus (n = 13; 16.9%) and other long bones (n = 11; 14.3%). However, tumour sites were not associated with the three-year OS (p = 0.805, Fisher's exact test). Almost half of the cohort presented with a pathological fracture at diagnosis (n = 32; 49,4%), which was not associated with three-year OS (p = 0.742, Fisher's exact test). Similarly, the median MRI tumour volume of 455.5cm^3 (IQR 241.6 to 969.5; range 36.50 to 14,489) was not associated with three-year OS (p = 0.141, Fisher's exact test). However, large tumours were predominant (n = 33; 50.8%), contrary to medium (n = 15; 23.1%) and small (n = 17; 26.2%). An osteosarcoma histological subtype was not associated with three-year OS (p = 0.936, Fisher's exact test), albeit a predominant osteoblastic (n = 41; 53.2%), followed by chondroblasts (n = 23; 32.5%) and other subtypes (n = 11; 14.3%).

Stage of disease

Notably, our cohort exhibited advanced disease (n = 45; 58.4%) presenting with metastases (i.e. Enneking stage III), and this was significantly associated with the three-year OS (HR 3.99; 95% CI 1.8 to 6.0; p < 0.001, Fisher's exact test) (Figure 2C). In all, 33 of these patients (75%) were demised within three years (Table III). In contrast, 36 patients (41.6%) did not have metastasis (i.e. Enneking stage IIB), and 66.7% (n = 22) were alive at three years. The lung was commonly metastasized (n = 34; 44.2%), contrary to bone (n = 9; 11.7%), liver (n = 1; 1.3%), and brain (n = 1; 1.3%). The metastatic site was not associated with the three-year OS (p = 0.241, Fisher's exact test).

The increased serum ALP was predominant (n = 41; 53.2%), contrary to decreased (n = 15; 19.5%), or normal (n = 21; 27.3%). In Cox multivariate regression, increased pre-treatment ALP emerged as a significant predictor, increasing the likelihood of mortality three-fold (HR 3.28; 95% CI 1.33 to 8.11; p < 0.010) (Figure 2D). In contrast, serum LDH was

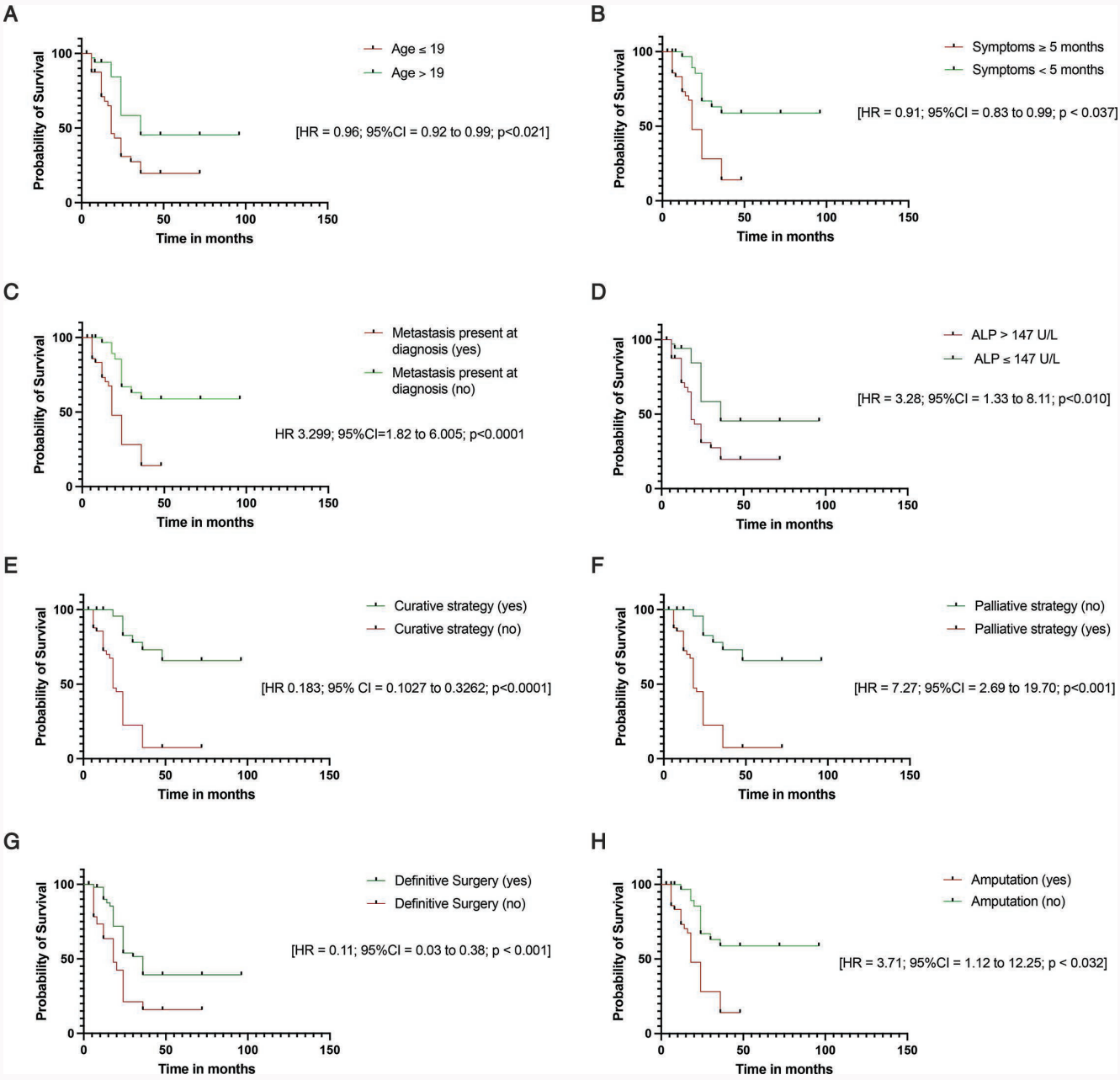


Fig. 2

Prognostic factors for overall survival of conventional osteosarcoma in South Africa. a) Osteosarcoma age; (b) osteosarcoma duration of symptoms; c) osteosarcoma metastasis at diagnosis; d) osteosarcoma serum alkaline phosphatase in units per litre; e) osteosarcoma curative strategy; f) osteosarcoma palliative strategy; g) osteosarcoma amputations; and h) osteosarcoma definitive surgery.

predominantly decreased (n = 50; 65.8%) than increased (n = 15; 19.7%) or normal (n = 11; 14.5%), and was not associated with three-year OS (p = 0.449).

Treatment-related factors

In all, 66 patients (68%) were available at three-year follow-up; this was not significant (p = 0.342) (Table IV). The reasons for loss to follow-up include seeking a second opinion, traditional medicine, refusal of amputation, or intolerance to chemotherapy. Therefore, 25 patients (32.5%) were available for curative treatment strategy; of those, 19 (57.6%) were still alive at three-year follow-up. Furthermore, there was a significant association between curative treatment and the three-year OS (HR 0.18; 95% CI 0.09 to 0.34; p < 0.001) (Figure 2E). On the other hand, 42 patients (54.4%) were available for palliative treatment strategy; of those, 34 (77.3%) died within three years. In the Cox multivariate regression, there was a seven-fold increase in mortality in patients treated palliatively within three years (HR 7.27; 95% CI 2.69 to 19.70; p < 0.001) (Figure 2F).

Overall, 52 patients (68%) had definitive surgery, which was not associated with the three-year OS (p = 0.182, Fisher's exact test). However, in the Cox multivariate regression, definitive surgery decreased the likelihood of mortality by 89% (HR 0.11; 95% CI 0.03 to 0.38; p < 0.001) at three-year follow-up (Figure 2G). Amputation procedures were predominant at 58.4% (n = 45), with a three-fold increase in mortality within three years (HR 3.71; 95% CI 1.12 to 12.25; p < 0.032)

Table II. Primary tumour factors associated with overall survival of the central high-grade conventional osteosarcomas of the appendicular skeleton in South African patients.

Patient-related factors	Univariate analysis				Multivariate analysis (stepwise regression)	
Three-year survival	**Overall (n = 77)**	**Alive (n = 33)**	**Died (n = 44)**	**p-value**	**HR (95% CI) adjusted**	**p-value**
Tumour location, n (%)				0.805		
Proximal tibia	19 (24.7)	9 (27.3)	10 (22.7)		1.87 (0.59 to 5.94)	0.289
Distal femur	34 (44.2)	15 (45.5)	19 (43.2)		1.04 (0.35 to 3.09)	0.944
Other	11 (14.3)	5 (15.2)	6 (13.6)		0.66 (0.15 to 2.80)	0.568
Pathological fracture, n (%)				0.742	1.08 (0.46 to 2.50)	0.865
No	39 (50.6)	16 (48.5)	23 (52.3)			
Yes	38 (49.4)	17 (51.5)	21 (47.7)			
MRI volume grouped in percentiles, cm^3, n %)				0.141	N/A	N/A
Small < 25%	17 (26.2)	11 (37.9)	6 (16.7)			
Medium 25 to 75%	15 (23.1)	5 (17.2)	10 (27.8)			
Large > 75%	33 (50.8)	13 (44.8)	20 (55.6)			
Histological subtype group, n (%)				0.936	N/A	N/A
Osteoblastic	41 (53.2)	18 (54.5)	23 (52.3)			
Chondroblastic	25 (32.5)	10 (30.3)	15 (34.1)			
Other	11 (14.3)	5 (15.2)	6 (13.6)			

CI, confidence interval; HR, hazard ratio; N/A, not applicable.

Table III. Factors relating to the stage of disease associated with overall survival of the central high-grade conventional osteosarcomas of the appendicular skeleton in South African patients.

Patient-related factors	Univariate analysis				Multivariate analysis (stepwise regression)			
Three-year survival	**Overall (n = 77), n (%)**	**Alive (n = 33), n (%)**	**Died (n = 44), n (%)**	**p-value**	**HR (95% CI) adjusted**	**p-value**	**HR (95% CI)**	**p-value**
Metastasis present at diagnosis, no: yes	32 (41.6): 45 (58.4)	22 (66.7): 12 (33.3)	10 (25.0): 33 (75.0)	< 0.001*	3.68 (0.36 to 37.54)	0.272	2.02 (0.86 to 4.76)	0.107
Site of metastasis grouped, lung only: multiple	33 (75.0): 11 (25.0)	10 (90.9): 1 (9.1)	23 (69.7): 12 (30.3)	0.241	N/A	N/A	N/A	N/A
Enneking staging, IIB: III	32 (41.6): 45 (58.4)	22 (66.7): 12 (33.3)	10 (25.0): 33 (75.0)	< 0.001*	3.68 (0.36 to 37.54)	0.272	2.02 (0.86 to 4.76)	0.107
Serum alkaline phosphatase, normal: increased: decreased	13 (39.4): 13 (39.4): 7 (21.2)	8 (18.2): 28 (63.6): 8 (18.2)	15 (19.5): 41 (53.2): 15 (19.5)	0.071	2.07 (0.54 to 7.89)	0.287	3.28 (1.33 to 8.11)	< 0.010*
Serum lactate dehydrogenase, normal: increased: decreased	4 (12.1): 26 (78.8): 3 (9.1)	7 (16.3): 24 (55.8): 12 (27.9)	11 (14.5): 50 (65.8): 15 (19.7)	0.079	N/A	N/A	N/A	N/A

CI, confidence interval; HR, hazard ratio; N/A, not applicable.

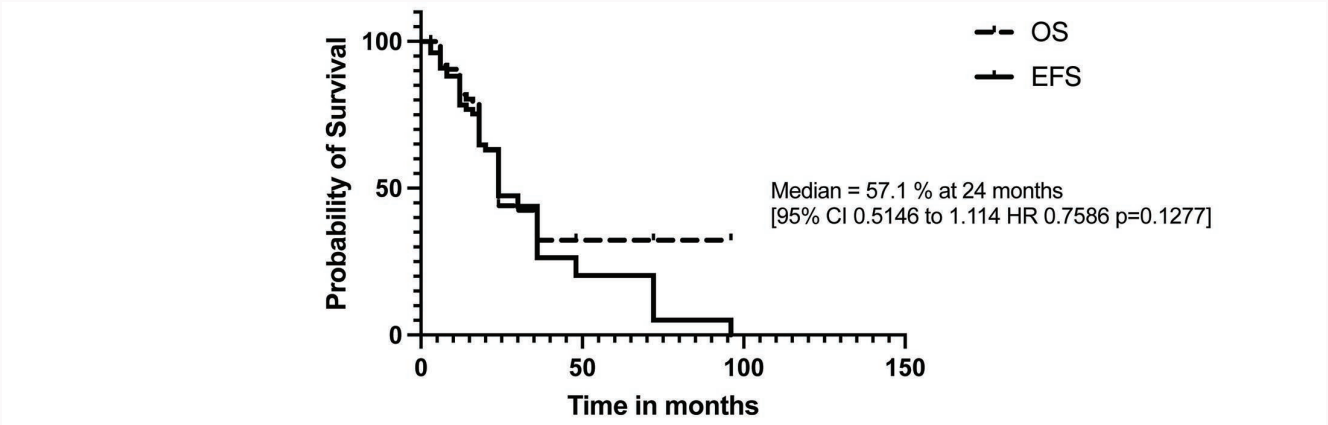
(Figure 2H). Lastly, the treatment was adjuvant chemotherapy at 75.3% (n = 58); however, this was not associated with OS (p = 0.066) at a three-year follow-up.

Event-free and overall survival

The Kaplan-Meier median survival time was 24 months, with an OS of 57.1% (44 events/deaths) at a three-year follow-up. There were non-significant differences between the projected five-year event-free survival (EFS) of 10.28% (58 events) and OS of 29.78% (HR 0.76; 95% CI 0.52 to 1.12; p = 0.128) (Figure 3).

Discussion

This retrospective, cross-sectional study interrogated the OS and predictive factors of poor prognosis central high-grade COS of the limbs in South African patients. Our overall patients' clinical characteristics of COS grossly mirror those exhibited globally, but discordances are observed.[4–11,17,20,21] For instance, our osteosarcoma failed to exhibit bimodal distribution. We observed that a single peak median age of 19 years (IQR 14.0 to 27.0) is similar to that previously reported in HICs.[4,20,21] Cole et al[4] and Duong et al[21] interrogated the epidemiology of osteosarcoma and emphasized bimodal distribution with an increased incidence rate in the second decade of life. In our series, increasing age was protective, reducing the likelihood of mortality by 4%. In contrast, Huang et al[20] noted an increased risk of mortality in patients over the age of 22 years. This finding should, however, be interpreted cautiously amid the small sample size and the small number



At risk	0.000	3.000	6.000	8.000	12.000	14.000	16.000	18.000	20.000	24.000	30.000	36.000	48.000	72.000	96.000
Overall Survival	77	77	74	66	63	52	51	50	41	40	27	25	13	8	1
EFS	77	77	74	66	63	52	51	50	41	40	27	25	13	8	1

Fig. 3
Kaplan-Meier event-free survial (EFS) and overall survival (OS) of osteosarcoma single centre within South Africa population.

Table IV. Treatment-related factors associated with overall survival of high-grade conventional osteosarcomas of the appendicular skeleton in South African patients.

Treatment factors	Univariate analysis				Multivariate analysis (stepwise regression)			
Three-year survival	**Overall (n = 77), n (%)**	**Alive (n = 33), n (%)**	**Died (n = 44), n (%)**	**p-value**	**HR (95% CI), uadjusted**	**p-value**	**HR (95% CI), adjusted**	**p-value**
Curative, no: yes	52 (67.5): 25 (32.5)	14 (42.4): 19 (57.6)	38 (86.4): 6 (13.6)	< 0.001*	0.41 (0.06 to 2.71)	0.352	N/A	N/A
Palliative, no: yes	35 (45.5): 42 (54.5)	25 (75.8): 8 (24.2)	10 (22.7): 34 (77.3)	< 0.001*	4.09 (0.87 to 19.19)	0.074	7.27 (2.69 to 19.70)	< 0.001*
Definitive surgery performed, no: yes	25 (32.5): 52 (67.5)	8 (24.2): 25 (75.8)	17 (38.6): 27 (61.4)	0.182	0.13 (0.03 to 0.58)	0.008*	0.11 (0.03 to 0.38)	< 0.001*
Limb ablation, no: yes	32 (41.6): 45 (58.4)	15 (45.5): 18 (54.5)	17 (38.6): 27 (61.4)	0.548	3.77 (0.83 to 17.22)	0.087	3.71 (1.12 to 12.25)	< 0.032*
Adjuvant chemotherapy, no: yes	19 (24.7): 58 (75.3)	11 (33.3): 22 (66.7)	8 (18.2): 36 (81.8)	0.127	0.36 (0.09 to 1.38)	0.135	0.39 (0.14 to 1.06)	0.066
Lost to follow-up, no: yes	66 (85.7): 11 (14.3)	N/A	N/A	0.342	N/A	N/A	N/A	N/A

*Statistical significance.
CI, confidence interval; HR, hazard ratio.

of patients aged over 30 years. A larger sample size could redefine the cut-off of age for our osteosarcoma presentation or peak age distribution.

Another discordance is that 58.4% of patients presented with metastases or Enneking stage III. In contrast, the figures reported globally that approximately 20% of patients have detectable metastases at presentation.[8-10] Our findings align with South African results that found metastases in 48%, 67%, and 80% of cases at presentation, respectively.[12-14] The question thus arises: why is there such a high rate of metastases at presentation in this geographical region? Delayed clinical presentations could be the main factor.[14,22] In the KwaZulu-Natal province, Phillias et al[22] presented a median duration of symptoms of four months. In our series, there was a somewhat longer delay to presentation, with the median duration of symptoms being five months (IQR 3 to 7). This is comparable to the 4.5 months reported by Lisenda et al,[14] when they retrospectively reviewed 61 patients with osteosarcomas. Previous investigators from LMIC have raised socioeconomic inequalities, inadequate referral systems, and poor access to quality healthcare as the main contributing factors; however, this is yet to be analyzed rigorously.[12-16] Our median duration of symptoms of less than five months was associated with a decreased likelihood of mortality by 9%. In contrast, Lawrenz et al[23] found an improved chance of survival with a longer duration of symptoms. While this may seem counterintuitive, it can be explained by the concept that less aggressive or lower-grade tumours may grow slower and thus be detected or cause symptoms later. However, in our case, this seems an unlikely explanation for the delay in the presentation when considering the high rate of metastasis at 58.4%. The long duration of symptoms in our series likely resulted from socio-economic and/or healthcare system-related reasons than low-grade malignancies.

The high rate of metastases (i.e. Enneking stage III) is reflected in the impoverished OS observed, with a median of two years, and OS at 57.1% at three-year follow-up. Our projected five-year EFS of 10.28% and OS of 29.78%, respectively. Our OS compares poorly to Western countries, with five-year OS 60% to 70% globally.[9-11] The latter survival rates are yet to be replicated in LMIC.[12-16] The RSA survival results, as reported previously by Hart et al,[12] Shipley et al,[13] and Lisenda et al,[14] were 58%, 53%, and 38%, respectively. Meanwhile, in Cambodia, as outlined by Noor et al,[15] the osteosarcoma

five-year survival rate is as low as 8%. In addition, our increased pre-treatment ALP was associated with a three-fold increase in the likelihood of mortality. This is in keeping with two previous meta-analyses that have also identified elevated ALP as an unfavourable predictor for osteosarcoma survival outcomes.[24,25 26,27]

Traditionally, the mainstay osteosarcoma treatment has been chemotherapy and wide tumour surgical resection of all sites,[8,28] a curative treatment strategy in our context with 32.5% (n = 25) treated like this. Of those, 57.6% (n = 19) were still alive at a three-year follow-up. There was a significant association between curative treatment and the three-year OS ($p < 0.001$). This treatment strategy has imparted 60% to 70% of five-year overall survival globally.[9-11] In our study, curative treatment and definitive surgery conferred a beneficial effect on OS. Furthermore, Kager et al[8] treated 202 patients with metastatic osteosarcomas at diagnosis and noted that the completeness of surgical resection of all tumour sites proved beneficial for overall survival. In the same vein, our definitive surgery was significantly predictive, decreasing the likelihood of mortality by 89%. The recent meta-analyses by Abdelgawad et al[24] and Papakonstantinou et al[25] suggested that limb salvage surgery (LSS) imparts better OS and functional outcomes and is more socially acceptable than amputation. In high-income settings, the LSS rate is > 80%.[24,25,29] On the contrary, our amputation rate was 58.4%; amputations had a three-fold increased risk of mortality within three years (HR 3.71; 95% CI 1.12 to 12.25; $p < 0.032$, Fisher's exact test). Again, selection bias as a confounding factor may play a role, such as advanced local disease requiring amputation.

The remainder of the cohort was treated palliatively (n = 42; 54.5%); of those, 34 (77.3%) were demised within three years. In the palliative cohort, the mortality rate was seven times within three years. However, selection bias needs to be considered. The indications for a palliative strategy in this series were multiple extensive lung metastases, multiple sites metastasis, poor response to chemotherapy, and refusal of surgical treatment, especially amputation, which remains socially unacceptable in our clinical setting. Monsereenusorn et al[30] noted treatment refusal and abandonment as bottlenecks to improving the overall survival of osteosarcomas in Southeast Asia.

There are numerous limitations to this study. The small sample size is a significant shortcoming, and our findings should be interpreted cautiously. The retrospective nature of the data collection meant that we could only analyze some possible factors that may have a bearing on the prognosis. Several cases were lost to follow-up, which precluded longer-term longitudinal prognostication. In our clinical environment, numerous contributory factors exist for patients' loss of follow-up, including refusing treatments, especially amputation, seeking alternative traditional medicines, socio-economic factors, and intolerance of chemotherapy drugs.

In conclusion, in this series of high-grade conventional osteosarcoma of the appendicular skeleton from South Africa of the single centre at a three-year minimum follow-up, 58.4% of cases had detectable metastases at presentation. The OS were 57.1% at three years and 29.8% at five years. More studies are needed to confirm the survival rate and prognostic factors in LMICs, and to determine the possible reasons for the apparent inferior outcomes in relation to other regions.

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