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The management of osteosarcoma in children and adolescents in a resource-limited setting: quality improvement considerations to improve treatment outcomes

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Abstract

Background The survival rates for children and adolescents with osteosarcoma in low-income countries are poor. Insufficient data regarding the challenges of managing osteosarcoma in resource-limited settings has been published. We evaluated the treatment of osteosarcoma in children and adolescents with the aim of improving the health system and management outcomes.

Methods We sourced data on children under 18 years treated for osteosarcoma at the Uganda Cancer Institute between January 2016 and December 2020. Descriptive statistics and Kaplan-Meier survival analysis were used.

Results Seventy-four osteosarcoma cases were identified, with a median age of 13 years (IQR 9.8–15). Referrals were made after a median of 28 days (range 1-147). Before appropriate referral, more than a quarter (26%) had undergone invasive procedures that could compromise tumour integrity and outcome. Half (50%) of the patients had metastatic disease at diagnosis, primarily to the lungs ($n=43$; 92%). Only 14 (33%) patients received neoadjuvant chemotherapy. Forty-three (58.1%) patients underwent limb amputation surgery, including 25 localized tumours and 18 patients with distant metastatic disease. No metastatectomies were performed. Adjuvant chemotherapy was delayed for longer than 21 days in 26 (61%) patients. No pathology reports described the status of resection margins or the degree of chemotherapy-induced necrosis. Twenty-six (35%) patients abandoned treatment, mainly due to pending radical surgery ($n=18/26$; 69%). Only 18% ($n=13$) were still alive; 46% ($n=34$) had died; and 37% ($n=27$) had an unknown status. The median overall survival was 1.1 years, and was significantly negatively affected by disease metastasis, timing of adjuvant therapy, and treatment abandonment.

Conclusions Osteosarcoma outcomes for children and adolescents at the Uganda Cancer Institute are extremely poor. The quality of care can be improved by addressing delayed referrals, high rates of prior manipulative therapy, metastatic disease, treatment abandonment, surgical challenges, and delayed resumption of adjuvant chemotherapy.

Keywords Osteosarcoma, Children, Adolescents, Low- and middle-income countries, Resource-limited setting, Uganda

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Background

Osteosarcoma is the most prevalent primary malignancy of bone in children and young adolescents [1]. It accounts for approximately 60% of all malignant bone tumours diagnosed before young adulthood with the peak incidence in puberty [2]. In low- and middle-income countries (LMICs) and Africa in particular, current literature on osteosarcoma and other bone tumours is scarce, occasioned by the lack of cancer registries in these settings and the low priority given to surgical oncology in Africa [3]. In Uganda, an early analysis of data from the 1960s is limited to epidemiological data confirming osteosarcoma as the most common primary malignant bone tumour [4].

The last fifty years have witnessed tremendous evolution in the treatment of osteosarcoma and an improvement in the survival rates of localized disease in high-income countries (HICs) [5]. From a poor 20% five-year survival in the 1950s, overall survival (OS) rates for patients with localized osteosarcoma now exceed 70% in HICs and 30% for those with metastatic disease [6–8]. Neoadjuvant chemotherapy-induced tumour necrosis has facilitated successful limb-salvage surgery by reducing the extent of the surgical margin required for tumour removal without compromising overall survival.

Similar advances in osteosarcoma treatment are not replicated in LMICs, where a number of inherent challenges in osteosarcoma treatment contribute to poor outcomes. Standard treatment regimens may not be accessible or too toxic in these settings. In addition, delayed and advanced disease presentation and the lack of expertise and resources for limb-salvage surgery frequently necessitate amputation, which is a common cause of surgical refusal and treatment abandonment [9, 10].

For optimal outcomes, osteosarcoma management avoids any invasive pre-surgical procedures that may compromise the outcome and involves neoadjuvant therapy, administered prior to surgery [11, 12], as well as adjuvant chemotherapy, begun within 21 days of definitive surgery [13, 14]. In addition, metastatectomies are recommended when there are fewer than four metastases (if non-mutilating) [6, 15, 16]. It suffices to state that assessing the surgical margin [17, 18] and the degree of necrosis as a histological response to neoadjuvant chemotherapy [19, 20] are critical, with prognostic implications in osteosarcoma treatment.

To date, there is a dearth of information in the literature about the salient characteristics and inherent determinants of treatment outcomes in children and adolescents with osteosarcoma in resource-constrained settings, such as Uganda. The absence of such context-specific data may limit the prioritization and planning for improving the quality of osteosarcoma disease management. The goal of the current study was to evaluate the treatment of osteosarcoma in children and adolescents with the aim of improving the health system landscape and management outcomes.

Methods

Study design

This was a retrospective study involving a review of records of children and adolescents aged below 18 years with osteosarcoma treated at the Uganda Cancer Institute (UCI) between January 2016 and December 2020. The UCI is Uganda's only national reference cancer treatment centre, treating nearly 80% of the children with cancer in the country. Anecdotal estimates suggest that around 15–20 of the approximately 500 new cancer cases seen at the centre annually are osteosarcoma. Patients with an uncertain or inconclusive diagnosis, incomplete medical records lacking clinical details, or an alternative diagnosis on histology review were excluded (Fig. 1).

Study procedure and data extraction

Individual patients' data were extracted from the time of cancer diagnosis to the date the patient was last seen in the clinic or died. Demographic information (age and sex/gender), duration of symptoms, pre-referral interventions, tumour characteristics and stage of disease, patient management, and clinical course and outcome were collected. Where the participant's status could not be ascertained owing to a lack of documentation or default, a phone call follow-up was made to the carer to enquire and ascertain the child's status.

Disease evaluation, staging and treatment

The diagnosis of osteosarcoma was made based on clinical presentations and radiological findings and confirmed by histological examination of tissue biopsy based on the morphologic criteria defined by the World Health Organization (WHO) classification [21]. The primary site and local extent of the tumour were assessed by a computed tomography (CT) scan or plain X-ray in some cases (where a CT scan was not accessible). The initial staging workup included a CT scan of the chest and a skeletal survey. Radionuclides technetium-99 m (Tc-99 m) scan during staging was not available.

All children with osteosarcoma included in the study were treated according to the local standard protocol, which is based on a two-drug combination chemotherapy regimen with Cisplatin and Adriamycin (AP) that does not involve high-dose methotrexate. The chemotherapeutic regimen entailed three courses of neoadjuvant induction chemotherapy and two courses of adjuvant maintenance chemotherapy administered every 21 days, regardless of histologic response to chemotherapy [22]. Each course comprised a combination of cisplatin

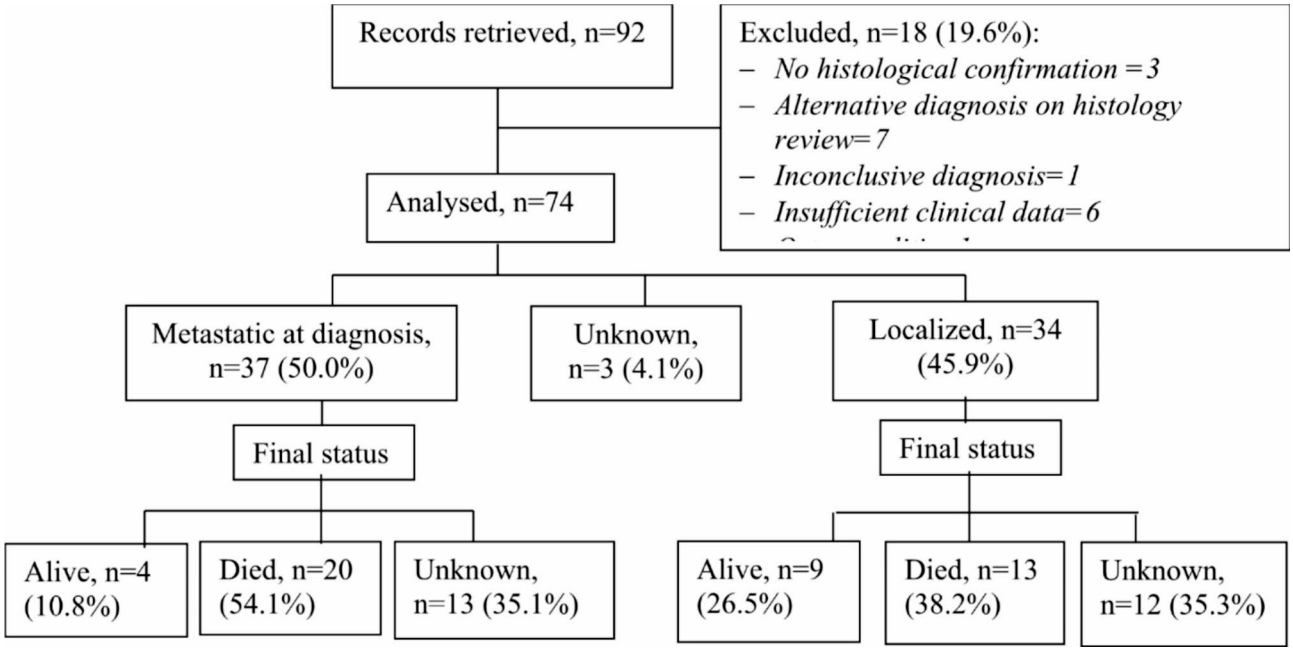

Fig. 1 Study profile

(100mg/m^2) and doxorubicin (25 mg/m^2). Interval radiological evaluations were performed prior to surgery, and individuals with resectable tumours were offered local control, often radical surgery (amputation or disarticulation). Physical examination, radiographic investigations, and biopsy, where feasible and appropriate, were used to confirm recurrences (local or systemic).

Clinical and outcome definitions

Manipulative therapy was defined as procedures that would damage the tumour or compromise outcome, including attempted incision and drainage, biopsy not based on oncological principles and local therapeutic cuttings over the tumour lesion with application of traditional medicines, among others.

Treatment refusal and abandonment were defined as failure to initiate or complete treatment. This excluded the decision of palliative treatment or discontinued treatment due to toxicity by primary oncologists.

Overall survival (OS) was defined as the time duration from the date of diagnosis to death from any cause or to the date the patient was last known to be alive.

Data management and statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) software package (SPSS for Windows, Version 20.0, Chicago, SPSS Inc.). Descriptive statistics for categorical variables were presented as frequencies and percentages, while continuous variables were summarized as mean with standard deviation if normally distributed or median with interquartile range if non-normally distributed. Median survival, with the associated 95% confidence intervals (CI), was estimated using the Kaplan-Meier method and compared using the log-rank test [23]. Statistical significance at multivariate analysis was defined as a p-value$<$0.05.

Results

Description of the study participants

During the study period, data for 74 children and adolescents treated for osteosarcoma were analysed (Fig. 1).

The participants ranged from four to 17 years of age, with a median age at diagnosis of 13.0 years (IQR 9.8–15). The median time from onset of symptoms to presentation to a health facility of first contact was 8.0 months (range 4.0–24.0). It took a median of 28 days (range 1-147) for patients to be referred from the facilities of first contact to the national reference cancer centre. Over half (55.4%; n=41/74) were male, and 22 (29.7%) had a preceding history of trauma. A quarter (25.7%; n=19) had had manipulative therapy for their lesions (invasive procedures such as local therapeutic cutting with application of local herbs, and attempted incision and drainage, that could compromise tumour integrity and outcome) for their lesions before presenting to the cancer treatment facility. The distal femur was the most common site of primary tumour (44.6%, n=33). Metastatic disease at the time of diagnosis was evident in 37 (50.0%) of the patients, 34 (91.9%) of which were pulmonary metastases, two (5.4%) were bone metastases, and one (2.7%) simultaneous pulmonary and liver metastases. The histological subtype was available for only 30 (40.5%)

Table 1 Baseline characteristics of children and adolescents with osteosarcoma ($n=74$)

Variable	Median	IQR
Age (years)	13.0	9.8–15.0
Duration of symptoms (months)	8.0	4.0–24.0
Time to referral (days)	28	1.0-147
Variable	***n***	**%**
Sex		
Male	41	55.4
Female	33	44.6
History of trauma		
Yes	22	29.7
No	52	70.3
Prior manipulative therapy¶		
Yes	19	25.7
No	55	74.3
Site of the primary tumour		
Distal femur	33	44.6
Proximal tibia	15	20.3
Proximal humerus	12	16.2
Other	14	18.9
Extent at diagnosis		
Localized	34	45.9
Metastatic	37	50.0
Unknown	3	4.1
Site of metastasis		
Lung	34	91.9
Bone	2	5.4
Lung & liver	1	2.7
Histological subtypes		
Osteoblastic	16	21.6
Chondroblastic	7	9.5
Fibroblastic	7	9.5
Not sub-typed	44	59.4

¶Manipulative therapy was defined as procedures that would damage the tumour or compromise outcome, including attempted incision and drainage, and local therapeutic cuttings over the mass with application of traditional medicines, among others

of the cases, while a substantial proportion of histological diagnoses were simply reported as osteosarcoma, without subtype specification. Overall, 16 (21.6%) of the patients had osteoblastic osteosarcoma (Table 1).

Treatment characteristics and clinical outcomes

The majority, 62 (83.8%) of the patients, received chemotherapy, and only 43 (58.1%) had surgical resection (local control). Forty-two (97.7%) of the surgeries were radical surgery (amputation or disarticulation), and only one patient (2.3%) had had limb salvage surgery. Among those who underwent surgical tumour resection, 29 (67.4%) were upfront surgeries, typically before being referred to the cancer treatment centre, and 14 (32.6%) were performed after pre-operative courses of chemotherapy. Twenty-five (58.1%) of the patients who had surgical resection had localized tumours, and 18 (41.9%) patients had distant metastatic disease. No metastatectomies were performed for the patients with metastatic disease, and none of the patients had a post-surgical pathology report describing the status of the resection margins or the degree of chemotherapy-induced necrosis. More than two-thirds (68.4%, $n=26$) of the patients who underwent surgery had delayed resumption of adjuvant chemotherapy of more than 21 days following definitive surgery, which was timely (within ≤21 days of surgery) in only 12 (31.6%) of the patients. The delay in adjuvant chemotherapy was highest among patients who had upfront surgery (75.9%; $n=22/29$) compared to those who received neo-adjuvant chemotherapy (28.6%; $n=4/14$). Overall, 50.0% (37/74) of the patients completed their course of initial chemotherapy treatment, 35.1% (26/74) abandoned treatment, and 14.9% (11/74) were discharged from therapy on total palliation because of disease progression with no possibility of cure. Twelve (32.4%) of the patients with metastatic disease refused or abandoned treatment, while 11 (29.7%) were palliated, two of whom were upfront. Of the 74 participants analysed, only 13 (17.6%) were alive at the time of this analysis, 34 (45.9%) had died, and 27 (36.5%) had been lost to follow-up, and their status could not be ascertained (Table 2).

Table 2 Treatment characteristics and clinical outcomes of children and adolescents with osteosarcoma ($n=74$)

Variable	*n*	%
Chemotherapy		
Yes	62	83.8
No	12	16.2
Surgery		
Yes	43	58.1
No	31	41.9
Timing of surgery		
Upfront	29	67.4
After neo-adjuvant chemotherapy	14	32.6
Timing of adjuvant chemotherapy		
≤21 days	12	31.6
>21 days	26	68.4
Treatment progress		
Completed treatment	37	50.0
Abandoned treatment	26	35.1
Discharged on total palliation	11	14.9
Clinical outcome		
Alive	13	17.6
Died	49	66.2
Unknown	12	16.2

Survival outcomes

The median follow-up time from the time of cancer diagnosis was 9.9 months (IQR 4.3–17.5). The median OS was 1.1 years (95% CI 0.5–1.7), while the two- and five-year probabilities of OS were 28% and 18%, respectively (Fig. 2).

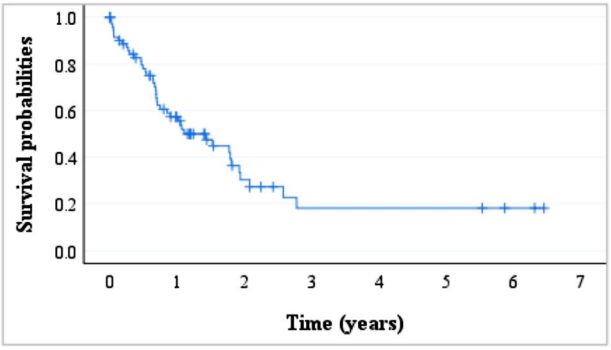

Fig. 2 Overall survival curves for children aged < 18 years with osteosarcoma

Table 3 Median survival for children and adolescents with osteosarcoma by key identified quality of care factors

Variable	Median survival¥	95% CI	*p*-value
Overall survival	1.8	1.4–2.2	-
Manipulative therapy			
Yes	1.0	0.8–1.3	0.961
No	1.8	1.3–2.2	
Metastatic disease at diagnosis			
Yes	1.1	0.1–2.1	**0.009**
No	-		
Upfront surgery			
Yes	1.8	1.7–1.8	0.273
No	2.1	0.6–3.5	
Timing of adjuvant chemotherapy			
≤21 days	2.8	1.4–4.1	**0.004**
>21 days	1.0	0.4–1.7	
Treatment abandonment			
Yes	0.8	0.4–1.3	**0.006**
No	1.9	1.4–2.5	

¥, survival in years

Metastatic disease at diagnosis ($p=0.009$), delayed resumption of adjuvant chemotherapy ($p=0.004$), and abandonment of treatment ($p=0.006$), resulted in statistically significantly lower median survivals. Likewise, patients who received prior manipulative therapy ($p=0.961$) and up-front surgery ($p=0.273$) had lower median survivals compared to those who did not receive manipulative therapy and those who received pre-surgical chemotherapy, respectively, although these differences did not reach statistical significance (Table 3).

Discussions

This study is the first review to characterize the management limitations and outcomes in Ugandan children and adolescents diagnosed with osteosarcoma. It demonstrates several important considerations for improving the quality of care at two levels that negatively impact survival: i). the pre-hospital level, encompassing delay in patient referral and high rates of manipulative therapy, and metastatic disease at diagnosis), and ii). In-hospital and/or therapy-related level, encompassing high rate of pre-chemotherapy surgical resection, high rate of treatment abandonment, lack of diagnostic and post-surgical histopathological assessments, lack of metastatic resection, and delay in adjuvant chemotherapy). In addition, our study reveals much poorer treatment outcomes among children and adolescents with osteosarcoma, with a high mortality rate and low overall survival.

Children with osteosarcoma in the current study were delayed in being referred from their facility of first contact to the national cancer treatment facility. This finding may not be surprising, and delayed referrals for children with cancer in LMICs have variously been reported [24]. This could be attributed to a lack of knowledge and a low index of suspicion among first-level health personnel, leading to unnecessary and often inappropriate attempts to manage patients based on misdiagnosis. In fact, in this study, over a quarter of the patients had manipulative therapy of varying nature before coming to the paediatric oncology centre. Dependence on alternative therapies, including traditional therapy, delays proper diagnosis and results in more advanced stages of disease at presentation [25]. Also concerning is the fact that these procedures pose a risk of damaging the tumour and forming micrometastasis due to hypervascularization [26–28]. This has the potential to compromise the chances for limb salvage surgery [26] and the overall patient outcome [28, 29]. It's thus necessary to raise community awareness and build the capacity of first-level health practitioners and traditional healers.

We found a higher rate of clinically detectable metastatic disease at diagnosis in our study population than has been reported in HICs [6, 30] and in a study in South Africa, an upper middle-income country [5]. The high rate of metastasis as found in the current study is concerning and could be due to poor health-seeking behaviour and delayed referral to the cancer treatment centre, among other reasons. In the current study, the median duration from onset of symptoms to presentation to a health facility was eight months, and patients who first presented to other facilities were later referred to the UCI after a median of 28 days. The clinical implication of the current study's finding relates to the fact that disease metastasis has an important bearing on survival in osteosarcoma, and the negative impact of metastatic disease in the current study was evidently clear. Patients with metastatic disease had a lower OS rate than those with localised disease, a finding consistent with other reports [6, 31]. Two of these patients received total palliation upfront, a decision based on their advanced disease stage and poor clinical status, and a discussion with the multidisciplinary team and their families.

None of the patients with metastatic disease in the current study had metastatectomy, which is a significant gap. There is evidence that the prognosis for patients with metastatic disease is influenced by the surgical resectability of metastatic disease, in addition to the metastatic site, and the number of metastases [32]. In international protocols, metastatectomies are encouraged when there are fewer than four metastases (if non-mutilating), with a complete metastatectomy being the best predictor of survival in osteosarcoma patients with pulmonary metastases. [6, 15, 16]. Patients with fewer pulmonary and unilateral lesions are more amenable to metastatectomy and are said to have a better prognosis compared to those with multiple lesions or bilateral lung metastases [6]. The majority of the metastases in the current study were in the lung, bilateral, with multiple lesions – features which make metastatic resection challenging, and are likely to have exacerbated the poor outcomes in our study population. While the foregoing is true, the lack of surgical infrastructures in the study setting, just as is the case in many resource-limited contexts, is a major challenge, and requires attention. Overall, in this study, lack of local control was associated with a lower survival than for patients who underwent local control (median survivals of 0.8 versus 1.8 years, respectively).

Over two-thirds of our patient population had pre-chemotherapy surgical resection, often amputation, performed before referral to the cancer treatment facility, at centres outside the UCI, and by individuals who may not be specialized in osteosarcoma surgical management. The improvement in survival among patients with osteosarcoma seen to date is partly a result of the current standard of care that involves pre-surgical (neo-adjuvant) chemotherapy [12, 33]. The high mortality rate witnessed in the 1970s when a surgery-only treatment approach was used were mainly due to the rapid progression of osteosarcoma due to micrometastases and lung metastases. Preoperative chemotherapy is thus important in the eradication of micrometastases and allows evaluation based on the histological response to chemotherapy, one of the most important predictors of the clinical outcome of osteosarcoma [34–36]. Neoadjuvant chemotherapy also results in a significantly higher margin negativity in the post-surgical specimen, a lower rate of local recurrence [12], and as many as 80–85% limb salvage surgery rates in HICs [33, 37, 38].

Another important finding in the current study is the high treatment abandonment rate – much higher than rates documented in other settings, including western Uganda [39, 40], attesting to the observation that the risk of treatment abandonment is high for bone sarcoma [41]. Although the reason for this may be multifaceted [39, 42], the lack of conservative surgery infrastructure necessitating radical surgery (amputation or disarticulation), especially in resource-limited settings, could be an important factor. In fact, over two-thirds of the patients who abandoned treatment in the current study were primed for amputation surgery. However, amputation is a frightening scenario for most families that may substantially impact treatment discontinuation. This is reinforced by the phenomenon of the child falsely appearing "cured" [39] following cycles of pre-surgical neoadjuvant chemotherapy. This poses a major barrier to improving outcomes among children with osteosarcoma in settings with limited resources where curative treatment options rely on radical surgery or amputation. As demonstrated in the Philippines, having a patient navigator involved with these patients from diagnosis throughout treatment may significantly reduce abandonment rates [43], in addition to bridging the gaps in the pre-surgical counselling process.

None of our patient population for whom surgical tumour resection was done had a histological report on the resection margin or the degree of chemotherapy-induced necrosis - an important prognostic indicator in modern-day treatment of patients with high-grade osteosarcoma [19, 20]. Likewise, an adequate or wide resection margin is associated with a lower risk of local recurrence in osteosarcoma [17, 18]. While we did not explore the reasons for this, we believe this could be partly attributed to the fact that surgeries for children with osteosarcoma are done outside of the UCI, and almost all patients are managed with radical surgery. This calls for strengthening multidisciplinary management and coordination among oncologists, surgeons, and pathologists.

There was a 64.3% reduction in the median survival when the resumption of adjuvant chemotherapy was delayed for more than 21 days compared to resumption within 21 days after the definitive surgery. This is concerning in light of a growing body of evidence showing that timely resumption of adjuvant chemotherapy within 21 days following definitive surgery improves survival in osteosarcoma [13, 14]. The notion that the actual dose and time intensity delivered impacts the outcome of osteosarcoma treatment has been used to explain the prognostic significance of adjuvant chemotherapy scheduling following definitive osteosarcoma surgery [44]. Consequently, a lengthy delay before the resumption of adjuvant chemotherapy after definitive surgery is believed to compromise the overall dose intensity [13]. As Imran et al. [13] point out, concerns over wound healing and infection risk are important factors in developing country environments, which make determining when to resume chemotherapy difficult.

The limitation of this study lies in the challenge innate to retrospective data, yet it serves as a motivation to standardize and improve clinical records at our institutions and in other similar contexts. Nonetheless, the current

study's fundamental merit is that it represents the first analysis of its kind in the country, laying the groundwork for future quality considerations along the whole osteosarcoma treatment pathway. The most important being increased medical education to health workers regarding timely referrals and avoiding detrimental medical procedures that compromise the outcome of cancer management.

In conclusion, the overall outcome for children and adolescents with osteosarcoma at the national reference cancer treatment centre is unacceptably low compared to developed countries. There is a need to bridge the quality gaps in the treatment pathway, including strengthening patient referral pathways for timely referrals, reducing the rates of prior manipulative therapy, reducing treatment abandonment, improving surgical and histopathological management, and improving the timeliness of adjuvant chemotherapy.

Abbreviations

HIC	High-income country
IQR	Interquartile range
LIC	Low-income countries
LMIC	Low- and middle-income country
OS	Overall survival
UCI	Uganda Cancer Institute
WHO	World Health Organization

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Author contributions
RN conceptualized and initiated the study, and contributed to the study design, data collection, and interpretation of results. FG, RA, and JBK supervised the study and reviewed the draft manuscript. JvH provided mentorship and critically revised the manuscript. All authors have read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All methods were carried out in accordance with relevant guidelines and regulations and the study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Uganda Cancer Institute Research and Ethics Committee (UCI-2022-44). Written informed consent and assent were accordingly waived by the research and ethics committee. Additionally, where a phone call was required to ascertain a child's status, verbal informed consent was obtained from the parents or guardians at the point of introduction during the call.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Belayneh R, Fourman MS, Bhogal S, Weiss KR. Update on Osteosarcoma. Curr Oncol Rep. 2021;23:71. https://doi.org/10.1007/s11912-11021-01053-11917.
2. Mascarenhas L, Siegel S, Spector L et al. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age including SEER incidence and survival: 1975–2000 National Cancer Institute. *NCI Report 2006*.
3. Hadley LG, Rouma BS, Saad-Eldin Y. Challenge of pediatric oncology in Africa. Semin Pediatr Surg. 2012;21:136–41.
4. Dodge OG. Tumours of bone and jaw. Recent Results Cancer Res. 1973;41:222–33.
5. Lisenda L, Linda ZA, Snyman FPJ, Kyte RD, Lukhele M. Osteosarcoma outcomes at a South African tertiary hospital. *SAMJ* 2017, 107(9):754–757. https://doi.org/10.7196/SAMJ.2017.v7107i7199.11424.
6. Kager L, Zoubek A, Po¨tschger U, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol. 2003;21(10):2011–8.
7. Jaffe N. Osteosarcoma: a review of the past, impact on the future. The American experience. Cancer Treat Res. 2009;152:239–62.
8. Bielack S, Kempf-Bielack B, Schwenzer D, Birkfellner T, Delling G, Ewerbeck V, et al. Neoadjuvant therapy for localized osteosarcoma of extremities. Results from the Cooperative osteosarcoma study group COSS of 925 patients. Klin Paediatr. 1999;211:260–70.
9. Slone JS, Chunda-Liyoka C, Perez M, et al. Pediatric malignancies, treatment outcomes and abandonment of pediatric cancer treatment in Zambia. PLoS ONE. 2014;9:e89102.
10. Mosaku KS, Akinyoola AL, Fatoye FO, Adegbehingbe OO. Psychological reactions to amputation in a sample of Nigerian amputees. Gen Hosp Psychiatry. 2009;31:20–4.
11. Sameer Rastogi A, Aggarwal A, Tiwari. Vinod Sharma: Chemotherapy in Non-metastatic Osteosarcoma: recent advances and implications for developing countries. J Global Oncol 2017: https://doi.org/10.1200/JGO.2016.007336
12. Bandyopadhyay R, Mukherjee A, Basu B. Role of Neo-adjuvant Chemotherapy in the Treatment of Osteosarcoma. Open J Orthop. 2012;2:25–9. https://doi.org/10.4236/ojo.2012.22005.
13. Imran H, Enders F, Krailo M et al. Effect of time to the resumption of chemotherapy after definitive surgery on prognosis for non-metastatic osteosarcoma. *J Bone Joint Surg Am* 2009, 91(3):604–612. https://doi.org/10.2106/JBJS.H.00449.
14. Jianping Hu C, Zhang K, Zhu L, Zhang T, Cai T, Zhan, et al. Treatment-related prognostic factors in managing Osteosarcoma around the knee with limb salvage surgery: a lesson from a long-term Follow-Up study. Hindawi BioMed Res Int. 2019. https://doi.org/10.1155/2019/3215824.
15. Matsubara E, Mori T, Koga T, Shibata H, Ikeda K, Shiraishi K, Suzuki M. Metastasectomy of Pulmonary Metastases from Osteosarcoma: Prognostic Factors and Indication for Repeat Metastasectomy. *Hindawi Journal of Respiratory Medicine* 2015:ID 570314, http://dx.doi.org/570310.571155/572015/570314.
16. Diemel KD, Klippe HJ, Branscheid D. Pulmonary metastasectomy for osteosarcoma: is it justified? Recent Results Cancer Res. 2009;179:183–208.
17. He F, Zhang W, Shen Y, Yu P, Bao Q, Wen J, Et. al.: Effects of resection margins on local recurrence of osteosarcoma in extremity and pelvis: Systematic review and meta-analysis. *International Journal of Surgery* 2016, 36:283–292. https://doi.org/10.1016/j.ijsu.2016.1011.1016.
18. Bertrand TE, Cruz A, Binitie O, Cheong D, Letson GD. Do Surgical Margins Affect Local Recurrence and Survival in Extremity, Nonmetastatic, High-grade Osteosarcoma? *Clin Orthop Relat Res* 2016, 474:677–683. https://doi.org/10.1007/s11999-11015-14359-x.
19. Bacci G, Longhi A, Ferrari S, Briccoli A, Donati D, De Paolis M, et al. Prognostic significance of serum lactate dehydrogenase in osteosarcoma of the extremity: experience at Rizzoli on 1421 patients treated over the last 30 years. Tumori. 2004;90:478–84.
20. Petrilli AS, de Camargo B, Filho VO, Bruniera P, Brunetto AL, Jesus-Garcia R, et al. Results of the Brazilian Osteosarcoma Treatment Group studies III and IV: prognostic factors and impact on Survival. J Clin Oncol. 2006;24(7):1161–8.

21. Stefan DC. Patterns of distribution of childhood cancer in Africa. J Trop Pediatr. 2015;61:165–73.
22. Bajpai J, Chandrasekharan A, Talreja V, Simha V, Chandrakanth MV, Rekhi B, et al. Outcomes in non-metastatic extremity osteosarcoma treatment-naive patients treated with a novel non-high-dose methotrexate-based, dose-dense combination chemotherapy regimen 'OGS-12'. Eur J Cancer. 2017;85:49e58.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Ass. 1958;53:457–81.
24. Buckle GC, Collins JP, Sumba PO, et al. Factors influencing time to diagnosis and initiation of treatment of endemic Burkitt Lymphoma among children in Uganda and western Kenya: a cross-sectional survey. Infect Agents Cancer. 2013;8(36). https://doi.org/10.1186/1750-9378-1188-1136.
25. Kamal AF, Pitarini A, Prabowo Y. Megaprosthesis limb salvage surgery: outcome and challenges in treating advanced bone tumour cases in vast archipelago in Indonesia. A case series. Int J Surg Open. 2018;11:30–6. https://doi.org/10.1016/j.ijso.2018.1004.1004.
26. Miwa S, Kamei M, Yoshida S, Yamada S, Aiba H, Tsuchiya H et al. Local dissemination of osteosarcoma observed after massage therapy: A case report. *BMC Cancer* 2019, 19(1):993. https://doi.org/10.1186/s12885-12019-16246-12884.
27. Wu PK, Chen WM, Lee OK, Chen CF, Huang CK, Chen TH. The prognosis for patients with osteosarcoma who have received prior manipulative therapy. *J Bone Jt Surg Br* 2010, 92(11):1580–1585. https://doi.org/10.1302/0301-1620X.1592B1511.24706.
28. Wang J-Y, Wu P-K, Chen PC-H, Yen C-C, Hung G-Y et al. Manipulation Therapy Prior to Diagnosis Induced Primary Osteosarcoma Metastasis—From Clinical to Basic Research. *PLoS ONE* 2014, 9(5):e96571. https://doi.org/10.91371/journal.pone.0096571.
29. Wayan Arya Mahendra Karda, Ismail WFW. Achmad Fauzi Kamal: Massage manipulation and progression of osteosarcoma, does it really correlate: a combination of prospective and retrospective cohort study. *Scientific Reports* 2023, 13:18541. https://doi.org/10.11038/s41598-18023-45808-18547.
30. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol. 2002;20(3):776–90.
31. Bacci G, Briccoli A, Longhi A, Ferrari S, Mercuri M, Faggioli F, Picci P. Treatment and outcome of recurrent osteosarcoma: experience at Rizzoli in 235 patients initially treated with neoadjuvant chemotherapy. Acta Oncol. 2005;44(7):748–55.
32. Bacci G, Rocca M, Salone M, et al. High-grade osteosarcoma of the extremities with lung metastases at presentation: treatment with neoadjuvant chemotherapy and simultaneous resection of primary and metastatic lesions. J Surg Oncol. 2008;98:415–20.
33. Yang Y, Han L, He Z, Li X, Yang S, Yang J, et al. Advances in limb salvage treatment of osteosarcoma. J Bone Oncol. 2018;10:36–40. https://doi.org/10.1016/j.jbo.2017.1011.1005.
34. Bacci G, MercuriM, Longhi A, Ferrari S, Bertoni F, Versari M, et al. Grade of chemotherapy-induced necrosis as a predictor of local and systemic control in 881 patients with non-metastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy in a single institution. Eur J Cancer. 2005;41:2079–85.
35. Bacci G, Bertoni F, Longhi A, Ferrari S, Forni C, Biagini R et al. Neoadjuvant chemotherapy for high-grade central osteosarcoma of the extremity. Histologic response to preoperative chemotherapy correlates with the histologic subtype of the tumour. *Cancer* 2003, 97:3068–3075. https://doi.org/10.1002/cncr.11456.
36. Bacci G, Longhi A, Versari M, Mercuri M, Briccoli A, Picci P. Prognostic factors for osteosarcoma of the extremity treated with neoadjuvant chemotherapy: 15-year experience in 789 patients treated at a single institution. Cancer. 2006;106:1154–61.
37. Li X, Ashana AO, Moretti VM, Lackman RD. The relation of tumour necrosis and survival in patients with osteosarcoma. *Int Orthop* 2011, 35(12):1847–1853. https://doi.org/10.1007/s00264-00011-01209-00267.
38. Li X, Moretti VM, Ashana AO, Lackman RD. Impact of close surgical margin on local recurrence and survival in osteosarcoma. *Int Orthop* 2012, 36(1):131–137. https://doi.org/10.1007/s00264-00011-01230-x.
39. Atwiine B, Busingye I, Kyarisiima R, Baluku E, Mbabazi R, Bamwine B et al. Money was the problem: Caregivers' self-reported reasons for abandoning their children's cancer treatment in southwest Uganda. *Pediatric Blood & Cancer* 2021, 68(11):e29311. https://doi.org/10.21002/pbc.29311.
40. Chalinee Monsereenusorn AP, Alcasabas AH, Pheng KWP, Leung C, Dhamne et al. Predictors and Treatment Outcomes of Pediatric Osteosarcoma in Diverse Socioeconomic Backgrounds in Southeast Asia: A Retrospective Multicenter Study. *Asian Pac J Cancer Prev* 2022, 23(2):631–640. https://doi.org/10.31557/APJCP.32022.31523.31552.31631.
41. Mirutse MK, Tolla MT, Memirie ST, Palm MT, Hailu D, Abdi KA et al. The magnitude and perceived reasons for childhood cancer treatment abandonment in Ethiopia: from health care providers' perspective. *BMC Health Services Research* 2022, 22:1014. https://doi.org/10.1186/s12913-12022-08188-12918.
42. Vasquez L, Diaz R, Chavez S et al. Factors associated with the abandonment of therapy by children diagnosed with solid tumors in Peru. *Pediatr Blood Cancer* 2018, 65:e27007. https://doi.org/10.21002/pbc.27007.
43. Gaston CL, Taleon K, Bersales K, Dimayuga C, Estanislao J, Fajardo P et al. The Effect of a Patient Navigator on Treatment Abandonment and Follow-up for High Grade Osteosarcoma Patients in the Philippine General Hospital. *Asian Pac J Cancer Prev* 2021, 22(9):2873–2877. https://doi.org/10.31557/APJCP.32021.31522.31559.32873.
44. Bacci G, Picci P, Avella M, Dallari D, Ferrari S, Prasad R et al. The importance of dose-intensity in neoadjuvant chemotherapy of osteosarcoma: a retrospective analysis of high-dose methotrexate, cisplatinum and Adriamycin used preoperatively. *J Chemother* 1990, 2(2):127–135. doi: 110.1080/1120009x.1121990.11738996.

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