



Determinants of Delayed Presentation of Patients with Primary Malignant Musculoskeletal Tumours Managed in a Tertiary Referral Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. Author AN designed the study, wrote the protocol, performed the statistical analysis and wrote the first draft of the manuscript. Authors MG, SP and WG reviewed the study protocol and managed the analyses of the study. Author ADBB managed the literature searches and reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Malignant musculoskeletal tumours are comparatively rare tumours and delays in diagnosis and treatment are common. Understanding the factors that influence delay is important so as to improve the outcomes for cancer patients.

Aim: To describe factors associated with delay in presentation of patients with primary musculoskeletal tumours.

Study Design: Descriptive cross-sectional study.

Setting: The study was conducted in a tertiary referral hospital from July to December 2014.

Methodology: 56 patients with a confirmed histopathological diagnosis of a primary malignant musculoskeletal tumour and who had consented to the study were included.

Data was collected using a pre-tested questionnaire. The clinical findings, laboratory results and radiographs of the lesions and the chest, as well as histopathological results were used to stage the musculoskeletal tumour.

Data was analyzed using SPSS software version 20.0. Univariate and bivariate analysis was done for associations and results presented in the form of tables, pie charts and bar graphs.

Results: A total of 56 patients were studied, 34 (60.7%) males and 22 (39.3%) females with a male to female ratio of 1.5:1. 73.2% (41) of the patients were adults while children comprised 26.8% (15). The age range was 4yrs-78yrs, with a mean of 32.25yrs.

The mean patient delay was four months with 50% (28) of the patients seeking care for the first time after three months.

Males were twice as likely to present late compared to females (OR 2.5, $P=0.10$) while patients younger than 40 years were more likely to present late (OR 1.4, $P=0.59$). Low educational level (OR 3.7, $P=0.15$) and low family income (OR 2.3, $P=0.38$) were associated with delayed presentation.

Conclusion: Delayed presentation of patients with MS tumours is influenced by a multitude of factors ranging from the socio-demographics (age, sex, education level), socio-economic status and tumour knowledge, beliefs and perception.

Keywords: *Delayed presentation; delayed diagnosis; musculoskeletal tumours; osteosarcoma; multiple myeloma.*

1. INTRODUCTION

The management of bone and soft tissue tumors remains a major challenge to Orthopaedic surgeons and other health professionals all over the world. The challenge is heightened in developing countries due to limited diagnostic and therapeutic facilities, delayed presentation which may be as a result of ignorance in the community; caused mainly by underlying cultural and religious beliefs [1–3].

Failure to recognize symptoms which signal cancer may delay contact or presentation of the patient to the health facility, thus decreasing the chances of diagnosis at an early stage of disease. There is evidence that delayed presentation of symptomatic cancer is associated with poor survival [4,5].

In a study conducted in the United States, patient delay was defined as waiting more than 3 months following symptom onset. Patient delay was considered as the time that passes between first symptoms and first consultation of a physician [5].

Understanding the factors that influence delay is important so as to improve the outcomes for cancer patients. In developing countries, these factors appear to be largely due to paucity of appropriate health care, poor information, cultural beliefs and fears about cancer [6].

Early recognition of cancer symptoms and prompt treatment are generally associated with increased survival [7]. Even when symptoms are recognized as potentially serious, many people delay seeking medical care. Earlier studies aimed at identifying factors leading to delay in health seeking focused on psychosocial factors such as fear and anxiety [8,9].

In Uganda, a study conducted in 1964 showed the prevalence of musculoskeletal (MS) tumours to be 1% [8]. There is no current literature documenting the prevalence of these tumours and data from cancer registry is lacking.

This study aimed to describe the clinical stage at presentation and factors associated with the delayed presentation of patients seen with primary malignant musculoskeletal tumours.

2. METHODS

This was a hospital based descriptive cross-sectional study that included a sample size of 56 patients. The sample size was calculated using the modified Kish-Leslie formula basing on previous study done in Tanzania [6]. The inclusion criteria was any patient managed at the study site, with a confirmed histopathological diagnosis of a primary malignant musculoskeletal

(MS) tumour who consented to participate in the study.

Patients with secondary or metastatic tumours of the MS system were excluded because of the possibility of having various confounding factors that may affect their presentation to the health facility. As an institutional protocol, patients had their histopathological diagnosis confirmed by another independent and accredited laboratory to avoid bias.

A study-generated pre-corded questionnaire was administered to the patients. Data of the sociodemographic, clinical status, time to seek care, practices and beliefs, as well as knowledge and perception of MS tumours was collected.

A detailed history of the patient was obtained and a thorough general and systemic physical examination conducted. Based on the tumour type, other accompanying baseline investigations included; complete blood counts (CBC), liver and renal function tests, serum alkaline phosphatase, serum calcium, plasma protein electrophoresis with specific measurements of serum albumin and β 2-microglobulin.

Categorical data was expressed as percentages, means and ranges and presented in the form of tables, pie charts and bar graphs. Univariate and bivariate analysis was done to realize the associations.

Plain radiographs of the lesion as well as chest x-rays to detect metastases were done. These x-rays were reviewed and interpreted by the author and a qualified and practicing radiologist. The data obtained; in addition to the clinical findings was used to stage the patient. The use of chest x-rays to detect metastases was based on a study done in the United Kingdom in which the investigators detected two-thirds of all metastasis using this imaging modality, with a specificity of 60.8% and specificity of 99.6% [10]. This study had limitation in use of computed tomography (CT) scan to aide in staging of the patients, due to financial barriers.

A diagnosis of multiple myeloma was made based on the presence of clonal bone marrow plasma cells $\geq 10\%$, presence of serum monoclonal protein myeloma and evidence of end-organ damage that was attributed to the underlying proliferative disorder, specifically

hypercalcaemia, renal failure, anaemia and bone lesions. These patients were then staged based on the laboratory results of serum albumin and serum β 2-microglobulin in accordance with the International Staging System (ISS) for multiple myeloma [11].

The Enneking staging system was used for solid tumours [12]. Tumour histology was recorded and classified according to the WHO classification of bone and soft tissue tumours [13].

Delayed presentation in this study referred to a patient presenting for the first time with a primary tumour three (3) months or more from symptom onset. This time interval was based on previous documented literature published by Pack and Gallo (USA, 1938) who first described and classified the different stages of delay [5].

3. RESULTS

A total of fifty-six (56) participants were recruited over a period of 6 months.

The age range was 4-78 yrs, with a mean age of 32.25 (± 2.7). The male to female ratio was 1.5:1; with 41.1% (23) of patients below 21 years of age.

Majority of the patients had achieved at least a primary level of education, 44.6% (25) while 12.5% (7) had no formal education.

67.9% (38) of the patients were rural dwellers as compared to 32.1% (18) urban dwellers.

Osteosarcoma, 17 (30.4%) and multiple myeloma, 21 (37.5%) were the commonest tumours seen in this study (Fig. 1).

The solid tumours commonly presented in stage IIB, 17 (48.6%) and stage III, 16 (45.7%) (Fig. 2), whereas all patients with multiple myeloma presented with advanced disease (Fig. 3).

50% (28) of the patients had a delay of more than three (3) months prior to their initial consultation as seen in Table 2.

64.3% (36) reported to have first sought help from a government hospital (Fig. 4).

Table 1. Showing sociodemographic characteristics of the patients seen

Mean age	32.25 (CI=26.9-37.6)	Std. Err 2.7				
Age range	4-78yrs					
	Freq.	Percent	Early (n=28)	Delayed (n=28)	UOR(95%CI)	p-value
Age group						
1-20.	23	41.1	12(52.2)	11(47.8)	1	
21-40	14	25	6(42.9)	8(57.1)	1.4(0.4-5.7)	0.5875
41-60	11	19.6	5(45.4)	6(54.6)	1.3(0.3-5.7)	0.7180
61-80	8	14.3	5(62.5)	3(37.5)	0.6(0.1-3.5)	0.6190
Religion						
R/Catholic	19	33.93	8(42.1)	11(57.9)	1	
Muslim	5	8.93	4(80.0)	1(20.0)	0.2(0.0-2.3)	0.1399
Pentecostal	8	14.29	3(37.5)	5(62.5)	1.2(0.2-6.8)	0.8273
Protestant	24	42.86	13(54.2)	11(45.8)	0.6(0.2-2.1)	0.4374
Marital status						
Divorced	1	1.79	1(100.0)	0(0.0)		
Married	25	44.64	10(40.0)	15(60.0)		0.2429
Not applicable	15	26.79	11(73.3)	4(26.7)		0.5637
Single	13	23.21	6(46.2)	7(53.8)		0.3173
Widow/widower	2	3.57	0(0.0)	2(100.0)		0.1573
	Freq.	Percent	Early (n=28)	Delayed (n=28)	UOR(95%CI)	p-value
Gender						
Female	22	39.29	14(63.6)	8(36.4)	1	
Male	34	60.71	14(41.2)	20(58.8)	2.5(0.8-7.8)	0.1037
Education level						
No formal education	7	12.5	5(71.4)	2(28.6)	1	
Primary	25	44.64	10(40.0)	15(60.0)	3.7(0.5-25.6)	0.1472
Secondary	15	26.79	8(53.3)	7(46.7)	2.2(0.3-16.2)	0.4321
Tertiary	9	16.07	5(55.6)	4(44.4)	2.0(0.2-18.1)	0.5287
Residence						
Rural	38	67.86	17(44.7)	21(55.3)	1	
Urban	18	32.14	11(61.1)	7(38.9)	0.5(0.2-1.6)	0.2567
Region						
Central	19	33.93	10(52.6)	9(47.4)	1	
Eastern	16	28.57	8(50.0)	8(50.0)	1.1(0.3-4.3)	0.8784
Northern	8	5.36	4(50.0)	4(50.0)	1.1(0.2-6.0)	0.9024
Western	13	19.64	6(46.2)	7(53.8)	1.3(0.3-5.5)	0.7231
Employment status						
Employed	19	33.93	9(47.4)	10(52.6)	1	
School-going	22	39.29	14(63.6)	8(36.4)	0.5(0.1-1.8)	0.3012
Un-employed	15	26.79	5(33.3)	10(66.7)	1.8(0.4-7.6)	0.4160
Monthly family income						
>500,000Ushs	30	53.57	16(53.3)	14(46.7)	1	
100-500,000Ushs	20	35.71	10(50.0)	10(50.0)	1.2(0.4-3.6)	0.8190
50-100,000Ushs	6	10.71	2(33.3)	4(66.7)	2.3(0.3-15.1)	0.3778

* CI= Confidence Interval, UOR=Unadjusted odds ratio, Std. Err= Standard error, n= total number of patients

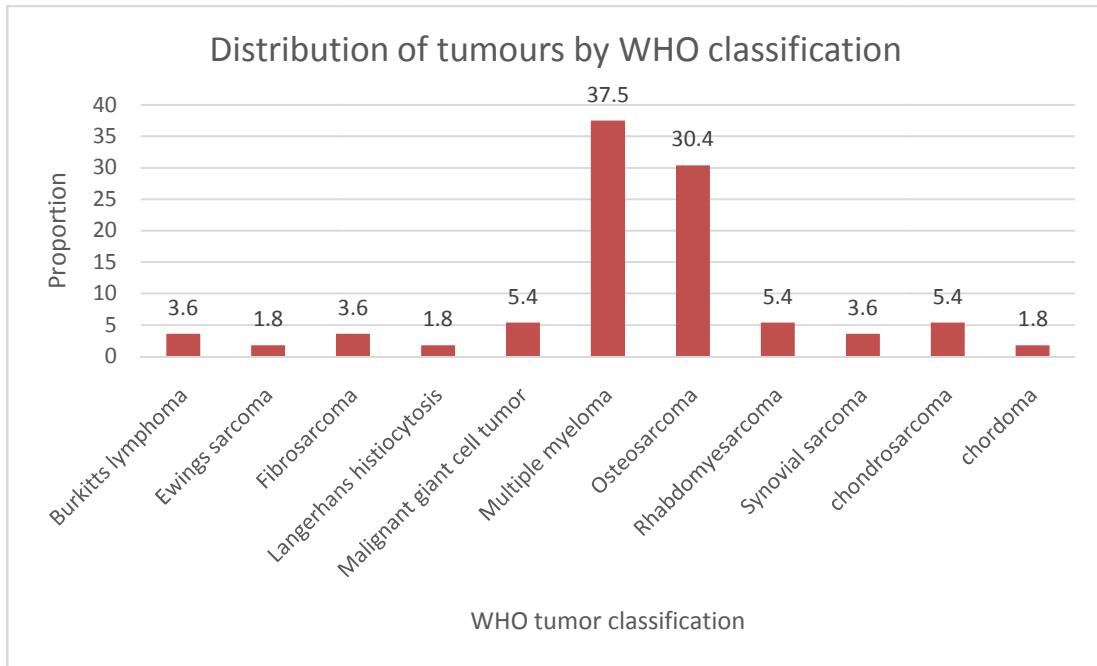


Fig. 1. Distribution of tumours by WHO classification

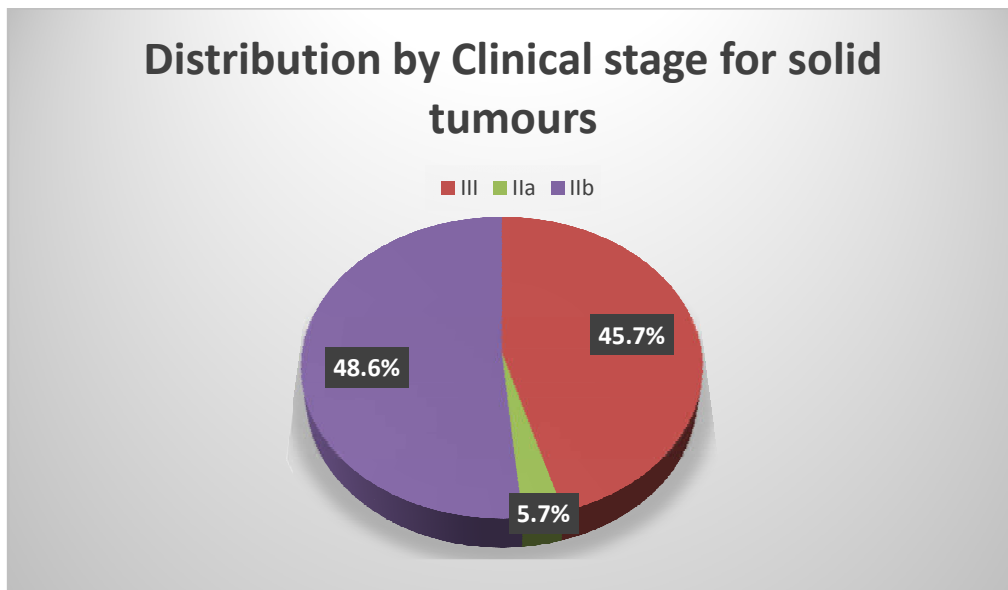


Fig. 2. Clinical stage at presentation of patients with solid tumours

Table 2. Showing the duration of symptoms

Before first consultation (patient delay)	Frequency (n=56)	Percentage (%)
Days (<7)	2	3.6
1-4 weeks	9	16.1
>4-12 weeks	17	30.4
>12 weeks	28	50.0
From first consultation to diagnosis		
>4-12 weeks	5	8.9
>12 weeks	51	91.1

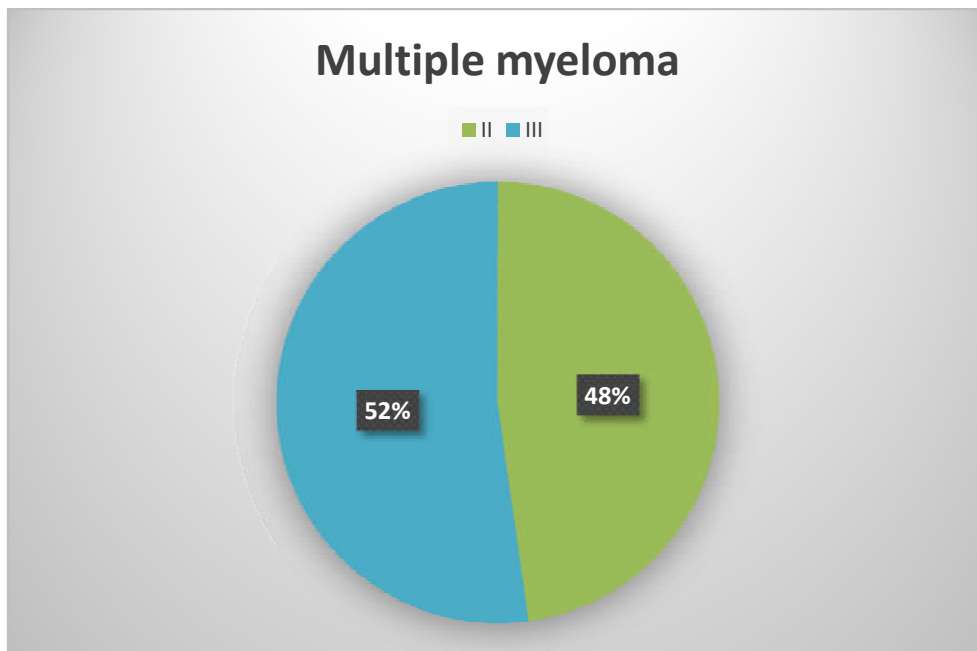


Fig. 3. Clinical stage at presentation of patients with multiple myeloma

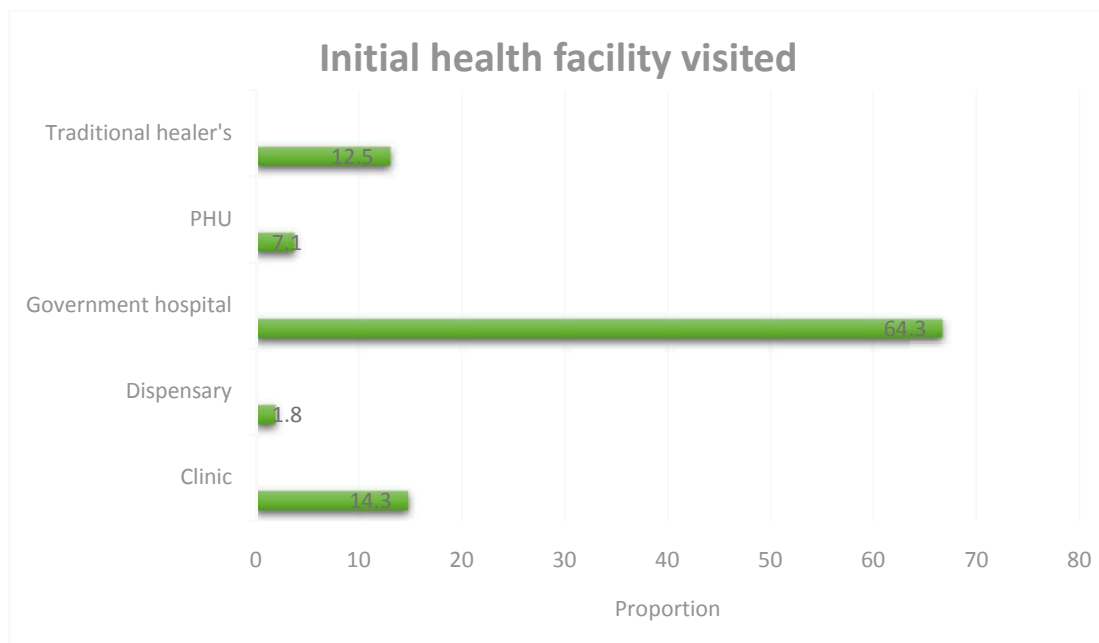


Fig. 4. Health facility visited at symptom onset
 *(PHU= Private Health Unit)

More than 90% (51) of the patients had not heard of bone tumours and 78.6% (44) reported no knowledge of causation (Table 3)

4. DISCUSSION

The delay in presentation is multifactorial and these subsequently have a bearing on the clinical stage at presentation. The clinical presentation of

patients with MS tumours is similar despite the variation in bone and soft tissue types.

There was a limitation to clinical staging of the tumours and detection of chest metastases which was done based on plain radiography; due to the financial constraints of obtaining computed tomographic and magnetic resonance images.

Table 3. Showing MS tumour knowledge and perception

	Frequency	Percentage
Heard about bone tumours		
Yes	5	8.9
No	51	91.1
Association of symptoms		
Other disease (than cancer)	28	50
Fracture due to trauma	11	22.9
Minor pain	9	18.8
Witchcraft	5	10.4
Abscess	3	6.3
Cited causes of bone tumours		
"I don't know"	44	78.6
Cigarette smoking	2	3.6
Genetics	2	3.6
Witchcraft	5	8.9
Alcohol consumption	1	1.8
Infections	1	1.8
Trauma	1	1.8
Perception of bone tumour as very serious disease	56	100

Table 4. Showing health facility factors and tumour knowledge

	Freq.	Percent	Early (n=28)	Delayed (n=28)	UOR(95%CI)	p-value
Distance to nearest h/f						
1-5km	42	75	19(45.2)	23(54.8)	1	
6-50km	14	25	10(71.4)	4(28.6)	0.4(0.1-1.4)	0.134
Decision to come to Mulago						
Referred	34	60.71	15(44.1)	19(55.9)	1	
Self-referral	22	39.29	13(59.1)	9(40.9)	0.5(0.2-1.7)	0.2781
Health facility visited first						
clinic	8	14.29	5(52.5)	3(37.5)	1	
dispensary	1	1.79	1(100.0)	0(0.0)		
Hospital	36	64.29	18(50.0)	18(50.0)	1.7(0.3-8.2)	0.5268
PHU	4	7.1	4(100.0)	0(0.0)		
Traditional healer	7	12.5	2(28.6)	5(71.4)	4.2(0.4-45.7)	0.2043
H/w seen first						
medical officer	39	69.64	21(53.9)	18(46.1)	1	
not sure	4	7.14	2(50.0)	2(50.0)	1.2(0.1-20.7)	0.9163
nurse	4	7.14	4(100.0)	0(0.0)		
specialist	2	3.6	0(0.0)	2(100.0)		
Traditional healer	7	12.5	2(28.6)	5(71.4)	2.9(0.5-17.7)	0.2232
Heard about tumours						
No	51	91.1	25(49.0)	26(51.0)	1	
Yes	5	8.9	2(49.0)	3(51.0)	1.0(0.1-7.5)	0.9701

* CI= Confidence Interval, UOR=Unadjusted odds ratio, Std. Err= Standard error, n= number of patients

This study looked at 56 participants, 60.7% (34) males and 39.3% (22) females of an age range between 4-78 years, all seen at a Tertiary Referral hospital.

4.1 Factors Associated with Delayed Presentation and Diagnosis

This study showed that majority of patients with MS tumours seek medical care with advanced stages of disease. In the case of solid tumours, a total of 35 patients were seen; with 45.7% and 48.6% seen in clinical stage III and IIB respectively. Two (5.7%) patients had stage IIA disease. These findings are in accordance with other studies done in Tanzania, Nigeria. This observation could partly be due to the gaps in the referral system that leads to patient delay, the long distance travelled by rural dwellers to get to the study site which in its right has cost implications and thus will keep most patients away. It could also be a reflection of the knowledge gap of both patient and health professional in identifying early signs of MS malignancy [1,6,14].

Patients with multiple myeloma constituted the majority of the older age group (40-78 years), a feature well documented in literature. In this group, all 21 patients were seen late with stage II (47.6%) and stage III (52.4%) disease. Other studies have documented comparable findings in Pakistan, Nigeria and Cameroon. Pain was the most commonly reported symptom (85.7%) while anaemia was detected in all 21 (100%) patients with multiple myeloma [15-17].

The mean patient delay in this study was found to be four (4) months with 50% of the patients seeking care for the first time after three (3) months of symptom onset. Only two (2) patients were seen within a week of symptom onset. These findings concur with other studies showing similar patient delay intervals [3,5,6,18]. This delay may be attributed to an interaction of several sociodemographic factors. However, a similar study conducted in Nigeria showed a mean patient delay of 56.4 weeks (14 months), which was attributed to the first person to attend to the patient [19].

41.1% (23) of the patients who presented late were below 20 years of age which is comparable to what was reported in several studies [2,18,20-21]. This could be as a result of delayed symptom recognition by the first clinician who in most developing countries, is not a specialist and

may have limited knowledge of signs and symptoms of early cancer. Also, symptoms in the younger age groups tend to be mistaken for common ailments like soft tissue or bone infections, or fractures due to trauma since they apparently appear young and healthy. Finances could also be a limiting factor since children under 20 years mostly do not earn any income in our environment and therefore reliant on their parents to seek health care which is usually challenging due to the level of poverty in our sub-region.

The male to female ratio of 1.5:1 was seen for each of the clinical stages and more so in the adult groups. This finding is similar to other studies in which males were the majority and seen late, more often than females [2,21,22]. This could be attributed to the fact that most MS tumours occur with increased frequency in the males than females probably due to biological reasons. In addition, in most African cultures the males are considered a stronger gender and as such they avoid seeking healthcare early. It has also been shown in other health-seeking behavior studies, that men actually have poor health-seeking habits as compared to females [6,23-25]. This is however at variance with what was observed by Schnurr et al in their study in which females actually presented late than males attributing it to females competing priorities with work, family and other unspecific physiological body changes [26].

Educational level appears to play a role in delay in presentation of patients with MS tumours. This is in accordance with other studies showing that the more educated are more likely to seek professional care and hence present earlier than the less educated [24,27,28]. The level of education may have an implied correlation with the level of knowledge and awareness of disease or symptoms. Also it suffices to say that in our sub-region, the more educated are likely to be more financially empowered to seek care early compared to less educated. There were twice as many rural dwellers (38, 67%, OR: 1, $P=0.26$) presenting with advanced disease as compared to the urban dwellers (18, 33%). This concurs with other studies that showed that urban dwellers were more likely to seek professional care earlier compared to rural dwellers due to easy accessibility and higher economic status of urban dwellers [29-32].

About 75% of the patients in this study lived within 5 km of the nearest government health

facility, which is a standard recommendation by the World Health Organization (WHO). Nonetheless, less than a third actually utilized these services at the onset of their symptoms. Delayed presentation was seen with increasing distance to the health facility (OR: 0.4, $P=0.13$). In Uganda, patients' utilization of government health services may be attributed to their perception of the quality of care at the facility, availability of diagnostic equipment and drugs as well as presence of cost-sharing opportunities [30,31].

Most patients had poor knowledge of MS tumours, with 91.1% having reported no prior knowledge. However, the odds of presenting late for a patient with no prior knowledge was similar to that of one who had some knowledge of bone tumours (OR: 1, CI 0.1-7.5, $P=0.97$). Generally, tumour knowledge and perception has been shown to affect the health seeking behavior of patients. Studies in Tanzania, Nigeria and other countries found that inadequate information pertaining to the symptoms and signs of MS tumours, as well as association of symptoms to other causes or diseases lead to delay in seeking specialized hospital care [4,6,7,23,33]. This similarity with our findings is probably due to similar cultural beliefs and practices in African sub region regarding the occurrence of "rare" diseases and association to supernatural powers, as well as seeking care from traditional bone setters [34].

5. CONCLUSION

Over 50% of patients with primary malignant musculoskeletal tumours in the study setting present late with majority presenting with advance stage of disease. This appears to be influenced by a multitude of factors ranging from the socio-demographics (age, sex, education level), socio-economic status (low family income) and tumour knowledge, beliefs and perception. A lot needs to be done in educating the population about cancer to increase awareness, knowledge and the need to report early for better outcomes in cancer treatment.

We recommend for further multi-center studies focusing on larger numbers of patients over a longer period of time that will be representative of the population in terms of tumour types, clinical presentation, clinical staging as well as diagnostic delays.

DISCLAIMER

The content of this article is the sole work of the authors and is a publication from a thesis work for the award MMED Orthopaedics. No benefits were received from a commercial party related directly or indirectly to the subject of this article.

CONSENT

A written informed consent was obtained from each patient or from the next of kin in the case of minors.

ETHICAL APPROVAL

This was obtained from the Institutional Review Board (IRB), Makerere University College of Health Sciences and the School of Medicine Research and Ethics Committee (SOMREC).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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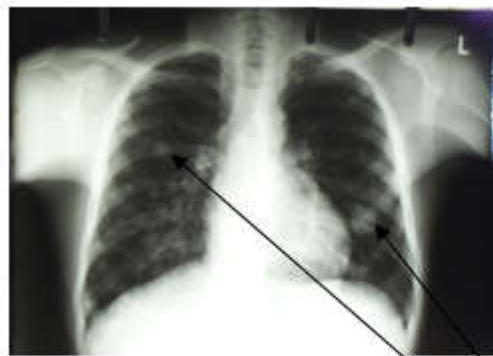
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APPENDIX 1: OSTEOSARCOMA



Clinical appearance of tumour

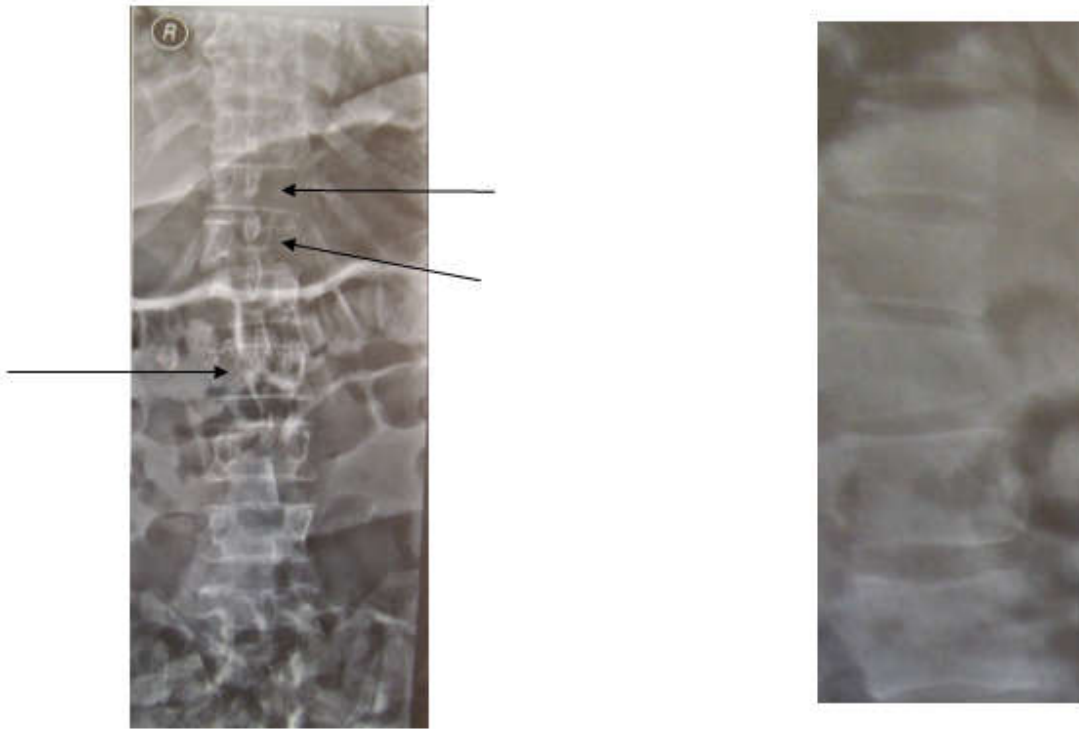


Metastases seen as 'Canon balls'

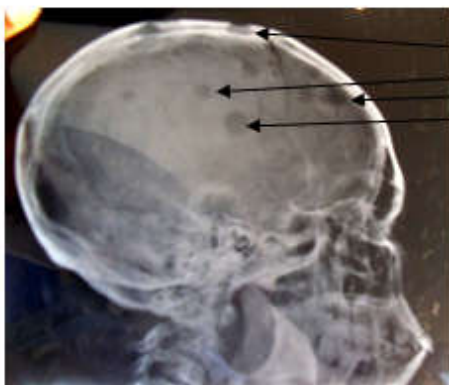


The figures above are of the left femur of a 16 year old male showing one of the common clinical presentations of osteosarcoma particularly in late stage disease. Lateral and anteroposterior views of the left femur showing lytic destruction with blastic areas, periosteal reaction giving the characteristic sun burst appearance, with preservation of the knee joint. Also note the pathological fracture.

APPENDIX 2: MULTIPLE MYELOMA



Radiographs demonstrating vertebral body destruction seen in multiple myeloma involving the spine, which is the commonly seen presentation. Marked osteopenia with lytic destruction involving the pedicles as shown by the arrows. Below is the classic punched out lesions seen in a skull radiograph.



Characteristic 'punched-out' lesions of the skull

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