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# Late Presentation, Advanced Disease and Severe Acute Malnutrition are Common Among Children with Cancer in Tanzania

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**Abstract**

***Background***

Majority of children with cancer live in low and middle-income countries (LMIC) where survival is disproportionately low compared to high-income countries (HIC). Among the challenges of managing childhood cancers in LMIC is late presentation, advanced disease, and the prevalence of severe malnutrition. Advanced disease and severe acute malnutrition are associated with poor treatment outcomes.

***Methodology***

This was a descriptive study conducted in Tanzania at Ocean Road Cancer Institute (ORCI) in 2010. Children and adolescents below 18 years were longitudinally enrolled in the study. Pathological diagnosis was made by examination of tissue biopsies, fine needle aspiration (FNAC) or bone marrow aspiration cytology (BMAC). Stage of disease at presentation was determined by physical examination and radiological investigations such as chest x-ray and ultrasonography. World Health Organization (WHO) anthropometric measurement chart was used to interpret measured Mid-upper arm circumference (MUAC) for age. Body mass index (BMI) is affected by tumour weight hence was not used to assess malnutrition in this study.

***Results***

One hundred and fifty-one (151) patients were enrolled in the study. The mean age at presentation was 5.8 years (range 3-17years), and 51.7% of participants were males. Three quarters (76.6%) of patients attended the first health facility within a month of onset of symptoms, but forty per cent (40%) of patients took six (6) months to reach ORCI for treatment. Eighty-six percent (86%) of patients presented with advanced disease (50.8% - locally advanced, 35.1% - metastatic disease). Metastatic disease was more frequent in patients with Neuroblastoma (NB) and Non Hodgikins Lymphoma (NHL) (66.6% each), Burkitt's lymphoma (BL) (50%), Soft tissue sarcoma (STS) (40%) and Wilm's tumour (WT) (35.3%). Severe wasting was seen in 12.6% of patients, and more prevalent among patients with BL (31.3%) and WT (25%).

***Conclusion***

Even though most patients sought health care early, they reached ORCI late with advanced disease (86%), and 12.6% had severe acute malnutrition.

***Keywords:*** *Children, Cancer, Advanced Disease, Malnutrition.*

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**Background**

Majority of the world children and children with cancer live in low- and middle-income countries (LMIC) (1, 2). These countries are dealing with the double burden of disease with non-communicable diseases (NCD) increasing despite the already high prevalence of infectious diseases such as HIV, malaria, pneumonia and diarrheal diseases (3). LMIC have limited resources to address NCD (4). Survival of children with cancer in LMIC is disproportionately very low, mainly below 50%, compared to above 80% in high-income countries (HIC) (5-8). Among the challenges of managing childhood cancers in LMIC is late presentation, advanced disease and high prevalence of severe acute malnutrition (9-11). Severe acute malnutrition is associated with increased treatment toxicities and poor treatment outcomes (13, 14). A study in Malawi showed that 59% of the children with cancer had severe acute malnutrition at admission by arm anthropometry (MUAC below 5Th percentile) and 44% were stunted (HFA < -2SD) (12).

**Methods**

This descriptive study was conducted at Ocean Road Cancer Institute (ORCI) in 2010 when ORCI was the only cancer hospital in Tanzania. Children and adolescents below 18 years attending ORCI with a malignancy diagnosis were longitudinally enrolled in the study. Morphological examination of tissue biopsies, fine needle aspiration (FNAC) or bone marrow aspiration cytology (BMAC) confirmed the diagnosis. Stage of disease at presentation was determined by physical examination and by radiological investigations such as chest x-ray and ultrasonography depending on the type and location of the tumour. Computerized tomography (CT) scans were not routinely done.

A digital weighing scale stationed in the ward was used to measure weight to the nearest 0.1kg. Mid-upper arm circumference (MUAC) was measured using special non-stretchable MUAC tapes to the nearest 0.1cm. World Health Organization (WHO) anthropometric measurement chart was used to interpret MUAC for age. Children and adolescents with MUAC below the fifth percentile for age were considered to have severe acute malnutrition. We did not use weight for height (WFH) to determine nutritional status because this can be misleading in children with large tumours, particularly intra-abdominal tumours (15, 16).

Data were collected for eight (8) months using a structured questionnaire, and analysis was done using Epi Info and SPSS 16.0 statistical programs.

MUHAS Senate Research and Publication Committee issued ethical clearance, and ORCI provided permission to conduct this study.

**Results**

Mean age at presentation was 5.8years. Almost half (46.4%) of the patients were 4 – 10 years old. Three quarters of the parents/guardians (76.4%) had attained either primary education or had no formal education. Severe acute malnutrition was seen in 12.6% of the participants (Table 1).

**Table 1: Demographic characteristics and Nutritional status of the study participants**

| Variables | Number | Percentage (%) |
|---|---|---|
| **Sex** | | |
| Male | 78 | 51.7 |
| Female | 73 | 48.3 |
| **Age group (Years)** | | |
| ≤ 3 | 55 | 36.4 |
| 4-10 | 70 | 46.4 |
| >10 | 26 | 17.2 |
| **Nutritional status (n=143)** | | |
| Normal* | 93 | 65 |
| Moderate wasting | 32 | 22.4 |
| Severe wasting | 18 | 12.6 |
| **Parent/Guardian level of education** | | |
| No formal | 23 | 15 |
| Primary | 92 | 61.4 |
| Secondary | 27 | 18.1 |
| Diploma and Degree | 9 | 5.5 |

**Normal includes mild wasting*

***Time from onset of symptoms to presenting to a health facility***

Seventy-six percent (76.6%) of patients attended the first health facility within a month of onset of symptoms, and about 30% reported during the first week of symptoms. The mean duration for seeking medical attention in the primary health facility was 1.5 months. The median duration of symptoms until patients reached ORCI was seven (7) months (range 1week-6 years). Forty per cent (40%) of patients presented at ORCI six (6) months after the onset of symptoms. Patients from Dar es Salaam had a relatively shorter duration of symptoms (mean four (4) months) when they reached ORCI (Table 2).

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**Table 2. Time from onset of symptoms to reporting at a health facility**

| Duration of symptoms (months) | First Health facility (n=145) (%) | ORCI (n=146) (%) |
|---|---|---|
| ≤ 1 | 111 (76.6) | 23 (15.8) |
| 2 - 6 | 29 (20) | 79 (54.1) |
| >6 | 5 (3.4) | 44 (30.1) |

***Stage of disease at presentation***

It was impossible to determine the disease stage at presentation for patients who needed surgical staging unless they had evident metastatic disease. For example, WT patients with lung metastasis were picked up by a chest X-ray. Due to lack of histology reports for some patients or incomplete reports (for example not reporting if the optic nerve's cut end is free of tumour cells or not in RB), it was impossible to assign stage for some patients accurately. To overcome this, all solid tumours were classified as either; early local disease, advanced local disease or metastatic disease. The early local disease was defined as primary tumour of less than or equal to 10cm in diameter. In contrast, the advanced local disease was defined as primary tumour larger than 10cm or local lymph nodes' involvement but without distant metastasis. The disease was considered metastatic when there was distance metastasis such as the lungs, liver, bone marrow or CNS.

Eighty-six per cent (86%) of patients presented with advanced disease, either locally advanced disease (50.8%) or metastatic disease (35.1%). Metastatic disease was more frequent in patients with NB and NHL (66.6% each), BL (50%), STS (40%) and WT (35.3%) (Table 3).

***The magnitude of severe acute malnutrition***

Results of nutritional status in relation to the type of malignancy are summarized in table 4. One hundred and forty-three patients (143), 95% of all participants, were evaluated for nutritional status. Patients with MUAC for age within median or showed mild wasting were classified together as “Normal”. Almost thirteen per cent (12.6%) of patients had severe wasting. There was variation in the magnitude of wasting by type of malignancy, and the difference was statistically significant (P=0.014).

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**Table 3: Stage of disease at presentation**

| Stage of Disease | | | | |
|---|---|---|---|---|
| **Diagnosis** | **Early local (%)** | **Advanced local (%)** | **Metastatic (%)** | **Total (%)** |
| Retinoblastoma | 12 (27.3) | 20 (45.4) | 12 (27.3) | 44 (100) |
| Wilms tumour | 1 (5.9) | 10 (58.8) | 6 (35.3) | 17 (100) |
| Burkitt lymphoma | 1 (6.2) | 7 (43.8) | 8 (50.0) | 16 (100) |
| Soft tissue sarcoma | 1 (6.7) | 8 (53.3) | 6 (40.0) | 15 (100) |
| Osteosarcoma | 0 | 5 (71.4) | 2 (28.6) | 7 (100) |
| Neuroblastoma | 1 (16.7) | 1 (16.7) | 4 (66.6) | 6 (100) |
| Non-Hodgkin Lymphoma | 0 | 2 (33.4) | 4 (66.6) | 6 (100) |
| Hodgkin's disease | 0 | 4 (100) | 0 | 4 (100) |
| Others | 2 (15.4) | 8 (61.5) | 3 (23.1) | 13 (100) |
| **Total** | **18 (14.1)** | **65 (50.8)** | **45 (35.1)** | **128 (100%)** |

**Table 4: Nutritional status by type of cancer**

| Nutritional Status | | | | |
|---|---|---|---|---|
| **Diagnosis** | **Normal (%)** | **Moderate wasting (%)** | **Severe wasting (%)** | **Total (%)** |
| Retinoblastoma | 36 (85.8) | 3 (7.1) | 3 (7.1) | 42 (100) |
| Wilms tumour | 7 (43.8) | 5 (31.2) | 4 (25) | 16 (100) |
| Burkitt lymphoma | 7 (43.8) | 4 (25) | 5 (31.3) | 16 (100) |
| Acute lymphoblastic lymphoma | 8 (50) | 7 (43.8) | 1 (6.3) | 16 (100) |
| Soft tissue sarcoma | 8 (57.1) | 5 (35.7) | 1 (7.2) | 14 (100) |
| Neuroblastoma | 3 (60) | 0 | 2 (40) | 5 (100) |
| Osteosarcoma | 3 (50) | 2 (33.3) | 1 (16.7) | 6 (100) |
| Acute myeloid leukemia | 5 (83.3) | 1 (16.7) | 0 | 6 (100) |

| | | | | |
|---|---|---|---|---|
| Non- Hodgkin Lymphoma | 4 (66.7) | 2 (33.3) | 0 | 6 (100) |
| Hodgkin's disease | 4 (100) | 0 | 0 | 4 (100) |
| Others | 8 (66.7) | 3 (25) | 1 (8.3) | 12 (100) |
| **Total** | **93 (65)** | **32 (22.4)** | **18 (12.6)** | **143 (100)** |

**Exact Chi square test P = 0.014 (95% CI 0.012-0.016)*

**Discussion**

Stage of disease at presentation is an important prognostic factor for childhood cancer, and advanced disease is associated with poor treatment outcome and overall survival (17). Unfortunately, most children with cancer in LMIC present late with advanced disease while treatment options are limited due to scarcity of resources (4, 8, 18).

In this study, 51% of patients with solid tumours presented with locally advanced disease and 35% had metastasis. There was a long delay between developing symptoms and a diagnosis of cancer, and starting treatment. The mean duration of symptoms before reaching ORCI was seven months (range 1week - 6 years). Similar findings have been documented before by Bekibele in Nigeria and Bowman in Tanzania where the mean duration of symptoms before diagnosis was six (6) months and ten (10) months, respectively for patients with RB (19, 20).

However, it is important to note that, in this study, despite the majority of patients presenting late at ORCI, more than 75% presented to the first health facility within a month of symptoms and 30% reported in the first week. From this finding, it is logical to speculate that the major causes of delay occur within the health care delivery system. The problem could be missed diagnosis or mismanagement before referral to ORCI. Other causes could be ignorance by parents/guardians, financial constraints and other family and social logistical challenges associated with leaving home to travel for treatment. Tanzania is a large country with challenges in infrastructure. Therefore, late presentation should be expected if all patients with childhood malignancies have to travel to Dar es Salaam for management.

Interestingly, no difference in the presentation stage was noted between Dar es Salaam patients and patients from far regions. However, the mean duration of symptoms before reaching ORCI was markedly different. Other studies have documented the lack of concordance between duration of symptoms and disease stage at presentation in children

with cancer (17). This may reflect differences in tumour biology and the aggressive nature of most childhood cancers.

Malnutrition is a big problem in developing countries and a significant contributor to childhood morbidity and mortality. In Tanzania, 4% and 1% of children under five years are moderately and severely wasted, respectively (2015-2016 TDHS-MIS). In this study, moderate and severe wasting was more prevalent (22.4% and 12.6%, respectively) compared to the general population. Other studies have also shown malnutrition to be more prevalent in children with cancer than in the general population, with the percentage of severe malnutrition ranging between 9% in Guatemala to 59% in Malawi (14). Patients who present with moderate wasting can easily fall into severe wasting during treatment. As reported before, patients with WT and NHL had a high proportion of severe wasting than patients with other malignancies (11). Combined WT and NHL accounted for half of all patients with severe wasting while only 4.5% of patients with ALL were severely wasted. The difference was statistically significant (P=0.016). This difference could be due to differences in tumour biology and relatively large tumour volumes seen in patients with intra-abdominal malignancies. Similarly, in developed countries, malnutrition is commonly seen in patients with advanced Neuroblastoma, WT and Ewing sarcoma (21)

**Conclusion and recommendation**

Despite most patients seeking health care within the first month of symptoms, most (86%) presented at ORCI late with advanced disease. Severe wasting was seen in 12.6% of children with cancer at ORCI. We recommend further studies to delineate causes for delay despite parents seeking health care early in order to plan appropriate interventions.

**List of abbreviation**

| | |
|---|---|
| ALL | Acute lymphoblastic lymphoma |
| BL | Burkitt lymphoma |
| BMAC | Bone marrow aspiration cytology |
| FNAC | Fine needle aspiration cytology |
| HIC | High-income countries |
| HL | Hodgkin Lymphoma |
| KS | Kaposi's sarcoma |
| LMIC | Low and middle-income countries |
| NB | Neuroblastoma |

| | |
|---|---|
| NHL | Non- Hodgkin Lymphoma |
| OS | Osteosarcoma |
| ORCI | Ocean Road Cancer Institute |
| RB | Retinoblastoma |
| RMS | Rhabdomyosarcoma |
| SAM | Severe acute malnutrition |
| STS | Soft tissue sarcoma |
| TDHS-MIS | Tanzania Demographic and Health Survey and Malaria Indicator Survey |

**Declarations**

**Ethics approval and consent to participate**

This study received ethical clearance from MUHAS Senate Research and Publication Committee and parents of involved children consented to participate in the study before children were enrolled.

**Availability of data and materials**

The data used in this study is available from the corresponding author.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

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**Authors' contributions**

LC, TK and EK designed the study. LC collected and analyzed data as well as prepared the first draft of the manuscript. All authors read and approved the final manuscript.

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