THE CLINICOPATHOLOGICAL CHARACTERISTICS OF CHILDHOOD MALIGNANCIES AT OCEAN ROAD CANCER INSTITUTE, DAR ES SALAAM, TANZANIA 2010.

By

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A dissertation submitted in Partial Fulfillment of the Requirements for the Degree of Master of Medicine (Pediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences

October 2011.

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled: **"The Clinicopathological Characteristics of Childhood Malignancies at Ocean Road Cancer Institute, Dar es salaam, Tanzania, 2010"** in partial fulfillment of the requirements for the degree of Master of Medicine (Pediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Dr. Lulu Chirande** declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature…… Date……

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DEDICATION

To my mother, Dr. Halima Mohamed Mwinsheikhe, for the values she installed in me that continue to guide my life and for filling our home with books.

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ABSTRACT

Background: More than 85% of childhood malignancies occur in developing countries where the burden of infectious diseases is also high. Cancer associated with viral infections, such as Burkitt lymphoma (BL), Hodgkin Disease (HD), Kaposi's sarcoma (KS) and Nasopharyngeal carcinoma (NPC) contribute a large percentage of cases in developing than in the developed countries. Worldwide one out of eight deaths is caused by cancer and in developed countries childhood cancers contribute 10% of all childhood deaths.

Outcome of childhood malignancies in developing countries has remained poor as opposed to developed countries where more than 70% of children with cancer are cured. Poor outcome in developing countries is related to late presentation and lack of sufficient and appropriate resources to provide specialized and comprehensive services needed to manage these children.

Despite the fact that cancers in children are common, very few studies have been done on this topic in Tanzania. Also the magnitude of malnutrition in children with cancer in our setting and the association of HIV/AIDS and childhood malignancies have not been systematically documented. This study addressed these gaps.

Objectives: The study aimed at describing the clinicopathological characteristics of childhood malignancies at Ocean Road Cancer Institute (ORCI). The magnitude of malnutrition and HIV infection were also studied.

Methodology: A descriptive cross-sectional hospital based study was conducted at Ocean Road Cancer Institute, the only specialized cancer hospital in Tanzania. Data was collected for eight months (May to December 2010). Participants were enrolled consecutively as they presented to the hospital. Demographic data, parents/guardians level of education, HIV status and clinical diagnosis were determined and recorded. Nutritional status was assessed using mid upper arm circumference (MUAC). Data collection for each patient was completed when a final diagnosis was reached and investigations for staging the patient were done.

Results: A total of 151 patients were enrolled in this study where 51.7% were males. Mean age at presentation was 5.8 years (range 3-17years). Age at presentation influenced the

type of malignancy with Retinoblastoma contributing 58.2% of patients aged 3 years or younger. Mean duration from symptoms to reaching ORCI was 7 months (range one week to six years). There was a significant delay between the first time a patient presented to a health facility and the time he/she reached ORCI (mean difference 5.5 months). Sixty three percent of patients had their diagnoses confirmed by either histology or cytology. Retinoblastoma was the commonest malignancy (29.1%) followed by Nephroblastoma (11.3%), Burkitt lymphoma (10.6%) and Acute Lymphoblastic Leukemia (10.6%). The majority of patients with solid tumors presented with either locally advanced or metastatic disease (86%). Only 4 patients (2.8%) were HIV positive; three patients with Kaposi's sarcoma and one patient with Burkitt lymphoma. Twelve percent of patients had severe wasting.

Conclusion and Recommendations: Retinoblastoma was the leading childhood malignancy at ORCI during the study period followed by Nephroblastoma. Despite more than 75% of parents/guardians seeking health services within one month of symptoms, majority of patients reached ORCI late with advanced disease. There was no significant association of HIV infection and childhood malignancies at ORCI.

There is need for affirmative actions to facilitate patients' access to proper treatment early. This can be achieved by regular training of primary health care providers on presentation of childhood malignancies throughout the country. A bigger multicenter study is needed in order to establish the prevalence of different types of childhood malignancies in Tanzania.

TABLE OF CONTENTS

LIST OF ACRONYMS.

AIDS	Acquired immunodeficient syndrome
ALL	Acute lymphocytic leukemia
ARV	Antiretroviral drugs
BL	Burkitt lymphoma
BMAC	Bone marrow aspiration cytology
CSF	Cerebral spinal fluid
CML	Chronic myeloid leukemia
CNS	Central nervous system
CT	Computed tomography
CXR	Chest X-ray
ES	Ewing's sarcoma
FNAC	Fine needle aspiration cytology
HAART	Highly active antiretroviral therapy
HD	Hodgkin disease
HFA	Height for age
HIV	Human immunodeficiency virus
KS	Kaposi's sarcoma
MDG	Millennium Development Goals
MRI	Magnetic resonance imaging
MUAC	Mid upper arm circumference
MUHAS	Muhimbili University of Health and Allied Sciences
NB	Neuroblastoma
NCD	Non-communicable diseases

NHL	Non-Hodgkin lymphoma
NPC	Nasopharyngeal carcinoma
ORCI	Ocean Road Cancer Institute
PET	Positron emission tomography
RB	Retinoblastoma
TDHS	Tanzania Demographic Health Survey
UK	United Kingdom
USA	United States of America
USS	Ultra sound scan
WFL	Weight for length
WT	Wilm’s tumour

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Background

Cancer imposes a major disease burden worldwide, with considerable variation among countries and regions. More than 85% of childhood cancers occur in developing countries, a region which has low resources for health.[1] Worldwide one out of eight deaths is caused by cancer, accounting for more death than those caused by HIV, Malaria and Tuberculosis combined. Cancer associated with biological agents such as, Non-Hodgkin lymphoma (NHL) in particular Burkitt lymphoma (BL), Hodgkin Disease (HD), Nasopharyngeal carcinoma (NPC), cervical, liver and stomach cancer, contribute a larger percentage of total cases in developing than in developed countries. At the same time developing countries are struggling with the burden of infectious diseases, hunger, poverty and conflicts.[2, 3] Because of the heavy burden imposed by infectious diseases, little has been done on Non-Communicable Diseases (NCD) including cancer.

Childhood malignancies constitute two percent of all cancers in Western industrialized countries, yet it accounts for 10 percent of childhood deaths and is second only to accidents as a cause of death in US children. Cancer is an important cause of childhood morbidity and mortality in developing countries as well.[4-6]

Poor nutritional status can influence the course of malignant diseases and therefore the prospects for survival. The majority of children with cancer live in developing countries where the prevalence of malnutrition in children may reach 50%. Malnutrition in children with cancer is influenced by factors such as the prevalence and severity of malnutrition in the general population, socioeconomic disadvantage, the type and grade of malignancy.[7]

Outcomes for childhood cancer in developing countries have remained poor largely because of late presentation[8-12] and the competition for resources between oncology services and many other health services which are considered to be of more public health importance such as care for HIV/AIDS, malaria, diarrheal diseases and other infectious diseases. In countries where infectious diseases have been brought under control, cancer in all ages is rising in importance but the cure rates are dismal in the underdeveloped world. The situation is quite different in Western countries where expectation for survival has increased from little in the 1960s to 80% cure rates for many childhood cancers. This is

due to tremendous improvement in early and accurate diagnosis as well as availability of treatment for childhood malignancies.[13, 14]

Oncology services in resource poor countries are faced with a lot of difficulties such as late presentation, delayed diagnosis or non-confirmed diagnosis. There are few specialized oncology hospitals (only ORCI in Tanzania with five Oncologists) and few Pathologist/ Hematologists to speed up diagnosis and staging of cancer patients. Tanzania has a total of fifteen Pathologists and five Hematologists. For tumors requiring surgery such as Wilm's Tumor (WT) and Neuroblastoma (NB) management is even more difficult due to delayed diagnosis or never performed surgeries. Banda et al., in Malawi showed that only 41.8% of the registered malignancies had a positive histology report.[15]

UNICEF has reported that about eleven million children die each year worldwide.[16] Majority of these preventable childhood deaths occur in developing countries.[17] Millennium Development Goal (MDG) number four addresses child mortality. Target one is to reduce under-five mortality by two thirds; that is from 93/1000 live births in 1990 to 31/1000 live births in 2015.[16] Efforts to achieve this goal have largely been directed at infectious diseases such as diarrhea, malaria, neonatal infections, pneumonia, measles, tetanus, and HIV/AIDS. NCD such as childhood cancer, which contribute significantly to deaths of children, have not received the attention they deserve. The current failure of the MDG number four to be achieved as planned, calls for the need to also look at NCD such as cancer more broadly and identify appropriate interventions.

1.2 Epidemiology of childhood malignancies

The distribution of childhood malignancies is affected by genetics as well as environmental factors. Malignancies with a genetic component tend to remain clustered in particular ethnic groups while those with environmental associated etiology cluster in certain geographical areas or cohorts with similar exposures.[18, 19] White children in Cape Town, South Africa have been shown to have the same age specific incidence rate for Acute Lymphocytic Leukemia (ALL) as white children in the United States of America (USA). Malignancies such as Ewing's sarcoma (ES) are common among white populations whereas WT and RB affect black children relatively more often. However, most cancers show an interaction between genetic susceptibility and environmental factors.[18-24] NHL

and BL in particular, are common in tropical Africa as well as Papua New Guinea. These are related to Epstein Barr Virus (EBV) infection and malaria endemicity in these areas.[25-27] The relatively low incidence of Central Nervous System (CNS) malignancies in developing countries is thought to be partly due to under diagnosis because of lack of expertise and facilities.[21] A comparative study between Nigerian, American Blacks, Ugandan and Caucasian children in the United Kingdom (UK) showed that American black children living in Washington, D.C. and Caucasian children living in Manchester UK, had similar frequencies for leukemia and glioma, whereas the incidence of lymphoma and RB was low. African children living in Nigeria or Uganda had the opposite frequency patterns. These differences in frequency of tumors between two ethnologically related population groups, (American blacks and Nigerians), suggested an influence of environmental factors in the etiology of these tumors. The rarity of ES and testicular tumors in American black children and Nigerian children suggested a genetic influence.[28]
The pattern of childhood malignancies in the developing countries of Africa is characterized by a high incidence of lymphoma (40%-60%) and a low incidence of leukemia (2%-8%).[29-31] However, a retrospective review of hospital data (1999-2007) in Sudan showed leukemia (26%) to be second to lymphoma (35%).[32] A comparative study in Nigeria showed a relative increase of intracranial neoplasias and leukemia with a relative decrease of BL between the years 1960-1972 and 1973-1990.[33] An exponential increase of Leukemia among Egyptian children less than five years was reported in 2002 by Hosny et al.[34] A retrospective study in Libya showed that malignant lymphoma (31.2%) was the commonest cancer among children ten years and below, followed by CNS tumors (19.2%) and WT (16.8%).[35] A retrospective analysis of 600 pediatric histopathological specimens done in Kenya in 1996 showed the following prevalence: BL (33.5%), NHL (21.8%), RB (11.5%) and KS (6.1%).[36] In 1998 Carneiro et al., published a retrospective study that showed the pattern of childhood malignancies in Tanzania over a period of 22 years (1973-1995). The results were similar to other African countries with lymphoma leading (38.9%) followed by Soft STS (13.1%) and RB (11.1%).[37] In the year 2000, Mgaya and Kitinya [38] published results of a histopathological study where the commonest malignant tumors were lymphoma (53%), of which 31.4% were BL, 14.9% HD and 6.6% NHL. Others were RB (12.9%), Carcinoma (not otherwise specified) (9%), WT and STS each 6.7% and KS (5.9%). Bone, germ cell and CNS tumors were rare.

A review by Draper et al., in 1994[39] showed no good evidence for any large increase in incidence of any childhood cancer over the past 20-30 years with the exception of KS in Uganda and thyroid carcinoma in Belarus. The increase of childhood KS in Uganda was attributed to the HIV pandemic. A high incidence of lymphoma with low incidence of leukemia has been associated with poor living standards and EBV infection.[5, 40]

1.3 Aetiology and risk factors for childhood malignancies

Known genetic predisposition accounts for only five percent of childhood malignancies. Genetic conditions associated with increased risk for malignancy include: Down's syndrome, Klinefelter's syndrome, Beckwith-Wiedemann syndrome, Neurofibromatosis, Tuberous sclerosis, von Hippel-Lindau syndrome, Xeroderma pigmentosa, Albinism, Fanconi's anemia, Ataxia telangiectasia, Bruton's agammaglobulinemia and Severe combined immunodeficiency (SCID).[40-42]

Some environmental exposures are associated with increased risk of developing certain malignancies where the exposure can be prenatal or postnatal. Such exposures include ionizing radiation, UV radiation, drugs and viruses.[5]

Prenatal exposure to ionizing radiation has been associated with increased risk of childhood cancer. A 38% increase in childhood cancer was reported following the Hiroshima and Nagasaki atomic bombs in 1945. In utero exposure to diagnostic X-rays during first trimester has also been associated with an increase in childhood cancer. Postnatal exposure to radiation increases risk to leukemias and radiation therapy for a primary tumor is a known risk for secondary malignancies later in life.[40, 43, 44] This might not be much appreciated in our setting because of the current poor survival but as we advance this is expected to happen.

UV radiation in susceptible individuals (Albinism, Xerodema pigmentosa) is associated with increased risk for skin malignancies such as basal cell carcinoma and squamous cell carcinoma.[41]

Epstein Barr Virus (EBV) is associated with B cell lymphoid malignancies (BL and NHL). In certain geographical areas B cell lymphomas constitute up to 50% of all childhood malignancies. EBV has also been linked to HD particularly in children below ten years of age. HIV/AIDS is associated with increased risk of KS in both children and adults.[45, 46]

Hepatitis B Virus (HBV) infection is associated with hepatocellular carcinoma. Infection occurs early during childhood but cancer occurs many years later. As a control measure children are vaccinated against HBV.

Immunosuppressive drugs such as used in renal transplantation are associated with a 20-40 increased risk for lymphomas. Alkylating agents such as Cyclophosphamide increase the risk of developing acute non - lymphoblastic leukemia 5-10% fold.[41]

1.4 HIV/AIDS and childhood malignancies

HIV infected children are at increased risk of developing malignancies and more often of the rare types compared to HIV uninfected children. These children are also forty times more likely to develop a malignancy than the general population.[45, 47] Two percent of children with AIDS have malignancy recorded as their AIDS defining illness as per Center for Disease Control (CDC) definition.[46] Tanzania has adopted the WHO staging of HIV/AIDS which includes KS and primary CNS tumors or peripheral B-cell NHL as AIDS defining illnesses (Tanzania HIV/AIDS treatment guidelines 2008).

There are regional variations in the prevalence of HIV related malignancies. The reasons for such differences are not clear but it could be related to the different distribution of etiological agents such as HHV-8. In Sub Saharan Africa the commonest HIV/AIDS related childhood malignancy is KS while in the United States of America it is NHL.[48, 49]

Uganda has reported a forty fold increase in childhood KS with 78% of cases being HIV related and majority (79%) with oral - facial presentation.[50] A retrospective study by Kaaya et al., in 2006, demonstrated a slight increase of malignant lymphoma in Tanzania during the HIV epidemic (1992-1994). However, they commented on the difficult to ascertain the prevalence of AIDS-related lymphoma due to lack of routine HIV screening of all lymphoma patients.[51] An unpublished study at Ocean Road Cancer Institute (ORCI) for the year 2005 showed that out of the 81 children with malignancies that were screened, 22% were HIV infected. Another study done in Malawi by Sinfield et al., showed that for children with cancers known to be associated with HIV infection (KS and NHL), 84% (386/461) were tested for HIV, compared to 42% (103/246) of the other malignancies. Among those who were tested, HIV prevalence was 93% (52/56) for children with KS, 4% (11/289) BL, 31% (8/26) NHL, 7% (1/15) HD and 5% (5/103) for the remaining cancers

combined. During the study period, none of the HIV - infected children had their immune status investigated and no child received anti-retroviral therapy.[52] A study in Zimbabwe has shown a seroprevalence rate of 42.2% with all 12 KS patients being HIV positive.[53]

The selective HIV testing done in the past means that more children with clinical characteristics suspicious of HIV/AIDS were screened compared to children without HIV/AIDS indicators. The effect of this practice is having a relative high proportion of HIV infection among the screened children. With routine testing a better approximation of HIV infection among children with malignancy will be obtained.

The pathogenesis of HIV related malignancies is attributed to a number of factors. HIV weakens the immune system, thus diminishing the body's innate tumor surveillance capacity, much in the way that immunosuppressive agents put transplant patients at risk of cancers. Furthermore, viruses such as EBV, Human Papilloma Virus (HPV), and HHV - 8 are re-activated by HIV from latency and initiate cell replication and transformation. The relationship between HIV - related malignancies and certain viruses is well established. For example, nearly every case of KS is associated with HHV-8, and nearly every case of HIV-related primary CNS lymphoma is associated with EBV infection. Additionally, EBV is frequently isolated from HIV - related Leiomyosarcomas, systemic NHL, and HD. [45, 47, 54]

In the current era of highly active antiretroviral therapy (HAART), early diagnosis and treatment of opportunistic diseases, more HIV infected children will live longer. The duration of immunosuppresion might play a role for a child's risk to develop malignancy by allowing completion of the multistep carcinogenetic cascade necessary for malignancy to occur.

Tanzania started to provide free HAART to children six years ago and HIV related malignancies pose a challenge in management due to drug interactions and the associated renal and liver toxicities of ARVs as well as the HIV effects to these organs.

1.5 Malnutrition and childhood malignancies

The majority of children with cancer live in developing countries, where malnutrition is prevalent. In Tanzania 3% of underfives were severely wasted in 2004/2005 and 22% were stunted (TDHS 2004-2005). Severe wasting has increased to 4% while moderate wasting was found to be 4.8% in the underfive children (TDHS 2010). Children with cancer might

present with even more severe malnutrition compared to their counter parts in the population. However, the magnitude of chronic malnutrition (stunting) is usually the same. Poor nutritional status can influence the course of a malignant disease and the prospects for survival. Malnutrition can affect tolerance of therapy, increase the risk of co-morbidities and influence the overall survival of cancer patients. Cancer increases the risk of malnutrition by reducing dietary intake (anorexia, vomiting, intra-abdominal tumors), increasing caloric expenditure and inducing changes in fat, carbohydrate and protein metabolism. Some of these changes have been ascribed to the production of tumor necrosis factor (TNF) by macrophages in response to the tumor. Malnutrition is more prevalent in patients with WT, NB, Rhabdomyosarcoma (RMS), NHL and Ewing's sarcoma (ES).[7, 55, 56]

A review paper by Alessandra in 2004 showed that there are few data on nutritional status of pediatric oncology patients in developing countries and that most of the studies on nutritional status in children with cancer have been done in children with ALL.[55]. In resource limited countries it is accepted that the prevalence of malnutrition averages 50% in children with cancer.[7] 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).[57] Unfortunately the authors did not show the relationship between the type and stage of malignancy to malnutrition. In industrialized countries the degree of malnutrition is related to the type of tumor and extent of disease and is common in children with advanced NB, WT and ES.[56]

There are different ways of evaluating nutritional status. It can be evaluated by dietary, clinical/anthropometric or biochemical measurements. However, there is no gold standard for doing this. Anthropometric measurements commonly used to assess nutritional status are weight for length (WFH), weight for age (WFA), height for age (HFA), mid upper arm circumference (MUAC) and triceps skin fold thickness (TSFT). In children with large abdominal tumors WFH is misleading because the abdominal tumors can weigh more than 10% of their total body weight. MUAC is not affected by tumor mass hence can reliably be used to assess nutritional status of children with solid tumors. In a large prospective, controlled study of 100 newly diagnosed children with cancer, the mean WFH ratio did not differ from the control reference values. However, the results of MUAC differed markedly

between the patients and control values: Twenty three percent (23%) of patients had TSFT (a measure of fat mass) more than 2 SD below the mean value for controls, and 20% had MUAC (a measure of lean body mass) less than the 5th percentile of the control distribution. In another study the result was very similar; whereas no statistically significant differences were found using WFH values between the patients and the control group, TSFT and MUAC measurements were significantly lower among the children with cancer (*P* 0.001), and this was even more evident in patients with intra abdominal solid tumors.[58] Thus MUAC is a simple, efficient and acceptable way of assessing nutritional status in children with cancer.

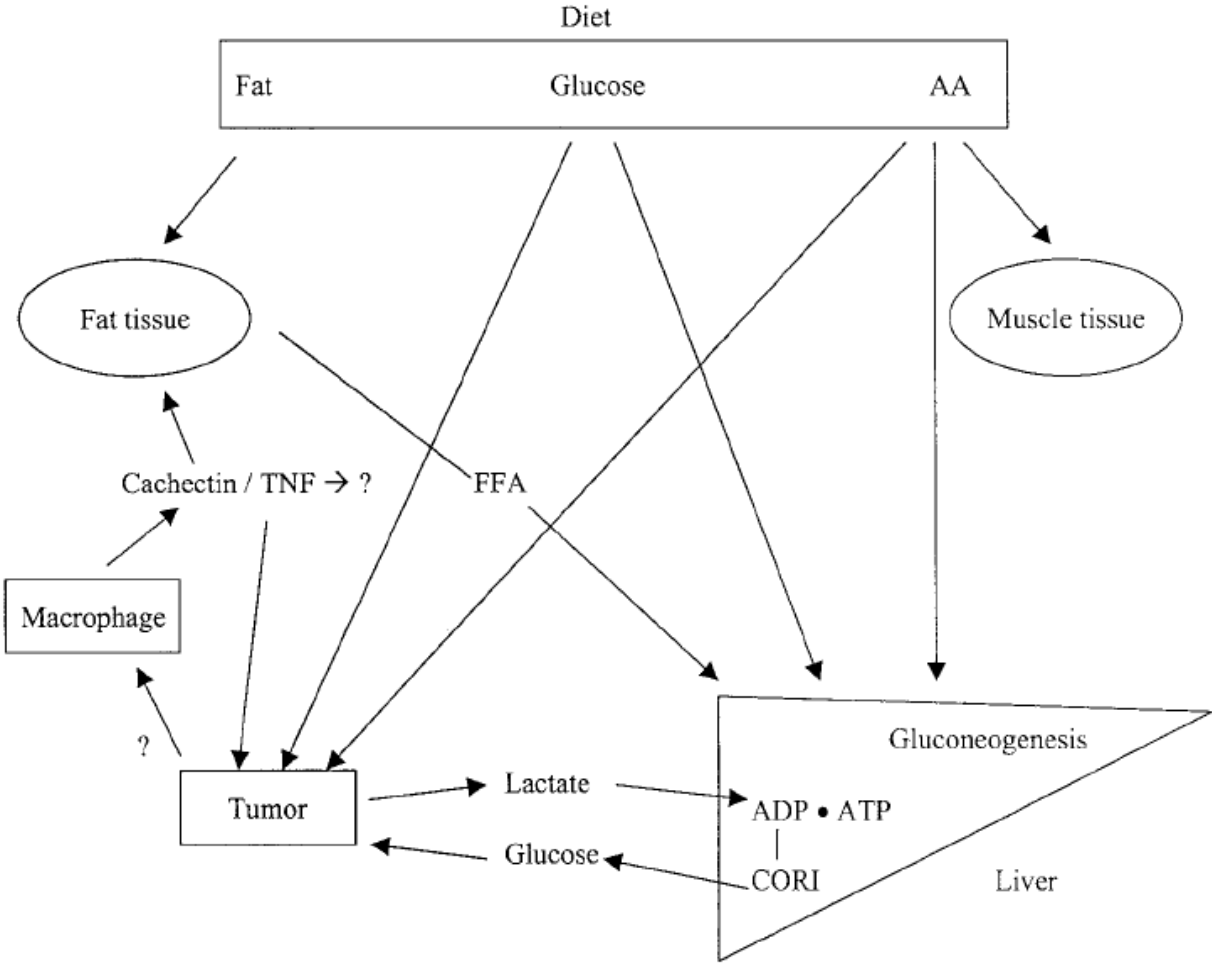
The pathophysiology of malnutrition in cancer patients

The pathogenesis of malnutrition in cancer patients comprise a triad of diminished intake, increased losses and increased demand. This is a consequence of the tumor, host response to the tumor, TNF and treatment (chemotherapy, surgery, radiation). The wasting syndrome seen in these patients is commonly referred to as cancer cachexia.

Cancer cachexia presents with weight loss, anorexia, organ dysfunction and tissue wasting. Tumor factors and host response leads to significant alterations in carbohydrate, lipid and protein metabolism. Patients with cancer commonly have anorexia attributable to TNF and other cytokines such as interleukin-1 (IL-1). Due to anorexia there is decreased food intake despite the hypermetabolic state caused by the tumor. Gastrointestinal disorders primarily of tumor origin or secondary to therapy further impair intake, digestion and absorption of nutrients.

Tumor cells release nonspecific peptides such as serotonin (5-HT) which cause anorexia and weight loss. In a vicious cycle the cytokines such as TNF, IL-1, IL-6 and interferon – gamma (IF-ɣ) released by host macrophages induce increased energy expenditure, lipolysis, and muscle proteolysis in addition to anorexia. Hepatic glycogenolysis occurs hand in hand with gluconeogenesis. Muscle breakdown provides glucogenic amino acids that are used by the liver for gluconeogenesis. Tumor cells metabolize glucose and produce lactate. Lactate in turn is recycled back to the liver to produce more glucose (Cori cycle). The Cori cycle uses a lot of energy and therefore adds to increased demand and expenditure. The usual mechanism for conserving energy seen in starvation are lost in patients with malignancies.[59-61]

Figure1: Metabolic changes induced by tumor (Adopted from Allessandra S. et al.)[55]



KEY: *AA: Amino acids, ADP: Adenosine diphosphate, ATP: Adenosine triphosphate, FFA: Free fatty acids, TNF: Tumor necrosis factor.*

Malnutrition leads to poor outcome in some children with cancer. It is associated with delayed therapy, prolonged bone marrow suppression after therapy, poor tolerance to therapy, suppressed immunity with frequent and severe infections and increased rate of disease relapse. Early nutritional diagnosis and proper dietary intervention has been shown to improve outcome in these patients. Nutritional support can be in the form of high caloric enteral feeds, semi digested foods or frequent normal balanced diet. These feeds can be given orally, by nasogastric tube or through a gastrostomy. Total parenteral nutrition can be used in patients who cannot tolerate enteral feeds.[62-65]

1.6 Diagnosis and staging of childhood malignancies

The diagnosis of childhood malignance starts with a detailed history and physical examination. The definitive diagnosis of cancer and its type must be confirmed by histopathology and other morphological studies. In the diagnostic work up of a child suspected to have cancer, early collaboration between the attending physician, pediatric oncologist, pathologist and hematologist is important to ensure accurate diagnosis and avoid inappropriate treatment. Histopathology provides the type as well as the grade of the tumor. Staging which is done clinically describes the extent of the disease and in some cancers the grade influences the stage. The type, grade and stage are all important prognostic indicators and determine the treatment modality.

Different methods are used to confirm the diagnosis of cancer. These include peripheral blood smears and Fine Needle Aspirates (FNA), needle biopsies, bone marrow aspirates (BMA) and open biopsy or surgical specimens. Each one of these has its advantages and disadvantages with increasing level of invasiveness from FNA to surgical specimens. The diagnostic accuracy of FNA in the diagnosis of pediatric tumors has been assessed and it has been found to be a simple, safe, rapid and accurate investigation. [66, 67] However, negative or uncertain results should be interpreted as non-diagnostic and open biopsy should then be performed. [68, 69]

To determine the extent (stage) of disease (local spread as well as metastasis), different imaging techniques are used. These include plain radiograms, CT scans, MRI, radionuclear scans and PET scans. Some types of cancer require analysis of the bone marrow and CSF as well. Each patient should be analyzed and worked out individually and some may need surgical staging.[70, 71]

In resource poor countries accurate diagnosis and proper staging of patients is often not achieved. A study in Malawi showed that only 41.8 % of patients had a positive histology.[15] Analysis of pediatric histology reports at ORCI in 2005 showed that 25% of the FNAs reported at MNH were non - diagnostic (unpublished).

2.0 PROBLEM STATEMENT

Childhood cancer constitutes 5.5% of all life years lost from cancer and collectively is the fourth most important cancer worldwide.[72] Eighty five percent of childhood cancer occurs in resource poor countries like Tanzania with mortality of over 80%. These are the same countries burdened with malnutrition, HIV/AIDS and other infectious diseases. Research and prevention strategies are directed to such problems with a consequent neglect to NCD such as cancer.

Most research on childhood malignancies and cancer in general is from developed countries. The real magnitude of the problem in our setting remains unknown. Community surveys are better at providing prevalence but have proven to be difficult to conduct even in resource rich countries. Hospital based studies provide an estimate of the problem but translation to the general situation is difficult due to unavoidable bias.

Few retrospective studies have been done at ORCI to address childhood malignancies. Because of deficiencies in documentation, storage and retrieval of patients' files, missed data is a common problem in such study design.

Previous studies were done when HIV screening was not a common practice hence for a number of patients this important information was missed. Improved survival of HIV infected children due to HAART and better care through care and treatment clinics (CTC) and the mere long time interval since the last study might have changed the presentation as well as the prevalence of childhood malignancies in our setting. Uganda has reported an increase in pediatric HIV associated KS but the situation in Tanzania is yet to be documented. Given those situations we needed a study which will indicate the actual magnitude of the problem.

Childhood malnutrition is a significant problem in developing countries and an important co-morbid factor in many childhood diseases. Poor nutritional status is associated with delayed and poor tolerance to therapy, increase disease relapse and an overall poor survival in children with cancer. Nutritional support can however, reverse this. We do not know the magnitude of malnutrition in these patients in our setting.

3.0 STUDY RATIONALE

Ocean Road Cancer Institute is the only specialized cancer hospital in Tanzania and receives cancer patients from all over the country. The last study on childhood malignancies was done at Muhimbili National Hospital over ten years ago.[37] Changes might have occurred over time that could change the frequency and presentation of childhood malignancies in our setting. HIV/AIDS is one among the factors which could have created a different frequency of childhood malignancies. As a result of improvement in the survival of HIV infected children due to provision of HAART and general better care through CTC, the incidence and prevalence of HIV associated childhood malignancies might have increased. This study aimed at establishing the real magnitude of HIV infection in children with cancer at ORCI by doing routine screening of all eligible patients during the study period. Patients found to be HIV infected were sent to CTC for treatment and follow up.

Since participants were screened for malnutrition at enrollment, this helped to know the exact magnitude of malnutrition in children with cancer and this information can be used in planning for nutritional support of these children.

Most studies on childhood malignancies in Africa are retrospective studies using available hospital data. Due to problems in recording, storage and retrieval of data, important information could be missed in such study designs. This study was different in that it prospectively recruited patients and actively collected data.

It is also expected that the results of this study will raise awareness in the community and among health care providers and encourage further research in childhood malignancies.

4.0 OBJECTIVES

4.1 Broad objective

To determine the clinicopathological characteristics of childhood malignancies at Ocean Road Cancer Institute (ORCI).

4.2 Specific objectives

1. To determine the proportion and presentation of different types of childhood malignancies at ORCI.
2. To determine the proportion of confirmed diagnoses among patients with childhood malignancies at ORCI.
3. To determine the proportion of patients with malnutrition among children with malignancies at ORCI.
4. To determine the proportion of patients with HIV infection among children with malignancies at ORCI.

5.0 METHODOLOGY

5.1 Study design

This was a descriptive cross-sectional hospital based study.

5.2 Study setting

This study was conducted at Ocean Road Cancer Institute (ORCI). ORCI is the National Cancer Institute and the only cancer hospital in Tanzania. It receives about 250 new patients per year. These patients are referred to ORCI from different hospitals throughout the country. About 70% of patients come through Muhimbili National Hospital (MNH) where histological diagnosis is usually done before referral to ORCI. Few hospitals offer first line chemotherapy for BL patients instead of referring them straight to ORCI. At ORCI fine needle aspiration for cytology (FNAC) is done for patients without histological diagnosis. This is done by a visiting Pathologist from MNH who goes there twice a week. FNAC slides are processed at Muhimbili National Hospital and the results sent back to ORCI when ready. This is a special arrangement to minimize delays in diagnosis and treatment once children reach ORCI. Children requiring surgical intervention such as open biopsy or pre/post operative surgery must be sent to MNH because ORCI doesn't have the capacity to do surgeries. Investigations such as chest x-ray (CXR), abdominal pelvic ultrasound and bone marrow aspiration cytology (BMAC) are done to assess the extent of disease. After histological diagnosis and staging, or in special cases before that, appropriate treatment is initiated. Treatment offered is mostly chemotherapy and radiotherapy or a combination. The cost of treatment is incurred by the government and some donors as all cancer patients and children below five years are exempted from cost sharing as a national policy. Most patients and their parents/guardians usually stay as inpatients until they finish treatment.

5.3 Study population

All children (0-17 years) attending pediatric department at ORCI during the study period with clinical/confirmed diagnosis of malignancy were eligible for this study.

5.4 Inclusion criteria

Children up to 17 years attending ORCI with clinical diagnosis or histologically confirmed diagnosis of malignancy and with parental consent.

5.5 Exclusion criteria

i. Patients with clinical and/or histological diagnosis of malignancy who die before it is possible to enroll the patient and do appropriate investigations.
ii. Patients with histological proof of non - malignant disease.

5.6 Sampling and sample size

Every eligible patient with consent was enrolled in the study. Convenient sampling was used because of the limited number of children with malignancies and the limited time within which this study had to be completed. Data collection was done for eight months. The expected number of participants for this duration was 180 (an average of 25 patients per month).

The following formula was used to calculate the minimum sample size (**n**) that was required.

$$\mathbf{n} = \frac{\mathbf{Z^2P(1-P)}}{\mathbf{E^2}}$$

Where:-

Z= percent point corresponding to significance level 5% which is 1.96

P= Proportion of patients with the characteristic of choice which in this study it was the proportion of patients with severe acute malnutrition as seen in Malawi 59%.

E= corresponds to maximum likely error allowed, 7% in this study.

Substituting these values in the above formula **n** becomes 193.

5.7 Study procedures

5.7.1 Data collection instruments

A structured questionnaire was developed in English and translated into Swahili. Pilot testing of the questionnaire was done at MNH before commencement of the study. The questionnaire had two parts: one part for interviewing the parents/guardians and second part for recording relevant clinical findings as well as investigation results.

One digital weighing scale stationed in the ward was used to weigh patients and special non stretchable tape measures were used to measure the MUAC. World Health Organization (WHO) anthropometric measurement chart was used for interpretation of

MUAC for age. Only MUAC was used to determine the nutritional status and MUAC below fifth percentile for age was considered as severe acute malnutrition.

5.7.2 Research assistants

There were two research assistants. These were qualified nurses who are working at ORCI in the pediatric ward. Both were trained on the study objectives and procedures a week before the start of data collection. The author practically demonstrated to the research assistants how to measure MUAC and observed them practice. The main tasks of the assistants were to enroll patients, administer first part of the questionnaire, take anthropometric measurements and facilitate completion of investigations.

5.7.3 Participant recruitment and data collection

All children with clinical or histological diagnosis of cancer were recruited in this study as they arrived at ORCI. Recruitment time was between 8 am and 10 pm so as not to disturb patients late at night. Anthropometric measurements were then taken and the author filled the second part of the questionnaires personally. The author went through ward registry books of pediatric ward at ORCI once a week and the main hospital registry book once a month to make sure no eligible patient was missed.

The author and research assistants explained about the study to the parent/guardian and requested for informed consent. For those who consented an interview was done and a structured questionnaire administered. Weight without shoes to the nearest 0.1kg and MUAC to the nearest 0.1cm was measured. MUAC was measured on the right hand at the midpoint between the acromial process of the scapula and the olecranon process of the ulnar. These were filled in the questionnaire and patient files. Each questionnaire had a serial number and patient file number for identification. Contact information for the parent/guardian was also recorded to help in follow up.

The author and research assistants facilitated completion of indicated investigations and follow up for results in order to complete data collection and facilitate patients' management. On admission each patient had blood collected for FBP, a form written for CXR which was done on the same day or next day and a booking was done for abdominal pelvic ultrasound which usually was done within a week or urgently on the same day when indicated. Pretest counseling was done and consent obtained for HIV screening.

Counseling was done by the investigator or nurses in the ward. HIV antibody tests (cappilus and determine) were used. For children below eighteen months with positive antibody test, a DNA PCR test was planned to be done at MNH however, there was no such a patient. HIV positive patients were enrolled into the CTC as required for proper management.

The author reviewed patient files once a week to check if results were back and she recorded the results in the questionnaires. Missing results were traced in the laboratory at ORCI or at MNH for BMAC and histopathology reports. When indicated investigations were repeated. For patients whose HIV results were missing an effort was made to trace the patient and find out when the patient is coming again in case of out patients, and an arrangement was made to take specimen for HIV screen when blood was collected for pre-chemotherapy FBP. For specimen sent to Ireland the author requested and discussed the results with the Pediatric Oncologist at ORCI who usually received the results through e-mail. The author participated in doing procedures such as venepunctures, BMA, biopsy taking and CSF cytospin preparation and examined patients when she first saw them and compared her findings with those recorded in patients' files. When the findings did not tally, she consulted doctors in the ward for clarification. Physical examination findings were recorded in the questionnaires and in the patients' files if such information was not yet recorded in the file. Each patient was followed up until all investigations were completed and a definitive diagnosis was reached. The author discussed with the Pediatric Oncologist about diagnosis and staging of difficult patients.

Trucut biopsies were done for patients with easily accessible solid tumors who had no histopathology report. Specimens were processed and read by qualified and experienced Pathologists either at MNH or in Ireland. For patients with hematological malignancies a BMAC was done and reported at MNH by Hematopathologists. BMAC was also done for patients with RB, Lymphoma and NB to assess for bone marrow metastasis. CSF for cytospins was done for patients with RB, NHL, Leukemia and NB to assess for CNS disease. These investigations were done within a week from admission unless there were unavoidable circumstances such as critically ill patients.

5.7.4 Diagnosis and staging of patients

Each patient had an initial clinical diagnosis which was then confirmed or mordified by histopathology results. For solid tumors tissue biopsies and sometimes FNAC was used for diagnosis whereas for hematological malignancies peripheral blood smears and BMAC was used. Immunohistochemical studies were not done because of lack of equipments and reagents. Staging was done by physical examination assessment as well as by investigations such as CXR, ultrasound, BMAC, CSF cytospins and bone scans depending on the type of malignancy. CT scans and MRI were not routinely used for staging, again because of high costs of these investigations. Only three patients had CT scans done, two of the abdomen and one of abdomen and chest. CNS involvement was assessed clinically by physical examination and by CSF cytospins analysis. Initial white blood cell (WBC) count was used, among other factors, to determine risk category for ALL.

Investigations done for diagnosis and staging of patients included:-

1. Trucut biopsy for histology
2. Bone marrow aspiration for cytology
3. Peripheral blood smear
4. Lumber puncture for CSF cytospins and cytology
5. Chest X Ray and other X-rays as required.
6. Abdominal Pelvic Ultrasound
7. CT scan when mandatory
8. Complete blood count

5.9 Data entry and analysis

Data was entered by the author into computer data base Epi Info version 3.5.1 consecutively as data collection continued. Data analysis was done using Epi Info and SPSS 16.0 statistical programs. Preliminary data analysis was done after four months of data collection and final analysis was done after completion of data collection.

Frequency tables were used for demographic, education level, nutritional status and types of malignancy. The mean age at presentation was calculated for the various types of malignancies. The proportion of HIV positive patients was determined as the percentage

of the total screened patients and the magnitude of malnutrition was expressed as a percentage of the total patients screened for malnutrition. Association between variables was tested using Chi square and Fishers' exact tests. Confidence interval was taken at 95% and P value less than or equal to 0.05 was considered to be statistically significant.

5.10 Data quality control

The investigator cross-checked the questionnaires weekly for missing data and outliers.

6.1 Ethical consideration

Each eligible parent/guardian had a full explanation about the study and its purpose and was assured that his/her acceptance or refusal to participate in the study will by no means affect care to his/her child. At any point participants could change their mind and withdraw from the study.

Pretest counseling for HIV screening was done and for those who consent results were confidential. Participants decided to whom the results could be disclosed to.

Informed consent forms were filled and signed by parents/guardians after they were satisfied and comfortable with the study. One copy remained with the parent/guardian. Verbal assent was obtained from patients who were old enough to understand about the study. No investigation or procedures were done that were of no benefit to the patient. There were no payments for participating and this was clearly explained to patients, parents or guardians.

During the study other conditions which were identified were referred to appropriate health care worker for management and all participants who tested positive for HIV were referred to HIV care and treatment clinics after appropriate counseling for proper management.

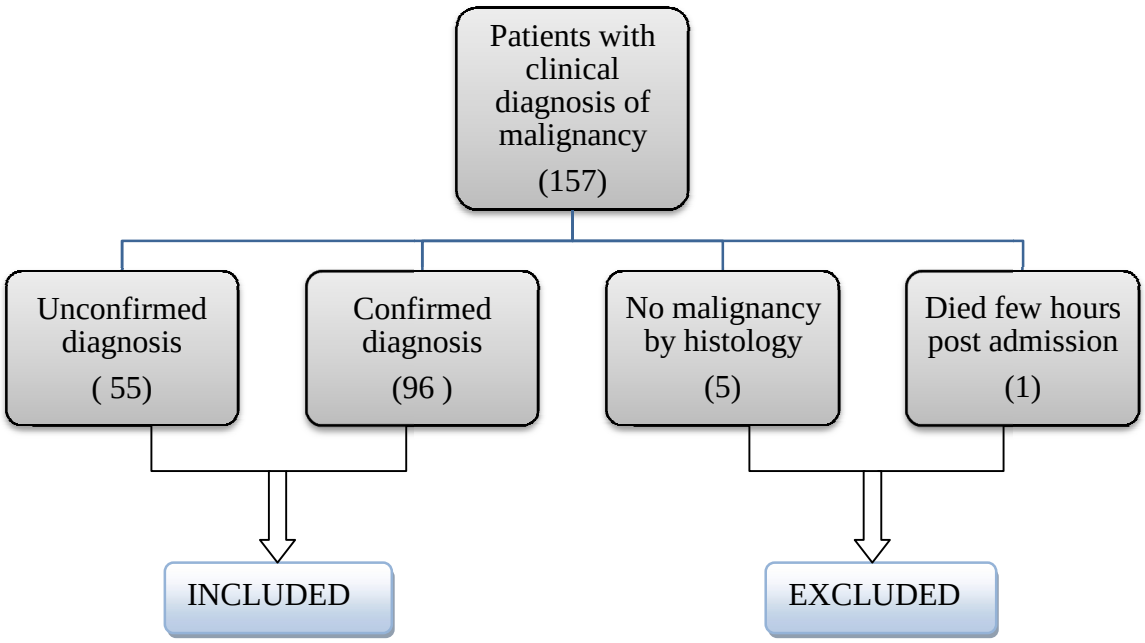
6.2 Ethical clearance

Ethical clearance was obtained from the MUHAS Senate Research and Publication Committee (SRPC). Permission to conduct this study at ORCI was obtained from the hospital management.

7. RESULTS

Data collection was done for 8 months (May to December 2010). A total of 157 patients were recruited into the study of whom six were excluded. See flow chart below.

Figure 2: Patient flow chart



7.1 Basic characteristics of the study population

A total of 151patients were enrolled in the study among which 78 (51.7%) were males. The mean age at presentation was 5.8 years (range 3months-17years). The majority of the patients (82.8%) were ten years old or younger with a median age of five (5) years. Thirty patients (20%) came from Dar es Salaam. MNH was the immediate referring hospital in 39.1% of the patients followed by CCBRT which accounted for 18.5% of patients. The median duration of symptoms until patients reached ORCI was seven (7) months (range 1week-6years). Forty percent (40%) of patients presented six (6) months after onset of symptoms. Patients from Dar es salaam had a relatively shorter duration of symptoms (mean 4 months) at the time they reached ORCI.

More than 75% of the patients attended the first health facility within a month after onset of symptoms and about 30% reported in the first week. The mean duration for seeking medical attention in the primary health facility was 1.5 months. Sixty one percent (61%) of the parents/guardians had attained primary education. The basic characteristics are summarized in table 1.

Table 1: Baseline demographic characteristics of the study population

Variables	Number	Percent
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
HIV status (n=145)		
Negative	141	97.2
Positive	4	2.8
Parent/Guardian level of education		
No formal	23	15
Primary	92	61.4

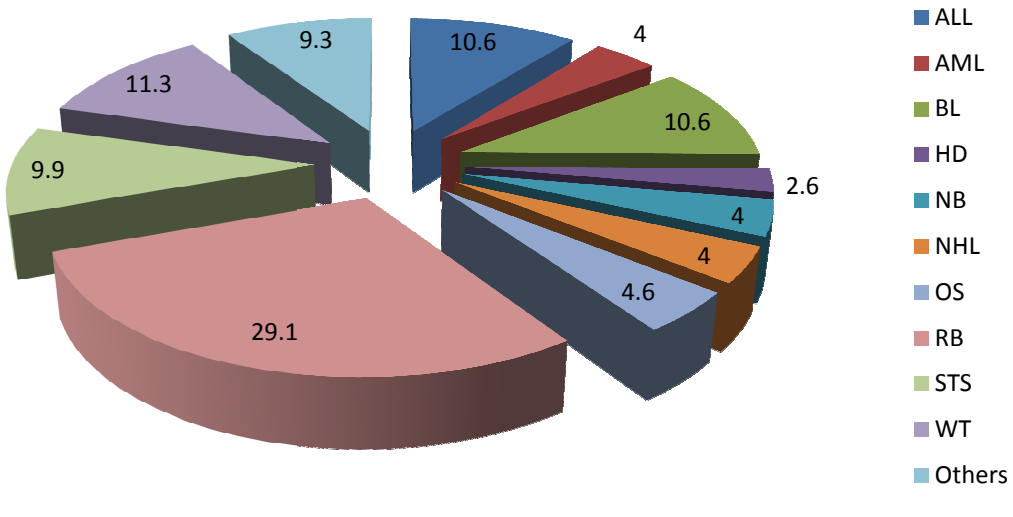
Secondary	27	18.1
Diploma and Degree	9	5.5
Duration (months)	**First Health facility (n=145)**	**ORCI (n=146)**
	Number (%)	Number (%)
≤ 1	111 (76.6)	23 (15.8)
2 - 6	29 (20)	79 (5.1)
>6	5 (3.4)	44 (30.1)

*Normal includes mild wasting.

7.2 Proportion and clinical presentation of childhood malignancies seen during the study

Retinoblastoma (RB) was the commonest malignancy accounting for 29.1% followed by WT (11.3%), ALL and BL each contributing 10.6% of the study population. The proportions of the different childhood malignancies are demonstrated on figure 3.

Figure 2: Percent propotion of different types of childhood malignancies



Others included: Squamous cell carcinoma (3), NPC (3), Hepatocellular carcinoma (HCC) (2), Renal cell carcinoma (1), Ovarian cancer (1), CML (1) and Uncertain diagnosis (3).

Of the three (3) patients with Squamous cell carcinoma, two (2) had Xeroderma Pigmentosa and one (1) had Ocular Cutinious Albinism. There was no patient with brain tumor during the study period.

Age at presentation had influence on the type of malignancy. RB, WT and NB accounted for three quarters of patients 3 years old or younger, 58.2%, 11% and 7.2% respectively. Only one (1) patient with Osteosarcoma (OS) was younger than10 years. The age distribution for different childhood malignancies is summarized on table 2.

Table 2: Type of malignancy by age group

	Age group (years)			
	≤ 3	**4-10**	**>10**	**Total**
Diagnosis	Number (%)	Number (%)	Number (%)	Number (%)
RB	32 (58.2)	12 (17.2)	0	44 (29.1)
WT	6 (11.0)	10 (14.3)	1 (3.8)	17 (11.3)
BL	1 (1.4)	10 (14.3)	5 (19.2)	16 (1o.6)
ALL	3 (5.5)	12 (17.2)	1 (3.8)	16 (10.6)
STS	4 (7.2)	8 (11.4)	3 (11.5)	15 (9.9)
OS	0	2 (2.9)	5 (19.3)	7 (4.6)
NB	4 (7.2)	1 (1.4)	1 (3.8)	6 (4.0)
NHL	2 (3.6)	4 (5.7)	0	6 (4.0)
HD	0	1 (1.4)	3 (11.5)	4 (2.6)
Others	1 (1.8)	7 (10.0)	6 (23.1)	14 (9.3)
Total	**55 (100)**	**70 (100)**	**26 (100)**	**151 (100)**

7.2.1 Stage of disease at presentation

The results for the stage of disease at presentation are summarized on table 3.

It was not possible to determine the stage of disease at presentation for patients who needed surgical staging unless they had obvious metastatic disease for example WT patients with lung metastasis picked up by a chest X-ray. Due to lack of histology reports in some patients or incomplete reports (for example not reporting if the cut end of optic nerve is free of tumor cells or not in RB) it was not possible to accurately assign stage for many patients. There are different staging systems for different malignancies hence comparisons of disease extent across different diagnoses was not feasible unless they shared staging system. To overcome this all solid tumors were classified as early local disease, advanced local disease or metastatic disease. Early local disease was defined as primary tumour of less than or equal to 10cm in diameter where as advanced local disease was defined as primary tumour larger than 10cm but without distant metastasis. Disease was considered metastatic when there was distance metastasis such as of the lungs, liver, bone marrow or CNS. Eighty six percent (86%) of patients presented with advanced disease, either locally advanced (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%) in that order.

Table 3: Stage of disease at presentation (Solid tumors)

	Stage of Disease.			
	Early local	**Advanced local**	**Metastatic**	**Total**
Diagnosis	Number (%)	Number (%)	Number (%)	Number (%)
RB	12 (27.3)	20 (45.4)	12 (27.3)	44 (100)
WT	1 (5.9)	10 (58.8)	6 (35.3)	17 (100)
BL	1 (6.2)	7 (43.8)	8 (50.0)	16 (100)
STS	1 (6.7)	8 (53.3)	6 (40.0)	15 (100)
OS	0	5 (71.4)	2 (28.6)	7 (100)
NB	1 (16.7)	1 (16.7)	4 (66.6)	6 (100)
NHL	0	2 (33.4)	4 (66.6)	6 (100)
HD	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%)**

7.2.2 Clinical presentation of selected childhood malignancies

(a) Retinoblastoma (RB)

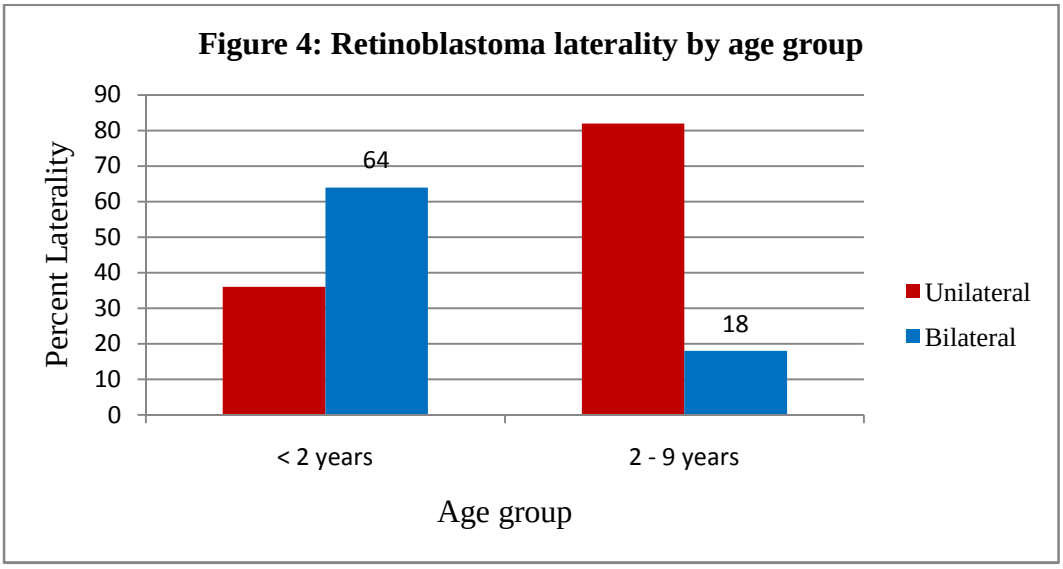
A total of 44 patients with RB were seen during the study period contributing 29.1% of the study population. The mean age at presentation was 2.6 years (range 3 months-9 years) and the male to female ratio was 0.6:1. Seventy three percent (73%) of the patients were three years old or younger. Seven percent (7%) of patients had severe wasting.

Table 3 and figure 4 below summarizes proportion of bilateral RB by age group. Bilateral disease was found in 29.5% of the patients and it was more common in younger patients. Patients younger than 2 years were more likely to have bilateral disease compared to older patients. This difference was statistically significant (P 0.008). Almost all patients less than one (1) year old had bilateral disease (6/7).

Table 4: Retinoblastoma laterality by age group

	Age group (years)		
	< 2	**2-9**	**Total**
Laterality	Number (%)	Number (%)	Number (%)
Bilateral	7 (63.6)	6 (18.2)	13 (29.5)
Unilateral	4 (36.4)	27 (81.8)	31 (70.5)
Total	**11 (100)**	**33 (100)**	**44 (100)**

***Fisher's exact test, P = 0.008 (95% CI 1.38-47.4)



Distinction between intraocular and extraoccular disease was done using histology reports when available or it was done clinically in cases of no histology reports or incomplete reports. This might have caused under staging because microscopic extraoccular disease was likely to be classified as intraocular disease. Metastasis was assessed by clinical examination for obvious lesions such as punched out bone lesions or enlarged regional lymph nodes as well as by BMAC and CSF cytospins cytological confirmation.

Table 5 shows the proportion of different stages of disease at presentation. Twenty seven percent (27%) of patients had metastatic disease.

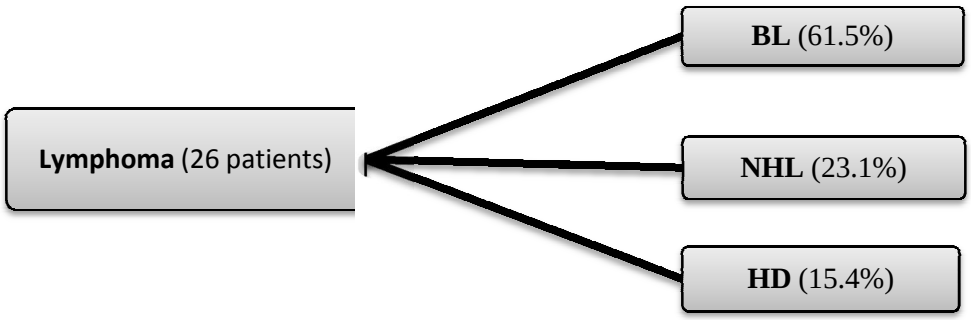
Table 5: Retinoblastoma stage at diagnosis

Stage	Number	Percent
Intraocular	18	40.9
Extraocular	14	31.8
Metastatic	12	27.3
Total	44	100

(b) Lymphoma

Figure 5 summarizes the proportion of the different types of lymphoma seen during the study. Twenty six (26) patients with lymphoma were seen accounting for 17.2% of the study population. Seventy seven percent (77%) were males. BL was the commonest type accounting for 61.5% of all lymphoma patients and this was equivalent to 10.6% of the total study population.

Figure 5: Different types of lymphoma seen during the study



The mean age at presentation was 7.8 years (range 3-13 years) for BL and 6.6 years (range 1-13 years) for NHL. Isolated abdominal disease was found in 25% of BL patients, 31.3% had isolated head and neck disease, 12.5% had trunk disease (1shoulder and 1chest wall) while 31.3% had both abdominal and head/neck disease. One patient with BL (13 years old) was HIV positive. Almost a quarter (23%) of patients with NHL had severe wasting.

All patients (4) with HD were males with mean age at presentation of 12.3 years (range 4-17 years).

Table 6 shows the stage at presentation for NHL using St. Jude staging system. Patients were staged by plain chest radiographs, abdominal pelvic ultrasound, BMAC, CSF cytospins and physical examination. More than 75% of patients with NHL presented with advanced disease (stage III and IV). All patients with intra - abdominal disease had metastasis at presentation.

Table 6: Burkitt Lymphoma and Non - Hodgkin Lymphoma stage at presentation (*St. Jude Staging System)*

	BL	**NHL**	**Total**
Stage	Number (%)	Number (%)	Number (%)
I	3 (18.8)	0	3 (13.6)
II	2 (12.4)	0	2 (9.0)
III	3 (18.8)	2 (33.3)	5 (22.7)
IV	8 (50)	4 (66.7)	12 (54.5)
Total	**16 (100)**	**6 (100)**	**22 (100)**

(c) Leukemia

Acute leukemia ranked third (14.6%) in frequency during the study duration. There were twenty two (22) patients; almost three quarters (72.7%) had **ALL** while the remaining patients (6) had **AML**. The mean age at presentation for ALL and AML was 6.4 years (range 1-15 years) and 6.3 years (range 2-15) respectively. ALL was categorized into low and high grade depending on the initial WBC, age and sex. Male sex, age less than 1 year or greater than 10 years and initial WBC greater than 50000/µL indicated high risk disease. Fifty six percent (56%) of patients with ALL presented with high risk disease. Severe malnutrition was not common with only 4.5% of patients being severely wasted though 36.4% had moderate wasting.

There was one patient with chronic myeloid leukemia **(CML)**. This patient was a five years old girl who presented four months from onset of symptoms. She presented with

(d) Wilm's Tumour (WT)

During the study period 17 patients had WT which is equivalent to 11.3% of the study population. Mean age at presentation was 4.3 years with 75% of patients being 5 years old or younger. Majority (94%) of patients with WT presented with late disease (local spread or metastasis). Twenty five percent (25%) of patients had severe wasting.

(e) Soft Tissue Sarcoma (STS)

STS (15 patients) accounted for 9.9% of the study population and the mean age at presentation was 7 years (range 1-16 years). **Rhabdomyosarcoma (RMS)** was the most frequent STS encountered during the study accounting for 67% of STS patients and 6.6% of the total study population. Mean age at presentation for RMS was 5 years with75% of patients 6 years old or younger. Among patients with Rhabdomyosarcoma, seven (7) had head and neck disease while three (3) had abdominal disease. Two of the three patients with abdominal disease were two years old or younger. Forty percent of STS patients had metastatic disease at presentation.

Three patients had **KS** and all of them were HIV positive. Two of the KS patients had generalized muco - cutaneous disease and the other patient had bilateral cutaneous nodular disease. Mean age at presentation for KS was 12.3 years. One patient (10 years old) had **Ewing sarcoma (ES)** of the hip and another patient had **Sinovial cell** sarcoma. Both patients had metastatic disease.

(f) Osteosarcoma (OS)

Seven patients had OS which was equivalent to 4.6% of the study population. The mean age at presentation was 12.8 years. The lower limbs were the commonest site of disease. Six patients had disease on the lower limbs while one patient had mandible disease. Two patients (28.6%) had metastatic disease of the lung. The remaining patients had advanced local disease.

(g) Neuroblastoma

Of the 151 patients seen during the study period, six (4%) had NB. The mean age at presentation was 4.3 years (range 0.9-12years). Majority of patients (67%) presented with metastatic disease. Forty percent of patients had severe wasting.

7.3 Proportion of patients with pathological confirmation of diagnosis

Pathological confirmation of diagnosis was done by examination of tissue biopsies, FNAC or BMAC. Table 7 summarizes the proportion of patients with confirmed diagnosis by the type of malignancy and the diagnostic modality used. Diagnosis was confirmed in 64.2% of the patients of which 43% were histopathology reports and 21.2% were cytology reports. Tissue for biopsy in contrast to FNAC was frequently used for diagnosis of solid tumors even though sometimes this was done after an inconclusive FNAC report. For solid tumors with confirmed diagnosis, 89% were diagnosed by histopathology. Hematological malignancies were diagnosed by BMAC and all of them had positive reports. Other patients were diagnosed clinically, but in 3 patients a diagnosis could not be reached and therefore these patients were classified as uncertain diagnosis. RB and WT had less proportion of patients with pathological confirmation of diagnosis, 36.4% and 29.4% respectively.

Availability of tissue for biopsy was the most important factor determining the likelihood of confirming the diagnosis. In turn this was greatly influenced by the site of tumor. Easily accessible tumors such as OS and HD had all diagnoses confirmed while patients with intraabdominal malignancies were largely diagnosed clinically except when there was easily accessible peripheral metastasis such as orbital metastasis in NB. At ORCI WT patients are usually given pre-operative chemotherapy before surgery and any invasive procedure of the tumour is discouraged to avoid intra- abdominal seeding of tumour cells. As a result we do not expect histopathology diagnosis in these patients before nephrectomy is done. WT patients who had histopathology reports in this study are those who had nephrectomy before going to ORCI.

Table 7: Diagnosis confirmation status by type of malignancy

Diagnosis	Confirmed		Not Confirmed	
	Histology Number (%)	Cytology Number (%)	Clinical Number (%)	Total Number (%)
RB	16 (36.4)	0	28 (63.6)	44 (100)
WT	5 (29.4)	1 (5.9)	11 (64.7)	17 (100)
ALL	0	16 (100)	0	16 (100)
BL	9 (56.3)	2 (12.4)	5 (31.3)	16 (100)
STS	12 (80)	1 (6.7)	2 (13.3)	15 (100)
OS	6 (85.7)	0	1 (14.3)	7 (100)
NB	2 (33.3)	2 (33.3)	2 (33.3)	6 (100)
AML	0	6 (100)	0	6 (100)
NHL	3 (50)	3 (50)	0	6 (100)
HD	4 (100)	0	0	4 (100)
Others	8 (57.2)	1 (7.1)	5 (37.7)	14 (100)
Total	**65 (43.0)**	**32 (21.2)**	**54 (35.8)**	**151 (100)**

7.4 Proportion of patients with malnutrition

The results of nutritional status in relationship to type of malignancy are summarized by table 8. One hundred and forty three patients (95%) were evaluated for nutritional status. Patients with MUAC for age within median or showed mild wasting were classified together as “Normal”. Severe wasting was found in 12.6% of patients. The percentage of children under five years who had severe wasting was 12.5%. There was variation in the magnitude of wasting by type of malignancy and the difference was statistically significant (P=0.014). BL, NHL and WT contributed 50% of all patients with severe wasting.

Table 8: Nutritional status by type of malignancy

	Nutritional Status			
	Normal	Moderate wasting	Severe wasting	Total
Diagnosis	Number (%)	Number (%)	Number (%)	Number (%)
RB	36 (85.8)	3 (7.1)	3 (7.1)	42 (100)
WT	7 (43.8)	5 (31.2)	4 (25)	16 (100)
BL	7 (43.8)	4 (25)	5 (31.3)	16 (100)
ALL	8 (50)	7 (43.8)	1 (6.3)	16 (100)
STS	8 (57.1)	5 (35.7)	1 (7.2)	14 (100)
NB	3 (60)	0	2 (40)	5 (100)
OS	3 (50)	2 (33.3)	1 (16.7)	6 (100)
AML	5 (83.3)	1 (16.7)	0	6 (100)
NHL	4 (66.7)	2 (33.3)	0	6 (100)
HD	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)

7.8 Proportion of patients with HIV infection

One hundred and forty five patients (96%) were tested for HIV infection. Only 4 patients (2.8%) were HIV positive. Even though very few patients had HIV infection still they presented with expected HIV associated malignancies. All three KS patients were HIV infected and the other patient had abdominal BL. One patient with KS had bilateral nodular disease of lower limbs. The other two KS patients had disseminated ocular cutinious disease. All three KS patients were already on HAART; two had started recently while the

one with lower limb KS was on treatment for many years. The patient with BL was diagnosed during the study and presented with metastatic disease (CNS and bone marrow).

7.9 Summary of results

RB was by far the commonest malignancy. In general most of the childhood malignancies seen during this study had clinical presentation as expected from literature regarding age at presentation, stage at presentation and magnitude of malnutrition. Late presentation was a remarkable finding with mean duration from onset of symptoms to reaching ORCI of seven (7) months. A problem with diagnosis was also noted where by 35.8% of diagnoses were not confirmed. HIV infection was notably low (2.8%) so was the proportion of patients with KS. See table below.

Table 9: Summary of selected findings

Diagnosis	% Total	Mean age (years)	Age range (years)	% Male	% Metastatic disease	% Severe wasting.
RB	29.1	2.6	0.25-9	36.4	27.3	6.8
WT	11.3	4.3	0.75-13	47.1	35.3	23.5
NB	4.0	4.3	0.9-12	50	66.7	33.3
RMS	6.6	5	1-14	40	30	10
AML	4.0	6.3	2-15	50	-	0
ALL	10.6	6.4	1-15	56.3	-	6.3
BL*	10.6	7.8	3-13	62.5	50	31.3
HD	2.6	12.3	4-17	100	0	0
KS**	2.0	12.3	10-16	66.7	0	0
OS	4.6	12.8	8-17	28.6	28.6	14.3
NPC	2.0	14	13-16	33.3	0	0

***One patient was HIV positive.

****All three patients were HIV positive.

8.0 DISCUSSION

8.1 Proportion and presentation of different types of childhood malignancies.

This study has observed a change in the proportion of childhood malignancies at ORCI as compared to other studies in similar settings. Retinoblastoma was by far the commonest childhood malignancy (29.1%) followed by WT, BL, ALL and STS in that order. ALL had similar proportion to BL. This is the first time RB is documented to be the commonest childhood malignancy in a general cancer hospital. From ORCI records BL used to account for almost half of all childhood malignancies seen in a year. In previous studies RB ranked at most third with percent proportion ranging between 11%-13%.[36-38] The usual spectrum of childhood malignancies in Africa has been characterized by high incidence of lymphoma and a low incidence of leukemia.[29-31] In this study if BL, NHL and HD are put together then lymphoma will be the second common childhood malignancy but still with a much smaller proportion compared to findings of previous studies where lymphoma contributed about half of all childhood malignancies. The three malignancies (BL, NHL and HD) are commonly grouped together as lymphomas but these are distinct entities and should be considered separately. BL is usually the predominant type of lymphoma in the tropics including East Africa.[36-38] Similarly in this study BL constituted more than half of all lymphoma patients.

The observed difference in the proportions of the different types of childhood malignancies seen in this study is most likely a reflection of access to ORCI by patients rather than true differences in the incidence of childhood malignancies in the general population. Most of the RB patients seen in this study were referred from CCBRT (a specialized rehabilitation and ophthalmology hospital) while only one RB patient came from MNH. This can explain the lower percent of RB observed in the previous two studies conducted at MNH. The two studies at MNH referred above reviewed histopathology reports. As seen from this study a significant proportion of RB patients (63.6%) did not have histopathology reports and therefore in such a study design a significant number of patients could be missed. Almost all literature addressing the spectrum of childhood malignancies in Africa and other developing countries are retrospective studies. Due to problems in documentation, storage and retrieval of patients' data the results of retrospective studies might not represent the true picture of patients seen in these hospitals. Another possible explanation for the

observed increase in RB patients in this study is the fact that in recent years CCBRT has been actively facilitating referral of RB patients to their hospital by using “focal personnel” in various upcountry health facilities. In addition the proportion of RB patients that are referred from CCBRT to ORCI for preoperative and postoperative chemotherapy has increased due to the close collaboration that has been established between the two hospitals. The decrease in patients with BL seen during this study could as well be a result of difficulties in access to ORCI. Since BL is a fast growing tumor delays in accessing proper treatment can lead to death before patients reach ORCI. However, there could be a true decrease of BL which needs further studies to prove. A retrospective study in Nigeria in 2009 showed a relative increase of leukemia with a relative decrease of BL over a period of 30 years.[33] Two other studies; one in Sudan and another in Egypt have shown an increase in the frequency of leukemia whereby in the Sudan study leukemia (26%) was second to lymphoma.[32, 34] In the current study the proportion of patients with ALL was similar to that of BL (10.6%) and both ranked third. Excluding RB patients, lymphoma would have been first (24.3%) and leukemia second (20.6%), which compared to previous studies it tallies with a relative increase of leukemia and a relative decrease of lymphoma. From the findings of this study no explanation can be given for the observed increase in ALL. Because poor living standards are associated with more lymphoma and less leukemia,[40] the observed increase of leukemia perhaps reflects improvement in the living standards of our people.

A five years old girl who had CML in this study presented after four months of symptoms with moderate anemia and massive splenomegaly. CML is common in adults but rarely encountered in children however there are few case reports of childhood CML and the presentation is similar to our patient. Ewing sarcoma (ES), a rare tumor in African children, was seen in one patient during the study period. This patient had ES of the hip with metastasis. No patients with CNS tumor were seen during this study. A possible explanation is that such patients are usually referred first to Neurosurgeons for surgery and the outcome of surgery has so far been poor therefore they don’t reach ORCI. In addition the incidence of CNS tumors is believed to be low in Africa.[21]

RB, WL and NB are known as tumors of early childhood.[8, 40] In this study the three malignancies accounted for three quarters of patients aged three years or younger. HD, OS,

KS and NPC were common among adolescents as expected from literature. The interaction between genetic predisposition and environmental factors[8, 41, 42] could probably explain the three patients with SCC where two had Xeroderma pigmentosa and one had ocular cutaneous albinism.

Mutation in the RB1 gene is associated with hereditary RB which commonly presents in the first year of life and is often bilateral.[41, 42] In this study all but one, patients below one year had bilateral disease and this decreased to 63.6% in patients below two years. The difference in the proportion of bilateral disease between patients less than two years old and those two years or older was statistically significant (P=0.008) but the 95% CI was wide (1.38-47.4). This could be due to the increase of sporadic RB by two years of age which usually presents as unilateral disease. In our setting where genetic studies are not done to determine RB1 mutations, clinical finding of bilateral RB in patients less than two years can be used as a surrogate for hereditary disease. Distinguishing between hereditary and sporadic RB is important because siblings of patients with hereditary RB are at increased risk for developing RB hence they need regular screening from early infancy.

Stage of disease at presentation is the most important prognostic factor for childhood malignancies and is even more important in countries where treatment options are limited. Advanced disease is associated with poor outcome. Unfortunately most children with cancer in developing countries present late with advanced disease and therefore poor outcome.[7-9, 12, 14] This study had similar findings where more than three quarters of patients with solid tumors presented with either locally advanced disease (51%) or metastasis (35%). There was a long delay between development of symptoms to the time the diagnosis of cancer was made and appropriate treatment started. The mean duration of symptoms before reaching ORCI was seven months (range 1week - 6 years). Similar findings have been documented before by Bekibele[10] in Nigeria and Bowman[11] in Tanzania where the mean duration of symptoms before diagnosis was six (6) months and ten (10) months respectively for patients with RB.

It is however important to note that, in this study, despite 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 cause of delay is within the primary health care providers and the health care

delivery system in general. The problem could be missed diagnosis or mismanagement like what has been observed in this study where some of RB and WT patients had multiple surgeries before referral to ORCI for adjuvant chemotherapy. Other causes could be ignorance by parents/guardians, financial constraints and other family and social logistics associated with leaving home and travel miles away for treatment. Tanzania is a large country with underdeveloped infrastructure therefore late presentation should be expected if all patients with childhood malignancies have to go to ORCI for management. Interestingly, no difference in the stage at presentation was noted between patients from Dar es Salaam and nearby regions and patients from distant regions but the mean duration of symptoms before reaching ORCI was markedly different.

8.2 Pathological confirmation of diagnosis

Among the challenges faced by developing countries in the management of childhood malignancies is the difficulty in confirming diagnosis.[7, 15] A confirmed diagnosis is important for deciding appropriate treatment, prognosis, parent and patient counseling as well as for research purposes. During this study 63.6% of patients had confirmed diagnoses. All patients with leukemia were diagnosed by BMAC but it was often not possible to determine the morphological type of leukemia with accuracy because immunohistochemical studies were not done. This is an important set - back and in one patient treatment had to be changed from that for ALL to AML after unsatisfactory response to ALL chemotherapy. Half of patients with solid tumors had diagnostic histopathology reports and the rest of the patients were diagnosed clinically. Sixty four percent (64%) of patients with RB did not have histology reports despite most of them having undergone eye removal surgery (enucleation or exenteration). A retrospective study done at CCBRT and ORCI in 2005 had similar findings where almost half of RB patients did not have histology reports.[11] Even though clinical diagnosis for RB is acceptable and almost always accurate, histopathology is important for staging of patients and therefore decision on treatment protocol.

Tumor site had a significant influence on the availability of histopathological diagnosis where by patients with easily accessible tumors such as HD, OS and head and neck tumors had the highest proportion of confirmed diagnoses while intra abdominal malignancies had the least. This, among other causes, reflects limited resources in pediatric surgeons,

anesthetists, operating theatres and supportive care in general. The treatment protocol for WT used at ORCI starts with preoperative chemotherapy and any invasive procedure to the tumor is discouraged before nephrectomy to prevent intra-abdominal seeding of tumor cells. This contributed to the low proportion of confirmed WT seen in this study.

8.3 HIV/AIDS and Childhood malignancies

HIV/AIDS is a worldwide pandemic but sub-Saharan Africa is more severely affected. HIV infected children are at an increased risk of developing malignancies.[45] In Africa childhood malignancies commonly associated with HIV infection are KS and B-cell NHL.[48, 49] During this study only four patients (2.8%) were HIV infected. This is low compared to the 22% found at ORCI in 2005 (unpublished study) and 42.2% in Zimbabwe.[53] During the 2005 study at ORCI there was selective screening of patients for HIV therefore determining the actual magnitude of HIV infection was difficult. Those with HIV associated malignancies were more likely to be screened hence skewing the results towards higher prevalence of HIV infection. In the current study HIV screening was done routinely to all patients and 96% of the study population was screened. Kaaya et al.,[51] demonstrated a slight increase of malignant lymphoma at MNH during the HIV epidemic (1992-1994).

Even though there were few patients with HIV infection, they all presented with the commonly described HIV associated malignancies in our region. One patient had bilateral cutaneous nodular KS of the lower limbs, two had generalized mucocutaneous KS and one had metastatic BL. A study in Malawi showed the prevalence of HIV infection to be 93% for children with KS, 4% for BL and 5% for the remaining cancers combined.[52] This is relatively similar to findings of this study because HIV infection was 100% for KS patients and 6.3% for BL patients. Uganda reported a forty fold increase in pediatric KS during the AIDS epidemic.[50] No increase in KS or other HIV associated malignancies was noted in the current study. Possible explanation for this could be the increased use of ARVs among HIV infected children which prevents immune suppression and therefore reduces the susceptibility to developing malignancies.

8.3 Malnutrition and childhood malignancies

Malnutrition is a big problem in developing countries and a major contributor to childhood morbidity and mortality. In Tanzania 3.8% of children under five years are severely wasted (TDHS 2009/2010). In this study severe wasting was more prevalent (12.6%) 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 percentage of severe malnutrition ranging between 9% in Guatemala to 59% in Malawi.[57] The pathogenesis of malnutrition in children with malignancies is related to the triad of reduced intake, increased losses and increased demand. Tumor factors and host response leads to alterations in carbohydrate, lipid and protein metabolism.[55] Similar to what was reported before[56] patients with WT and NHL had high proportion of severe wasting compared to patients with other malignancies. 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 tumor biology and as a result of relatively large tumor 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.[55] The only patient with Ewing's sarcoma in this study had severe wasting.

9.0 STRENGTH AND LIMITATIONS OF THE STUDY

9.1 Strength of the study

This study was done prospectively and the author was involved in data collection and she personally entered and analyzed data therefore she assured the authenticity and completeness of data collected as well as the results obtained.

9.2 Limitations of the study

In one third of patients diagnosis was not confirmed therefore there is a possibility of misdiagnosis in some patients.

Financial limitations of some investigations such as CT scan and MRI scan, and unavailability of histological reports may have lead to under staging of some patients.

10.0 CONCLUSION

1. Retinoblastoma was the leading childhood malignancy at ORCI during the study period in contrast to previous years where Burkitt lymphoma used to be the commonest malignancy.
2. Majority (85%) of patients reached ORCI late with advanced disease.
3. Diagnosis was not confirmed in one third of patients during the study.
4. Severe wasting was seen in 12.6% of children with cancer at ORCI.
5. HIV infection was not common (2.8%) among pediatric patients with cancer at ORCI.

11.0 RECOMMENDATIONS

1. A bigger multicenter study is needed to establish the prevalence of the different types of childhood malignancies in Tanzania.
2. It is important to study why patients present late at ORCI with advanced disease and plan appropriate interventions.

REFERENCES:

1. Yaris N, Mandiracioglu A. Childhood Cancer in Developing Countries. Pediatric Hematology Oncology. 2004;21(3):237-53.
2. Adrian Burton. The UICC My Child Matters Initiative Awards: Combating Cancer in Children in the Developing World. Lancet Oncology. 2006;7:13-14
3. Morris K. Cancer? In Africa? Lancet Oncology. 2003;4(1):5.
4. Philip AP, David GP, editors. Principles and Practice of Pediatric Oncology. Fourth ed: Lippincott Williams & Wilkins; 2002.
5. Wessels G, Hesseling PB. Outcome of children treated for cancer in the Republic of Namibia. Med Pediatr Oncol. 1996;27(3):160-4.
6. Rojers T, Bowley DM, Poole J. Experience and outcomes of nephroblastoma in Johannesburg, 1998-2003. Eur J Pedtiatr Surg. 2007;17:41-4.
7. Barr R, Ribeiro R, Agarwal B, Masera G, Hesseling P, Magrath I. Pediatric Oncology in Countries with Limited Resources. In: Pizzo P, Poplack D, editors. Principles and Practice of Pediatric Oncology. Fourth ed: Lippincott Williams & Wilkins; 2002. P. 1541-52.
8. Abuidris DO, Elimam ME, Nugud FM, Elgaili EM, Ahmed ME, Arora RS. Wilms tumour in Sudan. Pediatr Blood Cancer. 2008;50(6):1135-7.
9. Allan Davidson, Patricia Hartley, Farieda Desai. Wilm's Tumor Experience in a South African Center. Pediatr Bloob Cancer. 2006;46:465-71.
10. Bekibele CO, Ayede AI, Asaolu OO, Brown BJ. Retinoblastoma: The Challenges of Management in Ibadan, Nigeria. J Pediatr Hematol Oncol. 2009;31(8):552-5.
11. Bowman R.J, Mafwiri M, Luther P. Outcome of Retinoblastoma in East Africa. Pediatr Bloob Cancer. 2008;50:160-2.
12. Brown BJ, Bamgboye EA, Sodeinde O. Causes of Death in Childhood Cancer at the Department of Paediatrics, University College Hospital, Ibadan. Afr J Med Sci. 2008;37(1):7-13.
13. Gatta G, Capocaccia R, Coleman MP, et al. Childhood Cancer Survival in Europe and the United States. Cancer 2002;95:1767-72
14. Levi F, La Vecchia C, Lucchini F, Negri E, Boyle P. Patterns of Childhood Cancer Mortality: America, Asia and Oceania. Eur J Cancer. 1995;31A(5):771-82.
15. Banda LT, Parkin DM, Dzamalala CP, Liomba NG. Cancer incidence in Blantyre, Malawi 1994-1998. Trop Med Int Health. 2001;6(4):296-304.
16. UNICEF's Participation in Millenium Development Goal: Reduce Child Mortality. Available from: http://www.unicef.org/mdg/childmortality.html.;[updated 2007]
17. Millenium Development Goal 4: Reduce Child Mortality. Target 1: Reduce by two thirds, between 1990 and 2015, the underfive Mortality. Available from: http://www.unicef.org/mdg/28184-28230.htm.; [updated 2007]
18. Stiller CA, Parkin DM. Geographic and Ethnic Variations in the Incidence of Childhood Cancer. Br Med Bull. 1996;52(4):682-703.
19. Stiller CA, Parkin DM. International Variations in the Incidence of Childhood Soft-Tissue Sarcomas. Paediatr Perinat Epidemiol. 1994;8(1):107-19.
20. Stiller CA, Parkin DM. International Variations in the Incidence of Neuroblastoma. Int J Cancer. 1992;52(4):538-43.
21. Stiller CA, Nectoux J. International Incidence of Childhood Brain and Spinal Tumours. Int J Epidemiol. 1994;23(3):458-64.

22. Stiller CA. International Variations in the Incidence of Childhood Carcinomas. Cancer Epidemiol Biomarkers Prev. 1994;3(4):305-10.
23. Cohen C, Hamilton DG. Epidemiologic and histologic patterns of Hodgkin's disease: Comparison of the Black and White Populations of Johannesburg, South Africa. Cancer. 1980;46(1):186-9.
24. Hesseling PB, Hartley P, Zietsman L, van Lill S, Preston-Martin S, Wessels G. Incidence Of Acute Lymphoblastic Leukaemia in White and Coloured Children in the Western Cape. S Afr Med J. 2004;94(7):533-6.
25. Rochford R, Cannon MJ, Moormann AM. Endemic Burkitt's Lymphoma: A Polymicrobial disease? Nat Rev Microbiol. 2005;3(2):182-7.
26. Rainey JJ, Omenah D, Sumba PO, Moormann AM, Rochford R, Wilson ML. Spatial Clustering of Endemic Burkitt's Lymphoma in High-risk regions of Kenya. Int J Cancer. 2007;120(1):121-7.
27. Stiller CA, Parkin DM. International Variations in the Incidence of Childhood Lymphomas. Paediatr Perinat Epidemiol. 1990;4(3):303-24.
28. Olisa EG, Chandra R, Jackson MA, Kennedy J, Williams AO. Malignant Tumors in American black and Nigerian children: a Comparative Study. J Natl Cancer Inst. 1975;55(2):281-4.
29. Agboola AO, Adekanmbi FA, Musa AA, et al. Pattern Of Childhood Malignant Tumours in a Teaching Hospital in South-Western Nigeria. Med J Aust. 2009;190(1):12-4.
30. Ekanem IA, Asindi AA, Ekwere PD, Ikpatt NW, Khalil MI. Malignant Childhood Tumours in Calabar, Nigeria. Afr J Med Med Sci. 1992;21(2):63-9.
31. Mukiibi JM, Banda L, Liomba NG, Sungani FC, Parkin DM. Spectrum of Childhood Cancers in Malawi 1985-1993. East Afr Med J. 1995;72(1):25-9.
32. Abuidris DO, Ahmed ME, Elgaili EM, Arora RS. Childhood Cancer in Sudan: 1999-2007. Trop Doct. 2008;38(4):208-10.
33. Akang EE. Tumors of childhood in Ibadan, Nigeria (1973-1990). Pediatr Pathol Lab Med. 1996;16(5):791-800.
34. Hosny G, Elkaffas SM. Patterns in the Incidence of Pediatric Cancer in Alexandria, Egypt, from 1972 to 2001. J Egypt Public Health Assoc. 2002;77(5-6):451-68.
35. Akhtar SS, Abu Bakr MA, Dawi SA, Huq IU. Cancer in Libya - A Retrospective Study (1981-1985). Afr J Med Med Sci. 1993;22(1):17-24.
36. Makata AM, Toriyama K, Kamidigo NO, Eto H, Itakura H. The Pattern of Pediatric Solid Malignant Tumors in Western Kenya, East Africa, 1979-1994: An Analysis based on Histopathologic Study. Am J Trop Med Hyg. 1996;54(4):343-7.
37. Carneiro PM, Kalokola FM, Kaaya EE. Paediatric Malignancies in Tanzania. East Afr Med J. 1998;75(9):533-5.
38. Mgaya EM, Kitinya JN. Histopathology of Malignant Tumors of Childhood in Tanzania. East Africa Medical Journal. 2000;77(8):435-9.
39. Draper GJ, Kroll ME, Stiller CA. Childhood cancer. Cancer Surv. 1994;19-20:493-517.
40. Kadan-Lottick N. Epidemiology of Childhood and Adolescent Cancer In: Kliegman R, Behrman R, Jenson H, Stanton B, editors. Nelson Textbook of Pediatrics. 18 ed. Philadelphia: Saunders Elsevier; 2007. P. 2097-100.

41. Tim E, Guy M. ONCOLOGY. In: Neil M, peter J, Rosalind L, editors. Forfar and Arneil's Text Book of Paediatrics. 6th ed. London: Churchill Livingstone; 2003. p. 1095-149.
42. Worth L. Molecular and Cellular Biology of Cancer. In: Behrman R, Jenson H, Stanton B, editors. Nelson Textbook of Pediatrics. 18th ed. Philladelphia: Saunders Elsevier; 2007. p. 2100-4.
43. Yashimoto Y, Kato H, Sihall W. Risk of Cancer Among Inutero Children Exposed to a-Bomb Radiation 1950-84. Lancet 1988;2:665.
44. Stewart A, Webb J, Giles D. Malignant Disease in Childhood and Diagnostic Radiation in Utero. Lancet. 1956;ii:447.
45. Biggar R, Frisch M, Goedert J. Risk of Cancer in Children with AIDS. JAMA. 2000;284(2):205-9.
46. CDC. US HIV and AIDS case reports through December 1997. HIV/AIDS Surveillance report. Year end edition 1997;9:1-44.
47. Granovsky M, Mueller B, Nicholson S. Cancer in HIV-infected Children: A Case Series from the Childrens Cancer Group and National Cancer Institute. JCO. 1998;16(5):1729-35.
48. Chintu C, Athale UH, Patil PS. Childhood Cancers in Zambia before and after the HIV Epidemic. Arch Dis Child. 1995;73(2):100-4.
49. Newton R, Ziegler J, Beral V, Mbidde E, et al. A Case-Control Study of Human Immunodeficiency Virus Infection and Cancer in Adults and Children residing in Kampala, Uganda. Int J Cancer. 2000;92(5):622-7.
50. Ziegler JL, Katongole-Mbidde E. Kaposi's Sarcoma in Childhood: An Analysis of 100 cases from Uganda and Relationship to HIV infection. Int J Cancer. 1996;65(2):200-3.
51. Ephata E Kaaya, Esmeralda CV, Marianne E, et al. AIDS and non AIDS-related Malignant Lymhoma in Tanzania. Afr Health Sci. 2006;6(2):69-75.
52. Sinfield RL, Molyneux EM, Banda K, et al. Spectrum and Presentation of Pediatric Malignancies in the HIV era: Experience from Blantyre, Malawi, 1998-2003. Pediatr Blood Cancer. 2007;48(5):515-20.
53. Chitsike I, Siziya S. Seroprevalence of Human Immunodeficiency Iirus type 1Infection in Childhood Malignancy in Zimbabwe. Centr Afr J Med. 1998;44:242-5.
54. Pollock B, Jenson H, Leach C. Risk Factors for HIV-related Malignancy. JAMA. 2003;289(18):2393-9.
55. Alessandra S, Paul P, Ronald D. Children, Cancer, and Nutrition - A Dynamic Triangle in Review. Cancer. 2004;100(4):677-87.
56. Lori J. Berchard, Jaksic T. Nutritional Supportive Care. In: Pizzo P, Poplack G, editors. Principles and Practice of Pediatric Oncology. Fourth ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 1285-99.
57. Trijn I, Chawanangwa C, Huib C. Nutritional Status at Admission of Children with Cancer in Malawi. Pediatric Blood Cancer. 2008;51:626-8.
58. Oguz A, Karadeni ZC, Pelit M. Arm Anthropometry in Evaluation of Malnutrition in Children with Cancer. Pediatr Hematology Oncology. 1999;16(1):35-41.
59. Theologides A. Anorexins, Asthenins and Cachectins in Cancer. Am J Med. 1986;81:296-8.

60. Picton S. Aspects of Altered Metabolism in Children with Cancer. Int J Cancer. 1998;Suppl 11:62-4.
61. Kurzer M, Meguid M. Cancer and Protein Metabolism. Surg Clin North Am. 1986;66:969-1001.
62. Rickard K, Godshall B. Integration of Nutritional Support into Oncologic Treatment Protocols for High and Low Nutritional Risk Children with Wilms' Tumor. Cancer. 1989;64(49):491-509.
63. Gomez-Almaguer D, Ruiz-Arguelles G. Nutritional Status and Socio-Economic Conditions as Prognostic Factors in the Outcome of Therapy in Childhood Acute Lympoblastic Leukemia. Int J Cancer. 1998;Suppliment 11:52-5.
64. Murry D, Riva L, Poplack D. Impact of Nutrition on Pharmacokinetics of Anti-neoplastic Agents. Int J Cancer. 1998;Suppliment 11:48-51.
65. Rickard K, Loghmani E. Short and Long Term Effectiveness of Enteral and Parenteral Nutrition in Preventing or Reversing PEM in Children with Advanced Neuroblastoma: A Prospective Randomized Study. Cancer. 1985;56:2881-97.
66. Orford J, Gollow I, Brennan B. Fine Needle Aspiration Biopsy in Children. Austr N Z J Surg. 1997;67(11):785-8.
67. Shonubi A, Akiedo O, Salami B. A preliminary Report of Fine Needle Aspiration Biopsy in Superficially accessible Lesions in Children. West Afr J Med. 2004;23(3):221-3.
68. Steel B, Schwartz M, Ramzy I. Fine Needle Aspiration Biopsy in the Diagnosis of Lymphadenopathy in 1,103 Patients. Role, Limitations and Analysis of Diagnostic Pitfalls. Acta Cytol. 1995;39(1):76-81.
69. Wakely P, Kerdos J, Frable W. Application of Fine Needle Aspiration Biopsy to Pediatrics. Human Pathology. 1988;19(12):1383-6.
70. Vietti TJ, Steuber CP. Clinical Assessment and Differential Diagnosis of the Child with Suspected Cancer. In: Pizzo P, Poplack D, editors. Principles and Practice of Pediatric Oncology. Fourth ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 149-59.
71. Richard M. Braverman, Parker BR. Imaging Studies in the Diagnosis and Management of Pediatric Malignancies. In: Pizzo AP, Poplack GD, editors. Principles and Practice of Pediatric Oncology. Fourth ed. Philadelphia: Lipincott Williams & Wilkins; 2002. P. 205-36.
72. Craft A. Childhood Cancer-mainly Curable so Where Next. Acta Pediatr. 2000;89:386-92.

APPENDIX –I

QUESTIONNAIRE Part I.

NAME: ……..... REGISTRATION NO: ……

DATE OF BIRTH: --/--/---- **AGE:** Years…… Months……..

SEX: M/F

RESIDENCE: Region……. District……

INFORMANT: Mother/Father/Other, specify: …….

CONTACT INFO (Tel No.): …….

LEVEL OF EDUCATION: a) Father …… b) Mother…..……....

CLINICAL DIAGNOSIS: ……

1. What are the symptoms? (Mention)

   ……..

   ……

2. When did symptoms start: Date/Duration

   ……..

3. What did you do first?

   ……..

4. When did you attend health facility? Date/Duration.

   ……..

5. Duration from onset of symptoms to first seeking medical care:

   Months…….. Weeks……

6. Time from onset of symptoms to reaching ORCI:

   Months……. Weeks……

7. Name of the immediate referring hospital to ORCI:

……

QUESTIONNAIRE Part II.

NAME: ……...REGISTRATION No: ……

1. CLINICAL DIAGNOSIS: …….

2. ANTHROPOMETRIC MEASUREMENTS:

MUAC (cm) ……. MUAC/Age ……

CONCLUSION: …….

3. STAGE OF DISEASE AT PRESENTATION

a) Extend of disease by physical examination

I. Tumor size

……

II. Metastasis (LNs, Liver,..)

……

III. CNS involvement (nerve palsy, hemiplegia,..)

…….

b) CXR

…….

c) Abdominal-pelvic US

……

d) CSF cytospin

……...

e) BMAC

……..

f) Other (specify)…….

CONCLUSION (Stage): ……

4. HISTOPATHOLOGY REPORT

a) FNAC

…….

…….

b) Tissue Biopsy

……

……

5. FBP

a) WBC count: …… Neutrophils (%): ……. Lymphocytes (%): ……..

b) RBC count: ……. Hb: ……

c) Platelet count: …….

8. HIV Antibody test: …… **DNA-PCR:** …….

9. Treatment Received (Select all that apply)

a) Chemotherapy

b) Radiotherapy

c) Surgery

d) Palliation

10. CONCLUSION

a) DIGNOSIS: .....

b) STAGE: ……

c) NUTRITIONAL STATUS: ……

d) HIV STATUS: …….

REMARKS (data completed, patient died…)

……..

DATE: …… ……

SIGNATURE: ……

APPENDIX - II.

QUESTIONAIRRE Part I. **(Swahili version)**

JINA: …….. Namba ya Mgonjwa: ……

TAREHE YA KUZALIWA: --/--/---- **UMRI**: Miaka ……..… Miezi …..…….

JINSIA: MKE/MME ……

MAKAZI: MKOA …….. WILAYA ……

MSAILIWA: Mama/Baba/Mengineyo, eleza: ……

MAWASILIANO (NAMBA YA Simu): …….

KIWANGO CHA ELIMU: a) Baba: …… b) Mama: ……

UGOJWA WA MTOTO: ……..

1. Dalili za ugonjwa ni zipi? zitaje

……

……

2. Dalili zilianza lini (tarehe/muda)?

……

3. Ulifanya nini mtoto alipoanza kuumwa?

……

4. Lini ulimpeleka mtoto kituo cha afya? (Tarehe/muda)

……

5. Muda tangu dalili kuanza mpaka kwenda kituo cha afya.

Miezi: …..……... Majuma: …….

6. Muda tangu dalili kuanza mpaka kufika ORCI.

Miezi: ……...…. Majuma: …….

7. Jina la hospitali iliyotoa rufaa kuja ORCI.

…….

APPENDIX –III

CONSENT FORM FOR PARTICIPATION IN A STUDY (English version).

Study No……

Title: The Pattern and Clinicopathological Characteristics of Childhood Malignancies at ORCI.

To the Parents/ Guardians of ……..

Greetings!

I am Dr. Lulu Chirande a postgraduate student at MUHAS, the principle investigator of the above mentioned study.

Purpose of the Study

This study aims at generating information on the different types of cancer in children at this hospital (ORCI) and find out important characteristics of these patients such as nutritional and HIV status. This information will help in the management of the current patients and planning for future patients.

Participation

Parent/Guardian will fill a questionnaire administered by the PI or assistant. The child will be examined thoroughly and findings documented in the questionnaire. Weight, height and MUAC will be measured. Important findings will be documented in the patient's hospital file and communicated to the attending physician.

You are free to agree or disagree to participate in this study. Even after signing this form you may withdraw from the study at any time. You don't have to explain why you decided so. Your decision will not affect care to your child in any way.

Risks

No danger or risk is expected to occur to your child as a result of participating in this study. Except for HIV testing, all other investigations done and medication given will be those required for the proper management of your child as offered by ORCI.

Benefits

Participating in this study will benefit your child by having extra people who follow up and see to the timely completion of his/her investigations. Problems identified by the research team will be addressed to the ward team for proper management.

There won't be any payments (in money or kind) for participating in this study.

Consent

I have read and understood the explanation of the study. I accept for my child to be examined and participate in the study.

Signature of the Parent/Guardian.....

Relationship to the child.....

Signature of the interviewer.....

Date.....

For more information or clarification feel free to contact one of the Doctors mentioned below:

Dr. Lulu Chirande (0715378308)

Dr. T. Kazimoto (o713315051)

APPENDIX -IV

FOMU YA RIDHAA YA KUSHIRIKI KATIKA UTAFITI (Swahili version).

Namba ya utafiti ……..

Kichwa cha Utafiti: Aina na sifa za kitibabu na kipatholojia za saratani za watoto katika Taasisi ya Saratani ya Ocean Road, Dar es salaam.

Kwa Mzazi/Mlezi wa……

Salaam!

Mimi Dr.Lulu Chirande ni mwanafunzi wa udhamili Chuo Kikuu cha Sayansi za Afya cha Muhimbili. Ninafanya tathmini ya hiari kwa watoto wenye saratani kuhusu aina na sifa za kitibabu na kipatholojia katika hospitali hii (ORCI).

Dhumuni la Utafiti

Utafiti huu utasaidia kuainisha aina mbalimbali za saratani za watoto wanaotibiwa katika hospitali hii na hali za watoto hawa kama vile lishe na maambukizi ya virusi vya UKIMWI (VVU). Taarifa hii itasaidia kuboresha mipango ya tiba kwa watoto hawa na watakaougua baadae.

Participation

Mzazi/Mlezi atashiriki kujaza dodoso litakalotolewa na mtafiti mkuu au msaidizi wake. Mtoto atapimwa na kuchunguzwa. Matokeo yatajazwa kwenye dodoso na kuwakilishwa kwa madaktari wa wodi ili kuboresha matibabu ya mtoto.

Una uhuru kamili wa kukubali au kukataa kushiriki na haulazimiki kujieleza kwa nini umeamua hivyo. Pia unaweza kujitoa katika tafiti hii wakati wowote hata baada yakusaini form hii. Uamuzi wako hautaathiri huduma kwa mtoto kwa njia yoyote ile.

Madhara

Hakuna madhara inayotarajiwa kumpata mtoto wako kutokana na kushiriki katika utafiti huu. Vipimo vitakavyofanywa na dawa atakazopewa ni zile tuu anazostahili kutokana na ugonjwa wake kufuatana na muongozo wa tiba wa hospitali hii.

Utafiti huu umepata kibali kutoka kwa kamati ya jopo la madaktari wa Chuo kikuu cha Tiba cha Muhimbili wanaohusika kutoa idhini kwa tafiti mbalimbali.

Faida

Mtoto anaeshiriki katika utafiti huu atafaidika kwa kuwa na watu wa ziada wanaofuatilia kufanyika na kukamilika kwa vipimo vyake. Matokeo yote ya muhimu yatawakilishwa ili kuboresha tiba kwa motto.

Hakutakuwa na malipo yoyote (fedha au zawadi) kwa kushiriki katika utafiti huu.

Ridhaa ya makubaliano kushiriki

Nimesoma na kuelewa maelezo kuhusu utafiti huu. Nakubali mwanangu apimwe na kushiriki katika utafiti huu.

Sahihi ya mzazi/mlezi.....

Uhusiano na mtoto.....

Sahihi ya Mdahiri.....

Tarehe.....

Kwa ufafanuzi au maelezo zaidi jisikie huru kuwasiliana na mmoja kati ya madaktari wafuatao.

Dr. Lulu Chirande, namba ya simu 0715 378 303

Dr. T. Kazimoto , simu namba 0713 315 051