FACTORS ASSOCIATED WITH DELAYED PEDIATRIC CANCER DIAGNOSIS AT KIGALI UNIVERSITY TEACHING HOSPITAL.

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A dissertation submitted in partial fulfilment of the requirements for the degree of
MASTER OF GENERAL PEDIATRICS

In the college of medicine and health sciences

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March, 2019

DECLARATION

I declare that this Dissertation contains my own work except where specifically acknowledged

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Signature……..

Date 29th, March, 2019

DEDICATION

To my beloved husband Jean Claudien HATEGEKIMANA

To my beloved daughter Anny Maelys INEMA

To my friends and family

I dedicate this work.

ACKNOWLEDGEMENTS

My thanks goes first to Almighty God for giving me the courage and perseverance to pursue my dream

My respectful thanks goes to Dr Aimable KANYAMUHUNGA my supervisor, and Dr Aimable MUSAFILI my co-supervisor for their guidance and support all along the finalisation of this work

I thank to Dr Jean Damascene TWAGIRUMUKIZA for his help for data analysis

I am grateful to University of Rwanda and Kigali University Teaching Hospital (CHUK) for the knowledge and competence acquired during the four years of my postgraduate training.

I acknowledge the role of the pediatric staff in the referral hospitals for their continuous training.

I would like to thank the Ministry of health of the Republic of Rwanda for supporting me.

Many thanks to my family especially my husband Jean Claudien HATEGEKIMANA, my daughter Anny Maelys INEMA and my friends for their support and warm encouragement all along my studies.

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ABSTRACT

Background

Although no study has been done in Rwanda investigating delay in diagnosis of childhood cancer, early diagnosis is a fundamental goal as it allows time for treatment and prevent unnecessary complications.

Our study determines the diagnosis delay and factors influencing the time to diagnosis at Kigali University Teaching Hospital (CHUK)

Methods: This cross- sectional hospital based study included 100 children diagnosed with cancer at Kigali University Teaching Hospital from January 2018 to December 2018.The interval between symptoms onset and final diagnosis for each child was calculated. This was correlated by univariate and multivariate analyses with the child's age at diagnosis, sex, type and site of malignancy, family residence, distance to health care facility, family size, socioeconomic status, parents' age, parental educational level, qualification of the first healthcare provider consulted as well as duration of investigations at CHUK.

Findings: The median total diagnosis delay was 34 days categorized into patients and/or parents related delay (12 days) and health system related delay (18 days). Statistically significant patients' factors associated with delayed diagnosis were age of the child at diagnosis, large family size, low parental education, low socioeconomic status, consulting traditional healers, residence and geographical distance from home to primary health care. There is a moderate positive linear correlation between patient delay and both mother's age and family size. The qualification of first health care provider consulted and duration of investigations at CHUK influenced health system related delay. Sex and parents' age didn't show any statistically significant influence on the delay. Malignancy type and tumor site significantly affected the time of diagnosis. The lowest median delay was associated with lymphomas (18 days) and leukemias (24 days). The highest delay was observed in children with osteosarcoma (54 days).

Conclusion: There is a significant delay in diagnosis of childhood cancer at Kigali University Teaching Hospital. Education of parents and health workers on early warning signs of cancer and accurate diagnosis are recommended.

LIST OF SYMBOLS AND ACRONYMS

ALL: Acute Lymphoblastic Leukemia

AML: Acute Myeloid Leukemia

BL: Burkitt Lymphoma

CHUK: Centre Hospitalier universitaire de Kigali

CMHS: College of Medicine and Health Sciences

IRB: Institutional Review Board

KS: Kaposi Sarcoma

LIC: Low Income Countries

RSM: Rabdomyosarcoma

SD: Standard Deviation

UCH: University College Hospital

CHAPTER I. INTRODUCTION

1.1. Background

Though cancers are relatively rare in children, they constitute an important cause of morbidity and mortality (1) . One way of reducing the mortality of childhood cancers is early diagnosis and treatment, because they are known to have a better response to treatment and progress faster if not treated. In developing countries, early and accurate diagnosis of cancer remains a great challenge due to social economic factors as well as weaknesses in the health systems. The impact of the delay of diagnosis on the cancer related morbidity and mortality is, as expected to be tremendous. Many scholars have discussed this subject and found that the factors associated with the delay can be grouped into three main categories: those related to patient and/or parent, to the disease and to the healthcare(2)(3)(4) Health care system factors include access to services, knowledge of providers, as well as availability of diagnostic capabilities. Patient-related factors include age, gender, socioeconomic status of the parents, and parent's level of education whereas cancer-related factors are mainly related to its clinical presentation and progression (3)(5).

We determined the various types of delay intervals seen among pediatric oncology patients at Kigali university teaching hospital, and investigated factors that influence the time to diagnosis.

1.2. Problem statement

Rwanda as a developing country has made great achievements regarding child health, but early and accurate diagnosis of cancer remains a great challenge due to social economic factors as well as weaknesses in the health systems. The impact of the delay of diagnosis on the cancer related morbidity and mortality is as expected to be tremendous. Early stage diagnosis has a positive effect on prognosis and the quality of life of children with cancer .This study is expected to provide data that will help to understand different factors associated with diagnostic delay in childhood cancer, as to our knowledge no similar study has been done in Rwanda. Thereafter, evidence based recommendations will be issued to address the problem.

1.3. Study Questions

- Is there any patient/Parent related or healthcare system related delay in diagnosis of pediatric cancer for patients admitted at Kigali University Teaching Hospital (CHUK)?

-Are factors related to patients or parents causes of diagnostic delay?

-Are factors related to health care system causes of diagnostic delay?

- Is the type of the tumor/cancer related to the diagnosis delay?

1.4. Study Objectives

1.4.1. Broad Objective

To assess the factors associated with childhood cancer diagnosis delay at CHUK

1.4.2. Specific Objectives

1. To determine the types of pediatric cancers diagnosed at CHUK during the study period.
2. To evaluate the mean duration of pathology diagnosis from first consultation at health facility to pathology result delivery.
3. To evaluate the association between patient and parental factors with diagnosis delay.
4. To determine the health-care system related factors associated with diagnosis delay

CHAPTER 2: LITERATURE REVIEW

2.1. Childhood cancer epidemiology

Childhood cancer account for 0.5% of all cancers worldwide. In 2014 in The United States, 15,780 incident cases of pediatric cancer were diagnosed among children and adolescents aged 0–19 years, with 10,450 cases in children aged 0–14 years and 5,330 cases in adolescents aged 15–19 (6)(7) Incidence rates of cancer differ between various countries. Differences may be due to genetic predisposition, exposure to infectious diseases, and other environmental factors (8)(9) Poor disease reporting remains the main challenge to the knowledge on cancer epidemiology in low in-come countries.

The mean annual leukemia incidence per million children was 16.4 (SD13.6) in low income country, 36.5 in Middle income country, and 40.9 in high income country (8). An observation that suggest that leukemia incidence is systematically underestimated in Low income country.

In contrast, the incidence of non -leukemia cancers was 85 (SD 37) in Low income country, 70 (SD 20.5) in Middle income country, and 89 (SD 14) in High income country, which does not support a pattern of systematic underestimation of non-leukemia in low income country. After exclusion of Kaposi sarcoma, which is common in Uganda and Zimbabwe, the incidence rates of non-leukemia cancers in Low income country decreases to 76. LIC with the lowest reported incidence rates of leukemia have a very high incidence of malaria (>200 cases per 100 population per year), suggesting that patients with leukemia may die with anemia and fever that is attributed to malaria, which is 10,000 times more common than leukemia in endemic areas (8).

The proportion of childhood cancer is higher in Africa, than in the developed countries, at 4.8% of all cancers and is mainly due to the higher proportion of children of the total population. In parts of Africa, Burkitt's Lymphoma (BL) is the most commonly occurring cancer, with an incidence rate estimated at 40–100 per million per year in children under 15 in equatorial Africa whereas the southern and western parts of Africa have a low overall incidence of all childhood cancers . The high incidence of BL is commonly associated with Epstein–Barr virus and holoendemic malaria (10).

A study of 21 centers in 19 sub-Saharan African countries analyzed the distribution of childhood cancer in Africa between 1985 and 2011. In Southern Africa, Kaposi sarcoma was the most common paediatric malignancy in Mozambique 15.8%, and the second most common in Zambia 15.6%, with 12.4% in Malawi. In eastern Africa, Uganda recorded KS as the most common tumour

in children 22.0% while two Kenyan centers reported mainly BL 25.1% and 37.1%, respectively (10). Epidemiology data from western Kenya confirmed non- Hodgkin lymphoma as being the most common childhood cancer in the region (10)

In Western Africa, Non –Hodgikin lymphoma was the most common in Ghana (53.6%), in the Ivory Coast 73.6%, and in Mali 32.7% (4). Nephroblastoma remains one of the most common solid tumours in Africa, exceeding 10% of all pediatric cancers in many countries:Rwanda 26%,Ivory Coast 14.5%, Mali 17.6%, Congo 15.5% (10)(11)

However, Cancer incidence in developing countries is lower than what is expected mostly due to low level of awareness about cancer among clinicians and populations, inadequate access to health care, lack of diagnostic equipment and incomplete recording cases.(12)

2.2. Review on the delay of childhood cancer diagnosis

Many studies have been done on factors associated with delayed pediatric cancer diagnosis, in different parts of the world especially in developing countries (1,3,13–16)(4)

In Kenya, F. Njuguna et al recruited 99 children diagnosed with cancer between August 2013 and July 2014, and determined the factors that influence the time to diagnosis and start of treatment. In their study they found that Median total delay was 102 (9–1021) days.

The Median patient delay (4 days) was significantly shorter than health care system delay (median 87 days; $P < .001$). Lack of health insurance at diagnosis and use of alternative medicine before attending conventional health services were associated with a significantly longer patient delay (3).

A retrospective study was conducted in Egypt and included 172 children from two pediatric oncology units, this study also investigated the interval between symptoms onset and final diagnosis for each child, they found that the median total diagnosis delay period was 47 days caused by patients and/or parents (8 days) and diagnosis (28 days)(1). Statistically significant patient factors associated with delayed diagnosis were age (<5 years), lower parental education, and socioeconomic status. Malignancy type and tumor site significantly affected the time for diagnosis(1).

A Nigerian study done at the University College Hospital (UCH), Ibadan.by Biobele Jotham Brown et al, found that the Delay in diagnosis of childhood cancer is a significant problem in Ibadan, with a Median parent delay of 2 weeks, median health system or physician delay of 8 weeks, and median overall delay of 15.5 weeks(17). Overall delay had a negative correlation with age of child at diagnosis,

a positive correlation with the number of health facilities visited before diagnosis, and was shorter in mothers younger than 40 years of age (17).

Overall delay was significantly different among the diagnostic tumor categories, with Burkitt lymphoma having short time and retinoblastoma with long time (17).

In South Africa, Dr. Daniela Cristina Stefan and Femke Siemonsma Combined prospective and retrospective study of 194 children with cancer at Tygerberg Hospital, Cape Town, diagnosed between 2000 and 2009. 126 patients were included through review of the medical charts and 68 through interviews with the parents. They found That there was a considerable delay in childhood cancer diagnosis mostly due to physician delay of 20 days average(13)

The median total diagnosis delay was 34 days. The median patient delay was 5 days

Gender, age or ethnicity of the children, as well as parental level of education did not have a significant influence on the total time to diagnosis(13)

In south-eastern Turkey, a study done aiming to identify factors associated with delay in diagnosis in children with cancer was done. Clinical records of 682 patients with cancer were evaluated, they found that parent delay, physician delay and total delay were determined at 20, 23 and 60 days. Delay in diagnosis was associated with age, type and stage of the tumor, the first physician consulted and area of residence.(4)

Though there are variations between different countries but in general physician delays were longer than those related to parents 'or patients. Among the patent factors associated with the delay a positive association between the patient's age at diagnosis and diagnosis delay was observed. Sex and ethnicity were not consistently associated with patient delay. High parents' level of education, low parental age was positively associated with shorter delays of diagnosis.

When grouped according to different cancer types, delays in diagnosis were also found to be variable with nephroblastoma, Leukemia, having the shortest and brain tumors having the longest (2)(4)

In Indonesia, K. Handayani et al. analyzed both diagnosis and treatment delays. The diagnosis delay combining the patient and physician delays respectively followed a similar pattern as in above mentioned settings, the latter being longer. Again, alternative healthcare is an important player in this country (15).

CHAPTER 3. METHODOLOGY

3.1. Study Site

This study was conducted in the Department of Pediatrics at Kigali University Hospital(CHUK) CHUK is one of the national referral hospitals, located in Kigali the capital city of Rwanda. CHUK being the one referral hospital which has Hemato-oncology unit receives many children transferred from all over the country in different District Hospitals for further investigations and management.

3.2. Study Design

This was a cross-sectional hospital-based study.

3.3. Study Period

The data collection was done during a period of 12 months from January 2018 to December 2018.

3.4. Study population

Children diagnosed with cancer in the Department of Pediatrics from January 2018 to December2018.

3.5. Inclusion Criteria

All children admitted at Kigali University Hospital(CHUK) in study period to whom a diagnosis of malignancy was made.

3.6. Exclusion Criteria

In this study we have excluded:

- Those who did not consent for study participation
- Children died before the confirmation of malignancy

3.7. Procedures at enrollment

All Parents or Legal Guardians who had children diagnosed with malignancy during the study period, were explained the study objectives and benefits. If they accepted to participate in the study and fulfilled the inclusion criteria, a consent form was signed and a structured questionnaire was administered to participants using a face-to-face interview by the main investigator.

3.8. Definition of Variables

3.8.1. Dependent variables

A Total delay was defined as time in days from the first cancer symptoms to the time of cancer diagnosis.

Patient or parent delay was defined as time in days from first cancer symptoms to the time of first consultation to primary healthcare.

Health care system related delay was defined as time in days from first consultation to primary health care to final diagnosis of cancer

3.8.2. Independent variables

The following independent variables were collected: Sex of the child, age of the child, mother's age, father's age, social economic status, educational level of the parent's(mother and father), family size, geographical distance from home to primary health care.

3.9. Data management and statistical analysis

Data were collected using a well-designed and pre-checked questionnaire then entered in Epidata software version 3.1 and exported to IBM SPSS statistics version 25 for analysis. Univariate analysis was done by frequencies, percentages and bar charts for categorical variables and for continuous variables (patient delay, healthcare system delay and total delay), median values were used as they were not normally distributed (meaning they were skewed). Continuous variable measurements were compared for linear correlation using Pearson's correlation. Comparison of continuous measurements and categorical variables was done using Non-parametric tests where Mann Whitney U test was used for ordinal variables with 2 groups and the Kruskal Wallis test was used for ordinal variables with more than 2 groups. The confidence level was set at 95% meaning that the statistical significance was set at $p<0.05$.

3.10. Sample Size

We used convenience sampling with goal of meeting the calculated sample size of 70 patients (see below).

We conducted a survey at CHUK in the Department of Pediatrics. In the year 2016, there has been 2914 admissions, 85 of them (3 %) were cancer cases. A sample size was calculated from this proportion as following:

$N=[Z^2 X p X (1-p)] / \varepsilon^2$

Z: z value (example: 1.96 for 95% confidence interval)

p: Proportion (3%)

ε: Standard error: 0.04

$N= [(1.96)^2 X 0.03 X (1 - 0.03)] /0.04^2$

$N\approx 70$

CHAPTER 4: RESULTS

A total of 1660 children were admitted at CHUK, Department of Pediatrics during the study period starting from January 2018 to December 2018. Among them, 108 patients presented with malignant tumors representing 6.5% of the admissions. One hundred patients/guardians were interviewed; 4 others refused to participate and other remaining 4 were discharged before being interviewed. Among the 100 patients/guardians interviewed, 56 were male and 44 were female. They were aged 3 months to 15 years.**(Figure 1)**

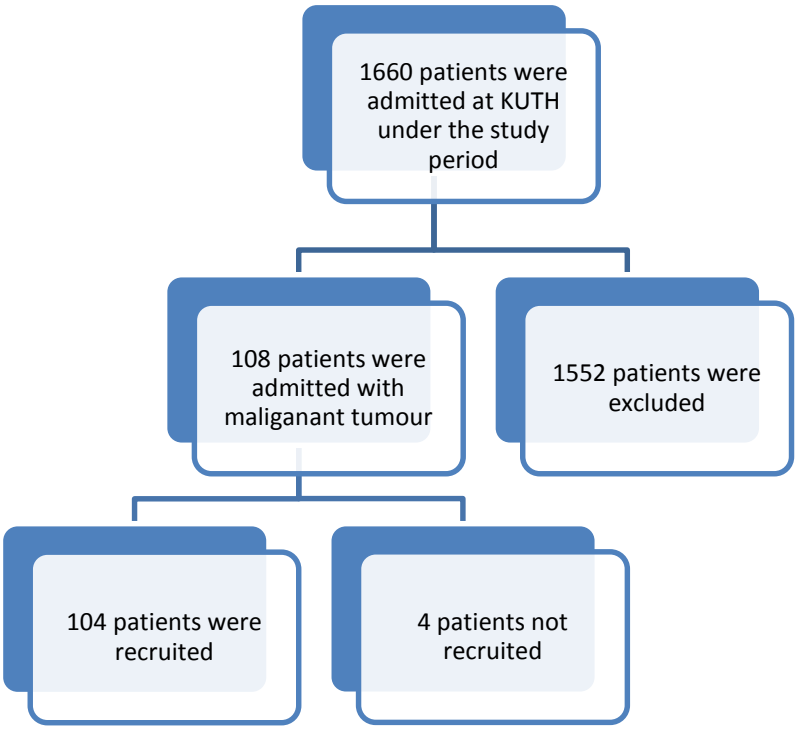

Figure 1: *Screening and recruitment of patients in our study*

4.1. Parents/patients and sociodemographic characteristics

Analysis of family social demographic characteristics showed that, parents/patients delay was longer in mothers and fathers with low level of education, than those with a high level of education (Kruskal Wallis test, P<0.001)

There was no significant difference in maternal and paternal age with respect to parents/patients delay (Mann-Whitney test, P=0.538, and 0.334). A significant difference was noted in parents/patient delay with respect to parent's economic status, residence and travel distance from home to primary health care (Mann–Whitney test, P<0.001). Those in Ubudehe category I, II have a longer delay than those in Ubudehe category III with a P<0,001

Patients walking for more than 2 hours to reach the primary health care facility have a longer delay than those who used less than 2 hours. Patient living in rural areas have a longer delay compared to those living in urban areas

There was a significant difference in parents/patients delay with regard to family size (Kruskal Wallis test, P<0.001). Where Families with a large size have a longer delay than families with small size.

Patient's sex did not show any statistical significance (Mann-Whitney U test, P=0.105), but patient's age showed a greater significance (Kruskal - Wallis test, P<0.001) where children more than 10 years old have a longer delay than children 5 years and less.

Traditional healers consultation influenced significantly parents/patients related delay with a mean of 20 days for those who first consulted traditional medicine, and 6 days for parents who did not consult traditional healers (Mann-Whitney test, P<0.001). (Table 1)

4.2. Frequency of pediatric cancer at CHUK

The most observed cancer was leukemia representing 29% with 34.6% of them were AML cases, and 65.4% of ALL. The less frequent type of cancer was RSM representing 2**%.** (Figure 2)

4.3. Overview of delay interval in days

Health care system related delay was longer than parents/patients related delay. The median patient/parent delay was 11.5 days (2-62). The median healthcare system delay was 17.5 days (4-60). The median total delay was 33. 5 days (7-99). (Table 2)

4.4. Diagnostic delay by site and type of cancer.

There was a significant difference in total delay for different types of cancer (P<0,001). Greater delay was observed in patients with Osteosarcoma with a median of 54 days, than in patients with leukemia with a median of 24 days. (Table 3)

4.5. Relationship between healthcare factors and healthcare system related delay in days.

The first health care provider significantly affected health care system related delay (Kruskal – Wallis test, P<0,001) where patients who consulted pediatrician first had a shorter delay than those who were first seen by nurses. (Table 4)

Variables	Categories	N	Mean (SD)	Median	Range	P value
Mother's education	No school	26	24 (12.6)	22	4-50	<0.001
	Primary	53	17.2 (15.0)	12	3-62	
	Secondary	18	5.8 (4.1)	5	2-16	
	University	3	3 (1.0)	3	2-4	
Father's education	No school	19	21.2 (13.2)	20	4-50	<0.001
	Primary	56	18.4 (14.2)	14	3-62	
	Secondary	19	7.5 (7.3)	5	2-33	
	University	5	3 (0.7)	3	2-4	
Mother's age	<40 years	97	15.7 (12.9)	10.5	2-60	0.538
	≥40 years	3	28.6 (29.9)	20	4-62	
Father's age	<40 years	81	15.4 (13.1)	10	2-60	0.334
	≥40 years	18	19.2 (15.9)	16	3-62	
Economic status	Cat I & II	55	22.2 (15.6)	20	3-62	<0.001
	Cat III & IV	45	9.5 (7.0)	7	2-33	
Residence	Urban	43	10.9 (10.9)	7	2-60	<0.001
	Rural	57	20.6 (15.1)	18	3-62	
Family size	Small	5	22.8 (23.1)	10	6-60	<0.001
	Medium	61	12.2 (11.5)	7	2-60	
	Large	34	23.2 (14.7)	20	4-62	
Travel distance to health facility	<2 hours	61	11.0 (9.8)	7	2-60	<0.001
	≥2 hours	39	25.0 (15.9)	26	17-99	
Gender	Male	56	18.5 (15.3)	13.5	2-62	0.105
	Female	44	13.9 (12.5)	10	2-60	
Age of the child	<5 years	36	13.4 (12.2)	8.5	2-60	0.001
	5-10 years	38	13.2 (11.5)	9	2-50	
	>10 years	26	25.5 (16.8)	20	7-62	
Traditional healer consultation	Yes	54	23.3 (15.2)	20	4-62	<0.001
	No	46	8.5 (7.5)	6	2-32	

Table 1: *Parents/Patients delay and social demographic characteristics*

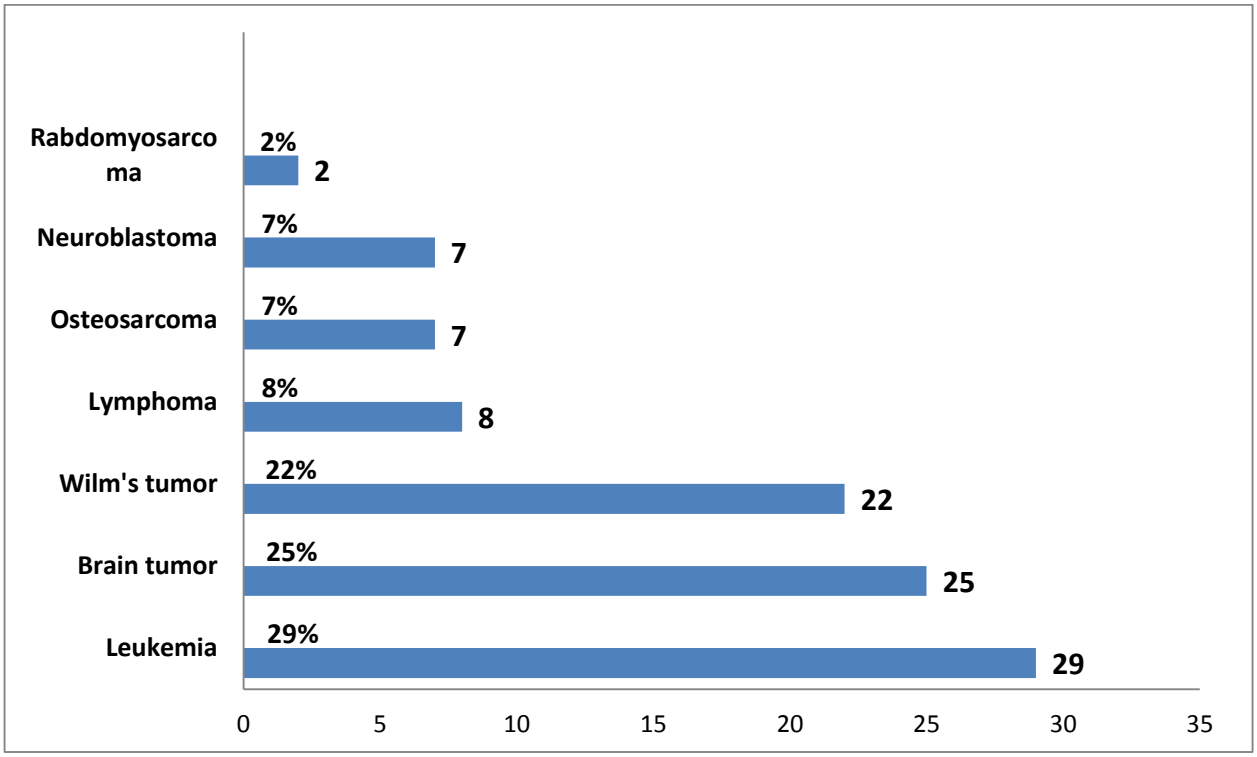

***Figure 2**: Types and proportion of pediatric cancers*

Statistical measure	Parent/patient delay	Health system delay	Total delay
Mean	16.5	18.8	35.5
Standard deviation	14.3	9.25	20.2
Median	11.5	17.5	33.5
Range (Min-Max)	2-62	4-60	7-99

***Table 2:** Overview of Delay interval in days*

4.6. Parents/Patients delay, Health care system delay with type of cancer.

There was a significant difference in patients/parents delay and health system related delay with regard to type of cancer diagnosis where patients who had leukemia had a shorter parents/patient delay of 4 days median, and 17 days of health system related delay. (Table 5)

4.7. Time from Investigations to Results Delivery.

Analysis of duration of investigations at CHUK with regards to types of cancer showed that patients presenting with solid tumors had a longer delay in diagnosis than patients presenting with Lymphoma

and Leukemia with Osteosarcoma having a median delay of 17 days, Lymphoma and leukemia having 6 and 9 days respectively. (Table 6)

Characteristics of cancer	N	%	Median total delay (range: min-max) in days	P value
Site of cancer				
Abdomen	33	33.0	38 (9-93)	
Hematological	30	30.0	23.5 (7-61)	
Brain	25	25.0	40 (16-99)	<0.001
Bone	7	7.0	54.0 (26-96)	
Neck	4	4.0	17.5 (17-42)	
Type of cancer				
Leukemia	29	29.0	24 (7-61)	
Brain tumor	25	25.0	40.0 (16-99)	
Wilm's tumor	22	22.0	25.5 (9-93)	
Lymphoma	8	8.0	17.5 (7-70)	0.001
Osteosarcoma	7	7.0	54.0 (26-96)	
Neuroblastoma	7	7.0	41.0 (26-54)	
Rhabdomyosarcoma	2	2.0	42.5 (35-50)	
Clinical stage at diagnosis				
Early stage	21	21.0	18.0 (7-28)	<0.001
Advanced stage	79	79.0	38.0 (9-99)	

Table 3*: Length of Delay in days by Type and site of cancer*

Healthcare factors	N	Mean (SD)	Median (range)	P value
Level of first health care provider Consulted				
Nurse	85	20.2 (7.5)	19 (7-39)	
General practitioner	10	13.1 (10.6)	7 (4-60)	0.001
Pediatrician	5	7.0 (2.0)	8 (4-9)	
Total turn -around times				
<5 times	56	16.2 (7.2)	15.5 (4-34)	0.002
≥5 times	44	22.2 (10.4)	19.5 (6-60)	

Table 4*: Relationship between healthcare factors and healthcare system related delay in days*

Type of tumor/cancer	N (%)	Median Patients/parents delay in days	Median Healthcare system delay in days
Leukemia	29 (29.0%)	4 (2-40)	17 (4-35)
Brain tumor	25 (25.0%)	21 (5-62)	20 (10-37)
Wilm's tumor	22 (22.0%)	14 (2-60)	13 (6-33)
Lymphoma	8 (8.0%)	7 (3-20)	11 (4-60)
Osteosarcoma	7 (7.0%)	20 (7-60)	32 (19-39)
Neuroblastoma	7 (7.0%)	20 (4-31)	20 (13-37)
Rhabdomyosarcoma	2 (2.0%)	23.5 (14-33)	18 (17-19)

Table 5*: Parents/Patients delay, Health care system delay with type of cancer*

Characteristics of cancer	n	%	Time from investigations to Results [Median (min-max)]	P value
Site of cancer				
Abdomen	33	33.0	9 (5,60)	
Hematological	30	30.0	9 (4,20)	
Brain	25	25.0	10 (4,18)	0.001
Bone	7	7.0	17 (10,20)	
Neck	4	4.0	6 (5,16)	
Type of cancer				
Leukemia	29	29.0	9 (4,20)	
Brain tumor	24	24.0	10 (4,18)	
Wilm's tumor	22	22.0	7.0 (5,13)	
Lymphoma	8	8.0	6.0 (4,60)	0.001
Osteosarcoma	8	8.0	17 (10,20)	
Neuroblastoma	7	7.0	10 (8,20)	
Rabdomyosarcoma	2	2.0	11 (10,12)	

Table 6*: Time from Investigations to Results Delivery*

CHAPTER 5. DISCUSSION

This study was querying a possible delay in childhood cancer diagnosis and different factors related to this delay. To our best knowledge, it is the first to analyze that problem in Rwanda. It has demonstrated that the delay in childhood cancer is a big issue to be addressed in order to ensure an optimal management.

At a satisfactory extent, we have achieved our sample size target. Moreover, CHUK is the largest referral hospital in Rwanda. Therefore, our findings can be reflection of the countrywide situation. However a population based study is recommended.

Some of our findings are in support of those earlier described in other studies done in developing countries, but also have some other peculiarities.

There is a remarkable similarity of relative frequencies of the most important childhood malignancy published by different scholars. In our case, similarly to other publications, leukemias are more frequent followed by CNS, Wilm's tumors and lymphoma(18–20)

One exception is noted in Cote d'Ivoire where Burkitt lymphoma is largely the most frequent (21)

5.1. Overview of diagnostic delay

In our study the median total delay of 34 days, the median health care related delay of 18 days are similar to the study done in South Africa by Stefan and Siemonsma, where the total delay was 34 days, and median physician delay of 20 days. However, the 12 days patient-related delay in our study was two times longer than what was observed in South Africa (13). This difference may be due to a higher capacity of South Africans to afford the cost of medical care.

On the other hand, we observed a shorted mean total delay than what was seen in Nigeria and Kenya (109 and 102 days respectively) (3). This shorter delay compared to some other countries in Africa may be explained by the recent Rwandan government's policies aiming at improving child health and reduce under-five mortality rates. These policies includes Community health insurance which allows a relatively early consultation.

Our findings are also in keeping with other studies done in in different countries (1,3,13)(22) revealing that health care system related delay is longer than parent delay(17) with exception of Nigeria where parents/patients' delay is longer than healthcare related delay(17)(23)

5.2. Parental level of education and socio-economic status.

Parent's level of education and social economic status were found to be factors affecting patient related delay. Liliana Vasquez et al. described the same tendency in Peru(24) Parents with higher level of education and higher social economic status tend to consult earlier than those with low education level. This demonstrate how both health awareness and financial status affect the time of consultation.

Moreover, most of parents who don't have the community health insurance for all family members and those who consult traditional healers before consulting the government's primary health care are found in low social economic level and this has contributed to the delay.

Parents with a high level of education have tendency to consult pediatricians first, which also shortened the healthcare system related delay in this category. A similar observation was made in Egypt, where families with higher level of education and socioeconomic status tended to request private hospitals and clinics for care with higher levels of clinical expertise (1). However, studies done in Kenya, Nigeria and South Africa, showed that level of education did not have any effect on the total delay (3,13,17).

5.3. Type of cancer and patient related delay.

We noted that the median patient delay was affected by the type of cancer which was shorter in patient with lymphoma and Leukemia, and longer in tumors presenting as masses (Brain tumor, bone tumor, and rhabdomyosarcoma).This can be explained by the fact that the features of leukemias and lymphomas present with more alarming symptoms to the parents than deep-seated brain tumors which often present with non-specific symptoms. But this is different from what was found in South Africa, where the type of tumor did not have a significant influence on any type of the delay(13). Our findings also differ to what was seen in Peru ,where significant differences in the latency to diagnosis for different types of cancer showed that Hodgkin lymphoma had a longer delay than Wilms tumor (24)

5.4. Demographic parameters and patient related delay.

There was no significant effect on patient/parent delay between male and female children in our study. This is consistent with most reports in literature(1,3). This show that there is no difference in health seeking behavior of parents regardless of the gender of the child.

In contrast to the patient sex, this study noted that the younger the children the shorter the parents/ patient related delay and total delay. Children younger than 5 years had shorter delay compared to

children older than 10 years. Jette Møller Ahrensberg et al., Amos Hong Pheng Loh et al. and Liliana Vasquez et al. reported the same findings in Danmark, Singapour and Peru respectively(25,26)(24) An exception is noted in Nigeria where there was no difference among the age groups(17). This can be due to the nature of aggressive malignancies affecting young children which lead to rapid appearance of symptoms and therefore, families tend to consult earlier.

Parent's age did not have a significant influence on any type of the delays ,and this is similar to what was found in many studies (1,13,17)

5.5. Number of consultations

Our study also showed that patients who consulted many times before being admitted at CHUK for diagnosis had a longer delay than those who consulted few times. This is again similar to the findings of Haimi et al in Israel (17) who observed that the higher the number of doctors the child had visited before the diagnosis, the longer the lag time (17).

5.6. Family size and patient delay

Family size affected significantly the patient/parent related delay, where larger families had long delay than small and medium ones. In our settings parents with larger families have difficulties in having health insurance, most of them are in low social economic categories and all of these affect the time for them to consult earlier.To our best knowledge, no previous study has looked at this important parameter

5.7. Geographical distance

Patients living in urban areas, consult earlier than those living in rural areas, and this affected the patients/parents delay as the patients from urban had shorter delay than those from rural.

Geographical distance to the primary health care also contributed to the patient/parent delay with patients coming from far and walking for an estimated two hours time had a longer delay compared to those walking for less than two hours. F. Njuguna et al. considered the geographical distance with means of transport and patients' perception on whether the transport to the hospital is expensive. No significant difference was found between geographical distance to health facilities and any type of delay(3)

5.8. Alternative healthcare consultation

In our case, 54% of patients consulted traditional healers resulting in a longer delay than those who consulted conventional health facility first with a delay of 20 and 6 days respectively. This can be explained by the misbelief in our society that disease presenting with non-specific symptoms or rapid growing disease are due to poisoning which they think is only treated by traditional medicines. Seeking

alternative healthcare has also been noted by different authors especially in Africa: 59% and 37% of patients sought different types of non convetional medicine in Kenya and Nigeria respectively (3,14)

5.9. Health workers qualification and healthcare related delay

The qualification of the first health care provider consulted affected significantly the health Care system related delay, where the patients first seen by pediatrician had a shorter delay than those seen by a nurse or a general practioner, this is similar to the study done in Nigeria, Peru (17)(22)and in Canada(27).

There is therefore the need to educate health care providers at primary and secondary care levels on the need for early referral of cases that constitute diagnostic difficulties to them.

In our situation the longer healthcare system delay was due to the fact that the patients are admitted for many days at health centers and district hospitals before consulting referral hospitals and tertiary level hospitals with diagnostic capabilities.

5.10. Factors related to the disease influencing the delay

A longer delay from the time of first symptoms to the time of diagnosis was found in children diagnosed with bone tumors followed by brain tumors than those who had Lymphoma and leukemia. This findings documented by different authors(24)(23)(26)a shorter diagnosis period for patients with acute leukemia than for those with brain and bone tumors (1) In our setting with high sensibilization with community health workers, children who present with symptoms like fever, joint pain, vomiting and diarrhea if not treated at primary level are fast transferred to secondary or tertiary level than children who present with unspecific symptoms.

Leukemia was the most frequent malignancy in this study representing 29% of all cancer cases with 65.4% being acute lymphatic leukemia and 34.6% of Acute Myeloid Leukemia. The median total diagnosis delay for leukemia in this study was 24 days, the median physician delay was 17days and the median parents/patients related delay was 4 days. In similar studies done in South Africa and Canada showed that the median diagnosis delay in South Africa was 31 days, median physician delay was 22 days. In Canada the median total delay was 18 days, physician delay was 3 days(13). Reasons for this big difference with developed country, could be that health worker providers at primary and secondary facilities may have difficulties to recognize the onset symptoms of leukemia, and tend to hospitalize patients for many days treating them as sepsis, before transfer to CHUK And also leukemia investigations might not be as easy to perform in our settings as in developed countries.

CHAPTER 5. CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

Delay in childhood cancer diagnosis is an issue in our settings. Even though, health care system related factors, as level of first health care provider consulted, time period of admission at primary and secondary level before consulting CHUK and time it takes before diagnosis at CHUK contributed to longer delay than parents/patients delay, parents/patients factors as level of education, social economic status, family size, age of the child at diagnosis and geographic distance to primary health care affected also parents/patients delay significantly.

The results of our study were comparable to the findings published in other scholars.

Effort should be made to raise the level of knowledge on signs and symptoms of pediatric cancer among health care providers as well as among parents.

6.2. Recommendations

To patients:

We recommend early consultation for any health complaint and avoid non accredited alternative medicine.

To medical training institutions:

In view of a big gap existing between different levels of health workers regarding early suspicion of malignancy, there is a need to extend training on signs and symptoms of malignancy to nurses and general practitioners as they have the opportunity to see the patient on first consultations. This recommendation goes to the Ministry of Health and universities which can organize further training on cancer.

To the Ministry of Health:

A statistically significant gap also exists between parent's education level and urban versus rural origin of parents. This can be addressed by integrating cancer awareness education to the already existing programs which have been successful countrywide like immunization, nutrition, contraception, etc.

To CHUK and other hospitals with cancer diagnosis facilities:

The longer health system delay has been seen in different countries especially in developing countries. This is in part related to laboratory diagnosis. I underscore the need of well organized, staffed and equipped laboratory services.

BIBLIOGRAPHY

1. Abdelkhalek ER, Sherief LM, Kamal NM, Soliman RM. Factors Associated with Delayed Cancer Diagnosis in Egyptian Children. Clin Med Insights. 2014;8:39–44.
2. Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer: A review. Cancer. 2007;110(4):703–13.
3. Njuguna F, Martijn H, Langat S, Musimbi J, Muliro H, Skiles J, et al. Factors influencing time to diagnosis and treatment among pediatric oncology patients in Kenya Factors influencing time to diagnosis and treatment among. Pediatr Hematol Oncol [Internet]. 2016;33(3):186–99. Available from: http://dx.doi.org/10.3109/08880018.2016.1169566
4. Araz NC, Guler E. Delays in Diagnosis of Childhood Cancer in Southeastern Turkey and the Associated Factors. Pediatr Hematol Oncol. 2015;
5. Arnautovic A, Billups C, Broniscer A, Gajjar A, Boop F, Qaddoumi I. Delayed diagnosis of childhood low-grade glioma: causes, consequences, and potential solutions. Child's Nerv Syst. 2015;31(7).
6. Whelan K, Alva E. Epidemiology of Childhood Cancer. In: Pediatric Cancer Genetics. 2017.
7. Steliarova-foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. Articles International incidence of childhood cancer , 2001 – 10 : a population-based registry study. 2017;719–31.
8. Howard SC, Metzger ML, Wilimas JA, Quintana Y, Pui CH, Robison LL, et al. Childhood cancer epidemiology in low-income countries. Cancer. 2008;112(3):461–72.
9. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li CK, et al. Paediatric cancer in low-income and middle-income countries. The Lancet Oncology. 2013.
10. Kruger M, Hendricks M, Davidson A, Stefan CD, van Eyssen AL, Uys R, et al. Childhood cancer in Africa. Pediatr Blood Cancer. 2014;61(4):587–92.
11. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5).
12. Hossain MS, Begum M, Mian MM, Ferdous S, Kabir S, Sarker HK, et al. Epidemiology of childhood and adolescent cancer in Bangladesh, 2001-2014. BMC Cancer. 2016;16(1).
13. Dr. Daniela Cristina Stefan MD, PhD, 1 and FS. Delay and Causes of Delay in the Diagnosis of

Childhood Cancer in Africa. Pediatr Blood Cancer. 2011;56:80–5.

14. Brown BJ, Adeleye AO, Ibeh JN, Brown BJ, Adeleye AO, Ibeh JN. A Prospective Study on the Causes of Delayed Diagnosis of Childhood Cancer in Ibadan , Nigeria A Prospective Study on the Causes of Delayed Diagnosis of Childhood Cancer in Ibadan , Nigeria. 2015;0018.
15. Handayani K, Sitaresmi MN, Supriyadi E, Widjajanto PH, Susilawati D, Njuguna F, et al. Delays in diagnosis and treatment of childhood cancer in Indonesia. Pediatr Blood Cancer. 2016;63(12):2189–96.
16. Brown BJ, James BO, Ajayi SO, Ogun OA, Oladokun RE. Factors influencing time to diagnosis of childhood cancer in Ibadan, Nigeria. Afr Health Sci [Internet]. 2009;9(4):247–53. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3074401&tool=pmcentrez&rendertype=abstract
17. Brown BJ, Adeleye AO, Ibeh JN. A Prospective Study on the Causes of Delayed Diagnosis of Childhood Cancer in Ibadan, Nigeria. Vol. 32, Pediatric Hematology and Oncology. 2015.
18. Schonfeld SJ, Kellett P, Kielkowski D, Schüz J, Erdmann F, Stanulla M, et al. Childhood cancer incidence patterns by race, sex and age for 2000-2006: A report from the South African National Cancer Registry. Int J Cancer. 2014;136(11):2628–39.
19. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol. 2017;18(6):719–31.
20. Stefan DC ristin., Baadjes B, Kruger M. Incidence of childhood cancer in Namibia: the need for registries in Africa. Pan Afr Med J. 2014;17:191.
21. Couitchere L, Azagoh-Kouadio R, Yao JJA, Koné D, Stefan DC, Atimere Y, et al. Childhood cancer in Côte d'Ivoire, 1995 - 2004 – challenges and hopes. South African Med J. 2013;103(2):113.
22. L. V, M. O, M. T, I. M, G. P, J. G. Factors associated with time to diagnosis of childhood cancer: A retrospective cohort study. Pediatr Blood Cancer. 2015;
23. Chukwu BF, Ezenwosu OU, Ikefuna AN, Emodi IJ. Diagnostic Delay in Pediatric Cancer in Enugu, Nigeria: A Prospective Study. Pediatric Hematology and Oncology. 2015.
24. Vasquez L, Oscanoa M, Tello M, Tapia E, Maza I, Geronimo J. Factors associated with the latency to diagnosis of childhood cancer in Peru. Pediatr Blood Cancer. 2016;63(11).
25. Ahrensberg JM, Schrøder H, Hansen RP, Olesen F, Vedsted P. The initial cancer pathway for

children - One-fourth wait more than 3 months. Acta Paediatr Int J Paediatr. 2012;101(6):655–62.

26. Ahrensberg JM, Olesen F, Hansen RP, Schrøder H, Vedsted P. Childhood cancer and factors related to prolonged diagnostic intervals: A Danish population-based study. Br J Cancer. 2013;108(6):1280–7.

27. Gupta S, Gibson P, Pole JD, Sutradhar R, Sung L, Guttmann A. Predictors of diagnostic interval and associations with outcome in acute lymphoblastic leukemia. Pediatr Blood Cancer. 2015;62(6).

ANNEXES

1. Data collecting tool

I. Patient's particulars

1. Data collection sheet number						
2. Hospital registration number						

3. Date of birth (years):

4. Sex	M	F

5. Province Region

II. Factors related to the patient

1. Age of the patient at diagnosis:
2. Number of consultation before diagnosis:

a. Health Center

b. District hospital

c. Provincial hospital

d. Referral Hospital

e. Private Clinic

f. Traditional healers

3. Geographic Distance from home to primary Healthcare facility (in walking or driving hours)

III. Parental characteristics and socio-economic status

1. Parent's age
    a. Father (years):
    b. Mother (years):
2. Family size (number of children and parents):

4.Ubudehe category	1
	2
	3
	4

5.Mother's highest level of education	No school
	Primary education
	Secondary education
	University Education
Father's highest level of education	No school
	Primary education
	Secondary education
	University education

IV. Clinical Data

1. Date of the first cancer symptom: (MM/YY)
2. Date of the first health care provider (medical, nurse) visit, type of health facility contacted:
3. Duration of symptoms before consultation to primary health care (in days):
4. Duration (in days) of illness before consultation at KUTH:
   ii. Provincial hospital:
   iii. District hospital:
   iv. Health center
5. Duration of illness from admission to KUTH to histological diagnosis report or radiological diagnosis (in days):

V. Factors related to the type of cancer.

1. Histology diagnosis
2. Radiological diagnosis
3. Site of the tumor
4. Clinical stage on admission

5. Clinical stage at histology results delivery

VI. Factors related to healthcare.

1. Level of 1st health care provider contacted
2. Total turn-around time from first consultation to final diagnosis of cancer

Consent form for care taker of child, English version

Study no……

I, ……hereby, fully consent on behalf of my child to participate in this study on the **"**FACTORS ASSOCIATED WITH DELAYED PEDIATRIC CANCER DIADNOSIS AT KIGALI UNIVERSITY TEACHING HOSPITAL".

I understand that I will incur no additional medical costs as a result of participation in this study. I have been fully informed about the purposes of the evaluations that will be done. I have had a chance to ask questions and they have been answered satisfactorily. I also understand that I may withdraw my child at any time with no adverse consequences whatsoever. I agree that on condition of anonymity, the information obtained from these assessments shall be used for educational and research purposes only. I am also aware that in case of any further clarification or queries, I can contact Dr Yvonne Nyangabo, Tel: +250788569675 , Dr Aimable Kanyamuhunga, Tel: +250788670200, Prof Kato J Njunwa, Tel: +250788490522 and Prof Jean Bosco Gahutu, Tel: +250783340040 in case of any further clarification or queries.

……..	……..	…../…./……
Name of the participant	Signature of participant	Date

……..	……..	…../…./……
Name of the researcher	Signature of the researcher	Date

Consent form for care taker of child, Kinyarwanda version

Amasezerano yo kwemera kujya mu bushakashatsi

Ubushakashatsi no……

Jyewe …….... nemeye ko umwana wanjye ajya mu bushakashatsi bwitwa **"**FACTORS ASSOCIATED WITH DELAYED PEDIATRIC CANCER DIADNOSIS AT KIGALI UNIVERSITY TEACHING HOSPITAL**",** Ubushakashatsi bwo kumenya igitinza ibipimo bya kanseri z'abana bivuriza mu Kigo cy'Ubuvuzi cya Kaminuza cya Kigali.

Nasobanuriwe ko kujya muri ubu bushakashatsi ari ubushake bwacu, ko nta gihembo ntegereje guhabwa, kandi ko nzagirirwa ibanga ku makuru yose nzatanga. Nasobanuriwe kandi ko ibizava muri ubu bushakashatsi bizatangazwa mu rwego rwo guteza imbere imyigishirize n'ubushakashatsi. Mfite uburenganzira bwo kuva muri ubu bushakashatsi igihe cyose nabishakira kandi ntibigire ingaruka mu mivurirwe y`umwana wanjye. Ikindi kandi, nziko nshobora kuba nahamagara Dr Yvonne Nyangabo, Tel: +250788569675, Dr Aimable Kanyamuhunga, Tel: +250788670200, Prof Kato J Njunwa, Tel: +250788490522 na Prof Jean Bosco Gahutu, Tel: +250783340040 ndamutse ngize ikibazo.

…… /…… …….

Amazina n'umukono by'uwasobanuriwe/Icyo apfana n'umurwayi Italiki

…….. …….

Amazina n'umukono w'umushakashatsi Italiki

2.IRB approval

UNIVERSITY OF RWANDA — COLLEGE OF MEDICINE AND HEALTH SCIENCES

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 14th /08/2018

Dr NYANAGABO Yvonne
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 296/CMHS IRB/2018

Your Project Title ***"Factors Associated With Delayed Pediatrics Cancer Diagnosis At Kigali University Teaching Hospital"*** has been evaluated by CMHS Institutional Review Board.

Name of Members	Institute	Involved in the decision		
		Yes	No (Reason)	
			Absent	Withdrawn from the proceeding
Prof Kato J. Njunwa	UR-CMHS		X	
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS	X		
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 16th August 2018, **Approval has been granted to your study.**

Please note that approval of the protocol and consent form is valid for **12 months**.

EMAIL: researchcenter@ur.ac.rw P.O. Box: 3286, Kigali, Rwanda WEBSITE: http://cmhs.ur.ac.rw/ www.ur.ac.rw

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 17th August 2018

Expiration date: The 17th August 2019

For Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR