RETINOBLASTOMA: CLINICAL PICTURE AND GROUPING AT THE TIME OF FIRST PRESENTATION IN PATIENTS ATTENDING PAEDIATRIC ONCOLOGY WARD AT MUHIMBILI NATIONAL HOSPITAL

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By

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A Dissertation Submitted in Partial Fulfillment of Requirement for Degree of Master of Medicine (Ophthalmology) of the Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that she has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation titled **"*Retinoblastoma: Clinical picture and grouping at the time of first presentation in patients attended pediatric oncology ward at Muhimbili National Hospital*"** in (partial) fulfillment of the requirement for the degree of Master of Medicine (Ophthalmology) of the Muhimbili University of Health and Allied Sciences.

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I, **Jacqueline Ngalula**, 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, and is not previously or currently under copyright.

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DEDICATION

This work is dedicated to my family, with special thanks to my beloved husband Dr. John Mbanga Bihagala and my lovely children Brighton, Brightness and Brigitte.

ABSTRACT

Introduction

Retinoblastoma (Rb) is the most common intraocular and life threatening eye cancer that affects mainly children under the age of five years. In developing countries including Tanzania, 50-70% of affected children die because they are diagnosed too late to save their lives. Delay in diagnosis, referral, treatment and follow up increase morbidity and mortality rate. The aim of this study was to identify clinical picture and group the eye according to the International Classification at the time of first presentation in patients attending pediatric oncology ward at Muhimbili National Hospital (MNH).`

Methodology: Descriptive cross sectional study was conducted in oncology ward at MNH, Dar es Salaam from April to December 2016.The study involved 72 patients with retinoblastoma. Parents/caretakers of every patient were interviewed in detail. Patients were examined under general anesthesia to measure horizontal corneal diameter, intraocular pressure, anterior segment of the eye and fundoscopy with indentation was performed using indirect ophthalmoscope. International classification of Retinoblastoma (ICRB) was used for grouping the disease. Ultrasonography, neuroimaging and histology to confirm the tumor were also performed.

Results: 72 patients were found to have Rb with a median age of 28 months, Interquartile Range (IQR) of (17-42 months). Out of 72 patients, 39(54.2%) were males and 33(45.8%) females. Majority of cases were from Coastal and Lake Zones. Family history of Rb was positive in only one patient who had bilateral Rb. Unilateral Rb was the most predominant type of the disease seen in 54(75.0%) patients. The commonest first clinical presentation noted by the family was Leukocoria reported in 56(77.8%) patients though at MNH about 30(41.7%) patients presented with proptosis. At the time of presentation at MNH, both bilateral and unilateral cases had advanced disease (group E and extraocular extension) where 84 eyes out of 90 eyes were indicated for enucleation. The median lag time was 4 months.

Conclusion: Leukocoria is the commonest first sign of retinoblastoma at home. Majority of the patients presented to MNH in advanced stage of the disease though they were taken to local peripheral hospitals early enough. Programs to raise awareness on retinoblastoma to both health workers and the community are important for early case detection, referral, diagnosis and treatment.

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ABBREVIATIONS

MNH	Muhimbili National Hospital
ICRB	International Classification of Retinoblastoma
RB1 GENE	Retinoblastoma gene
B-scan	Ultrasonography scan
MRI	Magnetic resonance imaging
PFV	Persistence Fetal Vasculature
COG	Children's Oncology Group
MUHAS	Muhimbili university of Health and Allied Sciences
EBRT	External Beam Radiation Therapy
SL	Slit Lamp
SPSS	Statistical Package for Social Sciences
IQR	Interquartile Range
Rb	Retinoblastoma
EUA	Examination under Anaesthesia
KCMC	Kilimanjaro Christian Medical College
CCBRT	Comprehensive Community Based Rehabilitation in Tanzania
PNET	Primitive neuroectodermal tumor
PTNM	Pathological staging tumor, nodes, metastasis

OPERATIONAL DEFINITIONS

Leukocoria: White pupillary reflex, an abnormal white reflection from the retina of the eye.

Strabismus: A visual condition in which the visual axes of the eyes are not parallel and the eyes appear to be looking in different directions (squinting).

Rubeosis iridis: Neovascularization of the iris**.**

Hyphema: Presence of blood within the anterior chamber of the eye.

Two hit model hypothesis: Is the hypothesis that cancer is the result of accumulated mutations to a cell's DNA, first and second mutation have to occur to have retinoblastoma**.**

Nystagmus: Is a condition of involuntary, rapid and oscillatory movements of the eyes.

Lag time: Time since disease onset to presentation to ophthalmologists

Peripheral health units: Dispensary, Health center, District hospital, Regional hospital.

Interquartile range: Is a measure of variability, based on diving data set into quartiles, quartiles divide a rank-ordered data set into four equal parts.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Retinoblastoma is a rare and unique cancer that forms in one or both eyes of child. If left untreated it is a deadly disease, tumor grows to fill the eye and destroys the globe which sometimes necessitates removal of the eye (1,2). In severe cases it causes death. It is triggered by genetic mutations in one or more cells of the retina as a result of mutational inactivation of both alleles of the retinoblastoma (*RB1*) gene. RBI gene is a tumor suppressor gene located at long arm of chromosome 13q14 and encodes a nuclear protein (Rb) which acts as a tumor suppressor (3,4). If the retinoblastoma gene is not active, cells can divide out of control leading to tumor formation. This gene may be inherited (Familial) or may develop at random (sporadic) when the child is growing in the womb (5).

Out of the newly diagnosed cases of retinoblastoma only 6% are familial while 94% are sporadic (5). Bilateral retinoblastoma involves germinal mutations in all cases where by all bilateral cases and 15% of unilateral cases occur due to this mutation (3). Retinoblastoma is the most common primary intraocular malignancy of childhood. The incidence of retinoblastoma is approximation of 40 – 60 per million live births worldwide, corresponding to 1 in $16,000 – 24,000$ live births (6). Studies show that the incidence is similar in boys and girls and among blacks and whites (7,8).

The median age at diagnosis of retinoblastoma is 18 months; with an average of 12 months for bilateral disease and 24 months for unilateral tumor (9). In addition, cases of newly diagnosed retinoblastoma have been reported in children as old as 18 years(7) and rarely, even in adults (10).

Survival rates for retinoblastoma vary in different countries and races. A general 5 year survival is 83% – 97% in some developed countries but much lower 20% – 48% in developing countries such as Africa and India (11).The most important contributing factor for

high mortality in developing countries is delayed diagnosis and advanced presentation of retinoblastoma which is interconnected with multiple cultural and social economic factors. In addition, poor compliance and follow up with medical care increases mortality in developing countries (6,12).

In about 56% of the patients with retinoblastoma leukocoria serves as the first clinical presentation, but other presentations may also occur like strabismus, poor vision, red eye and proptosis (10,13). Below figure shows a child with bilateral white pupillary reflex, presenting as whitish yellowish mass on the retina with prominent vessels over the lession.



Figure 1: Leukocoria in a child with bilateral retinoblastoma

The figure below shows inflammed left eye presenting with mild lid edema and hyperemic conjuctiva.



Figure 2: Retinoblastoma presenting with a red eye, left side.

Below figure shows advanced retinoblastoma presenting with proptosis of the right eye, eyelid edema, chemosis and hyperemic conjunctiva.



Figure 3: Late stage retinoblastoma presenting with proptosis, right eye.

The available evidence from Tanzania revealed mean lag time for presentation of about 10 months (14). Furthermore there is stigma associated with removal of the eye and parents may abandon early therapy altogether, just to present at metastatic stage (14). Other factors associated with poor outcome are inadequate treatment centers, poor referral pathway and protocol for the comprehensive management of early and advanced stages of retinoblastoma (15).

Excellent survival outcomes have been reported from the developed countries where the goals of treatment have shifted towards globe and vision salvage (16). Evidence based reports have shown that with timely screening, diagnosis, referral, treatment and follow-up delivered in a systematic way by a multidisciplinary team, 98% of children with retinoblastoma survive and their eyes and vision are preserved (17).

Successful treatment requires early diagnosis as well as availability of modern treatment modalities. The major goal should be to improve the delivery of ocular health care and general survival especially in developing countries. This is possible when early referral to ophthalmologist and other pediatric specialists is done to maximize visual outcome and survival (18).

1.2 Literature Review

Epidemiology

Prevalence/incidence

Retinoblastoma represents approximately 3% of all pediatric malignancies and is the most common primary intraocular cancer in children (19). In the United states incidence is reported to be 3.8 cases per million (20). In Africa it accounts for 10 to 15 % of cancer in children (21) In Bulgaria incidence rate of retinoblastoma for children aged 0 - 4 years varies from 3.4% per million to a very high 42.5 per million in Mali. Incidence estimates from Africa include 20 cases per million children under 5 in Malawi and 9.3 per million in Guinea Conakry (22). One study in Kenyan showed that incidence of retinoblastoma was 1:17, 030 live births (23).

Age

Approximately 95 percent of children with retinoblastoma present before the age of five years. Most children who are diagnosed with retinoblastoma are younger than 5 years old, it makes up 2% of all cancers diagnosed in children before the age of 15 (24). The median age at diagnosis is 18 months; an average of 12 months for bilateral disease and 24 months for unilateral cases. However, there is a broad spectrum of age at presentation for both bilateral and unilateral disease (24). Nonetheless, cases of newly diagnosed retinoblastoma have been reported in children as old as 18 years (7,24). A study carried out in Kenya by Nyamori J M et al (25) involving 132 patients with retinoblastoma showed that mean age at presentation was 33 months while another study from Nigeria done by Akhiwu WO et al revealed a mean age at presentation of 29 months with cases of bilateral Rb presenting at very younger age of 15 months (26). Kazadi Lukusa A. et al did a study in Congo Kinshasa and found a median age of 1.9 years for unilateral disease and 1.4 year for bilateral tumor at disease onset (27).

Sex

The incidence is similar in boys and girls and among blacks and whites (8). Most studies from different parts of the world suggest no sex discrepancy in the incidence of retinoblastoma. In the USA, studies by different workers have found an age adjusted incidence of 11.3 for males and 12.4 for females suggesting a mild female predominance (20). This difference however

was not significant. In Southern Africa studies there is a marked male predominance over females (3:1) in the bilateral cases. However, for the unilateral cases, the ratio of males to females is 1.2:1.0. Overall however the Male: Female ratio is 4:3 (28). Study from Congo by Kazadi Lukusa A. et al showed a Male: Female predominance for all cases of retinoblastoma seen over a 6 year period to be 2:1 (27). In Ilorin, Nigeria, there was a mild female predominance of 1.2:1. The mean age for females and males was also not significant at 31 months and 27 months respectively (26).

Tumor laterality

About one-third of retinoblastoma cases are bilateral, the remaining two-thirds are unilateral. Nyamori JM et al did a study in Kenya (25) involving 132 patients with retinoblastoma unilateral cases were 98 (74%) while bilateral ones were 34 (26%). Another study done in Congo Kinshasa involving a total of 49 children with retinoblastoma, 31 cases (77.5%) had unilateral disease and 9 cases (22.5%) had bilateral disease (27).

Survival rate

Survival rates for retinoblastoma vary in different countries and races. In some African or Asian countries the survival rate is virtually zero because most patients do not complete therapy or are lost to follow-up. Also pathologic evaluation of enucleated eyes is seldom done, and relatively intensive chemotherapy is not usually available (29). Survival in many middle-income countries (MICs) is over 70% and some upper MICs that have established multidisciplinary teams and adequate treatment facilities have survival rates near 90% (30).

Clinical Presentation

Leukocoria is the most common presenting finding in children with retinoblastoma in the United States; however, other presentations include strabismus, nystagmus, and a red eye which sometimes may herald the disease (31). Rare presentations include iris heterochromia, iris neovascularization, vitreous hemorrhage, hyphema, glaucoma, anisocoria, orbital cellulitis from tumor necrosis with proptosis, eye pain and fever (32). In the United States, more than one-half of new patients present with advanced intraocular disease while in developing countries most patients presents with extraocular disease (33). Classic presentation of early

retinoblastoma is a solitary or multifocal, well-circumscribed translucent intraretinal mass but as disease advances, the tumor becomes more pink in color, with dilated feeding blood vessels and may show different types of growth pattern as follows (34):
Exophytic – The vertical growth of the tumor is beneath the retina, toward and into the subretinal space often leading to exudative retinal detachment.

Endophytic – The vertical growth of the tumor is toward and into the vitreous cavity. The tumor is friable and often the vitreous is seeded with tumor cells.

Diffuse infiltrating Retinoblastoma – The tumor remains relatively flat and grows intraretinally.

In a study done in Congo Kinshasa by Kazadi Lukusa A et al (27) involving 40 patients with retinoblastoma Leukocoria and proptosis were the most frequent initial signs noticed by families. Other noted clinical signs were red eye and hyphema. However at diagnosis in institution the most frequent clinical findings were proptosis in 22 patients and leukocoria in only 10 patients.

Pathogenesis

Retinoblastoma is caused by mutational inactivation of both alleles of the retinoblastoma (*RB1*) gene. Absence of active, functional retinoblastoma gene causes cell cycle dysregulation (3).

A "two-hit" model has been proposed to explain various clinical features of germ line and sporadic cases of retinoblastoma (2,3). In the germ line form, a mutation at the RB1 locus or deletion of chromosome 13q is present in all cells of the body because it occurs before fertilization and a second "hit" occurs later after fertilization that affects the remaining *RB1* allele within retinal cells (35,36). These patients are at risk of multifocal and bilateral tumors. The genetic abnormality associated with heritable forms of retinoblastoma is highly associated with an increased risk of developing second primary tumors such as osteogenic sarcoma, soft tissue sarcomas (particularly leiomyosarcoma) and malignant melanoma (37).

In sporadic (nonhereditary) retinoblastoma, both hits arise spontaneously in a single somatic cell of the retina after fertilization resulting in unifocal unilateral tumor. Two independent postnatal events takes some time to develop this explain why sporadic retinoblastoma occurs at an older age than inherited tumor (12).

Two most common routes of metastatic spread are direct infiltration through the optic nerve to the central nervous system and spreading via the choroid into the sclera and orbit (18,38). Additional routes of spread include dispersion of the tumor cells through the subarachnoid space to the contralateral optic nerve or through the cerebrospinal fluid to the central nervous system. Hematogenous spread to the lung, bone, liver or brain and lymphatic dissemination if the tumor spreads anteriorly into the conjunctiva, eyelids or extraocular tissue. Metastatic spread may occur at around 4 months of diagnosis, and death may follow within a year following metastasis (39).

Diagnosis

Accurate clinical diagnosis of retinoblastoma is accomplished by taking a detailed history, physical evaluation, external ocular examination, slit lamp biomicroscopy and binocular indirect ophthalmoscopy with scleral indentation. This is generally performed either in the office or under anesthesia (5), the characteristic finding is a chalky, off-white retinal mass with a soft, friable consistency. Intrinsic tumor calcification, tumor microvasculature and seeding can also be seen.

Other ancillary tests which can be done to confirm the diagnosis include ocular B scan and/or tomography (CT) which demonstrate a solid intraocular tumor with calcification. Caution, CT scan is not recommended in patients with suspected bilateral retinoblastoma because of the risk of radiation-induced second cancers instead MRI can be helpful to confirm the presence of an intraocular mass. MRI will not demonstrate calcifications however, it is an important tool in revealing tumor size, potential optic nerve involvement, presence of an associated intracranial lesion and is generally recommended as part of the staging evaluation for all newly diagnosed retinoblastoma patients (40).

Differential Diagnosis

Conditions that produce leukocoria are considered as differentials of retinoblastoma. In a clinical review involving 2775 patients referred for management of retinoblastoma over a 40-year period about 22 percent were diagnosed with other conditions (41). The most common conditions included Coats disease (40%), PFV (28%), vitreous hemorrhage (5%), and ocular toxocariasis (4%). The frequency of the other conditions varied depending on the age at presentation (42).

Classification

Different systems have been developed to classify retinoblastoma into groups according to the likelihood of globe salvage; the Reese-Ellsworth, Essen, St. Jude, Philadelphia, and the Murphree classifications. With the advent of modern examination and treatment techniques, these systems have become outdated.

ICRB was developed in 2003, it is a clinical system of prognosticating organ salvage and a logical flow of sequential tumor grading devised to suit the current treatment strategy. The classification is based mainly on the extent of tumor seeding in the vitreous and sub retinal space, with consideration for tumor size and location. It elaborates the natural history of retinoblastoma (early disease, group A to late disease, group E) as well as the likelihood of salvaging the eye when systemic chemotherapy and adjuvant focal therapy are used as the primary treatment paradigm (19). The chances of retaining useful vision decreases from group A to E. Group A eyes have lesions that are small and are away from critical visual structures (Table 1) below. In both groups A and B, the tumor remains confined to the retina. In groups C and D, the tumor has spread into the sub retinal space and vitreous cavity. The tumor in group E eyes is extensive and has destroyed the eye. Risk of treatment failure and enucleation is very low in Group A eyes whereas group E eyes are rarely salvageable and require enucleation as the primary treatment.

Table 1: International Classification of Retinoblastoma (ICRB)

GROUP	ICRB FEATURES
GROUP A	Small intraretinal tumors (≤ 3mm) away from foveola and disc
GROUP B	Tumors > 3mm, macular location ≤ 3mm to foveola or juxtapapillary location ≤ 1.5 mm to disc, or with subretinal fluid ≤ 3mm from margin.
GROUP C	Tumor with focal subretinal seeds ≤ 3mm from tumour or vitreous seeds ≤ 3mm from tumour or both subretinal and vitreous seeds ≤ 3 mm from tumour.
GROUP D	Tumor with diffuse subretinal seeds > 3 mm from tumour or vitreous seeds > 3mm from tumor or both subretinal and vitreous seeds > 3mm from tumour.
GROUP E	Extensive retinoblastoma occupying >50% of the globe with or without neovascular glaucoma, opaque media from hemorrhage in anterior chamber,vitreous or subretinal space. Extension of tumor to post lamina optic nerve,CHOROID > 2 mm,sclera and anterior chamber.
EXTRAOCULAR/ORBITAL	Involvement of extraocular muscles and or orbit / CNS
UNCLASSIFIED	Destructed anterior segment or dense media opacity obscuring fundus view / patients who came already enucleated.

Furthermore ICRB addresses only the risk of loss of the eye and is not a staging system for the disease in the child therefore is not intended to predict life prognosis or visual outcome; rather it predicts globe outcome and the probability of avoidance of enucleation or EBRT after primary chemotherapy (43). In this classification each eye is staged independently and the tumor of high grade is used to classify the eye.

Therefore if both eyes are affected, each eye is staged independently and if only one stage is stated in patient's report for a bilateral child, this refers to the stage of the worst eye, as an indicator of risk to the child's life. In general ICRB is a classification for globe prognosis and not systemic prognosis as well as a good predictor of treatment success after chemo reduction (44,45). Grouping is done preoperatively to plan lines of management and prognosticate organ salvage in order to have common language at all Rb centers (19,43).

Prognostic Factors

Various clinical and histopathologic features determine prognosis in patients with retinoblastoma. Features associated with a poor prognosis include a delay in diagnosis of more than six months. a delay of more than 6 months from the first clinical sign to diagnosis is associated with 70% mortality recorded in developing countries. Example a study done in Kenya showed that due to resource-poor settings, Kenyan patients presented late, even those with family history (25). Another study which was done in East Africa by Bowman RJ et al (14) showed that mean lag time was 10 months. Other poor prognostic factors include history of intraocular surgery which may occasionally contribute to vitreous seeding or extraocular spread, cataract, use of external beam radiotherapy which contributes to the subsequent development of secondary cancers mainly in heritable form of the disease, choroidal, optic nerve, sclera or orbital invasion which increases the risk of metastatic disease and tumor anaplasia.

Histology Results

A careful histopathological examination of enucleated eyes is mandatory to confirm or rule out metastatic spread. Eyes are graded according to the pathological staging tumor, nodes, metastasis (PTNM) classification. A detailed examination of pathological changes in the enucleated eye is essential to assess risk of tumor spread and identifies whether adjuvant postoperative treatment or metastatic workup is necessary (23). Classic pathological features of retinoblastoma include a small round blue cell tumor with Flexner-Winter Steiner rosette formation with clear central lumen, Homer-Wright rosettes, and Fleurettes (16).

When the optic nerve, choroid or both are shown to be involved, curative adjuvant treatment and metastatic surveillance is recommended. By the time extraocular disease is clinically obvious, cure is very difficult. If extraocular disease is already present at diagnosis, intensive treatment is necessary to attempt to save the child's life (4). Bowman RJ et al (14) did a study in East Africa involving 36 cases, among them 31 patients had histology done and confirmed that, 19 (62%) already had choroidal invasion while 14 (45%) had retro-laminar optic nerve involvement and 14 (42%) had optic nerve resection margin involvement.

Management

Various treatment options are available for children with retinoblastoma, including several "vision-sparing" therapies. The choice of treatment depends upon visual prognosis, tumor size and location, presence or absence of vitreous or subretinal seeds, and patient age (5). Standard therapeutic options include enucleation and external beam radiotherapy (EBRT) for large tumors and cryotherapy, laser therapy and plaque radiotherapy for smaller lesions (46). Therapeutic modalities in retinoblastoma have changed to avoid invasive methods and reduce the rate of enucleation. Chemotherapy and chemoreduction are receiving increasing attention as effective methods for salvage of the eye. Chemotherapy is normally used to shrink small tumors which can subsequently be destroyed using adjuvant treatment such as laser therapy, cryotherapy, thermotherapy, chemothermotherapy and plaque radiotherapy. The drugs commonly used for chemotherapy and chemoreduction are vincristine, etoposide, carboplatin and cyclophosphamide (12).

Outcome

Retinoblastoma survival varies geographically, ranging from <30 % in the developing world to >90 % in industrialized countries. The overall five-year survival rate for children with retinoblastoma in the United States is 94 %. Retinoblastoma if left untreated is a deadly disease, tumors grow to fill the eye and destroy the globe. In the United States, due to early diagnosis with proper treatment and follow up, the survival rate for retinoblastoma is greater than 95 % (47). However, the prognosis for eye salvage is far less and depends on the stage of disease at diagnosis. Spontaneous regression has been reported to occur in a small number of

cases but is very rare (48). Generally common cause of death for patients with germ line retinoblastoma is a secondary malignancy, due to RB1 deletion, and not the initial primary malignancy.

Several studies shows that delay in seeking medical health and referral to ophthalmologist contribute to poor survival outcome in patients with retinoblastoma. Patients who develop metastatic disease usually do so within one year of diagnosis; a child who remains recurrence free for five years after diagnosis is considered cured (1). The prognosis for vision in bilaterally affected children depends upon the extent of tumor involvement and the effectiveness of therapy; the prognosis is better if the tumors are small, do not involve the fovea and there is a limited retinal detachment and seeding. The prognosis for vision in the unaffected eye of children with unilateral disease is excellent (38). The development of tumors in the contralateral eye after three years is rare.

Survivors of retinoblastoma require lifetime follow-up because of the risk to develop (and potentially die from) secondary malignancies. The risk of a second malignancy is 35 to 40 % at 50 years after the original treatment in patients with hereditary Retinoblastoma. Thus, patients with heritable retinoblastoma must be closely monitored for second malignancies throughout their lives. Again, for germline patients, this risk is highly increased in patients who were treated with radiation therapy when they were younger than one year of age compared with those who were treated with radiation therapy after one year of age or did not receive radiation therapy.

Long-term follow-up is best done by a multidisciplinary team such as pediatric oncologist, pediatric endocrinologist, pediatric ophthalmologist and other sectors. Ophthalmologic follow-up after treatment for retinoblastoma should occur at least every three months for a year (34). After this if stable without active disease, examinations can be tapered to every four and then every six months, and then annually. Many centers perform routine screening with MRI brain every six months for children <5 years of age with germline disease. The MRI should include images through the pineal region to look for signs of a midline primitive neuroectodermal tumor (PNET) (49).

Long-term survivors should also be followed for the development of second malignancies with periodic physical examination, laboratory screening and radiology testing, depending upon specific risk factor.

1.3 Problem Statement

Retinoblastoma is a deadly disease if not treated; tumor grows to fill the eye, destroys the globe, cause loss of vision and in extreme cases it causes death. Excellent evidence based survival outcomes have been reported from the developed countries that with timely screening, diagnosis, referral, treatment, and follow-up delivered in a systematic way by a multidisciplinary team, 98% of children with retinoblastoma survive and their eyes and vision preserved (17).

In developing countries including Tanzania, 50-70% of children affected with this eye cancer die because most are diagnosed too late to save their lives. About 100-120 new cases are seen in Tanzania per year. Parents and family members usually are the first to notice the symptoms, however a small proportion seeks medical advice on time. They often seek medical advice late in the course of the disease when vision is impaired and the eye is completely destroyed. The available evidence from Tanzania revealed that time delay between first seeing the sign and seeking medical help was about 10 months (14).

Furthermore, Tanzania like other African countries had no retinoblastoma program; that is, there was no infrastructure and multidisciplinary team to manage retinoblastoma. In March 2016, a national retinoblastoma program was created in an effort to coordinate the efforts of organizations interested in improving care for retinoblastoma patients. The team developed standard of care protocol/guideline for the country, developed a multidisciplinary team, identified centers that could treat Rb and started fund raising to purchase equipment.

Generally there was a need to establish baseline data to support the retinoblastoma program. The study ‘‘to determine the clinical picture of retinoblastoma and group the eyes according to the International Classification of Retinoblastoma’’ was proposed considering that there was no such a documented study done in Tanzania.

1.4 Rationale of the Study

Several cases of retinoblastoma are attended at MNH which is a tertiary referral center for children with eye conditions and pediatric cancer but there is paucity of data concerning the disease.

Also this study was done to provide baseline data for the retinoblastoma program at MNH which started in the year 2016 but also results obtained are expected to open doors for future studies on different areas of retinoblastoma and put forward a strategy to reduce morbidity and mortality from retinoblastoma in Tanzania.

1.5 Research questions

1. What is the proportion of patients with retinoblastoma in pediatric oncology ward at MNH?
2. What groups of ICRB classifications do patients with retinoblastoma present with at MNH pediatric oncology ward?
3. What is the lag time (time from fist sign to time they present to MNH) in patients with retinoblastoma at MNH pediatric oncology ward?
4. What is the first clinical presentation at home and at MNH in patients with retinoblastoma in pediatric oncology ward?
5. What is the distribution of social demographic data of the patients with retinoblastoma in MNH pediatric oncology ward?

1.6 Objectives

1.6.1 Broad Objective

To describe the clinical picture of retinoblastoma and ICRB grouping at the time of first presentation in patients at the paediatric oncology ward at Muhimbili National Hospital from April 2016 – December 2016.

1.6.2 Specific Objectives

1. To determine the proportion of patients with retinoblastoma in paediatric oncology ward at MNH.
2. To determine socio demographic features of the patients with retinoblastoma in paediatric oncology ward at MNH.
3. To identify the first clinical presentation at home and at MNH in patients with retinoblastoma in paediatric oncology ward at MNH.
4. To group the eyes with retinoblastoma according to ICRB in patients at MNH. Paediatric oncology ward.
5. To identify the lag time in patients with retinoblastoma in paediatric oncology ward at MNH.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 Study design

Hospital based Descriptive cross sectional study.

2.2 Study area

This study was conducted at Muhimbili National Hospital pediatric oncology ward. MNH is the national consultant and teaching hospital located in Ilala municipal in Dar es Salaam, Tanzania. It receives patients from different regions of the country, referrals and non-referrals.

Pediatric oncology ward is divided into Upendo and Tumaini wards and one hostel with a total of around 83 beds; bed state per day is 80 patients. Also it has a separate section of out-patient clinic receiving 10 to 15 patients per day. In general Oncology ward receives about 80-100 patients with retinoblastoma per year. Records from oncology ward in 2015 showed that, a total of 360 patients were admitted and diagnosed with different types of cancers, of these 75(20.8%) of the patients had Rb. For this year retinoblastoma was the leading cause of admission followed by Leukemia with 73(20.3%) patients.

In 2016, there were 418 admissions with different cancers, of which 78(18.7%) were confirmed to have retinoblastoma. That year it was a number two cause of admission at oncology ward at MNH. Active retinoblastoma program at oncology ward started in November 2015.

2.3 Study population

All patients confirmed to have retinoblastoma by a paediatric ophthalmologist during the study period were recruited. For the sake of the study, the study population was grouped according to zones and participants were labeled according to their respective zones. Tanzania has several zones as follows; Lake Zone included Tabora, Kigoma, Shinyanga, Kagera,

Mwanza and Mara. Coastal zone included Dar es Salaam, Zanzibar, Tanga, Morogoro and Coast. Southern zone had Lindi, Mtwara and Ruvuma regions. Northern highland zone comprises Arusha, Kilimanjaro and Manyara. Southern highland zone included patients from Iringa, Mbeya and Rukwa while Dodoma and Singida regions were categorized as Central zone (Figure 4).



Figure 4: Tanzania political map

2.4 Inclusion criterion

A newly diagnosed patient with retinoblastoma confirmed by pediatric ophthalmologist during the study period was included in the study.

2.5 Exclusion criteria

1. Patients whom their parents / care taker did not consent to participate in the study. (However all patients responded well and all were included in the study)
2. Retinoblastoma cases already on follow up category (at MNH oncology clinic) that is they were diagnosed and treated accordingly before study period.

2.6 Sampling technique

Consecutive sampling of patients was used. All patients with retinoblastoma attended during study period who met inclusion criteria were included in the study.

2.7 Sample size

Sample size was estimated by using the following formula; where prevalence of retinoblastoma was 4.8% obtained from a study done in Sudan; on Clinical presentation and outcome of retinoblastoma among children treated at the National Cancer Institute (NCI) in Gezira, Sudan.(50)

$$n = \underline{z^2 p(100 - p) / \varepsilon^2}$$

n = Minimum required sample size

z = percentage point of normal distribution corresponding to the level of confidence

£= Maximum likely error/ margin of error

p= expected proportion with the characteristic of interest (prevalence)

95% confidence interval (Z) = 1.96

Error rate (£) = 5%

P = 4.8 %

n = (1.96/5)2x (4.8(100-4.8) =70

Hence minimum sample size = 70.

2.8 Data collection methods

The study was done for a period of 9 months from April 2016 to December 2016. All parents/caregivers of the children with Rb were informed about the study. History of the disease was taken from the care giver. Data sheet designed for the study was used to obtain information from the parents of the study patients. Parents/care taker of every patient diagnosed to have retinoblastoma were interviewed in detail about age of onset, presenting complaints, time taken to seek medical advice since the disease onset, Where was the first visit to seek medical help, family history of eye diseases particularly retinoblastoma, history of enucleation and consanguinity practices. Systemic workup was done according to oncology ward protocol, which included general physical examination and a series of laboratory investigation like renal and liver function tests, lactate dehydrogenises levels, full blood picture and erythrocytes sedimentation rate. Serology for Hepatitis panel (A, B, C) and HIV were also done, Work up specifically for retinoblastoma were lumber puncture to obtain cerebrospinal fluid samples for cytospine analysis and bone marrow aspiration to identify if there was any extraocular disease. Computed tomography (CT scan) was ordered in patients to identify the presence of calcifications and extent of the disease.

Standardized ophthalmological evaluation was done under supervision of pediatric ophthalmologist at the pediatric eye clinic. At the clinic, visual acuity and general ocular examination was done to identify the symptoms and signs of retinoblastoma such as leukocoria, strabismus, red eye and proptosis. All patients were listed for examination under anaesthesia. Under general anesthesia thorough ocular examination was done including B scan to observe if there was intraocular calcification/ mass.

- Intraocular pressure (IOP) of each eye was measured by using I care machine. The IOP of 9 to 21 mmHg was considered as normal and IOP of more that 21mmHg was considered as high indicating glaucomatous stage while IOP below 9mmHg was considered as low IOP.
- Anterior segment of the eye was examined using operating microscope. Findings such as anterior chamber seeds, pseudohypopion, hyphema, iris neovascularisation, Iris corectopia and heterochromia were recorded.
- Horizontal corneal diameter (HCD) was measured by using vernier calliper, to determine its status depending on patient age.
- Posterior segment of the eye was examined by using binocular indirect ophthalmoscope with indentation done in 360 degrees. The following were documented about the tumour, location, size, tumor pattern (endophytic, exophytic or mixed tumor) and if there were retinal detachment and tumor seeding in the vitreous or subretinal space.

The EUA findings were interpreted by the paediatric ophthalmologist with special skills in retinoblastoma management to group the eyes according to International classification of Retinoblastoma (ICRB) with minor modification designed for this study (Table 1).

For patients who underwent enucleation as initial part of treatment, enucleation with orbital implant and conformer insertion was done at the same sitting. Specimen of enucleated eyes were fixed in formaldehyde, studied and reported by the pathologist according to retinoblastoma histology reporting protocol.

2.9 Study variables

Independent Variables

The independent variables were age, sex, time of disease onset, inheritance, tumor laterality and growth pattern of retinoblastoma.

Dependent Variables

Dependent variables included retinoblastoma and International Classification of Retinoblastoma disease group.

2.10 Data processing and analysis

Data was entered into the Statistical Package for Social Sciences (SPSS) software version 20. Before entering the data, the forms were checked again for completeness and consistency. Univariate analysis was done to assess characteristics of the study population. Bivariate analysis using Chi-square or fisher's exact tests were used to assess the association between the tumor laterality and patient age of disease onset. Any association was considered significant at 95% confidence interval.

2.11 Ethical Consideration

Permission to conduct the study was granted from Ethics and Research Committee of MUHAS, as well as from department of Ophthalmology and Pediatric Oncology ward at MNH. Informed consent was obtained from the patient parents/care taker. Refusal to be enrolled in the study did not affect patient treatment quality. Registration numbers instead of names were used for confidentiality except for academic purposes.

CHAPTER THREE

3.0 RESULTS

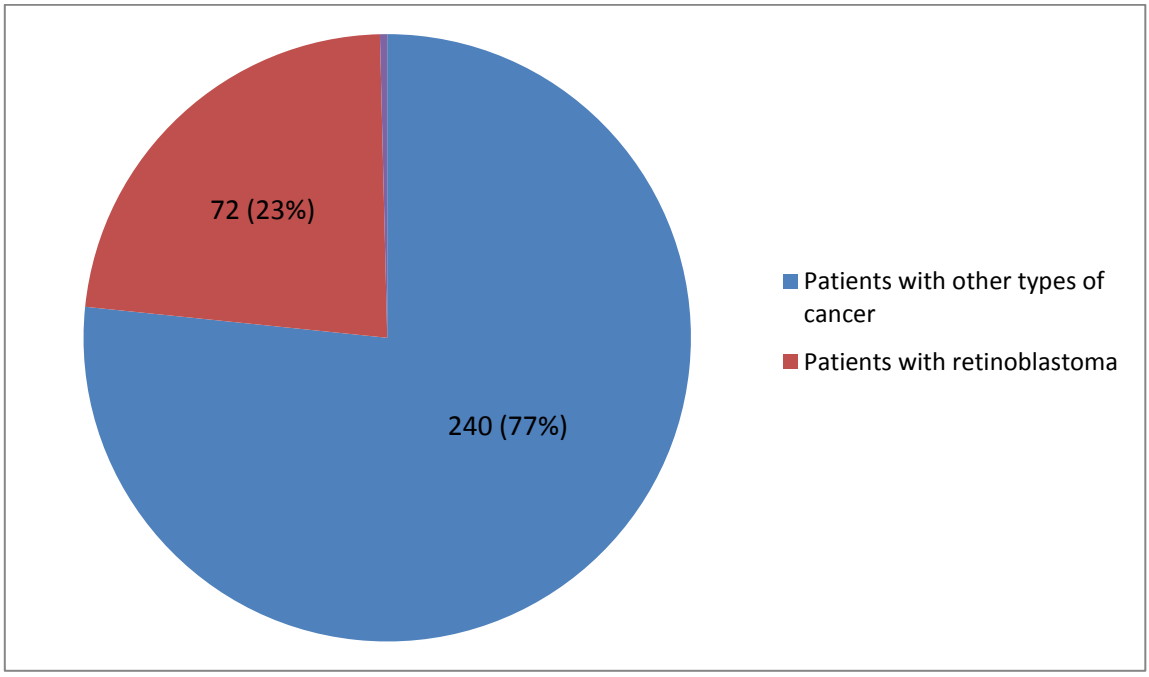


Figure 5: Proportion of patients with retinoblastoma among all patients with cancer during study period.

During study period a total of 312 patients were diagnosed with different cancer, of these 72 had retinoblastoma giving a prevalence of 23% (Figure 5).

Table 2: Characteristics of study participant stratified by sex

Characteristic	Male N = 39	Female N = 33	Total N = 72
	N(%)	N(%)	N(%)
Age group			
0-24 Months	18 (46.2)	16 (48.5)	34 (47.2)
25-48 Months	16 (41.0)	13 (39.4)	29 (40.3)
>48 Months	5 (12.8)	4 (12.1)	9 (12.5)
Median age (IQR)	30 (16 - 45)	26 (20 - 36)	28 (17 - 42)
Patient address			
Lake zone	12 (30.8)	9 (27.3)	21 (29.2)
Coastal zone	10 (25.6)	13 (39.4)	23 (31.9)
Southern zone	7 (17.9)	2 (6.0)	9 (12.5)
Southern highlands zone	4 (10.3)	4 (12.1)	8 (11.1)
Central zone	6 (15.4)	5 (15.2)	11 (15.3)
Family History of RB			
Yes	1 (2.6)	0 (0.0)	1 (1.4)
No	38 (97.4)	33 (100.0)	71 (98.6)
Consanguinity history			
Yes	1 (2.6)	0 (0.0)	1 (1.4)
No	38 (97.4)	33 (100.0)	71 (98.6)
Tumor Laterality			
Unilateral	29 (74.4)	25 (75.8)	54 (75.0)
Bilateral	10 (25.6)	8 (24.2)	18 (25.0)

Seventy two (N=72) patients with retinoblastoma were recruited during the study period. Of these, males outnumbered females with male to female ratio of 1.2:1. Most of the patients were in the age group of 0-24 months and majority had unilateral retinoblastoma. Most of the cases were from Coastal and Lake Zone. Almost all had neither family history of retinoblastoma nor consanguinity practices except 2 patients. (Table 2).

Table 3: Distribution of clinical features of the patients as first seen at home and MNH

Characteristic	Male N = 39	Female N = 33	Total N = 72
	N(%)	N(%)	N(%)
First sign noted by the family.			
Leucokoria	28 (71.7)	28 (84.9)	56 (77.8)
Strabismus	4 (10.3)	1 (3.0)	5 (6.9)
Red eye	4 (10.3)	3 (9.1)	7 (9.7)
Proptosis	1 (2.6)	1 (3.0)	2 (2.8)
Others	2 (5.1)	0 (0.0)	2 (2.8)
Sign noted at MNH			
Leucokoria	19 (48.7)	10 (30.3)	29 (40.2)
Strabismus	2 (5.1)	0 (0.0)	2 (2.8)
Red eye	1 (2.6)	2 (6.0)	3 (4.2)
Proptosis	12 (30.8)	18 (54.6)	30 (41.7)
Others	5 (12.8)	3 (9.1)	8 (11.1)

The commonest first clinical presentation noted by the family at home was leukocoria while proptosis associated with leukoria was the commonest presentation at MNH. (Table 3).

Table 4: Distribution of tumor group according to ICRB

Characteristic	Frequency	Percentage
Grouping unilateral Rb		
Group A	0	0.0%
Group B	0	0.0%
Group C	0	0.0%
Group D	6	11.1%
Group E	13	24.1%
Extraocular/orbital	21	38.9%
Unclassified	14	25.9%
Total	54	100%
Grouping bilateral Rb		
Group A	0	0.0%
Group B	1	2.8%
Group C	5	13.9%
Group D	7	19.5%
Group E	12	33.3%
Extraocular/orbital	8	22.2%
Unclassified	3	8.3%
Total	36	100%

In overall, 100% (eyes) of the unilateral cases and 83.3% (eyes) of bilateral cases presented with advanced disease group where vision and globe salvage was not possible (Table 4).

Table 5: Characteristics of study participants lag time stratified by sex.

Characteristic	Male N = 39	Female N = 33	Total N = 72
	N (%)	N (%)	N (%)
Age of disease onset in months			
0-24	24 (61.5)	20 (60.6)	44 (61.1)
25-48	12 (30.8)	10 (30.3)	22 (30.6)
>48	3 (7.7)	3 (9.1)	6 (8.3)
Time taken to decide seeking medical care			
6 months and below	35 (89.7)	26 (78.8)	61 (84.7)
above 6 months	4 (10.3)	7 (21.2)	11 (15.3)
First visit facility level			
Dispensary	7 (17.9)	10 (30.3)	17 (23.6)
Health center	14 (35.9)	12 (36.4)	26 (36.1)
Regional hospital	15 (38.5)	9 (27.3)	24 (33.3)
Referral hospital	2 (5.1)	1 (3.0)	3 (4.2)
Other places	1 (2.6)	1 (3.0)	2 (2.8)
Lag time			
0-6 months	30 (76.9)	18(54.6)	48 (66.7)
7-12 months	5 (12.8)	12(36.4)	17 (23.6)
>12 months	4 (10.3)	3 (9.0)	7 (9.7)
Median lag time in months, (IQR)	2 (1 - 6)	6 (2 - 10)	4 (1.5 - 8)

The commonest age at disease onset was between 0 – 24 months. Most parents decided to seek medical care within 6 months since the disease onset and the most common first visiting health facility was a health center (Table 5). Median lag time of 4 months.

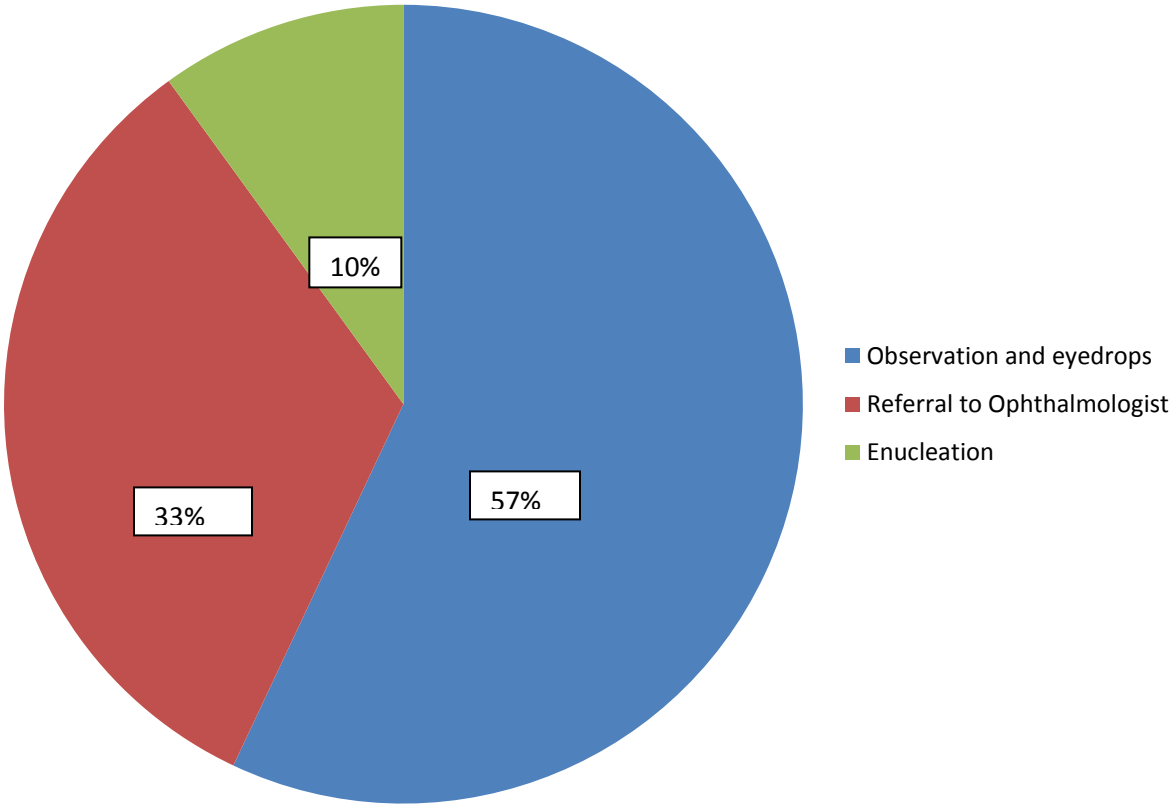


Figure 6: Treatment modalities provided at peripheral hospitals.

Observation and eye drops were the most common type of treatment given at peripheral health units at first presentation. Immediate referral to ophthalmologist was done to about a third of the children (Figure 6).

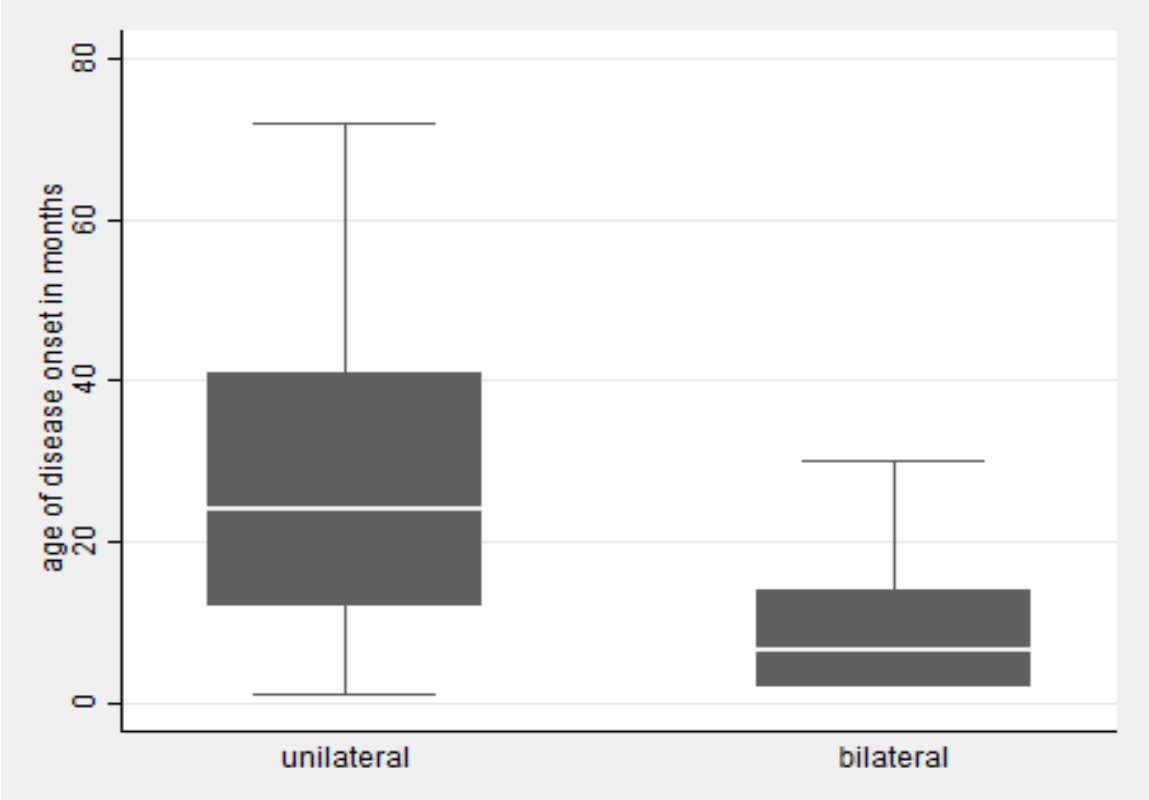


Figure 7: Box plot of median age of onset by tumor laterality

It is estimated that, those with bilateral tumor were 16.30 months younger than those with unilateral tumor. The difference range from 9 to 23 months and was statistically significant ($p<0.001$) (Figure 7).

CHAPTER FOUR

4.0 DISCUSSION

Among 321 children with a diagnosis of cancer in the pediatric oncology ward during the study period, 72(23%) were diagnosed to have retinoblastoma. This high prevalence of 23% is an expected reflection of a study done at the only well-established pediatric oncology centre in the country. Other studies reported variable range of proportion (21,22,26). The prevalence of retinoblastoma is not distributed equally worldwide. It appears to be higher in Africa, India, and among children of Native American descent in the North American continent (51). Whether these geographical variations are due to ethnic or socioeconomic factors is not well known. However, the fact that even in industrialized countries an increased incidence of retinoblastoma is associated with poverty and low levels of maternal education, suggests an environmental role (52). Although this study did not evaluate the social economic status and level of education of parents/care takers most of them came from poor rural areas. This justifies and gives a challenge to the program to plan another long term study to look into these factors in the future.

Establishment of retinoblastoma program at MNH required baseline data. It was important to find out where specifically Rb cases were coming from in order to plan for proper awareness public health campaigns and intervention programs. Most of the patients came from Coastal zone (31.9%) and Lake Zone (29.2%).This could be justified by the fact that MNH is located within the Coast area and this was the closest Rb facility for the people of the Coast zone. Despite that, Comprehensive Community Based Rehabilitation in Tanzania (CCBRT) is in the Coast zone and provides tertiary eye care, the management of the hospital recognizes the Rb program at MNH and agreed to refer all Rb cases since its establishment. There were also many patients coming from the Lake zone although there is a tertiary referral hospital in this zone. This is because the tertiary hospital (Bugando Medical Center) in Mwanza has not yet started to provide Rb services, they had to refer all to MNH. No patient came from Northern highland zone probably due to the availability of Rb services at KCMC hospital.

In this study there were slightly more boys than girls with retinoblastoma. The finding was similar to other studies which showed slightly male predominance (14,25,27,34,53) however, a study done by Balmer A et al (8) suggested no sex discrepancy. Another study done by E Broaddus et al (20) slightly suggested mild female preponderance; the difference however was not significant. Finding more males than females in this study may be related to the fact that our social and cultural situations in the African societies favor more a male child in education and health needs compared to a female child.

Evidence from literature show that retinoblastoma commonly affects children below the age of 5 years (3,24). Similar findings were noted by the current study, where 87.5% patients were below five years. Furthermore, several previous reports show that about one-third of retinoblastoma cases are bilateral and two third of cases are unilateral (2,27,28,54). Likewise this report found the same results where 75% of patients had unilateral retinoblastoma. Probably these cases were sporadic retinoblastomas considering most of them were generally unilateral and diagnosed at the late age of about two years since the median age for unilateral cases was 24 months. Furthermore, finding that almost all had neither family history of retinoblastoma nor history of consanguinity except 2 patients implies that they were most likely sporadic cases.

In this study only one (1.4%) patient with bilateral retinoblastoma had a strong positive family history of having 2 brothers who had had bilateral retinoblastoma and only 1(1.4%) patient came from a family and area where consanguinity is practiced and the parents were cousins. Apart from the Coast area of the Indian Ocean and especially Zanzibar, most part of Tanzania mainland do not practice consanguinity. These findings are similar to a similar study done in Malaysia where history of consanguinity was positive in only one patient (2).

The reported median age at presentation for Rb is 18 months with an average of 12 months for bilateral disease and 24 months for unilateral tumors (24) while for this report the median age for presentation was 28 months with an average of 6.5 months for bilateral cases an 24 months for unilateral cases.

Those with bilateral disease were 16.30 months younger than those with unilateral disease and the results were statistically significant ($p<0.001$). In other studies done, they showed variable ranges of age at disease presentation (2,27,28,53).

Available evidence shows that leukocoria is the most common presenting feature of retinoblastoma, followed by strabismus, painful blind eye and loss of vision (1,30). The findings of this study are not different from the literature (18, 26, 29, 47–49) since leukocoria was the commonest first sign noted by the parents and family members at disease onset. In the current report, though majority reported leukocoria as a first sign during disease onset, it was not a surprise that both bilateral and unilateral cases had advanced disease at the time of presentation at MNH. According to ICRB, 84 eyes out of 90 eyes with Rb were in group D, E, extraocular and unclassified and the outcome for the classification was enucleation, only 6 eyes were for organ salvage. All 84 eyes were enucleated due to advanced disease stage. Removal of eyes contributes significantly to childhood blindness and leads to impaired quality of life to survivors and their families. 3 patients had bilateral enucleations.

Late presentation for treatment in African countries has been documented in the literature (2,29). The reasons include, lack of awareness of the disease to the general population hence delay in presenting the children to health facilities and poor knowledge of health care providers at primary health care level revealed by misdiagnosis and unnecessary delay in referring patients with the disease to a specialized centers for treatment. The results of this study found that majority of patients (84.7%) sought medical advice within 6 months since the disease onset. Their first visiting point was at a nearby health facility (peripheral health units) which included dispensaries, health centers and district hospitals. These nearby public health facilities are manned by public health assistants with no or limited knowledge/education about retinoblastoma or other eye conditions. Majority of children were not timely referred to MNH as it should be, instead they were advised either to observe or use eye drops. They were referred late in the course of the disease probably when vision was impaired and the eye was completely destroyed. The findings are also a reflection of the structure of health referral system in Tanzania which follows a hierarchy system from primary to tertiary level.

The system does not allow a direct referral to a tertiary hospital these patients had to pass all the levels to reach the top level (MNH). This might have been a contributing factor for late presentation at MNH. The other factor that might have contributed to the late presentation at MNH, is the fact that a child with early retinoblastoma may be feeding and appear systemically well. The primary health workers and parents might have taken it easy to the early features of retinoblastoma.

The previous evidence from Tanzania revealed that time delay between the time a first sign of retinoblastoma is seen to the time of presentation to an ophthalmologist for expertise medical help was about 10 months (14) whereas an overall median lag time of 4 months was observed in this study. Other studies showed variable ranges of lag time (9,14,27,53). The decrease in lag time from 10 months to 4 months may be attributed to the awareness campaign done along with the establishment of Rb services at MNH in the beginning of the year 2016. In addition, presentation at advanced disease stage has poor prognostic factors and contributes to the high mortality reported to be as high as 50-70% in developing countries (14). Seven patients had central nervous system involvement and were not treated and died within the study period.

4.1 Limitations

This was a hospital based study at a referral pediatric oncology; it may be difficult to generalize the situation of retinoblastoma in Tanzania.

4.2 Mitigations

Despite having no patient from Northern highland zone, patients were coming from almost all Tanzania regions, so still this study provided general baseline information about retinoblastoma in Tanzanian setting.

CHAPTER FIVE

5.0 CONCLUSION AND RECOMENDATIONS

5.1 Conclusion

The prevalence of retinoblastoma at pediatric oncology ward is high at 23 % of all cancers. Majority of patients affected were below 5 years old and most of them had unilateral disease. Bilateral cases of retinoblastoma presented at very young age than those with unilateral disease. Leukocoria was the commonest first clinical presentation noted by the family members while most of them presented at MNH with advanced disease stages (group E and Extraocular extension), where globe and vision salvage was not possible. The Median lag time was 4 months.

5.2 Recommendations

1. Raising awareness on Rb to both medical practitioners and the public at large on the importance of early screening, diagnosis and referral of affected patients is recommended.
2. A further long term study is proposed on long term outcome and social economic factors of the cases under the program.

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APPENDICES

Appendix I: Questionnaire (English version)

TITLE: RETINOBLASTOMA: CLINICAL PICTURE AND GROUPING AT THE TIME OF FIRST PRESENTATION IN PATIENTS ATTENDING PAEDIATRIC ONCOLOGY WARD AT MUHIMBILI NATIONAL HOSPITAL FROM APRIL 2016 – DECEMBER 2016.

A: **Demographic characteristics**

1. Patient ID Number/Name …….

2. Age ……

3. Sex

   a) Male □

   b) Female □

4. Address

   a) Lake Zone (Tabora, Kigoma, Shinyanga, Kagera, Mwanza, Mara) □

   c) Coastal zone (Tanga, Morogoro, Coast, Dar es Salaam, Zanzibar) □

   d) Southern zone (Lindi, Mtwara, Ruvuma) □

   e) Northern Highland zone (Arusha, Kilimanjaro, Manyara) □

   f) Southern Highland zone (Iringa, Mbeya, Rukwa) □

   g) Central zone (Dodoma, Singida) □

5. Date of admission ……

6. Tumor laterality

   a) Unilateral □

   b) Bilateral □

   7. Eye affected

   a) Right eye □

   b) Left eye □

   c) Both eyes □

8. Patient/next of kin cell phone number ……

9. Is there any history of eye removal in the family?

a) Yes □

b) No □

10. Is there a family history of Retinoblastoma?

a) Yes □

b) No □

11. If yes (in question 9 above); what is the relationship with the patient……..?

a) Father □

b) Mother □

c) Siblings □

d) Others □

12. Is there any history of intermarriage (consanguinity) in the family?

a)Yes □

b) No □

13. Parents/ care taker level of education

a) Primary level □

b) Secondary level □

c) University level □

d) Others (specify)…….

B: Clinical assessment

14. Age of disease onset (in months) ……..

15. What was the first clinical presentation at disease onset noted by the family

a) Leucokoria □

b) Strabismus □

c) Red eye □

d) Proptosis □

e) Others (specify)……

f) Unknown □

16. Time taken by the patient to decide seeking medical help since disease onset.

a) Less than 6 month's □

b) More than 6 month's □

17. Where was the first visit patient attended to seek medical help (peripheral health units)?

a) Nearby dispensary □

b) Health Centre □

c) District hospital □

d) Regional hospital □

e) Referral hospital with ophthalmology center □

18. What type of treatment was given at peripheral health units (Dispensary, Health centre, district hospital, Regional Hospital?)

a) Observation and Eye drops □

c) Referral to Ophthalmologist □

d) Enucleation □

19. Total time spent by the patient moving around peripheral hospitals seeking medical help before reaching Ophthalmology center (lag time) in months……..

20. If patient attended peripheral health units (Dispensary, Health centre, district hospital, Regional hospital), in total after what period was the patient referred to ophthalmologist?

a) Within 2 weeks □

b) More than 2 weeks □

21. If referral was done in 2 weeks' time, did the patient reach ophthalmology centre within 2 weeks of referral.

a) Yes□

b) No□

22. If NO (question 21 above) what was the cause or delaying presentation to ophthalmologist?

a) Patient financial instability □

b) Lack of support from family members □

c) Negligence □

d) Others (specify)……

23. Examination under anaesthesia (EUA) findings;

Parameters	Right eye	Left eye
HCD		
IOP		
Anterior segment slitlamp examination.		
Fundus examination using indirect ophthlmoscope with indentation.		

24. Disease group (Classification by ICRB)

	Right eye	Left eye
Group A		
Group B		
Group C		
Group D		
Group E		
Extraocular/Orbit/ CNS		
Unclassified		

25. Modality of treatment given.

Treatment options	RE	LE
1. Enucleation 2. Chemotherapy 3. Radiations 4. Focal therapy(laser/cryotherapy) 5.Others		

C: Investigation results (If done)

26. Ultrasonography **(**B scan features)…….

27. CT scan features……

28. Pathological results of patient enucleated eye/s;

a) Confirmed Retinoblastoma by histology

1) Yes □

2) No □

b) Retinoblastoma risk parameter..

1) High Risk Retinoblastoma □

2) Low Risk Retinoblastoma □

KEY FEATURES:

● Fundus key features for ICRB

Group	ICRB features
A	Small intraretinal tumors (≤ 3mm) away from foveola and disc.
B	Tumors > 3mm, macular location ≤ 3mm to foveola or juxtapapillary location ≤ 1.5 mm to disc, or with subretinal fluid ≤ 3mm from margin.
C	Tumor with focal subretinal seeds ≤ 3mm from tumour or vitreous seeds ≤ 3mm from tumour or both subretinal and vitreous seeds ≤ 3 mm from tumour.
D	Tumor with diffuse subretinal seeds > 3 mm from tumour or vitreous seeds > 3mm from tumor or both subretinal and vitreous seeds > 3mm from tumour.

E	Extensive retinoblastoma occupying >50% of the globe with or without neovascular glaucoma, opaque media from hemorrhage in anterior chamber,vitreous or subretinal space. Extension of tumor to post lamina optic nerve,CHOROID > 2 mm,sclera and anterior chamber.
Extraocular /orbital/CNS	Involvement of extraocular muscles and or orbit
Unclassified	Destructed anterior segment or dense media opacity obscuring fundus view.

Presence of choroidal invasion, post lamina invasion of the optic nerve, sclera invasion, involvement of the anterior chamber and iris neo vascularization indicate high risk Retinoblastoma while absence of those mentioned features indicate low risk Retinoblastoma.

Appendix II: Consent forms (English version)

Dear Sir/ Madam

My name is **Dr Jacqueline Ngalula,** a resident in department of Ophthalmology at MUHAS. I have been authorised by MUHAS research committee and MNH to conduct a research as a necessary requirement for fulfillment of my post graduate studies.

Title: Retinoblastoma: Clinical picture and grouping at the time of first presentation among patients attending Paediatric oncology ward at Muhimbili National Hospital from April 2016 to December 2016

The study is aimed to determine demographic data such as age, sex, address and tribe, time onset since disease onset, stage at presentation and modality of treatment in patients with retinoblastoma. Therefore your participation will require you to provide information's to address those issues.

Confidentiality: All information collected in questionnaires and hospital register will not be disclosed to any one not related to this study. Initial of your names will be used and results will be presented as overall reflection of the community and not as a report of an individual.

Risk: There will be no risk associated with this study.

Benefits: Participant will be able to gain extra information about his/ her condition by being closer to the investigator. Since the report of this study is intended to open rooms for future studies about Retinoblastoma and have clear picture of the real situation in our community so as to have strategies in improving survival, the participant will be part of this effort.

Participation: Your participation in this study is purely voluntary that any decision you make will be respected and will not interfere with type of management you will get from the institute. You can chose to participate or not, answering or not answering some of the questions and withdraw from the study at any point. If you agree to participate in this study you will be interviewed.

Contacts: For any question about this study you can contact me **Dr. Jacqueline Ngalula.**

Phone: 0717990990

P. O. Box 65001, Dar es Salaam.

E-mail: jacquelinengalula@gmail.com

OR

Dr .Anna Sanyiwa (Lecturer MUHAS, consultant Ophthalmologist at MNH).

Phone: 0784717461

OR

Dr. Judith Mwende (Ophthalmologist at MNH)

Phone: 0754465216

For questions about your rights as a participant, you may contact Professor Said Aboud, Director of Research and Publication MUHAS, P.O Box 65001 Dar es Salaam.

Participant declaration:

I.....have read/ told and understand the content of this form. With my sound mind I do agree/ disagree to participate in this study.

Signature of participant. .....

Signature of investigator.....

Date. .....

Appendix III: Fomu ya Ridhaa (Insha ya Kiswahili)

Mimi naitwa **Dk Jacqueline Ngalula**, ni mwanafunzi wa udhamili chuo kikuu cha Sayansi za Afya Muhimbili, idara ya magonjwa ya macho. Ninafanya utafiti huu kama hitaji la lazima ili kukamilisha masomo yangu. Pia matokeo ya utafiti huu yatasaidia kufahamu kwa undani zaidi kuhusu ugonjwa huu na hivyo kuboresha zaidi matibabu yake.

Utafiti huu ni kuhusu kansa ya jicho kwa watoto (Retinoblastoma) kwa mwaka 2016/17. Taarifa zitakazokusanywa ni kuhusu umri, jinsia, kabila na anatokea wapi. Pia ugonjwa umedumu kwa muda gani kabla ya kutafuta huduma ya afya na kugundulika kuwa ni kansa ya jicho na mgonjwa amefika hospitalini akiwa na hali gani pia aina ya matibabu uliyopata.

Usiri: Taarifaza ugonjwa wako zitatunzwa kwa usiri mkubwa kwamba hazitaonekana kwa mtu asiyehusika na utafiti huu. Utambulisho wako utatumia herufi za mwanzo za majina yako.

Madhara: Hakuna madhara yoyote yanayotegemewa kutokana na utafiti huu

Faida: Ukishiriki kwenye utafiti huu, utapata fursa ya kufahamu kwa undani kuhusu ugonjwa wako. Kwa kuwa matokeo ya utafiti huu yatafungua milango kwa tafiti za kansa ya jicho kwa watoto (Retinoblastoma) na kujua hali halisi ya jamii yetu pia ukubwa wa tazizo ili kuboresha maisha, ukishiriki utakuwa ni sehemu ya juhudi hizi za kuisaidia jamii.

Uhuru wa kushiriki: kushiriki kwenye utafiti huu ni hiyari yako. Unahiyari ya kushiriki au kutoshiriki, kujibu au kutokujibu baadhi ya maswali au hata kujitoa wakati utafiti unaendelea. Kwa uamuzi wowote utakaofanya utaendelea kupata matibabu kama kawaida hapa hospitalini.

Taarifa: Endapo unahitaji kupata maelezo zaidi kuhusu utafiti huu, wasiliana na Dk. Jacqueline Ngalula simu namba 0717990990 au Dk. Anna Sanyiwa wa chuo kikuu cha Afya na Tiba Muhiimbili na Taasisi ya macho Muhimbili au Dk Judith Mwende Taasisi ya macho Mhimbili.

Kama una swali lolote kuhusu haki zako kama mshiriki wasiliana na **Profesa Said Aboud** ambaye ni

mkurugenzi wa bodi ya utafiti, chuo kikuu cha Afya na Tiba muhimbili, kwa S.L.P 65001 Dar es Salaam.

Tamko la mshiriki.

Mimi,.....nimesoma/nimeambi wa na kuelewa kilichomo kwenye fomu hii. Nikiwa na akili timamu nakubali/ nakataa kushiriki kwenye utafiti huu.

Saini ya mshiriki. .....

Tarehe...../...../.....

Thank you very much for completing all the questions in this questionnaire.