



THE UNIVERSITY OF ZAMBIA
SCHOOL OF MEDICINE
DEPARTMENT OF SURGERY

**MODES OF PRESENTATION, MANAGEMENT AND SHORT TERM OUTCOME
OF RETINOBLASTOMA AT THE UNIVERSITY TEACHING HOSPITAL (UTH),
LUSAKA**

BY

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DECLARATION

I hereby declare that this dissertation herein presented for the degree of Master of Medicine in Ophthalmology has not been previously submitted wholly or in part for any other degree at this or any other University nor is it being currently submitted for any other degree.

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STATEMENT

I hereby testify that this study is entirely the result of my own independent investigation. The various sources to which I am indebted have been acknowledged in this paper.

Signed :.....(Candidate)

Date

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LIST OF ABBREVIATIONS

CDH.....	Cancer Diseases Hospital
CT.....	Computerized Tomography
EBRT.....	External Beam Radiation Therapy
EUA.....	Examination Under Anesthesia
ENT.....	Ear Nose and Throat
HIV.....	Human Immunodeficiency Virus
ICRB.....	International classification of retinoblastoma
MD.....	Median
MRI.....	Magnetic Resonance Imaging
NVP.....	Negative Predictive Value
P.....	Probability
Rb.....	Retinoblastoma
SD.....	Standard Deviation
UNZABREC.....	University of Zambia Biomedical Research Ethics Committee
UTH.....	University Teaching Hospital
US.....	Ultrasound

ABSTRACT

Objectives: To establish the presentation, management and short-term outcomes of retinoblastoma at UTH from January 2006- December 2012

Method: This was a retrospective case series study of the modes of presentation, management of retinoblastoma and treatment outcomes 6 months after initiation of treatment at UTH from January 2006 – December 2012. The data was collected from registers for the eye unit inpatient and outpatient, histopathology laboratory, pediatric oncology department as well as patients' files. The data collected included demographics, clinical presentation, histopathology reports, treatment modalities, and treatment outcome at 6 months after initiation of treatment. The statistical analyses were performed using the statistical package SPSS version 20.

Results: There were 57 African participants in the study of which 26 (45.6%) were males and 31 (54.4%) were females. The youngest was 0.75 months old while the oldest was 132 month old. The average age of the participants was 31.1 months old (with a standard deviation of 21.96). The average time lag from the onset of symptoms to treatment at UTH was 9.27 months with a minimum of one month and a maximum of 36 months. 71.2% had unilateral retinoblastoma, 28.8% had bilateral retinoblastoma however no trilateral retinoblastoma was observed. The most common presentations were proptosis (47.3%), leukocoria (36.8%), phthisis bulbi (4%), hyphema (2%), orbital cellulitis (1%) and uveitis (1%). The common treatment regimens were enucleation and chemotherapy (28.8%), exenteration and chemotherapy (15%), enucleation, chemotherapy and radiotherapy (3.4%). Moreover, 8.5% had enucleation only whilst 3.4% had exenteration, chemotherapy and radiotherapy treatment regimen. In the study, the treatment outcomes 6 months post initiation of treatment were abandoned treatment 17.7%, while 49.1% died and 33.2% were alive.

Conclusion: The common presentation was proptosis (47.3%) and leukocoria (36.8%). The most common treatment outcome was death, alive followed by abandonment of treatment. Treatment was completed in 22% of the participants. Delay in diagnosis of retinoblastoma remains a challenge as seen in the study by the high mean lag time and late presentation. The diagnosis of retinoblastoma from the referral centers was accurate in 50 % of the patients. Awareness of retinoblastoma to primary health care givers and parents will help to improve early referrals. Further, we recommend the integration of knowledge of retinoblastoma into the curriculum of primary health care giver to facilitate quick referral of patient.

CHAPTER ONE

1.1 INTRODUCTION

Retinoblastoma is the most common primary ocular malignancy of childhood. The incidence of retinoblastoma is reported to ranges from 1:10 000 in South Africa to 1:34 000 in the Netherlands (Moll et al, 1995). In Zambia, a study done by Chintu et al showed that the most common cancer in children was Lymphoma (36.95%) followed by retinoblastoma (12.46%) then Kaposi sarcoma (12.17). There was a statistically significant increase in the incidence of retinoblastoma during the post-HIV period ($p=0.02$). Apart from this no other difference in the epidemiological features was noted. The age ranged from 3 months to 10 years, with an average of 3.35 years. The male to female ratio was 1.3:1. Most of the patients were diagnosed after their first birthday (Chintu *et al*, 1995). Various studies reveal no significance difference in male and female ratio (Onder *et al*, 1994).

Over 95% of children with retinoblastoma in developed countries survive the malignancy where as in developing countries as low as 6.8% survive (Kayambe *et al.*, 1986). The reason for this difference in survival rate in developed countries has been attributed to early detection and prompt treatment of retinoblastoma while the tumour is still located intraocular. In developing countries, 90% of patients with retinoblastoma present with extra-ocular disease due to late recognition and presentation. Several other factors play a role in late presentation resulting in poor prognosis. These included due a high mean age at diagnosis and lag-time (the interval between the onset of symptoms and treatment). This delay in diagnosis is attributed to lack of knowledge by parents and primary health care professionals resulting in late referral to tertiary hospital (Adio&Komolafe *et al.*, 2010).

The management of retinoblastoma requires a multi-disciplinary team of an ophthalmologist, pediatric oncologist, pediatric radiation oncologist, pathologist, nurse and social worker. The most important objective in the management of a child with retinoblastoma is survival of the patient, and the second most important goal is preservation of the globe. Treatment modalities include surgery, chemotherapy and radiotherapy. The major challenge faced in

treating children with retinoblastoma includes refusal and abandonment of treatment. In some cases parents refuse treatment and seek traditional and spiritual remedies while the tumor remains unchecked (Adio&Komolafe *et al.*, 2010). Thus temporal refusal has resulted in delay in treatment. The rate of 69.2% intra-ocular tumors at first admission versus only 15.4% at readmission and 30.8% extra-ocular tumors at first admission versus 73.1% at readmission shows significant inverse correlation between the delay caused by therapy refusal and progression to the extra-ocular stage of the tumors (Sitorus *et al.*, 2009).

Approximately 25% of cases of retinoblastoma are found in Africa (Kivela *et al.*, 1999) however the outcome and survival of patients is poor. Retinoblastoma is curable tumor if it is diagnosed early. The treatment of retinoblastoma is highly dependent on modes of presentation, timely diagnosis and stage of the disease.

This study looked at the modes presentation, management of retinoblastoma and treatment outcome 6 months after initiation of treatment at University Teaching Hospital in Lusaka.

CHAPTER TWO

LITERATURE REVIEW

2.1. GENETICS

Retinoblastoma can be inherited as a familial tumor in which the affected child has a positive family history of retinoblastoma or as sporadic tumor in which the family history is negative for retinoblastoma. Approximately 6% of newly diagnosed retinoblastoma cases are familial and 94% are sporadic. Retinoblastoma is classified in three different ways: familial or sporadic, bilateral or unilateral, and heritable or non-heritable (Shields & Shields, 2004).

The retinoblastoma gene is a tumor suppressor gene, which is located on the long arm of chromosome 13 (13q14). An intact gene protects against expression of retinoblastoma. It is believed that the gene is a recessive suppressor gene and may play a role in cell growth and development. In order for retinoblastoma to develop, both copies of the gene at the 13q14 locus must be lost, deleted, mutated, or inactivated. If either the maternal or paternal copy of the gene that is inherited by an individual is defective, then that individual is heterozygous for the mutant allele. Tumor formation requires both alleles of the gene to be mutant or inactive. These two mutations correlate to the two “hits,” theorized by Knudson. He proposed that the development of any retinoblastoma was caused by two complementary chromosomal mutations. Each of these genetic events could occur randomly with a frequency of 2×10^{-7} per year. In the case of familial retinoblastoma, the initial event or “hit” was a germinal mutation that was inherited and found in all cells of the offspring. The second “hit” occurred sometime during development, and if it occurred in a somatic cell, such as a retinal cell, then retinoblastoma would develop. (Knudson *et al.*, 1971)

Non-heritable retinoblastoma children are usually unilateral. These children have no germ line mutation in Rb gene, thus are not predisposed to second primary tumors and do not pass the gene to their children. The heritable form is associated with multiple, bilateral eye tumors and patients have a risk of developing second primary tumors cancers throughout their body and transmitting the Rb gene to their offspring. (Harbour *et al.*, 2001)

2.2

PRESENTATION

In developing countries, late presentation continues to be a challenge. Several studies showed that over 90% of patients presented late with extraocular disease (Kodilineye, 1964)(Olurin &Willam, 1972) (Abiose &Adido, 1985). According to a study done in Nigeria, Poor prognostic factors in the management of retinoblastoma included late presentation, delay in accepting treatment options offered, low socioeconomic status and low parental education. Thus widespread parental education and awareness campaigns are necessary as well as integrating the knowledge of retinoblastoma into the curricula of community health officers, as they are the ones who work in the interior areas where these patients and their guardians reside to facilitate quick referral (Adedlayo *et al.*, 2010).

The challenges faced in management of retinoblastoma include refusal and abandonment of treatment. Such behavior is responsible for many preventable deaths in these patients. Temporary Refusal of therapy inevitably results in a delay to treatment. Several factors have been identified leading to refusal of treatment. If the tumor presented as an intra-ocular disease, the parents tend to refuse the recommended treatment (especially enucleation) because of personal, psychological, cultural and financial reasons. Then they seek alternative medicine. When the tumor enlarges and the eye becomes proptotic, they return with the child for readmission. A number of parents refused therapy when the child already had a proptotic eye due to financial reasons rather than the ignorance or unawareness of the parent (Sitorus *et al.*, 2009).

Most patients delay accessing treatment even when symptoms are noticed for as long as one year as noted in a Belgian study (Wirix *et al.*, 2000). Thus most patients were diagnosed in that study with advanced disease. Several factors play a role in late presentation resulting in poor prognosis. These factors include; late presentation with high mean age at diagnosis, the interval between onset of symptoms and treatment being more than 5 months. This delay in diagnosis is attributed to lack of Knowledge of the parents and primary health care professionals resulting late referral to tertiary hospitals (Adio&Komolafe *et al.*, 2010). In China, the delay in the clinical diagnosis depended on the medical infrastructure and on the alertness of the parents as well as the pediatricians (Bai *et al.*, 2011).

Most studies indicate that the incidence of retinoblastoma among the various geographic populations is relatively constant. However in Zambia there was statistically significant

increase in the prevalence of retinoblastoma during post-HIV period ($p=0.02$) (Chintu *et al.*, 1995.) The role of environmental influences and HIV in the development of retinoblastoma is unclear.

2.2.1 MODES OF PRESENTATION OF RETINOBLASTOMA

The clinical presentation of retinoblastoma depends on the size, location, growth pattern and stage of lesion at diagnosis. Leukocoria is an abnormal typical white pupillary reflex .It is a classic typical manifestation of retinoblastoma. The white reflex is caused by tumor in the vitreous cavity. Strabismus occurs when the fovea is involved.

The most common presentation in developed countries is leukocoria (60%), strabismus (20%) and secondary glaucoma associated with buphthalmos. Early presentation to the eye clinic is not a prominent feature in retinoblastoma in most countries in Africa (Ajaiyeoba *et al.*, 1993) (Bekibele *et al.*, 2009). According to Badhu et al in Nepal, The commonest presentation was proptosis with orbital extension (40.42%) and leukocoria (29.78%). Further, 90.7 % had unilateral retinoblastoma and the rest had bilateral (Badhu *et al.*, 2009).

In another study done in China showed that the most frequent symptoms were leukocoria and poor vision. Presence of strabismus predicted a late diagnosis of the tumor. Strabismus was a late sign of retinoblastoma in this study suggesting that development of strabismus did not lead to an early ophthalmic consultation (Bai et al 2011). The clinical presentation of retinoblastoma in Malaysia was as follows: 51.6% were girls, leukocoria was most common presentation with 71% followed proptosis with 32.8% (Badhu *et al.*, 2009).

In Ghana, twenty-three patients were seen with retinoblastoma in a period of 20 months. The age ranged from 1 to 84 months, with a mean of 36.3 (± 22.15) months and median of 36 months. 82.6% of the patients had unilateral and the rest of the patients had bilateral disease. There was no trilateral (bilateral retinoblastoma and pinealoblastoma) retinoblastoma seen. The common presentations were leukocoria (87.0%), proptosis (34.8%), strabismus (21.7%) and red eye (21.7%). Other presentations included fungating and necrotic orbital mass 2(8.7%), buphthalmos with enlarged and cloudy cornea 2(8.7%) flat anterior chamber (13.1%), rubeosis 1 (4.4%), and hyphema (4.4%) (Essuman *et al.*, 2010)

2.3 DIAGNOSIS

Diagnosis of retinoblastoma is made by a clear history of leukocoria, fundoscopy usually under general anesthesia, Ultra Sound, CT and MRI. Ultra sound (US) can detect classic intra-tumoral calcifications providing high confidence rate regarding diagnosis. US detects calcifications in 92–95% of cases where it is present histopathologically, however, is limited in cases with small calcified masses due to the presence of intraocular interfaces associated with vitreous opacities, retinal mass with subretinal fluids and retinal detachment (Galluzzi et al., 2009). In settings where US are unavailable X ray is able to identify intraocular calcification in patients with opaque media. On CT scan, a mass may be located in the posterior ocular pole with distinct contours and an inhomogeneous structure. It may contain calcifications in 70.5% of cases (Pascott A et al., 2014). Several studies have demonstrated that MRI is the modality of choice for assessing the local extension of orbital tumours (Ainbinder et al., 1996)(Barkhof a et al., 2005) (Brisse et al.,2007).

2.4. CLASSIFICATION

The international classification of retinoblastoma ICRB and Management (appendix 3) is useful in prediction of chemoreduction and focal methods for intraocular retinoblastoma (Shield *et al.*, 2005).

2.5. TREATMENT OF RETINOBLASTOMA

Management of a child with retinoblastoma requires a multidisciplinary approach. Ophthalmologists, pediatric oncologists, pediatric radiation oncologists, pathologists, genetic counselors, social workers, nurses, and others play important roles in the cure of the disease, salvage of vision, and support of the child with vision loss and potential long-term sequelae. Management varies for children with intraocular disease from extraocular spread of the tumor (Chintagumpala *et al*, 2007).

Successful treatment of retinoblastoma depends on the ability of paediatricians to detect the disease while it is still confined to the eye and promptly refer children to an ophthalmologist for a fundoscopy examination. Additionally, the pediatric oncologist must provide adequate treatment according to the stage of the disease to preserve life and useful vision (Ali *et al.*, 2011). Although approximately 25% of the retinoblastoma cases in the world occur in African children (Kivela *et al.*, 1999), there is limited information about disease outcome in

this setting; however, most reports are consistent with lower survival. (Bowman *et al.*, 2008) The most important objective in the management of a child with retinoblastoma is survival of the patient, and the second most important goal is preservation of the globe. Therapy is tailored to each individual case and is based on the overall assessment. This includes assessing for threat of metastatic disease, risks for second cancers, systemic status, laterality of the disease, size and location of the tumor(s), and estimated visual prognosis. The currently available treatment methods for retinoblastoma include intravenous chemoreduction (sometimes combined with subconjunctival chemoreduction), thermotherapy, Cryotherapy, laser photocoagulation, plaque radiotherapy, external beam radiotherapy, enucleation, orbital exenteration, and systemic chemotherapy for metastatic disease (shield *et al.*, 2004).

Unilateral retinoblastoma (Reese-Ellsworth group V) is managed with enucleation however for those eye in groups I to IV, chemoreduction or focal measures are used. For bilateral retinoblastoma, chemoreduction is utilized in most cases unless there is extreme asymmetric involvement; with one eye having advanced disease necessitating enucleation while the other eye has minimal disease, treatable with focal methods. Bilateral retinoblastoma is treated with chemoreduction for at least one of their two involved eyes. Most pediatric oncologist use the chemotherapy regime of carboplatin, etoposide, and vincristine regimen. The chemotherapy regimen is generally given for 6 cycles to allow for adequate tumor reduction. Focal therapy to the individual tumors is delivered at cycle 2 after achieving adequate tumor reduction and sub- retinal fluid resolution. The objective of chemoreduction is to reduce tumor size so that focal treatments can be applied to a smaller tumor volume in order to preserve more vision and possibly avoid exenteration and external beam radiotherapy. Ocular salvage rates have improved with the addition of chemoreduction to treatment regimens (Shield *et al.*, 2004).

Following the initial observations on the usefulness of chemoreduction by Kingston et al chemoreduction permitted globe salvage in 85% of eyes classified as Reese-Ellsworth groups I to IV and 47% of those classified as group V. However, chemoreduction has recurrence of related vitreous or subretinal seeds, usually remote from the main tumors. For advanced eye disease external radiotherapy for salvage is required (Shield *et al.*, 2004). Wilson et al used chemoreduction (vincristine and carboplatin) without tumor consolidation for 36 eyes with

retinoblastoma for eight cycles over 6 months. Complete tumor control was found in only 8% of eyes, 92% showed recurrence of retinal tumor, subretinal seeds, or vitreous seeds. Tumor consolidation with thermotherapy or Cryotherapy following chemoreduction was provided for each retinal tumor, but the vitreous and subretinal seeds were treated with chemoreduction alone without consolidation. The 5-year Kaplan-Meier results showed that approximately 50% of the eyes with vitreous seeds at presentation showed at least one vitreous seed recurrence, 62% of the eyes with subretinal seeds at presentation showed at least one subretinal seed recurrence, and at least one retinal tumor recurrence per eye was found in 51% of the eyes. Children with advanced retinoblastoma in both eyes or in their only remaining eye are generally treated with systemic chemoreduction and a local periocular boost of subconjunctival Carboplatin. Currently the subconjunctival approach is combined with systemic chemotherapy for best results (Shield *et al.*, 2004).

Focal therapies include laser photocoagulation, thermotherapy, Cryotherapy, and plaque radiotherapy. Most of these therapies are employed for small tumors, especially those that have been reduced by chemoreduction (Shield *et al.*, 2004).

Retinoblastoma is radiosensitive tumor and external beam radiotherapy (EBRT) is a method used for treatment of advanced retinoblastoma. Recurrence of retinoblastoma after external beam radiotherapy is a problem that can develop within the first 4 years after treatment. External beam radiotherapy can also induce a second cancer in the field of irradiation. Abramson and Frank found that external beam radiotherapy increased the incidence of second cancers in the field of radiation but did not stimulate second cancers outside the field of irradiation. Patients treated with EBRT younger than 12 months of age have greater risk for second cancers than patients over 12 months of age (Shield *et al.*, 2004).

Enucleation is an important method for managing retinoblastoma. Enucleation is appropriate when there is advanced disease with no hope for useful vision in the affected eye or invasion of the tumor into the optic nerve, choroid, or orbit. Further, eyes with secondary glaucoma, pars plana seeding, or anterior chamber invasion are best managed with enucleation (Shield *et al.*, 2004).

A study from Senegal that examined the epidemiology and prognosis of childhood tumors including retinoblastoma observed that treatment was completed in only 18% of cases. The management of retinoblastoma was compounded by paucity of staff, absence of expert

centers, shortage of anticancer drugs, lack of financial resources, delayed treatment, and underlying malnutrition. This, further led to lower cure rates compared with the industrialized world (Ka *et al.*, 2003)

2.6. STATEMENT OF THE PROBLEM

In developed countries, over 90% of children with retinoblastoma are cured due to early presentation whilst the tumor is still intraocular. However, in developing countries patients tend to present late with very advanced disease, thus death from retinoblastoma is a major problem.

2.7. STUDY JUSTIFICATION

The majority of retinoblastoma cases live in low–middle and low-income groups. About 25% of retinoblastoma cases are found in Africa and is associated to a poor outcome. The risk factors in this setting include delay in the diagnosis and abandonment / refusal of enucleation. In Zambia, Anecdotal data at the UTH indicate that late presentations are common. Further, a statistically significant increase in retinoblastoma was noted (Chintu *et al.*, 1995). In view of the increase in cases and late presentation of retinoblastoma, it is important to understand the mode of presentation, management and the treatment outcome of Retinoblastoma at the University Teaching Hospital (UTH). In addition, it will give the clinicians a clear scope on how to improve the vision and survival of retinoblastoma patients by early detection and appropriate management.

Currently, no literature is available in Zambia of the presentation, management and treatment outcome of retinoblastoma.

2.8. RESEARCH QUESTION

What are the modes of presentation and short-term outcome of retinoblastoma treatment at UTH from 2006 to 2012?

2.9. OBJECTIVES

2.9.1. General objectives:

To establish the presentation, management of retinoblastoma and short-term outcome at UTH (2006 to 2012)

2.9.2. *Specific objectives;*

1. To determine the modes of clinical presentation of retinoblastoma at UTH.
2. To determine the time interval between on-set of symptoms to initiation treatment (lag-time).
3. To determine the treatment administered to retinoblastoma patients at UTH
4. To determine the treatment outcome up to 6 months after initiation of treatment.

CHAPTER THREE

3.0 METHODOLOGY

This was a retrospective case series study of the modes of presentation, management and short-term outcome of retinoblastoma at UTH from January 2006 – December 2012.

Patients with suspected retinoblastoma were managed by obtaining a clear history, examination under anesthesia (EUA) for fundoscopy, ocular ultrasound of both eyes and in some cases where metastasis was suspected a CT scan was performed. Depending on the tumor stage, the appropriate treatment was offered. Once the diagnosis of retinoblastoma was made histologically or clinically patients were sent to the Pediatric-oncology unit and Cancer Disease Hospital (CDH) for chemotherapy and radiotherapy respectively. The chemotherapy administered for retinoblastoma involved 6 cycles of vincristine, etoposide, and carboplatin (VEC) every 3-4 weeks. Chemotherapy protocols were derived from evidence-based protocols in the literature (Chantada GL et al, 2005) (Friedman DI et al, 2000)(Appendix4). External beam radiation therapy was administered in stage III and stage IV retinoblastoma, a total of 40 Grays in 20 equivalent fractions was administered for 5 days in week for a month

3.1 STUDY DESIGN

This study was a descriptive retrospective case series

3.2 STUDY POPULATION

Records of patients who were diagnosed retinoblastoma at UTH eye unit from January 2006-December 2012.

3.3 STUDY LOCATION

The study location was the University Teaching Hospital (UTH), Lusaka. Zambia health delivery has three level health systems, which comprises District, Provincial and Central hospitals. Primary health care is run by the district hospital. Thus, a patient requiring specialist treatment has to pass through the district and provincial hospitals before going to a central hospital. The University Teaching Hospital (UTH) is the highest health referral centre located in capital city of Lusaka, with an estimated population of 2 million. UTH has approximately 1655 beds and 250 Baby cots. UTH has 4 clinical departments which are Paediatrics, Surgery, Internal medicine, and Obstetrics. There are also specialized section under the aforementioned department units, which include Dental, Ear, Nose and Throat

(ENT), Ophthalmology, Chest, Urology, and Psychiatry. The UTH offers the basic diagnostic investigation, pathology laboratory, imaging facilities like X-ray, ultrasound, CT scan and MRI.

Within the department of surgery is a specialized eye unit with an outpatient service which sees about 100 patients per week and an inpatient service which has a bed capacity of 30 patients. The eye unit is also the country's principle training centre for several levels of eye workers who includes Ophthalmologist, Ophthalmic nurses, ophthalmic clinical officers and ophthalmic theatre nurses. The unit provides 24hour emergency eye care services. The staffing in the unit includes the consultant ophthalmologist, paediatric ophthalmologist, and a general ophthalmologist.

The oncology unit is under the department of paediatrics and also provides in and out- patient services. The in-patient facility has a 32 bed capacities and admits an average of 10-15 patients a week from all parts of the country. In collaboration with Surgery and Cancer Diseases Hospital (CDH) the unit is able to offer three treatment modalities; surgery, chemotherapy and radiation therapy. The cancer disease hospital (CDH) is located within UTH grounds and it provides radiotherapy and chemotherapy.

3.4 CASE DEFINITION

A case was defined as a patient with either clinical diagnosis or Histological diagnosis of retinoblastoma.

3.5 RETRIVAL OF PATIENTS RECORDS

Records of patients who presented to the eye clinic and pediatric oncology were collected. The data was collected from the eye unit inpatient and outpatient registry, patients' file, histopathology registry, and pediatric oncology registry.

The data collected included demographics, clinical presentation, pathology reports, treatment modalities, and treatment outcome at 6 months after initiation of treatment. Further, histological reports were retrieved from the histology laboratory. The treatment options were recorded as outlined from the patients file.

The information was compiled into the data collection form (Appendix 1)

3.5 INCLUSION CRITERIA

Any patient with 1 and 2 or /and 3 of the following

1. Clinical diagnosis of retinoblastoma
2. Patients aged of 15 years and below
3. Histology of retinoblastoma

3.6 EXCLUSION CRITERIA

1. Unclear clinical or histological diagnosis of retinoblastoma
2. Patients with missing files

3.7 ETHICAL ISSUES

1. Authority to conduct the research at the University Teaching Hospital and the Cancer Diseases Hospital was formally obtained from the offices of the respective Senior Medical Superintendent
2. Confidentiality - all specific patient identifiers were removed and destroyed from the data obtained. Sequential numerical study serials were allocated to all patients.
3. This study was a retrospective study and therefore did not require any interaction with the patient at any point, therefore consent to access information from patients was not sought.
4. Ethical approval was obtained from the University of Zambia Biomedical Research ethics committee (Appendix 5)

3.8 DATA ANALYSIS

Descriptive information for independent variables was expressed as mean, medians, 25th to 75th percentile, range and percentage. The statistical analyses were performed using the statistical package STATA version 12 (StataCorp, College Station, TX, USA).

CHAPTER FOUR

4.0 RESULTS

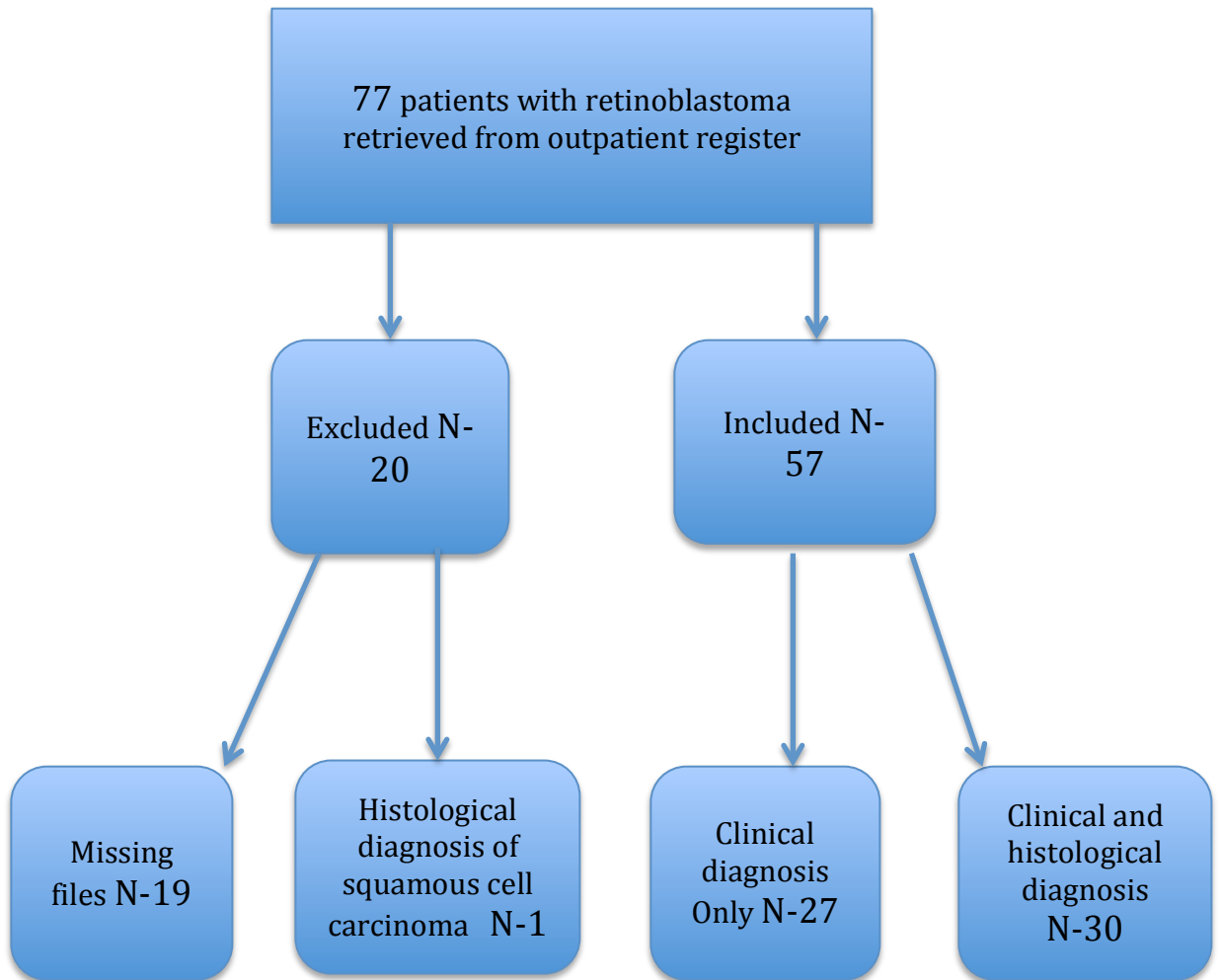


Figure 1: PATIENTS' FLOW DIAGRAM

4.1 DISTRIBUTION OF CASES BY PROVINCE

Thirty (51.1%) came from provincial hospitals, 17 (29.3%) came from district hospitals, 6 (10.3%) came from health centers, 3 (5.2%) were self-referrals, and 2 (3.4%) were from private hospitals. The majority of the patient from the district hospitals came from Southern province followed by Central and Northern province. Seventeen (29.3%) came from Southern Province, 8 (13.8%) each came from Western, Central, and Lusaka Provinces, 6 (10.3%) came from Eastern Province, 5 (8.6%) each came from Northern and Luapula Provinces, and 1 (1.7%) came from Copperbelt Province. None came from northwestern province due to presence of an eye hospital on the Copperbelt province which of closer proximity than Lusaka.

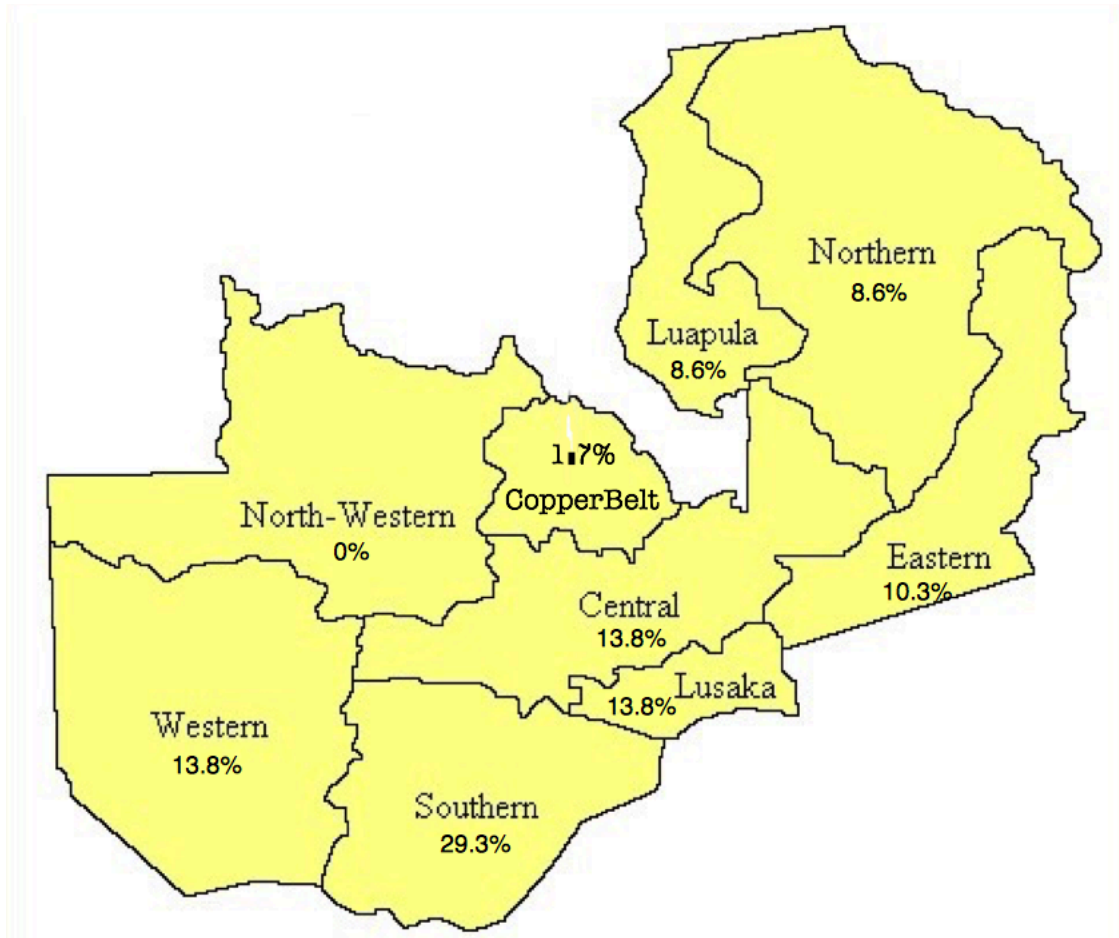


Figure 2: The Map of Zambia showing the percent frequency of Retinoblastoma by Province

4.2. DEMOGRAPHIC CHARACTERISTICS OF CASES

All the cases were African. Twenty-six (45.6%) were males while 31 (54.4%) were females. The youngest was 0.75months old while the oldest was 132 months old. The average age of the participants was 31.1 months old (with a standard deviation of 21.96).

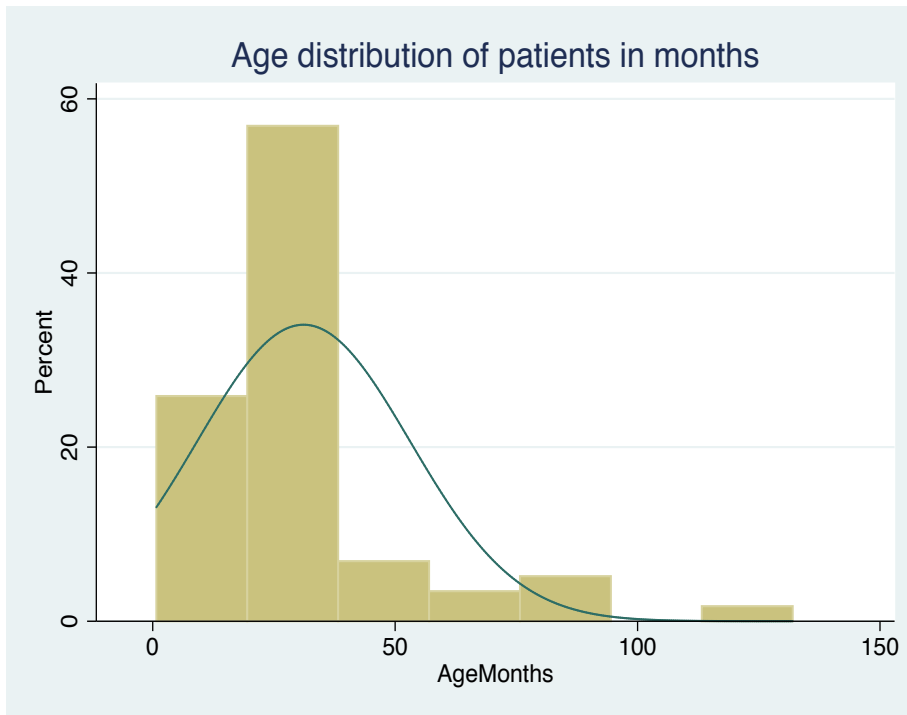


Figure 3: AGE DISTRIBUTION OF PARTICIPANTS

Age in months

Minimum: 0.75 months

Maximum: 132 months

Mean: 31.1 months

Median: 25.5 months

25-75% percentile - 19-36

4.2 MODES OF PRESENTATION

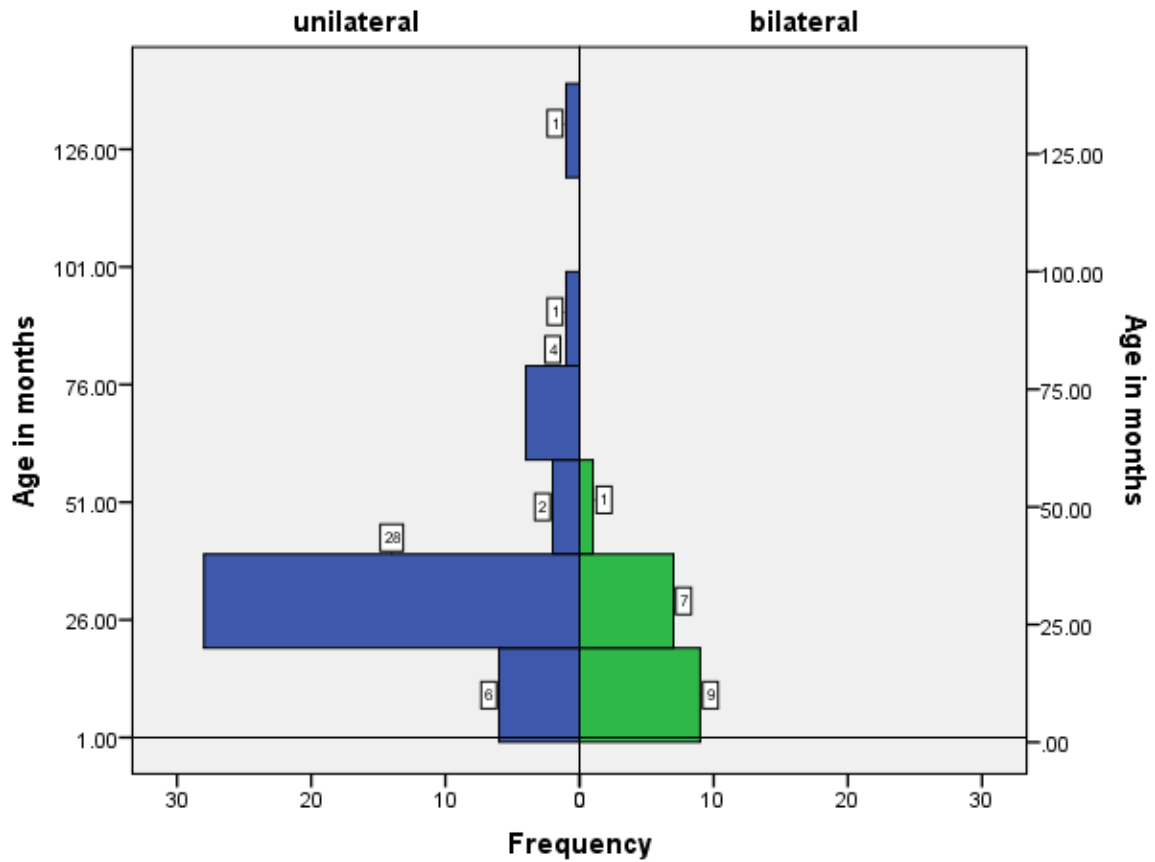


Figure 4: LATERALITY AND AGE OF PRESENTATION AT UTH

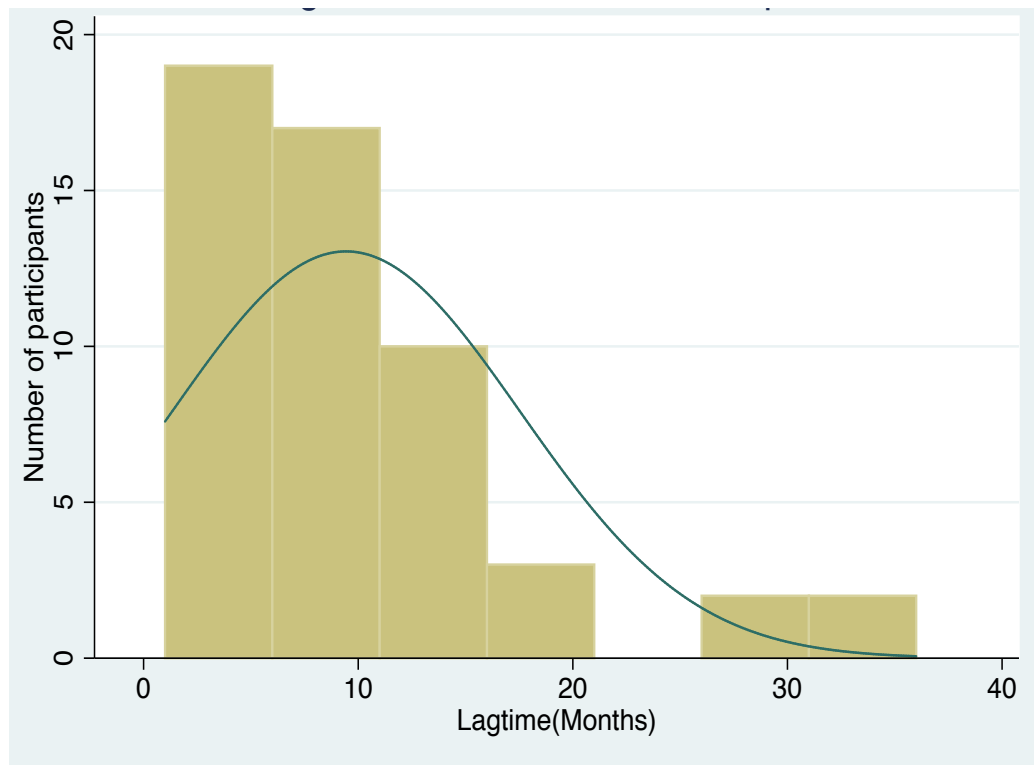
71.2% had unilateral retinoblastoma, 28.8% had bilateral retinoblastoma however no trilateral retinoblastoma was observed. The majority of the patients (28) with unilateral retinoblastoma presented between 24- 48 months. With regards to bilateral retinoblastoma cases the majority (9) presented to UTH between 0.75 months-24 months.

Table 1: MODES OF PRESENTATION

Presentation	Number of eyes	Percent (%)
Proptosis	45	47.37
Leukocoria	35	36.84
Phthisical eye	4	4.21
Anterior staphyloma	3	3.16
Hyphema	2	2.11
Fungating mass	2	2.11
Bone prominence in skull	1	1.06
Hypopion	1	1.06
Orbital cellulitis	1	1.06
Uveitis	1	1.06
TOTAL	96	100

4.3. LAG TIME

The average time lag from the referral institution to UTH was 9.27 months with a minimum of one month and a maximum of 36 months.

**Figure 5: LAGTIME DISTRIBUTION OF THE CASES**

Lag time in months

Minimum:	1	Mean:	9.3
Median:	7	Maximum:	36

4.4. INVESTIGATIONS

57.6% of the patients had Examination Under Anesthesia (EUA) of the fundus that confirmed retinoblastoma, however no staging and details of high risk were provided in the patients records.

The following types of investigations were conducted at UTH and confirmed the likelihood of retinoblastoma. Thirty-four (57.6%) were CT-Scan, 23 (39.0%) were ultrasound, and 4 (7.5%) were skull X-Rays. The imaging studies showed intraocular mass with calcification thus confirming the likelihood of the diagnosis of retinoblastoma. No MRI was conducted.

Twelve patients received both EUA and CT-scan; six patients received both EUA and ultrasound; seven patients received both CT-scan and ultrasound; and seven patients received EUA, CT-scan and ultrasound.

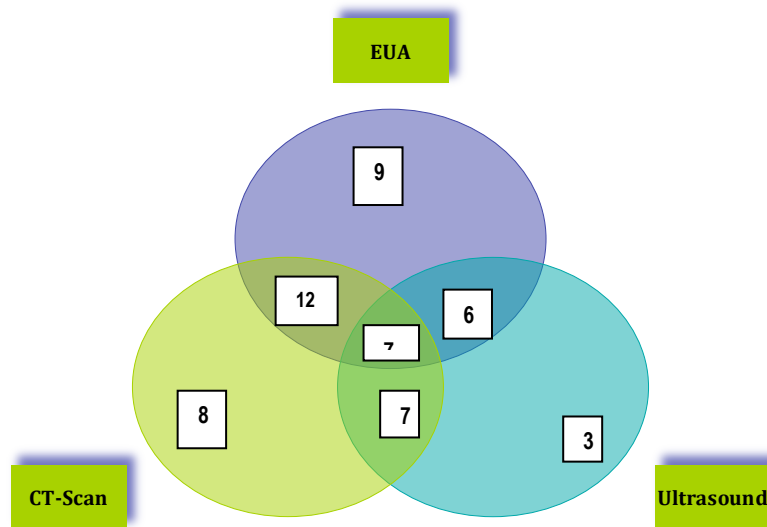


Figure 6; INVESTIGATION CONDUCTED AT UTH

Table 2: HISTOLOGICAL DIAGNOSIS

		Number of children	Percentage	Percentage
Valid	Retinoblastoma	12	21	40
	Retinoblastoma optic nerve involvement	8	14	26.7
	Retinoblastoma optic nerve clear of tumor	8	14	26.7
	Differentiated retinoblastoma	2	3.5	6.67
	Total	30	52.5	100
	No histology requested (advanced retinoblastoma)	16	28.0	
	Missing specimens	10	17.5	
	Squamous cell carcinoma with optic nerve involvement	1	1.75	
	Total	27	49.4	
Total		57	100	

4.5. COMPARISON OF DIAGNOSIS FROM REFERRAL CENTRE AND UTH

Table 3:DIAGNOSIS FROM REFERRAL CENTRE

DIAGNOSIS	Number of children	Percent
Retinoblastoma	24	42.2
Advanced Retinoblastoma	3	5.2
Bilateral Retinoblastoma	1	1.8
Retinoblastoma left eye, Eye ball atrophy right eye	1	1.8
Orbital tumor	14	24.6
Carcinoma left eye	2	3.5
Congenital Glaucoma	1	1.8
Congenital cataract	1	1.8
Conjunctivitis	1	1.8
Corneal Ulcer	1	1.8
Endophthalmitis	1	1.8
Red eye	1	1.8
Secondary glaucoma with anterior staphyloma	1	1.8
Septic lacerated globe	1	1.8
No diagnosis	3	5.3
TOTAL	57	100

Table 4: DIAGNOSIS AT UTH

DIAGNOSIS	Number of children	Percent
Retinoblastoma	30	52.6
Advanced retinoblastoma	12	21.0
Bilateral Retinoblastoma	11	19.2
Bilateral advanced Retinoblastoma	2	3.5
Congenital Retinoblastoma	1	1.7
Total	57	100

Table 5: COMPARISON OF DIAGNOSIS FROM REFERRAL CENTRE AND UTH

	Diagnosis of retinoblastoma	Percent
Not correct	25	43.9
Correct	29	50.8
Total	54	94.7
No diagnosis	3	5.3
Total	57	100

The above table compared diagnosis from the referring center and UTH. It was noted that diagnosis from referral center was correct 50.8 % of the cases. Further, 3 patients were self-referrals thus; no diagnosis from referral center was available

4.6. TREATMENT ADMINISTERED

The majority of the patients received surgical based treatment regimen that included: enucleation and chemotherapy regimen (28.8 %), exenteration and chemotherapy (15.3%) and enucleation only (8.5%). Patient that received chemotherapy regimen only (22.1%) were receiving neo-adjuvant chemotherapy and died before any surgical management could be initiated. One patient did not receive any treatment as guardians refused the treatment option offered (enucleation) and later abandoned treatment. Radiotherapy was administered in 10.2 % of the patients; moreover, this was in combination with enucleation and chemotherapy (3.4 %) or exenteration and chemotherapy (3.4%). The treatment regimen was administered in the sequence as shown in the table.

Table 6: TREATMENT REGIMEN

Treatment Regimen	No. of children	Percent
Enucleation and chemotherapy	17	28.8
Exenteration and chemotherapy	9	15.5
Chemotherapy only	13	22.1
Enucleation only	5	8.5
Exenteration, chemotherapy and radiotherapy	2	3.4
Chemoreduction, Enucleation and chemotherapy	1	1.7
Enucleation, chemotherapy and radiotherapy	2	3.4
Exenteration only	2	3.4
Chemoreduction, enucleation	1	1.7
Enucleation, Exenteration, chemotherapy	1	1.7
Exenteration, chemotherapy	1	1.7
Exenteration and radiotherapy	1	1.7
Chemotherapy and radiotherapy	1	1.7
Total	56	98.5
None	1	1.7
Total	57	100

Table 7: TREATMENT STATUS

Treatment status	Number of children	Percent
Incomplete treatment	43	75.4
Completed treatment	13	22.8
On treatment	1	1.8
Total	57	100

Table 8: TREATMENT REGIMEN AND TREATMENT OUTCOME

Treatment regime	Treatment out come			Total
	Died	Alive	Abandonment	
Enucleation,chemotherapy	10	5	2	17
Chemoreduction	6	1	0	7
Exenteration, chemotherapy	6	0	3	9
Exenteration,chemotherapy, radiotherapy	1	2	1	4
Chemotherapy	2	3	0	5
Enucleation only	1	2	2	5
Enucleation,exenteration,chemotherapy	1	0	0	1
Exenteration only	1	0	1	2
Enucleation,chemoreduction	0	1	0	1
Chemoreduction, enucleation,chemotherapy	0	1	0	1
Enucleation,chemotherapy,radiotherapy	0	2	0	2
Exenteration,radiotherapy	0	1	0	1
Chemotherapy, radiotherapy	0	1	0	1
None	0	0	1	1
Total	28	19	10	57

Most death occurred in patients who had following treatment regime administered: enucleation, chemotherapy regimen (10) and exenteration, chemotherapy regimen (6)

Table 9: TREATMENT OUTCOME

	Number of children	Percentage
Died	28	49.2
Alive	19	33.3
Abandoned	10	17.5
Total	57	100

Table 10: TIME TAKEN IN DAYS BEFORE THE ABANDONMENT OF TREATMENT

	N	Minimum	Maximum	Mean	Std. Deviation
Time taken before outcome (in days)	10	8	186	107.6	68.14

Table 11: ABANDONMENT OF TREATMENT AND DISTRIBUTION PER PROVINCE

	Number of patients	Percent
Northern	1	10.0
Western	2	20.0
Central	3	30.0
Southern	2	20.0
Eastern	2	20.0
Total	10	100.0

There was no patient from Lusaka province, Luapula province who abandonment treatment. The majority of the patients come from Central (30%), Southern (20%), Western (20%) and Eastern provinces (20%).

CHAPTER FIVE

DISCUSSION

5.0. DEMOGRAPHIC CHARACTERISTICS OF CASES

Fifty-seven African patients were included in the study with a male to female ratio of 1:1.2. The youngest was 0.75 months and the oldest was 132 months with a mean age 31.1 months and standard deviation of 21.96. In Brazil, the oldest child was 144 months, which was slightly lower than what was noted in the study (de Aguirre Neto *et al.*, 2007). However, our findings were similar to Gunalp *et al.* in Turkey where the youngest patient was 0.66 months and oldest was 192 months (Gunalp *et al.*, 1996). In contrast to this study, in Nigeria, the minimum age at presentation was 4 months and the maximum age was 60 months (mean 30.69 ± 14.2 months) (Bekibele *et al.*, 2009).

5.1. CLINICAL PRESENTATION OF RETINOBLASTOMA

In the study, the common presentation was proptosis with 47.3%. Proptosis is a feature of late presentation. Proptosis as presenting sign was also a common finding, in other developing countries including: Nigeria (84.6%), Zimbabwe (65%), Pakistan (52.2%), and India (25.5%) (Owoeye *et al.*, 2006)(Chitsike *et al.*, 2014)(Reddy *et al.*, 2009). The foregoing study findings are likely to be due to delayed presentation of patients. In contrast to the developed countries where proptosis as presenting sign was a rare occurrence: USA (0.5%) and South Korea (1.4%) (Reddy *et al.*, 2009).

Leukocoria as presenting sign in the study was 36.8%, which was of low frequency as compared to other countries: Ghana (87%) and China (77.1 %) (Essaman *et al.*, 2010)(Xin *et al.*, 2014). This low frequency of leukocoria as presenting sign was due lack of recognition as well as lack of knowledge of retinoblastoma by the parents and the health works. In most cases the patients would be seen in the health centers and commences on topical medication. These patients were only referred once proptosis appeared.

With the majority (70.2%) presenting with unilateral eye involvement, the study findings were similar to those of Congo (79%)(Kaimbo et al., 2006).

5.2. LAG-TIME

The average lag-time (from onset of symptoms to initiation of treatment) was 9.27 months with a maximum of 36 months. The lag time in the study was much higher than that reported in several studies (Epee E. et al., 2014) (Chang CY et al., 2006). However, in a study done in Tanzania, the mean lag time was 10 months which was slightly higher than that attained in the study (Bowman et al., 2008). It was noted in Honduras, that awareness campaigns increased the number of patients being referred to the pediatric oncology unit and a decrease in lag time (from 7.2 months to 5.5 months) (Leander et al., 2007). In order to achieve early detection of retinoblastoma, it is important that the first contact physicians and healthcare workers are able to recognize the common signs and symptoms of retinoblastoma early resulting in prompt referral. In the study, it was noted that the diagnosis of retinoblastoma from the referral centers accurate in 50.8% of the participants while 43.9% were inaccurate. Leal et al found that in developing countries an important factor that contributed to delay in diagnosis was lack of knowledge of the disease (Leal *et al.*, 2011). The Zambian health delivery comprises of a three level health care systems, which includes District, Provincial and Central hospitals. Patient with retinoblastoma pass through the established referral system prior to procuring definitive treatment at UTH. Going by the study findings, the referral system in its current form is fraught with impediments that delay the speed of access to definitive treatment for retinoblastoma.

5.3. INVESTIGATIONS

EUA of the fundus confirmed the likelihood of the diagnosis of retinoblastoma, however, the medical records lacked the staging of retinoblastoma and there was no mention on high-risk features. This was similar to a study done in Sudan where EUA findings were not comprehensive and lacking high-risk features (Ali A et al., 2011). There was no record of ICRB but it is important in predicting of chemoreduction and focal therapies. Thus, in our setting a comprehensive EUA with ICRB staging will help in offering the best treatment options for retinoblastoma patients.

The imaging studies done at UTH included CT scan (57.6%), ocular ultrasound (39.0%) and skull X-ray (4 %) demonstrated features consistent with the diagnosis of retinoblastoma. However, MRI was not available at UTH during the period of this study. Brisse *et al.* demonstrated that CT Scan sensitivity was very low even in patients with marked optic nerve invasion. Whilst, MRI was 60% sensitive to detect post laminar invasion in the normal sized optic nerve and had 95% Negative predictive value (NPV). Further, MRI reduces the risk of second tumors by avoiding ionizing radiation and has high resolution for soft tissue contrast (Brisse *et al.*, 2007). MRI is now available at UTH, thus MRI should be used in investigation of retinoblastoma patients as will give us important details of post laminar invasion of optic nerve.

5.4. HISTOLOGICAL DIAGNOSIS

The histological diagnosis is important in forming retinoblastoma therapy decision. In 52.5% of sample population had a histological diagnosis of retinoblastoma. Of those who had histological diagnosis 40% had diagnosis of retinoblastoma that was incomplete without comment of optic nerve status and no mention of differentiation of the tumor. Whilst a diagnosis of retinoblastoma with optic nerve involvement was made on 26.7% of the specimens, this was much lower in our study than reported by Biswas *et al* from India (32.3%) and Badhu *et al* (37%) from Nepal. Eye pathology examination done by experienced ocular pathologists is critical for identifying high-risk patients. High risk for extra-ocular recurrence on histopathological examination of enucleated eyes, include invasion of the post-laminar optic nerve, choroid, sclera and in some studies, involvement of the anterior chamber has also been considered high risk (Khelfoali *et al.*, 1996) (Uusitab *et al.*, 2001) (Hanever G *et al.*, 2002). In developing countries, it is estimated that the extra-retinal extension to the outer layers of the affected eye occurs in 50% of the cases (Chantada *et al.*, 2012).

5.5. TREATMENT ADMINISTERED AND TREATMENT OUTCOME

In the study, 6.4% of the cases received all three treatment modalities offered at UTH (surgery, chemotherapy and radiotherapy) and no death occurred in these cases. Further, patients that received chemoreduction, enucleation, chemotherapy regimen had a favorable outcomes. Chemoreduction administration reduced the need to perform exenteration due significant tumor reduction. However, there were very few patients to give any

recommendations on the management. The treatment regimen of exenteration with chemotherapy exhibited a high number of deaths. This could be attributed to extra-ocular extension with distant metastasis in these cases. Further, several studies have shown that overt extra-ocular extension of retinoblastoma is associated with a poor prognosis (Chantada et al, 2003) (Schvartzman et al, 1996)

The outcomes at 6 months were as follows: 49.4% of participants died, 23.7% were alive and 17% had abandoned treatment. Abandonment of treatment was a challenge and was similar to several studies (Belmekki et al., 1999)(Bekibele et al., 2009). In this study, Abandonment of treatment occurred at an average time of 107.6 days, the earliest to have abandoned treatment was at 8 days and the latest was 186 days. Abandonment of treatment can be attributed to lack of knowledge on retinoblastoma by the parents, long hospital stay and financial constrains. In a study conduct at UTH under the pediatric oncology unit from 2008 to 2010, Slone et al demonstrated that about 45% of the patient abandoned treatment and this was alluded to the distant from the treatment center. Close proximity to the treatment center was associated with a decreased risk of abandonment of treatment. Further, distance played a role in delaying the initial presentation of children who eventually abandon treatment (Slone et al., 2014). In Nigeria, abandonment of treatment was attributed to social and economic constrains (Meremikwu *et al.*, 2005). In Malawi, absence of the guardian from home and the extra cost of hospital stay were the reasons for abandoning treatment (Israel's T *et al.*, 2008). Death from retinoblastoma was the most common outcome in this study. Almost half of the entire study population patients died. This poor outcome can be attributed to several challenges that have been noted in this study. Firstly, the lack of knowledge on retinoblastoma by the primary health care workers who are first contact in the referral chain could have resulted in late presentation, high lag-time and delay in diagnosis. Secondly, factors like inadequate staging work-up, incomplete pathological reports, and absence of a team approach to the management of retinoblastoma were noted in this study. These challenges can be overcome by early detection campaigns to the parents and the primary health care workers. Reduction in lag time was achieved through awareness programs as seen in several studies (Leander et al., 2007) (Rodriguez et al., 2008). Twinning with developed countries to facilitate mentorship and supervision as seen in Jordan where twinning had a

positive impact on survival and ocular salvage was noted (Qaddoumi et al., 2008). Further, a multidisciplinary team approach is paramount to the successful treatment of retinoblastoma at UTH.

CHAPTER SIX

6.0 CONCLUSION, STUDY LIMITATIONS AND RECOMMENDATIONS

6.1 CONCLUSION

The common presentation was proptosis with 47.3%, leukocoria with 36.8% and phthisis bulbi with 4%. The most common treatment outcome was death, alive followed by abandonment treatment. Treatment was completed in 22% of the participants. Delay in diagnosis is a challenge as seen in the study by the high mean lag time and late presentation. Further, the diagnosis of retinoblastoma from the referral centers was accurate in 50 % of the patients. Awareness of retinoblastoma to the primary health care givers and parents will help to improve early referrals.

6.2 STUDY LIMITATIONS

1. This study was a retrospective study thus there was some missing records; the history, clinical examination and staging were not comprehensive in some cases.
2. The histological diagnosis was not comprehensive and not indicative of risk extra-ocular recurrence.

6.3 RECOMMENDATIONS

1. To advocate for early diagnosis of retinoblastoma through public awareness campaign to the parents and guardians.
2. To integrate the knowledge of retinoblastoma into the curriculum of the primary health care givers who are the first line in the health care referral structure in Zambia to facilitate quick referral of the patients
3. A retinoblastoma protocol needs to be implemented to standardize the management of the disease at university teaching hospital.

4. Further research will be required to find out what factors are associated with late presentation of retinoblastoma in Zambia.
5. Further research will be required to find out the factors associated with abandonment of treatment in retinoblastoma

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APPENDIX 1: Data Collection Form

PATIENT NUMBER			
AGE (IN MONTHS)			
SEX	()F	()M	
NATIONALITY	[]Zambian []Non Zambian		
REGION OF ORIGIN (Province)			
REFERRED BY INSTITUTION	1)Health centre 3)Provincial Hospital 2)District hospital 4)Self referral		
DIAGNOSIS FROM REFERRAL INSTITUTION			
DATE OF PRESENTATION AT UTH EYE UNIT			
LAG TIME (IN MONTHS)			

HIV STATUS	1) Positive	2) Negative	3) Unknown
CLINICAL DIAGNOSIS AT UTH			
INVESTIGATION DONE	1) EUA	2) CT Scan	3) MRI 4)Ultrasound
PRESENTATION	[] Unilateral [] Bilateral		
MODES OF PRESENTATION	(1)Leukocoria (2)Proptosis (3)Buphthalmos	(4) Squint (5)Blindness (6)Others_____	
DATE OF ENUCLEATION			
HISTOLOGY DIAGNOSIS	1)Poorly differentiated 2)Moderately differentiated 3)Well differentiated		
TREATMENT	1) Enucleation	2) Exenteration	3)Chemotherapy 4)Radiotherapy
TREATMENT STATUS	1)Completed treatment	2)Incomplete treatment	
TREATMENT OUTCOME	1)ALIVE	2)DIED	3)ABANDON
DATE OF OUTCOME			

APPENDIX 2: The Reese-Ellsworth Classification

The Reese-Ellsworth Classification (REC) is rarely used today as chemotherapy has superseded radiotherapy as the favoured treatment for eye salvage.

Group 1: very favourable for maintenance of sight

- A. Solitary tumour, smaller than 4 disc diameters (DD), at or behind the equator.
- B. Multiple tumours, none larger than 4 DD, all at or behind the equator.

Group 2: favourable for maintenance of sight

- A. Solitary tumour, 4 to 10 DD at or behind the equator.
- B. Multiple tumours, 4 to 10 DD behind the equator.

Group 3: possible for maintenance of sight

- A. Any lesion anterior to the equator.
- B. Solitary tumour, larger than 10 DD behind the equator.

Group 4: unfavourable for maintenance of sight

- A. Multiple tumours, some larger than 10 DD.

- B. Any lesion extending anteriorly to the ora serrata.

Group 5: very unfavourable for maintenance of sight

A. Massive tumours involving more than one half the retina.

B. Vitreous seeding.

APPENDIX 3: The International Classification of Retinoblastoma (ICRB) and Management

Group	Features	Management
A	Small tumor =<3mm Large tumor>3mm	Cryotherapy, Laser photocoagulation
B	Macula=<3mm to disc Juxtapapillary =<3mm to disc Subretinal fluid: =<3mm from the margin Focal seeds	Brachytherapy Chemothermotherapy Cryotherapy
C	Subretinal seeds;=<3mm Vitreous seeds=<3mm Diffused seeds	Chemoreduction Chemothermotherapy Cryotherapy
D	Subretinal seeds>3mm Vitreous seed>3mm Both subretinal and vitreous seeds ;>3mm	Chemoreduction Thermotherapy EBRT

E	Extensive retinoblastoma occupying more the 50% or neovascular glaucoma or opaque media from hemorrhage in the anterior chamber ,vitreous or subretinal space	Chemoreduction Thermotherapy EBRT
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The international classification of retinoblastoma

APPENDIX 4: Retinoblastoma protocol stage IV / Relapse CODE N0. 018

Name: Weight:kg
Age:yr Height:m
Sex: BSA:m²
Stage:
Date of starting chemotherapy.....

VEC: Administer every 3-4 weeks X6 Cycles total (Patients > 3 years old)

Drug	Dose	Route	Frequency
Vincristine	1.5mg/m ²	i.v. (bolus)	day 1
Etoposide	150mg/m ²	i.v (1hr inf)	days 1, 2
Carboplatin	560mg/m ²	i.v (1hr inf)	days 1

VEC: Administer every 3-4 weeks X6 Cycles total (Patients < 3 years old)

Drug	Dose	Route	Frequency
Vincristine	0.05mg/kg/d	i.v. (bolus)	day 1
Etoposide	5mg/kg/d	i.v (1hr inf)	days 1, 2
Carboplatin	18.6mg/kg/d	i.v (1hr inf)	days 1

Cycles 1

Drug	Date	Day 1	Day2	Signature
Vincristine		*		
Etoposide		*	*	
Carboplatin		*		

Cycles 2

Drug	Date	Day 1	Day2	Signature
Vincristine		*		
Etoposide		*	*	
Carboplatin		*		

Cycles 3

Drug	Date	Day 1	Day2	Signature
Vincristine		*		
Etoposide		*	*	
Carboplatin		*		

Cycles 4

Drug	Date	Day 1	Day2	Signature
Vincristine		*		
Etoposide		*	*	
Carboplatin		*		

Cycles 5

Drug	Date	Day 1	Day2	Signature
Vincristine		*		
Etoposide		*	*	
Carboplatin		*		

Cycles 6

Drug	Date	Day 1	Day2	Signature
Vincristine		*		
Etoposide		*	*	
Carboplatin		*		

Note: Sign when completed giving drugs for required days

APPENDIX 5: A waiver of ethics review from UNZABREC



THE UNIVERSITY OF ZAMBIA
BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
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Assurance No. FWA00000338
IRB00001131 of IORG0000774

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

24th May, 2013

Your Ref: 007-05-13

Dr. Mutale Nyaywa
School of Medicine,
Department of Surgery
PO Box 50110
Lusaka

Dear Dr. Mutale,

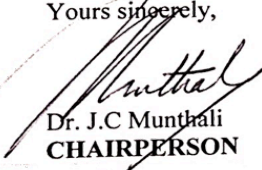
RE: SUBMITTED RESEARCH PROPOSAL: "A RETROSPECTIVE COHORT STUDY OF MODES OF PRESENTATION, MANAGEMENT AND SHORT TERM OUTCOME OF RETINOBLASTOMA IN CHILDREN AT THE UNIVERSITY TEACHING HOSPITAL (UTH) LUSAKA FROM 2006 - 2012"

Your application for a waiver of ethics review for the protocol "A Retrospective Cohort Study of Modes of Presentation, Management and Short Term Outcome of Retinoblastoma in Children at the University Teaching Hospital (UTH) Lusaka from 2006 - 2012" was reviewed. The waiver is hereby granted in accordance with the University of Zambia Biomedical Research Ethics Committee procedure on granting waiver of ethics review.

CONDITIONS:

- The waiver is based strictly on your submitted proposal. Should there be need for you to modify or make changes to the proposal you will need to seek clearance from the University of Zambia Biomedical Research Ethics Committee.
- This waiver does not release you from any other applicable obligations in ensuring confidentiality.
- If you need any clarifications please consult this office.
- **Ensure that a final copy of the results is submitted to this Committee.**

Yours sincerely,


Dr. J.C. Munthali
CHAIRPERSON

Date of approval: 24 May, 2013

Date of expiry: 23 May, 2014

APPENDIX 6: TNM Clinical classification

T- PRIMARY TUMOUR

T X- Primary tumour cannot be assessed

T0 No evidence of primary tumor

T1 Tumour(s) limited to 25% of the retina or less

T2 Tumour(s) involve(s) more than 25% but not more than 50% of the retina

T3 Tumour(s) involves more than 50% of the retina and /or tumour cells in vitreous body

T3b Tumour(s) involves optic disc

T3a Tumour (s) involves anterior chamber and/or uvea T4 Tumour with extraocular invasion

T4a Tumour invades the retrobulbar optic nerve

T4b Extraocular extension other than invasion of the optic nerve

N- Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph nodes metastasis

N1 Regional lymph node metastasis

M-Distant Metastasis

Mx distant metastasis cannot be assessed

M0 no distant metastasis

M1 Distant Metastasis