# DISSERTATION

## Survival among retinoblastoma patients at Kenyatta National Hospital: A retrospective audit.

A dissertation submitted as part fulfillment for the degree of Masters of Medicine University of Nairobi

by

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2008

## DECLARATION

This dissertation is my original work and has not been presented for a degree at any other university

Signed  Date 3 / 11 / 08

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## APPROVAL

This dissertation has been submitted for examination with our approval as university supervisors.

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## DEDICATION

This book is dedicated to Mfwana.

Your smile kept me going when the going got tough.

I hope to share with you one day about the making of this book and of the courage of the retinoblastoma survivors.

To Ben, my husband and my friend.

Thanks for cheering me on through the seasons of life.

To the courageous retinoblastoma survivors and to their parents,

I wish you God's blessing. You have inspired me.

To Christ, our Lord and saviour.

We can do all things through Him who gives us strength.

**ACKNOWLEDGEMENT**

1. Christoffel Blindenmission (CBM) – for sponsoring this study and my post-graduate studies.
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4. Colleagues, class of 2008- for your friendship and comradeship.

## LIST OF TABLES

## LIST OF FIGURES

## TABLE OF ABBREVIATIONS

1. CT Scan - Computerised Tomography Scan
2. MRI Scan - Magnetic Resonance Imaging Scan
3. CSF - Cerebrospinal fluid
4. KNH - Kenyatta National Hospital
5. EBRT - External Beam Radiotherapy
6. mm - Millimetres
7. SPSS - Student Package for Social Sciences
8. CNS - Central Nervous System

## ABSTRACT

### Aim

The purpose of this study was to estimate the survival of patients with retinoblastoma admitted at Kenya's national referral hospital, The Kenyatta National Hospital. The information obtained will provide a good audit into the management of retinoblastoma in our country.

### Methods

The study was a retrospective audit and was carried out at the Kenyatta National Hospital. All records of patients admitted with retinoblastoma in the period January 2000 to December 2004 were retrieved using ICD9 coding system. The files were coded 69.2 for retinoblastoma. Demographic data,clinical presentation, intraoperative finding and histology report were recorded in a provided questionnaire. Patient or their next of kin were contacted in order to find out the outcome of the disease. The data was stored in a computer for analysis and analysis carried out using the Statistical Package for Social Scientists (SPSS) version 12.

### Results

The cumulative 3-year survival rate was found to be 26.6%. The mean survival time for the 3-year survivors was 68 months (SD 16.6) and the Kaplan-Meier survival probability at 36-months follows up was 0.2. The factors that significantly influenced good outcome were; age at presentation of <12 months, early disease at presentation (leucocoria only) 4.13(1.48-11.68) $p<0.001$, intraocular disease on histology (compared with extraocular disease) 8.5(2.23-34.49) $p<0.001$ and total delay to management of ≤5 months 3.5(1.31-9.68) $p=0.005$. Proptosis and tumor recurrences were associated with 100% mortality. Multivariate analysis found early disease at presentation (leucocoria only) and intraocular disease on histology to significantly affect good outcome.

Accuracy in correlating intraoperative findings with histopathological report was found to be 69.9%. Only 48% of the histologies were reported within two week of the surgical intervention.

### Conclusions

The survival rate of patients treated for retinoblastoma was found to be very low compared to findings in studies done in the developed countries and developing countries outside Africa. The main reasons were the late presentation and presentation with recurrent disease. The factors associated with poor outcome were presentation with advanced or metastatic disease, extraocular disease on histology and total delay to management of more than five months. The accuracy in correlating the intraoperative findings with histopathological findings was moderate.

**TABLE OF CONTENTS** **PAGE NUMBER**

# 1 INTRODUCTION AND LITERATURE REVIEW

## About retinoblastoma

### Definition

Retinoblastoma is a primitive embryonal anaplastic tumour composed of undifferentiated retinal elements. It is the most common primary, intraocular malignancy of childhood.

### Incidence and Epidemiology

Retinoblastoma has a worldwide distribution affecting all races. Some evidence documents a higher incidence in some African-American population as in Haiti, Jamaica, Nigeria and South Africa [1,2,3]. Pendergrass in 1980 however found no difference between African-Americans and Caucasians[4]. It accounts for 3% of all childhood cancers and occurs in about 1:17,000 live births[5]. In Kenya, Klauss estimated the incidence to be 1:19,000 live births from hospital data and since this was not a population-based data this figure could be an overestimate. In the United States, the incidence is 1 in 15,000-20,000 live births or 300 cases per year[6]. No significant sex difference has been noted. In Kenya, Khan found the male to female ratio to be 1.3:1[7]. Kimani found 29 females and 23 males but the difference was not statistically significant ($p=0.94$)[11]. Bowman et al found a male to female ratio of 1.1:1[33].

### Clinical Presentation

Patients present with retinoblastoma within the first year of life in bilateral cases and about 2 years of age if the tumour is unilateral. However, 8.5% patients are children older than 5 years at initial diagnosis[8]. In Kenya, Khan found that majority of children (61.4%) were seen in the second and third years of life[7]. The mean age at diagnosis for all cases was 18 months. Retinoblastoma is extremely rare after 4 years[8].

Studies in Kenya show that majority of retinoblastoma patients present late[9, 10,11]. Gakuruh found 42.9% of cases presented in first year of life, 19.6% in the second and 30.4% in the third[9]. Klauss found the average age of presentation to be 32.4 months with a range of 6- 72 months[10]. Kimani found the mean age at admission in bilateral disease was 26.1 months and in unilateral cases, 35 months[11]. Khan found the average age at the time of diagnosis to be 32.4 months. Children with bilateral disease were younger (mean age of 21.4 months) than those with unilateral disease (mean age of 38.7 months of age) [9]. In India Shanmugan found the mean age of presentation in

India to be 23.98 + /- 23.37[12]. Ozhan found the mean age overall in the time of diagnosis to be 25 months, 29 months in unilateral cases and 16 months in bilateral cases[13].

Retinoblastoma is unilateral in approximately 67% of cases and bilateral in 33% of cases[14]. At Kenyatta National Hospital, Gakuruh found 59% of cases to have been unilateral and 41% of cases to be bilateral[9]. Klauss found it to be 63% unilateral and 36% bilateral (also in Kenyatta National Hospital)[10]. Kimani et al (2000) found 58% of patients to be unilateral and 42% bilateral[11]. Khan, also in Kenyatta National Hospital, found prevalence of laterality to have been 63.3% unilateral and 36.7% bilatera[17]. In a Nigerian study, Owoeye found bilaterality to have been 15%[15]. In India, Shanmugan) found unilaterality in 50% and bilaterality in 50%of the patients studied[12]. In Turkey, Ozhan found that 74.5% were unilateral and 25.5% were bilateral[13].

In the developed countries, leucocoria is the commonest presenting complaint (60%) while strabismus is the second most common (20%)[6]. Melamud reported leucocoria as the commonest presentation usually detected in primary care in the United States of America[6]. Other presentations include secondary glaucoma associated with buphthalmos. Diffuse retinoblastoma invading the anterior segment tends to be present in older children. It presents with pseudouveitis and iris nodules, which may be associated with pseudo-hypopyon. Orbital inflammation mimicking orbital or preseptal cellulitis may occur with necrotic tumor. Orbital invasion with proptosis and bone invasion occur in neglected cases. Other presentations include metastasis to regional lymph nodes and brain as well as raised intracranial pressure due to trilateral retinoblastoma. The prognosis of metastatic retinoblastoma is dismal[14].

In Kenya, Gakuruh found 73.2% to present with leucocoria, 16% with proptosis and 3% with inflammation[9]. Kimani found the most frequent initial symptom to be white reflex while the most frequent presenting complaint was swelling of the eye. Only 26% of patients presented with white reflex as a complaint[11]. Klauss found that over 90% of the patients presented late with only 3 out 99 eyes amenable to focal methods of treatment[10]. In Ilorin Nigeria, Owoeye found that proptosis with chemosis was the commonest clinical presentation (84.6%)[15].

Trilateral retinoblastoma is a well recognized syndrome that consists of unilateral or bilateral germ line retinoblastoma associated with an intracranial neuroblastic tumor. It has been observed that 5% to 15% of children with familial, multifocal or bilateral retinoblastoma may develop an intracranial neuroblastic tumor as well. Children with germline retinoblastoma have a particularly high incidence of trilateral retinoblastoma, which are nearly always fatal[16]. It has also been found that patients who are asymptomatic at the time of diagnosis with an intracranial tumor have a better overall survival than those who are symptomatic[17]. Use of chemotherapy to reduce the extent of intraocular tumor in bilateral cases may prevent the development of pineal tumor[18].

**Histopathology**

Histopathologically, retinoblastoma consists of small basophilic cells with large hyperchromatic nuclei and scanty cytoplasm. Many tumors are undifferentiated but varying degrees of differentiation is characterized by formation of Flexner-Wintersteiner rosettes, Homer-Wright rosettes and fleurettes. Plentiful rosettes are usually found in those tumours that had not extended beyond the choroid or as far as the resection line of the optic nerve and were, therefore, associated with a good prognosis[19]. The absence of rosettes did not, however, necessarily indicate a poor prognosis[19]. Neither the length of the optic nerve stump, tumour size, anterior chamber invasion, degree of ocular coat invasion correlated with increased risk of metastasis in a study done by Chantada[20]. Stannard found that choroidal invasion carried a 100% survival rate provided that the sclera, iris and whole optic nerve were not also involved.

**Investigations**

Ultrasound is used mainly to assess tumor size. It also detects calcification within the tumor and is helpful in the diagnosis of simulating lesions such as Coat's disease. Dudea studied doppler ultrasound performed in intraocular and orbital tumors. The association of vascular information to the 2-dimensional image allowed for an improved characterization of ocular and orbital tumors[21]. CT Scans also detect calcification but it entails a significant dose of radiation and performed only if ultrasound has not detected calcification. Magnetic resonance cannot detect calcification but it is superior to ultrasound for optic nerve evaluation and detection of extraocular extension or a pinealoblastoma especially with contrast and fat suppression. It is also useful in differentiating retinoblastoma from simulating conditions. Screening by neuroimaging

may improve the cure rate. Apushku studied 58 eyes with retinoblastoma found that screening by neuroimaging MR imaging is accurate for tumor staging and detection of metastatic risk factors. Detection of intraocular tumor volume, measured with MR imaging, was associated with prelaminar optic nerve and choroidal involvement[22]. It has been recommended that children with germline retinoblastoma should be screened using magnetic resonance neuroimaging every 6 months after diagnosis for the next 4 years. These tumors are not likely to occur after the age of 5 years[22]. Systemic evaluations include physical examination and magnetic resonance of the orbit and the skull, as a minimum in high-risk cases. In the presence of metastatic disease, then bone scans; bone marrow aspiration and lumbar puncture are also performed.

Genetic studies require fresh tumor tissue from the enucleated eye and a blood sample for DNA analysis. Blood samples from the patients relatives and a sperm sample from the father is also useful.

**Treatment Modalities**

Despite early tumor detection, improved and increased use of more conservative eye sparing treatments, enucleation remains a frequent treatment for retinoblastoma. It is indicated for all unilateral tumors that fill over half of the eye or when there is vitreous seeding, rubeosis or optic nerve involvement. It is also performed if chemoreduction fails or a normal fellow eye makes aggressive chemotherapy unsuitable. Enucleation is indicated for diffuse retinoblastoma because of poor visual prognosis and high risk of recurrence with other therapeutic modalities.

Retinoblastoma is extremely sensitive to radiation hence irradiation is an effective treatment. External beam radiotherapy is most often used to treat patients with bilateral retinoblastoma, which is not amenable to local treatment. It is preferred when tumor recurs or metastasis into the orbit, when the second eye contains a tumor larger than 16mm in diameter, when the tumor is nears the optic disc or fovea, when multiple tumors are present or when there is extensive vitreous seeding. It may also be used to treat the eye socket after surgical intervention if there is extension beyond the resection site. However, over the last ten years, treatment using external beam radiotherapy has been avoided due to its serious and often fatal complications[23].

Plaque radiotherapy delivers radiation in a localized manner. Theoretically, it should minimize exposure to other eye structures reducing complications. It is however, associated with more radiation-induced retinopathy, papillopathy than external beam radiotherapy. It is effective for tumors of up to 16mm in diameter and 8mm in thickness (small solitary tumors). Schueler found tumors treated with plaque radiotherapy to have a 5-year tumor control rate of 94.4%. Tumor recurrences occur frequently in eyes with vitreous seeding. The 5-year eye preservation rate in this study was 86.5%[24]. Phototherapy is used to treat selected small tumors that do not involve the optic disc or macula. It is successful for tumors less or equal to 3mm in diameter and 2mm in thickness confined to the retina. Cryotherapy is used as a primary or secondary treatment of peripheral retinoblastoma. It may be effective for vitreous seeding less than 0.5mm from the tumor apex.

Systemic chemotherapy is used as adjuvant therapy in children previously considered candidates only for enucleation or bilateral external beam radiotherapy. Use of chemotherapy for tumor reduction may make tumors amenable to focal treatment or permit lower dosage of radiation. There is role for pre-enucleation chemotherapeutic induction in children with high-risk features including orbital disease or suspected optic nerve disease. With the use of systemic chemotherapy, without radiation therapy or enucleation, recurrence is not uncommon and generally occurs in the first 6 months following therapy[25,26,27,28].

**Genetics of retinoblastoma**

Retinoblastoma results from malignant transformation of primitive retinal cells before final differentiation. Retinoblastoma may be inheritable or non-inheritable. The predisposing gene (RB1) is at 13q 14 – the gene is a tumor suppressor gene.

**Inheritable retinoblastoma**

This accounts for 40% of retinoblastoma cases. In inheritable retinoblastoma one allele of the RB1 is mutated in all body cells; when further mutagenic events (second hit) affect the second allele, the cell undergoes malignant transformation. According to Knudson's hypothesis, deletion or rearrangement of 13q 14 band might be associated with retinoblastoma through a specific derangement of normal retinal development which predisposes the retinal cell to a second mutation[29]. A child with familial retinoblastoma inherits faulty inactivated suppressor allele on one chromosome 13 and a functional gene is lost or inactivated by chance. All retinal

precursor cells contain the initial mutation. The children develop bilateral and multifocal tumors. They also have a predisposition to non-ocular cancers notably suprasellar primitive neuroectodermal tumor (PNET) which occurs in about 3%. The risk of second malignancy increases by about 6%[30]. This risk increases five fold if external beam irradiation has been used to treat the original tumor – According to a study done by Wong the cumulative incidence is about 26% (+ 10%) in non irradiated patients and 58% (+ 10%) in irradiated patients by 50 years after diagnosis of retinoblastoma – a rate of about 1% per year[31].

**Non-hereditary**

It accounts for 60% of cases. Tumors are unilateral and solitary tumors are the rule, they occur in patients with negative family history and normal karyotypes. This sporadic retinoblastoma reflects the chance inactivation of both 13 Q14 allele. Both mutational events occur in a single cell in the developing retina (somatic mutation) in 75% of cases resulting in a solitary unilateral tumor. The risk in each sibling and offspring is about 1%. In non-hereditary disease, both retinoblastoma mutations are somatic events that cause formation of a single tumor focus.

**Prognosis & Survival**

Children with retinoblastoma who have access to modern medical care have a very good prognosis for survival, with overall survival rates of over 95% for children in developed countries presenting with localized intraocular disease. Melamud found the 5-year survival rate of retinoblastoma patients in the United States to have been 93%[6]. Berger, in Rhone–Alpes, found the 5-year survival rate to be 94.1% for retinoblastoma[32]. In developing countries survival rate is variable with follow up poor. Bowman in Tanzania found a disease-free survival probability of 0.23 (Standard error = 0.07)[33]. Ozhan found the 3 year cumulative survival rate to be 89.9% [13]. In Omani children, Khandekar found a five-year survival rate for retinoblastoma of 89%[34].

**Prognostic Indicators**

Absence of extraocular disease is the most important prognostic factor [25,26,27,28]. The only independent factor indicating a poor prognosis is extraocular disease. If the recurrence or progression is extraocular, the chance of survival is probably less than 50%[25,26,27,28]. In Taiwan, survival rates of patients with intraocular and extraocular diseases were 96.9% and 39.2%

respectively[35]. In Sao Paolo, Rodrigues found that a 5-year overall survival rate were higher among patients with intraocular disease (94.6%)[36].

Stannard studied correlation of the optic nerve and choroids involvement with prognosis and metastases. The extent of optic nerve invasion was correlated with choroidal / scleral extension. Choroidal invasion carried a 100% survival provided that the sclera, iris and whole optic nerve were not also involved. Invasion of the optic nerve beyond the lamina cribrosa also carried 100% survival provided that the resection line was free and that invasion did not involve the sclera or iris[19]. Bouguila analyzed the factors influencing the prognosis of retinoblastoma. They reported a global survival rate of 87.5%. The main aggravating factors were the size of the tumor and the extraretinal involvement with extension within the choroids, the sclera and the optic nerve. They concluded that the prognosis of retinoblastoma mainly depended on the extraretinal involvement[34]. Further, in Turkey, Gunduz concluded that the prognosis for metastatic retinoblastoma is dismal and the presence of central nervous system involvement may portend an even worse outcome[14].

Chang carried out a retrospective study aimed at describing the survival characteristic and prognostic factors retinoblastoma cases diagnosed at the Taipei Veterans General Hospital between 1982 and 2004. The survival rate of patients with intraocular and extraocular disease was 96.9% and 39.2% respectively[35].

Laterality of the disease (whether it was unilateral or bilateral) depends mainly but not entirely on the genetics of the retinoblastoma- whether heritable or non-heritable. In the Turkey, Ozkhan found the 3- year cumulative survival rate to be 90.74% for unilateral cases and 87.25% in bilateral cases[13]. Chang found the 5-year survival rate to be 88.1% in unilateral cases and 64.3% in bilateral cases[35]. The age at diagnosis depends on whether the disease is heritable or non-heritable. Generally various studies have shown that younger age at diagnosis and family history of retinoblastoma are considered to be risk factors for recurrences[25,26,27,28].

Chang found that the survival rate of patients with an interval of between onset and treatment of <5 months was 90.9%, and that for an interval of >5 months was 60.9%. The mean duration of symptoms was 2.96 months in this study[35]. Lag time after diagnosis is the other factor affecting the prognosis of retinoblastoma. Chang concluded that a lag time before treatment of >2.5 months was an indicator of poor prognosis[35]. Rodrigues found a mean lag time of 5.8 months.

DerKinderen et al reported that early diagnosis in bilateral retinoblastoma improved survival and visual outcome[39]. Erwenne et al found that the risk of extraocular disease was dependent on the age at diagnosis and lateness of referral. The median overall lag time was found to be 5 months with a range of 0-45 months[40].

Children who survive bilateral retinoblastoma have an increased incidence of non-ocular malignancies later in life. The mean latency for second tumor development is approximately 9 years from management of the primary retinoblastoma. Estimates suggest that as many as 10-20% of patients who have bilateral retinoblastoma will develop an apparently unrelated neoplasm within 20 years and that 20-40% of such patients will develop an independent primary malignancy within 30 years[8]. By the age of 50 years, the second tumor incidence is reported as high as 58.3%. The prognosis for survival in retinoblastoma patients who later develop sarcomas are less than 50%. External beam radiotherapy to the eye appears to decrease the latency period of second tumor development, increase the proportion of tumors in the head and increase the incidence of second tumors in the first 30 years of life.

Individuals with intraocular retinoblastoma without trilateral retinoblastoma usually have a good 5-year survival. Those with extraocular retinoblastoma have less than a 10% chance of disease free survival. Patients with trilateral retinoblastoma who receive treatment have an average survival rate of approximately 8 months while those who remain untreated have an average survival rate of approximately one month. Patients with retinoblastoma who are asymptomatic at the time of diagnosis have a better prognosis than those who experience symptoms.
Patients with an inherited form of unilateral retinoblastoma have 70% chance of developing retinoblastoma in the other eye. Retinoblastoma reoccurs in the other eye in approximately 5% of people with a non-heritable form of retinoblastoma, so it is advisable for even those patients to be closely monitored.

People with an inherited form of retinoblastoma who have not undergone radiation treatment have approximately a 26% chance of developing cancer in another part of the body within 50 years of initial diagnosis. Those with an inherited form who have undergone radiation treatment have a 58% chance of developing a secondary cancer by 50 years of initial diagnosis.

## Study Rationale

Various factors have been found to influence the survival rate in patients with retinoblastoma. We need a study in our set up to determine the factors that influence the survival rate of retinoblastoma patients. Due to delays in histopathological reporting, decision-making on the consequent management of retinoblastoma patients is often based on gross appearance of the globe at the time of operation. It is therefore important to compare histology reports with the gross appearance of the globe as a retrospective audit of the accuracy of our decision making process.

## Study Justification

No study has been done on the survival rate among retinoblastoma patients in Kenyatta National Hospital. This is Kenya's national referral hospital where majority of retinoblastoma patients are referred to for management, hence a study of the survival rate of retinoblastoma would provide good audit into the management of retinoblastoma.

## Expected outcome

The data collected would also allow for comparison of survival of our retinoblastoma patients against those in other developing countries and the developed world and, therefore, provide a platform for addressing any gaps in our management.

An investigation into the factors contributing to the survival rate would enable us to highlight the main areas where new approaches are needed in order to improve the survival rate.

# 2 RESEARCH OBJECTIVES

## Objectives

1. To determine the 3-year survival rate of retinoblastoma patients admitted at the Kenyatta National Hospital between 1st January 2000 and 31st December 2004 and factors that influence survival rate in our set-up.

2. To relate gross appearance of globe after enucleation (as per theatre notes) with the histopathological report.

# 3 METHODOLOGY

## Place of Study

The Kenyatta National Hospital is located approximately 3.5 kilometres from the Nairobi city centre. It is Kenya's largest national and referral public hospital and therefore receives patients from all parts of the country who require specialized management. Kenyatta Hospital is also the teaching hospital for the University of Nairobi medical school and Kenya Medical Training College. It has bed capacity of 1800 patients.

## Study Design

A retrospective audit of treated cases of retinoblastoma

## Study Population

All patients admitted with retinoblastoma at Kenyatta National Hospital in the period between 1st January 2000 and 31st December 2004. The year 2000 was chosen as the commencement of the study as there will be increased likelihood of ability to contact the patients or the next of kin because of the availability of the mobile phone facility during this period.

## Inclusion Criteria

Records of patients with retinoblastoma confirmed clinically and or histopathologically.

## Exclusion Criteria:

Records of patients whose histology report ruled out retinoblastoma.

## Data Collection

All patient records of patients admitted with retinoblastoma in the period January 2000 to December 2004 were retrieved. Computer printouts of all the records disease coded for

retinoblastoma using ICD-9 methods were made and all the files retrieved manually by a medical clerk in the records department. A list of all patients admitted with retinoblastoma was manually made using the admission records in the ophthalmology ward and this was used to independently cross-check the retrieved files by another medical records officer. The following information from the socio-biographical data sheet and or the patient cadex was retrieved and recorded in the questionnaire (Appendix I):

i. Patient's name, age and sex

ii. Names of next of kin, postal address and telephone contact

iii. Patient's home (village), location, division and district.

iv. Patient's area of residence, name and telephone contact of relative or friend.

v. Date of admission and discharge

vi. Date of death (where applicable)

vii. Date of last follow up

viii. Age at presentation, the duration of symptoms,

ix. Whether the disease was unilateral or bilateral,

x. Presenting complaint and ocular findings on examination.

xi. Findings at surgery were recorded and indicated whether tumor was within the globe grossly, outside the globe and whether or not the optic nerve was thickened.

xii. Histopathological report where available was indicated. Of interest was whether the tumor was confined to the globe, involving the optic nerve but resection margin free of tumor or whether the margin was involved and also whether there was extrascleral spread and or cellular differentiation.

xiii. Time lag from onset of symptoms to treatment

xiv. Investigations done

xv. Mode of management

xvi. Secondary management where applicable.

The telephone contacts were used to find out whether the patients are alive or dead, date of death, place of death and cause of death (if known).

Where no telephone contacts are obtained, letters were written through the available post office boxes requesting the patient/friend/next of kin to contact the investigator through a telephone number provided( Appendix II ). The various coordinators in the integrated school programme were also contacted to help in identifying blind children in their institution who may have been treated for bilateral retinoblastoma during the study period. The above information was entered into the questionnaire.

The data was stored in a computer for analysis. Survival rate was calculated using the simple cumulative survival rate method and using Kaplan-Meier survival probability. Analysis was carried out using the Statistical Package for Social Scientists (SPSS) Version 12.

**Ethical and Medico-legal Consideration**

1. Approval from the Ethical Board was sought and obtained.
2. Patient's records were treated with confidentiality.

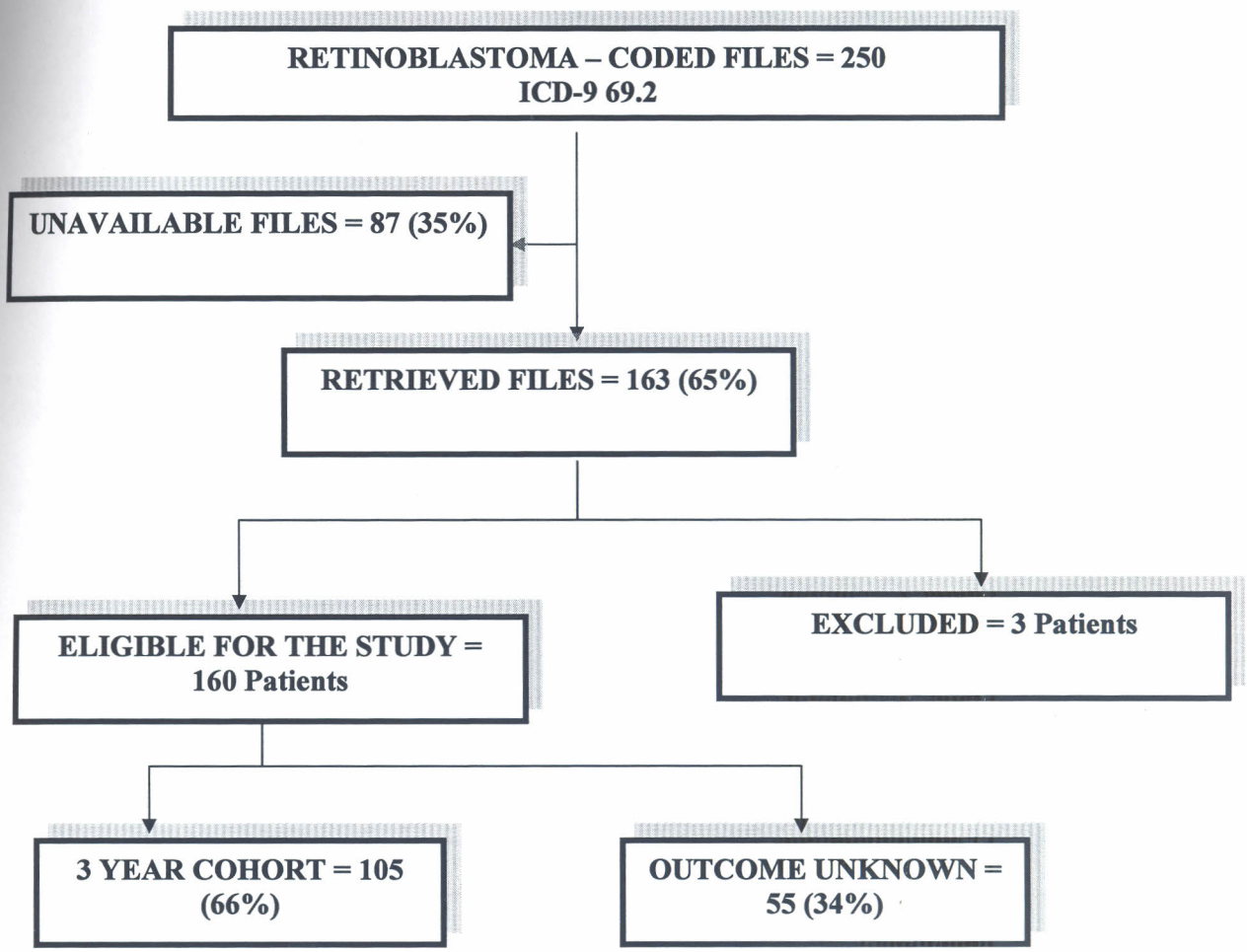
**Study Equipment**

- Patients' records
- Questionnaire
- Mobile phone

## 4 RESULTS

A total of 160 patients were included in this study. Out of these the outcome of 98 was known; 105 patients had been followed up for at least three years and hence qualified as the 3-year cohort.

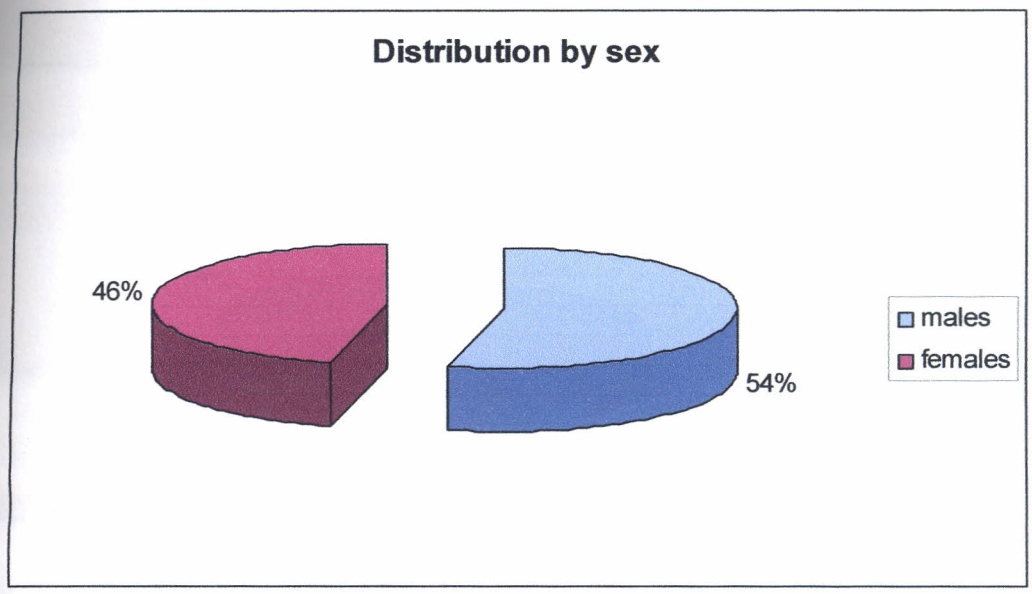
**Figure 1:Cohort Representation**




3 patients were excluded on the basis of histology reporting; two patients were found to have persistent hyperplastic primary vitreous and one had ocular trauma with organized vitreous haemorrhage.

**Figure 2: Distribution by sex**

n =160




Ratio of male: females was 1.16: 1

**Figure 3: Distribution by laterality**

n =160

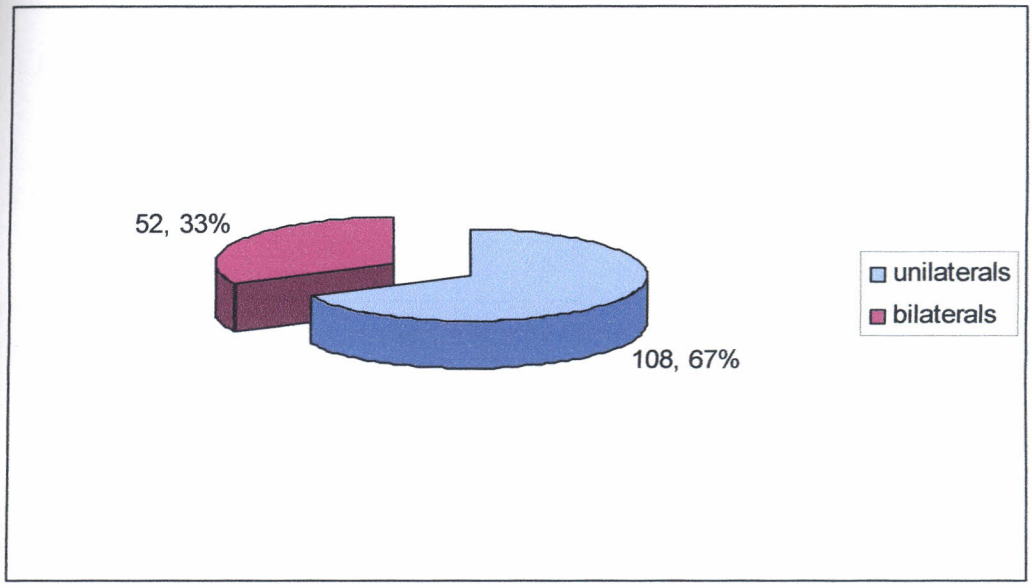
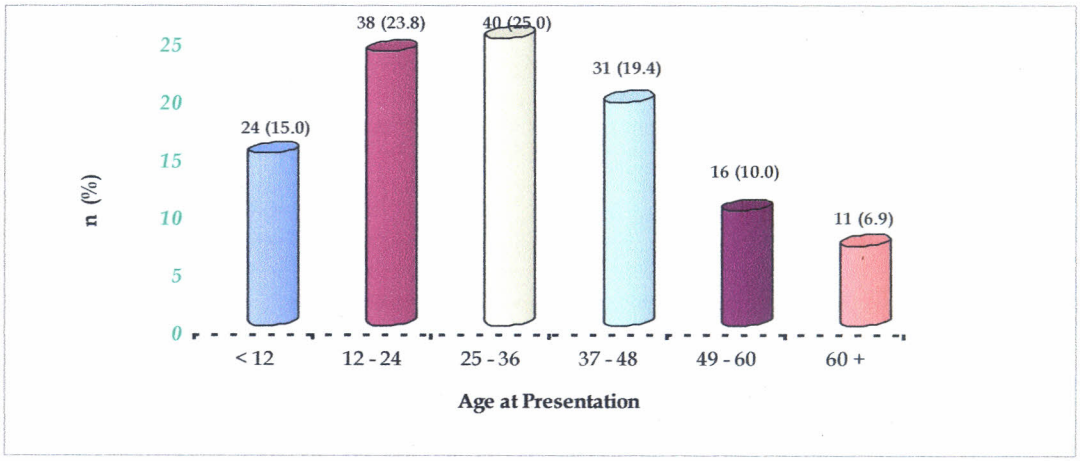



**Figure 4: Distribution by age at presentation**

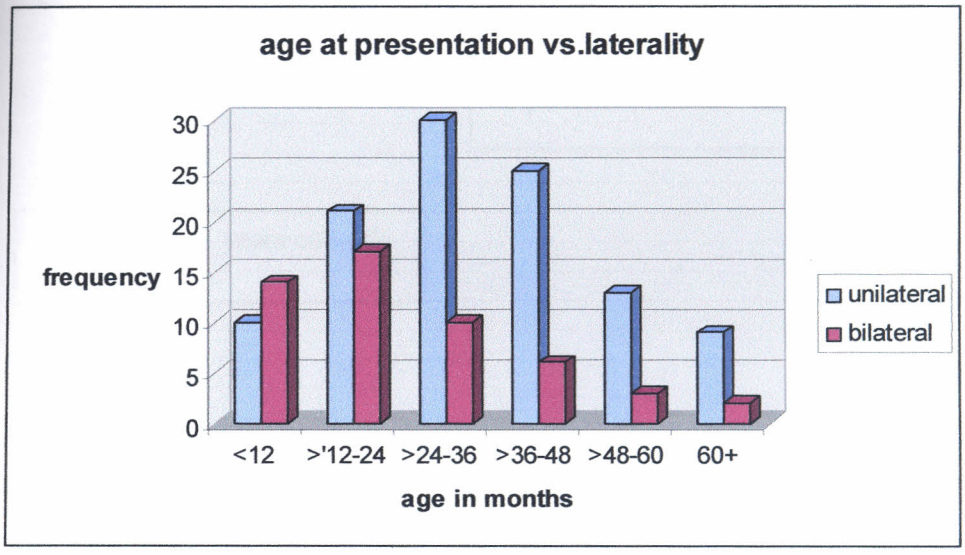
n =160




The mean age was 35 months (SD 25), median age 33.5 months, mode 36, and range 1-144 months

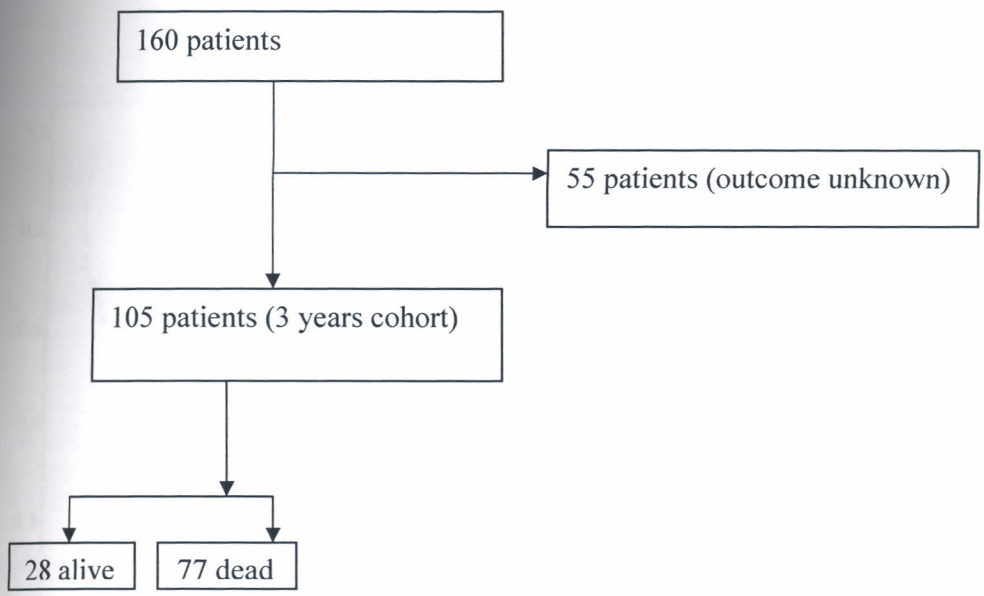
**Figure 5: Age at presentation: Age in months vs. laterality**

n =160




The mean age of the unilateral patients was 39.9 months (SD 26.1) compared to 24.4 (SD 18.1) months among the bilateral patients; the mean difference was 15.5 months with a p value < 0.001.

**Figure 6: Outcome**




**Cumulative 3-year survival rate: 28/105=26.6%**

**Person-time at risk:**

$$\frac{\text{Number of those known to be dead}}{\sum\text{Survival time for the dead + Survival time for all alive (months after presentation)}}$$

$$\frac{7}{393+1917}$$

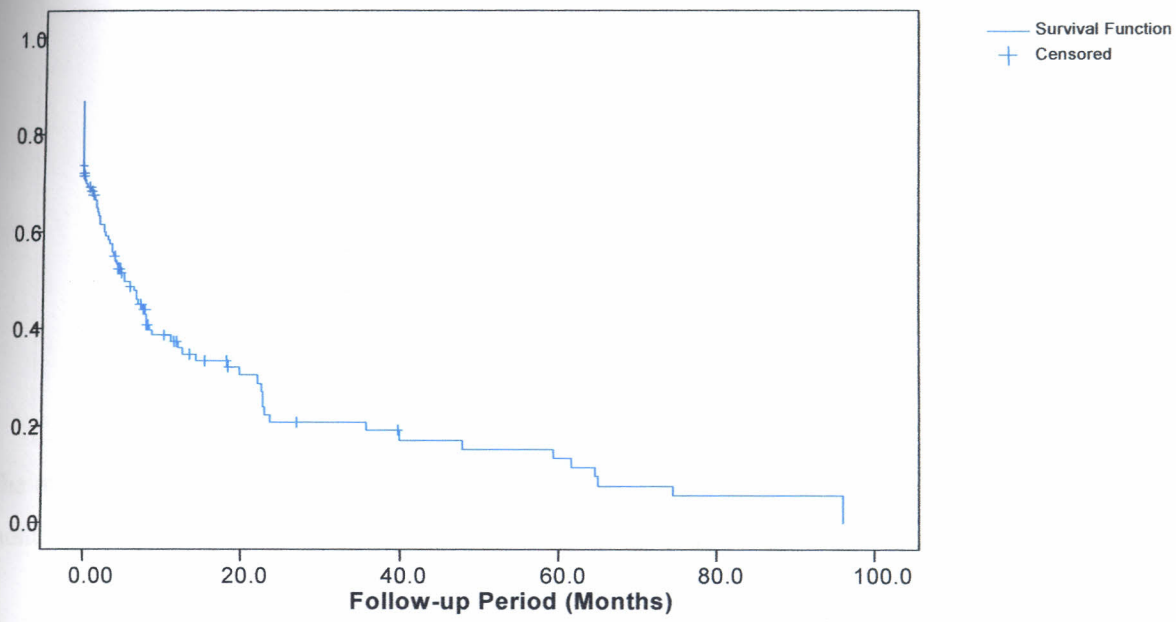
33 per 1000 person-time at risk (n=105)

Mean survival time of dead children after presentation was found to be 5.1 months (SD 6.4), range of 1-30 months (n=105).

Mean survival time for the 3-year survivors after presentation was found to be 68 months (SD 16.6), range of 41-96 months (n=105).

**Figure 7: Kaplan-Meier Survival probability curve**

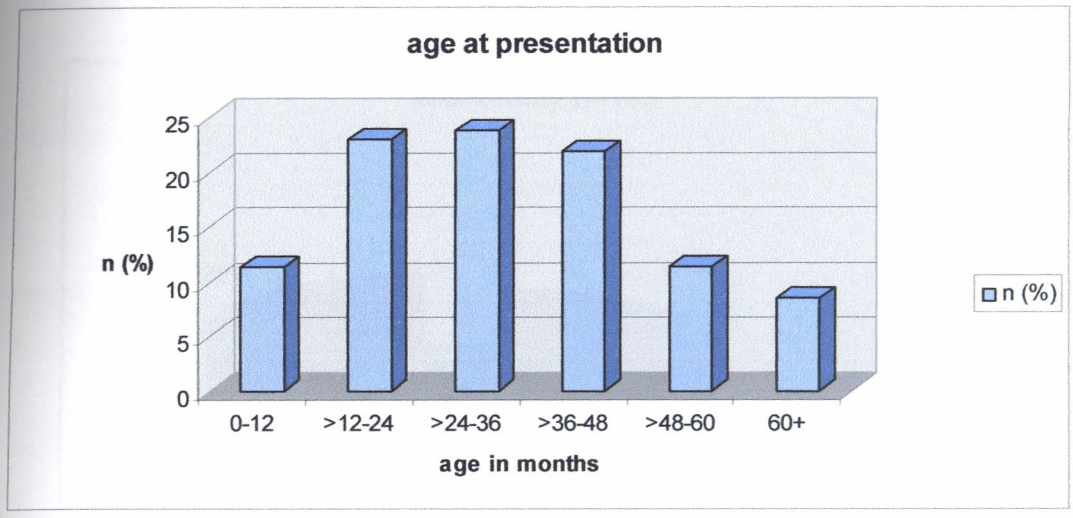
n=160




Probability of survival at 36 months is 0.2

**Figure 8: Age at presentation**

n =105




The mean age at presentation was 37.5 (SD 27). The mode was 36 months; the median was 36 months and range 1-144 months.

**Figure 9: Association between at age at presentation and survival rate**

n=105

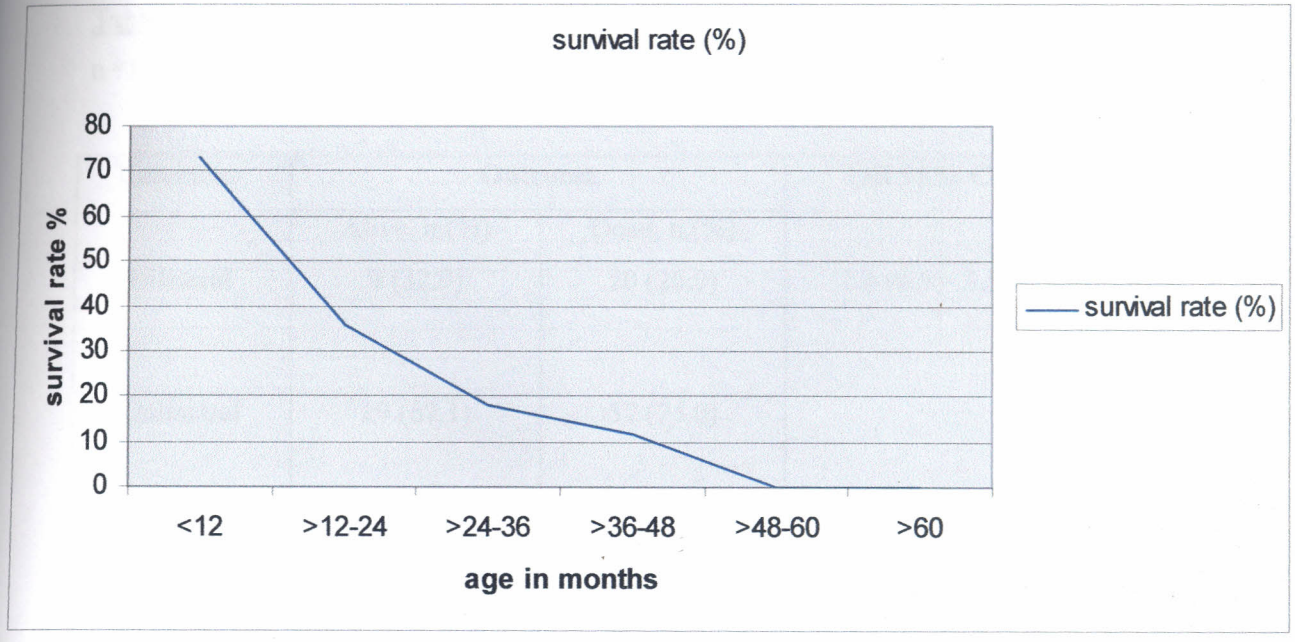
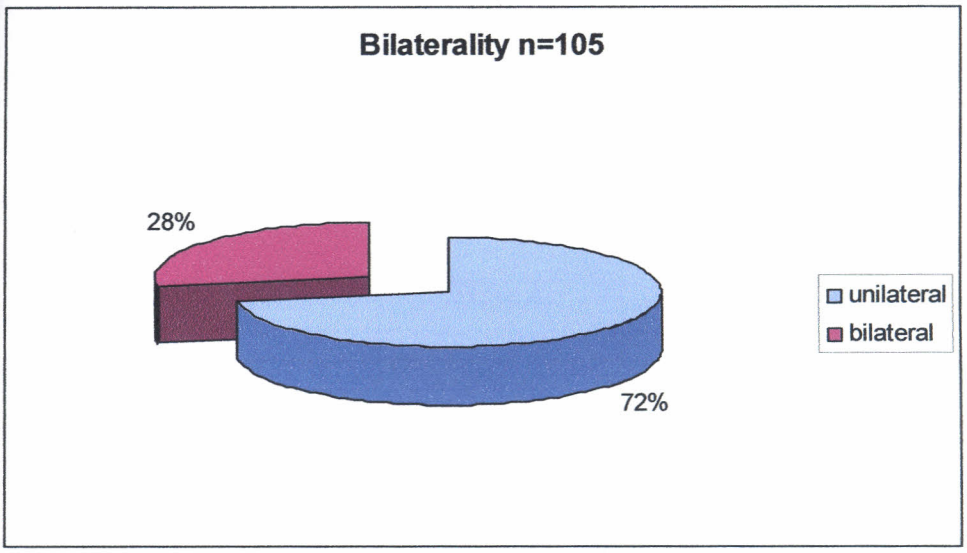


**Figure 10: Laterality**

n =105




No patient had trilateral disease.

**Table 1: Association between laterality and 3-year outcome**

n =105

| Laterality | Outcome | | OR 95% CI | P-values |
|---|---|---|---|---|
| | Alive, n (%) | Dead, n (%) | | |
| Bilateral | 9 (32.9) | 20 (26.0) | 1.4 (0.5 – 3.5) | 0.532 |
| Unilateral | 19 (67.1) | 57 (74.0) | | |

Patients with bilateral disease had a better 3-year outcome but this difference was not statistically significant.

**Table 2: Laterality vs. Family history of retinoblastoma**

n=105

| Family History | Laterality | | OR 95% CI | p value |
|---|---|---|---|---|
| | Bilateral | Unilateral | | |
| Positive | 4(14.2) | 5(6.5) | 2.04(0.37-11.30) | P=0.343 |
| Negative | 11(39.2) | 28(36.4) | | |
| Not stated | 14(50) | 44(57.1) | | |

8.5% of the patients had positive family history of retinoblastoma, 34.3% had negative family history. It is important to note however to note that 55.2% of the records did not indicate a family history status.

**Table 3: Association between family history and 3-year outcome**

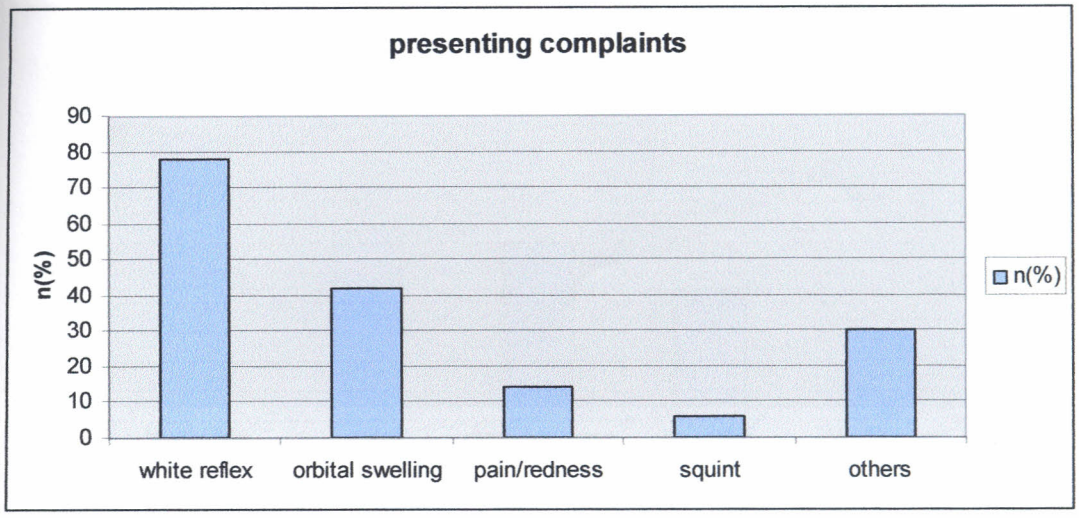
n =105

| Family history | Outcome | | OR 95% CI | P value |
|---|---|---|---|---|
| | Alive n (%) | Dead n (%) | 0.32(0.01-3.13 | P=0.285 |
| Positive | 1 (3.6) | 8 (10.4) | | |
| Negative | 11 (39.3) | 28 (36.4) | | |
| Not stated | 16 (57.1) | 41 (53.2) | | |

Positive family history was associated with poor outcome though this was not statistically significant.

**Figure 11: Presenting complaints**

n =105




The others included the following;

**Table 4 Other complaints**

| Other Complaints | Frequency |
|---|---|
| • Mass in the Socket | 7 |
| • Poor Vision | 10 |
| • Shrunken eye/small eye | 5 |
| • Discharge/itchiness/discharge | 4 |
| • Abnormal eye movements | 1 |
| • Swellings on head | 1 |
| • No complaints | 3 |

3 patients had no complaints as they had presented for routine examination under anesthesia because of family history of retinoblastoma.

**Figure 12: Ocular findings**

n =105

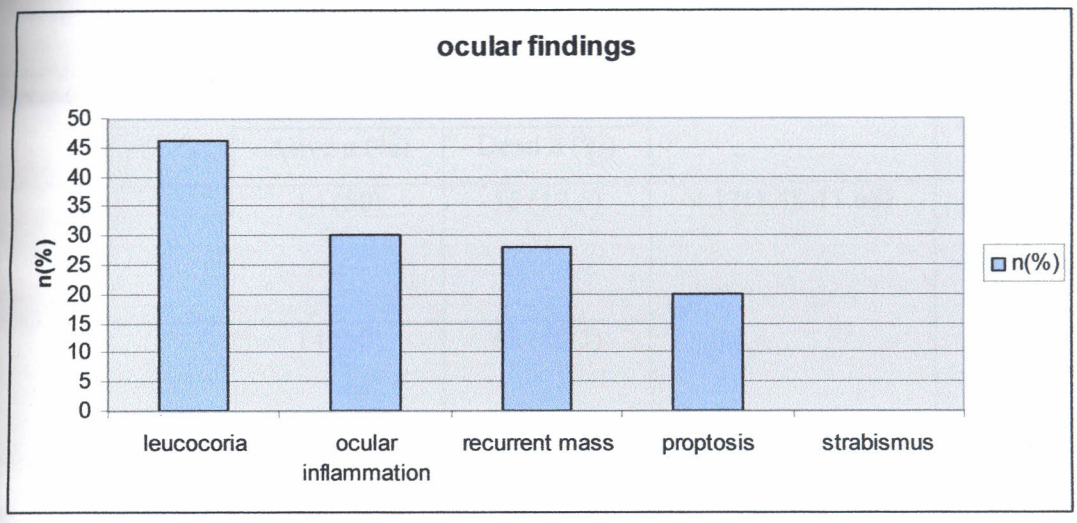



**Table 5: Association between clinical presentation and 3-year outcome**

n =105

| Clinical Presentation | Outcome | | OR 95% CI | P-values |
|---|---|---|---|---|
| | Alive, n (%) | Dead, n (%) | | |
| Proptosis | | | | |
| Yes | - | 21 (27.3) | - | ***<0.001*** |
| No | 28 (100.0) | 56 (72.7) | | |
| Recurrence | | | | |
| Yes | - | 29 (37.7) | - | ***<0.001*** |
| No | 28 (100.0) | 48 (62.3) | | |

50 out of these 105 patients (48%) had either proptosis or recurrent masses after enucleation and these two clinical features were associated with poor outcome (100% mortality within 12 months of presentation to the hospital).

**Table 6: Association between clinical presentation and 3-year outcome**...cont

n=105

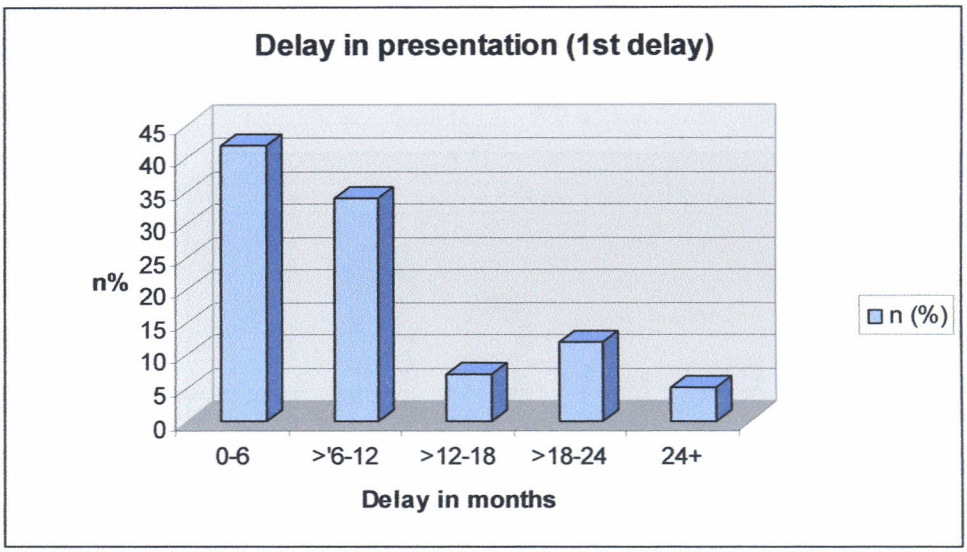
| Leucocoria only | Outcome | | OR 95% CI | p value |
|---|---|---|---|---|
| | Alive n (%) | Dead n (%) | | |
| Yes | 14 (50) | 15 (19.5) | 4.13(1.48-11.68) | p=0.001 |
| No | 14 (50) | 62 (80.5) | | |

Patients with leucocoria only were 4 times more likely to be alive than those who had other ocular findings. The difference was statistically significant (p=0.001).

## DELAY BETWEEN ONSET OF SYMPTOMS AND MANAGEMENT

**Figure 13: Delay in presentation (1st delay)**

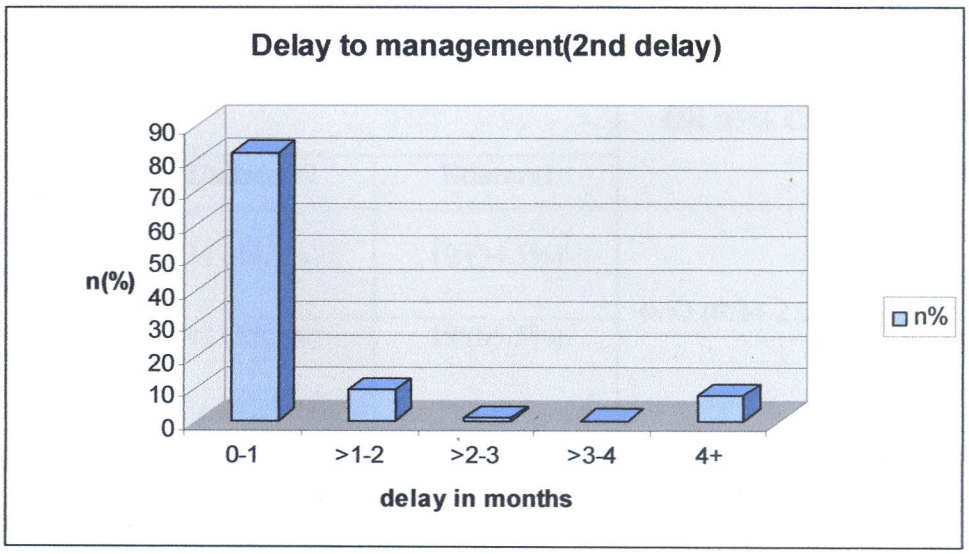
n =105




The mean delay between onset of symptoms and presentation was 10.5 months (SD 10.7), median was 8 months, 12 months was the mode and the range was between 7 days-60 months.

**Figure 14: Delay to management (2nd delay)**

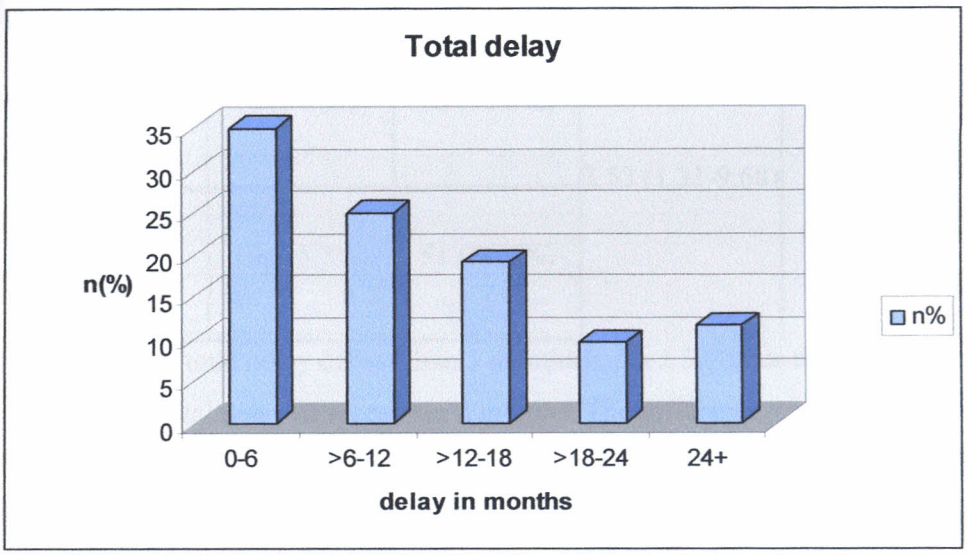
n =105



The mean delay between presentation and primary mode of management (2nd delay) was 1 month 6 days (SD 3.8), median of 7 days and range of 1-36 months

**Figure 15: Total delay**

n =105




The total delay between onset of symptoms and management had mean of 12 months (SD 11.5 months). The median was 8 months with a mode of 7 months. The range was 13 days-61 months.

**Table 7 : Total delay vs laterality**

| Durations in months | Laterality | | OR 95% CI | P value |
|---|---|---|---|---|
| | Unilateral | Bilateral | | |
| ≤ 5 | 34 (44.7%) | 10 (34.5%) | 0.73 (0.24-2.22) | 0.53 |
| >5 | 42 (55.3%) | 19 (65.5%) | | |

The difference in the total delay between those with unilateral and those with bilateral disease was not statistically significant.

**Table 8: Association between total delay and 3-year outcome**

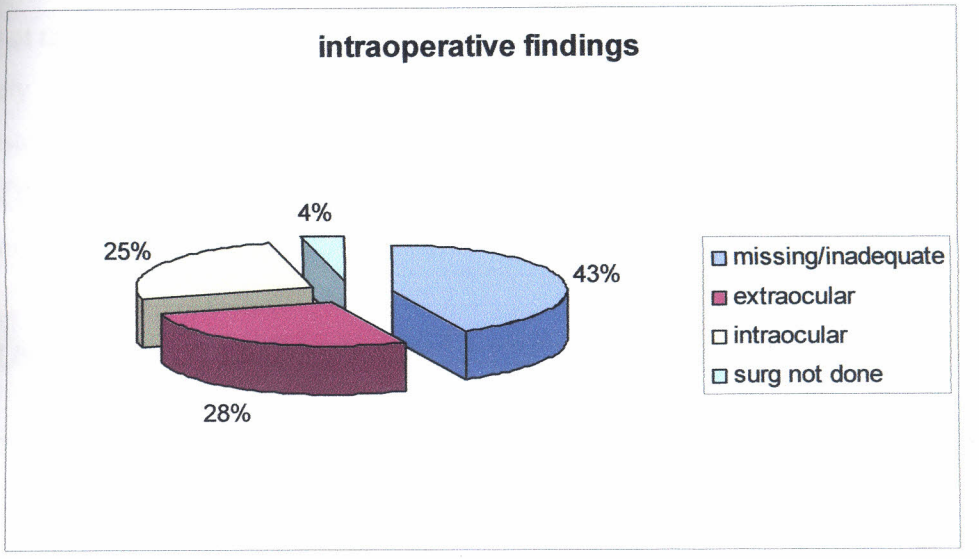
n =105

| Durations in months | Outcome | | OR 95% CI | P value |
|---|---|---|---|---|
| | Alive n (%) | Dead n (%) | | |
| ≤ 5 | 18 (64.3%) | 26 (33.8%) | 3.53 (1.31-9.68) | 0.005 |
| > 5 | 10 (35.7%) | 51 (66.2%) | | |

The patients who had a total delay of less than 5 months had a 3.53 times chance of being alive than those who had a total delay of more than 5 months. The difference was statistically significant.

**Figure 16: Intraoperative findings**

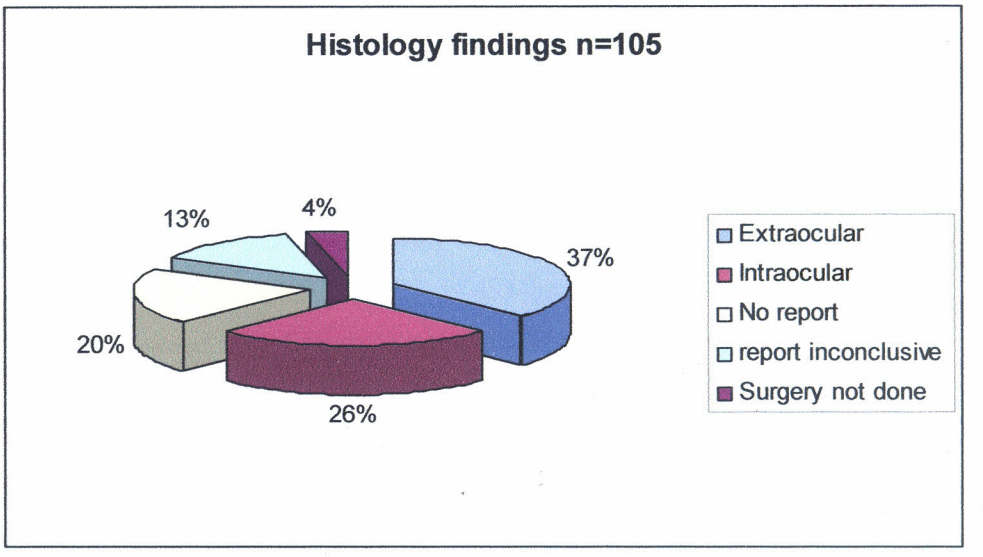
n =105




More patients were found to have extraocular disease intraoperatively than those that had intraocular disease.

**Figure 17: Histology findings**

n =105



In bilateral cases in which both eyes were enucleated, for the purpose of correlating the extent of tumour involvement with survival, the eye with the greater degree of tumour involvement was considered.

Majority of the patients had extraocular involvement. Only 2 out of 105 (1.9%) were reported as moderately differentiated retinoblastoma. The rest of the patients had poorly differentiated retinoblastoma. No patient had a well-differentiated tumor.

A fifth of the patients had no histology report while 13% had inconclusive reporting as the extent of the tumor was not indicated.

**Table 9: Association between histology and 3-year outcome**

n =105

| Histology Findings | Outcome | | OR 95% CI | p value |
|---|---|---|---|---|
| | Alive n (%) | Dead n (%) | | |
| Intraocular | 15 (53.6) | 12 (15.6) | 8.5(2.23-34.49) | P<0.001 |
| Extraocular | 5 (17.9) | 34 (44.2) | | |
| Inconclusive/missing results | 8 (28.5) | 31 (40.2) | | |

Patients with intraocular disease on histopathology examination of surgical tissues were 8.5 times more likely to be alive (95% CI 2.23-34.49) than those that were found to have extraocular disease. The difference was statistically significant (p<0.001).

**Multivariate Analysis**

The following variables were included in the model

- Sex
- Age
- Total delay
- Leucocoria only
- Histology both eyes

However only leucocoria only and histology had significant results as shown by * below

**Table 10: Multivariate Analysis**

n=160

| Variables | Hazard ratio | 95% Confidence interval hazard ratio | p-value |
|---|---|---|---|
| Sex | | | |
| - Female | ref | | |
| - Male | 0.762 | [0.459, 1.265] | 0.294 |
| Laterality | | | |
| - Bilaterality | ref | | |
| - Unilaterality | 1.354 | [0.743, 2.465] | 0.322 |
| Age | 1.005 | [0.997, 1.014] | 0.216 |
| Total delay | 1.007 | [0.987, 1.028] | 0.499 |
| Leucocoria only | | | |
| Yes | ref | | |
| No | 2.057 | [1.070, 3.957] | 0.031* |
| Histology | | | |
| - Others | ref | | |
| - No histology | 0.898 | [0.404, 1.997] | 0.792 |
| - Tumor confined to eye globe | 0.279 | [0.121, 0.645] | 0.003* |
| - Tumor involving optic up to resection margin | 0.745 | [0.359, 1.543] | 0.428 |
| - Extrascleral spread | 0.902 | [0.398, 2.042] | 0.804 |

Hazard ratio in survival analysis is the effect of an explanatory variable on the hazard or risk of an event. The explanatory variable were; sex, laterality, age, total delay, leucocoria only and histology reporting.

**Table 11: Histology vs. Surgical findings**

| At Surgery | Histology | | Total |
|---|---|---|---|
| | Intraocular | Extraocular | |
| Intraocular | 25 | 10 | 35 |
| Extraocular | 11 | 23 | 34 |
| Total | 36 | 33 | |

The sensitivity of the surgeons' findings at surgery when compared to the histological findings was found to be 69.4% while the specificity was 69.6%. The positive predictive value was 71.4% while the negative predictive value was 67.6%. The accuracy was 69.5%.

**Table 12: Intraoperative findings**

n =212 eyes

| Findings | Frequency | Percentage |
|---|---|---|
| Tumor within globe grossly | 50 | 23.6 |
| Tumor outside clinically | 31 | 14.6 |
| Thickened optic nerve | 27 | 12.7 |
| Inadequate information | 12 | 5.7 |
| Referrals with no surgical notes | 47 | 22.2 |
| Surgery not done | 50 | 23.6 |

50 eyes (23.6%) were not operated for various reasons:

Parents/guardian declined to consent.....10

Patients with bilateral disease lost to follow up after first operation .....17

Patients with metastatic disease not amenable to surgery (palliative care)....8

Phthisical eyes.....7

Tumor treated with sight saving procedures (laser and EBRT).....8

**Table 13: Histology findings**

| Histology Finding | Frequency | Percentage |
|---|---|---|
| Tumor confined up eyeball | 48 | 30 |
| Tumor involving optic but resection margin free | 5 | 3 |
| Tumor involving optic nerve resection margin | 34 | 21 |
| Choroidal extension | 6 | 5.7 |
| Extrascleral Spread | 39 | 24 |
| No Histology Report | 38 | 23.4 |
| Inconclusive reporting on tumor extent | 13 | 8 |
| Total number of specimen for examination | 162 | 100 |

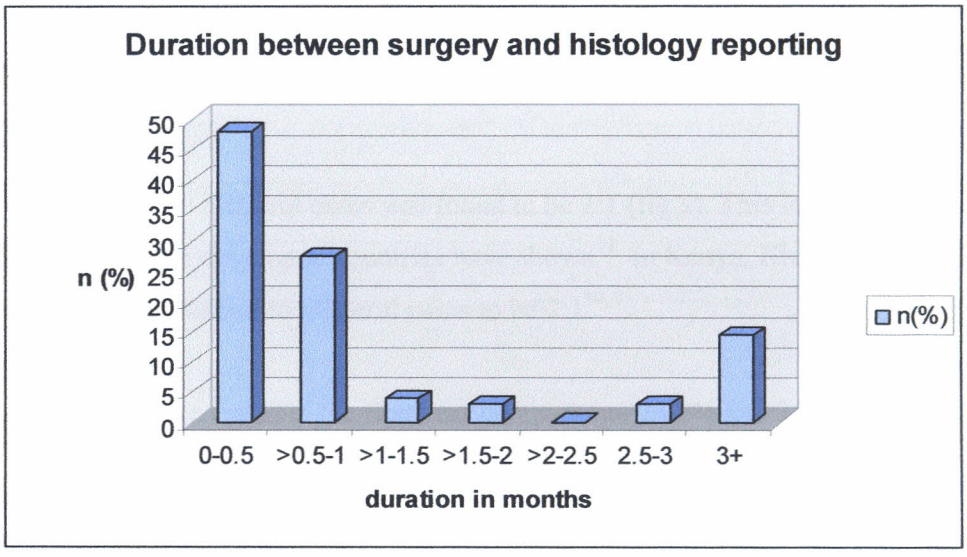
Moderate cellular differentiation was reported in 6 out of the 162 eyes. None of the eyes was reported as been highly differentiated. 13 specimens (8%) were confirmed, as having retinoblastoma but the extent of the tumor was not reported.

No histology report was available for 38 operated eyes (23.4%).

17 of the 162 specimen (10.4%) had choroidal extension of the tumor.

**Figure 18: Duration between surgery and histology reporting**

n =160




Mean duration was 2.5 months (SD 4.2), mode was 1 month, 48% of histologies were reported within 2 weeks of surgery. The range was 3 days-4 months.

# 5 DISCUSSION

## Basic Demographics

No significant sex differences were found in this study. The distribution of male to females was found to be 1:1.6 (fig 1), which was quite similar to the ratio of 1:1.3, found in the study by Khan et al done in Kenya[7].

The ratio of unilateral to bilateral cases was found to be 2:1 (fig 2). This is similar to what studies previously in the developed countries have shown[14]. In Kenya, Khan et al and. Klauss et al found the ratio of unilateral to bilateral cases to be 2:1[10, 7].

Only 15% of patients presented in the first year compared to 23.8% and 25% who presented in the second and third year respectively (fig 3). The mean age at presentation was 35 months (SD 25) with a median age of 33.5 months and the range 1-144 months. This is similar to findings of previous studies in Kenyatta National Hospital[7, 10 & 9]. However the patients in our study presented much later than those in other studies done in other developing countries like India and Turkey and it is very late presentation. In India Shanmugan et al found the mean age at presentation to be 23.98 +/- 23.37[12]. In Turkey Ozhan et al found the mean to be 25 months. This late presentation could be because of factors like parents' ignorance of the value of early medical intervention when symptoms are noted in the affected children, poor referral system and financial constraint that may have deterred parents from traveling to referral centres[11]. Kenyatta is a national referral centre so the patients that present here usually will have been seen in one or two peripheral centres so time may have been lost in the referral system.

The mean age at presentation of unilateral patients was 39.89 months compared to 24.35 months for the bilateral disease and the difference was statistically significant (fig 4). The bilateral patients presented earlier because the first symptom appears earlier than in unilateral cases.

Retinoblastoma is rare after the age of five years however one patient presented at 12 years of age with a history of leucocoria for two years. Histology had confirmed retinoblastoma with extra-scleral spread. This patient died within one year of presentation to the hospital.

The late presentation in Kenya is very similar to the findings in studies carried by Klauss et al and Khan et al fifteen years in the same institution [10,7]. The pattern of presentation had not changed significantly in that time period.

**Outcome and Survival rate**

The cumulative 3-year survival rate was found to be 26.6% .The probability of survival at 36 months was 0.2 as calculated using the Kaplan-Meier method (fig 7).

In calculation of the cumulative 3-year survival rate only the 105 patients whose outcome had been established at the end of the study were considered but in calculating the 36-month probability of survival all patients studied were included as Kaplan-Meier method takes into consideration those censored due to loss to follow up.

This is a very low survival rate when compared to the situation in developed countries where 5-year survival rate has been found to be 87.5% and over 95% in France and the United States of America respectively[32, 6]. Studies done in developing countries have similarly reported comparably good survival rates. Oman and Taiwan reported 5-year survival rates of 89% and 80.9% respectively[34, 35]. Turkey reported a 3-year survival rate of 89.9%[13].

There are several factors that could explain the poor survival of retinoblastoma patients in our set-up. Being a referral centre, Kenyatta National Hospital admits patients who have been seen and managed in peripheral centres previously. This results in both late presentations due to delays in the referral system and presentation with advanced disease both of which are associated with poor outcome. Late presentation by the patient in our set-up is primarily due to ignorance and lack of finances[11].

**a) Age at presentation**

The mean age of presentation for the 3-year cohort was 37.5 months with a range of 1 to 144 months (fig 6). This study found that survival rate was highest for the patients who presented at 12 months of age or less and reduced dramatically in the older age groups. Majority of patients in this group (65%) however presented between 12 and 48 months of age. The age of diagnosis has been found to be dependent on whether the disease was heritable or non-heritable. Studies have further shown that younger age at diagnosis is considered a risk factor for recurrences[25, 26, 27 & 28]. This finding may have been missed due to the poor follow up seen among our patients.

However two patients were noted to develop tumor in the second eye on follow up. One patient presented at 12 months of age and the other presented at 20 months of age.

**b) Association between survival and laterality and family history of retinoblastoma**

Laterality was not found to have any significant impact on the on the 3-year outcome (table 1). The 3-year cumulative survival rate was found to be 31% in those with bilateral disease and 25% in the patients who had unilateral disease. The difference between was not statistically significant (p=0.532). The marginally higher survival rate among the bilateral cases could be explained by the earlier presentation among these patients. In Turkey, Ozhan et al found the 3-year cumulative survival rate to be 90.74% for the unilateral cases and 87.25% for the bilateral cases[13].

Family history of retinoblastoma was not found to have any association with laterality of disease (table 2).

The association between family history of retinoblastoma and 3-year outcome was not statistically significant (table 3). In studies done elsewhere, positive family history was associated with risk of recurrences[25, 26, 27 & 28].

**c) Clinical presentation**

In this study majority of the patients presented with clinical features of advanced retinoblastoma. The most common presenting complaint was white reflex (72%) followed by orbital swelling (37%) then pain and redness (8%). Only 5% of patients presented with a complaint of deviated eye (Fig 11). It is important to note that of the 75 patients presenting with white reflex in the eyes, only 29 had leucocoria without associated proptosis, metastasis or recurrent tumor (table 6). This means that while majority of patients had white reflex as the first symptom, few presented early enough for leucocoria to be found on examination. By the time of presentation leucocoria had been distorted by proptosis or the patients had already been enucleated at other centres and were being referred to Kenyatta National Hospital with recurrent masses for secondary management. On examination of the patients, 30% had recurrent masses, 18% had proptosis, 43% had leucocoria, and 27% had ocular inflammation (fig 12). These presentations depict the advanced stage of disease in our set-up when compared with the findings in the developed countries where majority of the patients present with early disease. In the developed countries leucocoria followed by strabismus (60%&20% respectively) are the commonest presenting complaints[6]. A study in Nigeria also found similarly advanced stages of

retinoblastoma at presentation-proptosis with chemosis in 84.5% of the patients studied[15]. In Tanzania, 56% of patients presented with leucocoria, 30% with proptosis, 28% with lid swelling and 11% with strabismus. 8 patients had metastatic disease at presentation while 11 patients developed metastasis during follow up[33].

The advanced stage of disease was found to be associated with very poor outcome. Proptosis had 100% mortality and recurrent masses also had a 100% mortality rate within one year of presentation (table 5). It is important to note that 65% of the patients who died in the three-year cohort had either proptosis or recurrent masses. 17 patients had tumor cells seen on cerebrospinal fluid microscopy, 4 patients had computerized topography scan evidence of intracranial metastasis while one had ultrasonographic evidence of abdominal metastasis. All these patients died between 2 to 23 months of admission at the hospital. In Turkey Gunduz et al found that all patients with CNS metastasis (50% of all patients studied) were deceased within 24 months[14].

Patients who had early disease (leucocoria with no clinical evidence of proptosis, recurrent masses or metastatic disease) were 4 times 95% CI (1.48-11.68) more likely to survive than those with late presentation $p<0.001$ (table 6).

**d) Influence of delay to management on survival**

The total delay between onset of symptoms and institution of primary management had mean of 12 months (SD 11.5 months). The median was 8 months with a mode of 7 months. The range was 13 days-61 months (fig 15). The difference total delay to management between the patients with bilateral disease and those with unilateral disease was not statistically significant (table 7). The total delay to management was found to influence the 3-year outcome. Patients with a total delay of 5 or less months had 6 times 95% CI (2.12-17.35) more likely to be alive than those with a total delay of more than 5 months $p<0.001$ (table 8). The survival rate in those with a total delay of $\leq$ 5 months was 64% compared to 33% in those who had a total delay of >5 months. There may have been recall bias in the determination of delay to management as this depended on the parents/guardian Chang et al found the survival rate of patients with a total delay of $\leq$5 months to be 90.9% and 60.9% for those with a total delay of >5 months[35]. Erwenne et al found that the risk of extraocular disease was dependent on the age at diagnosis and lateness of referral. The median overall lag time was found to be 5 months with a range of 0-45 months. Nearly 50% of the patients had an overall lag time of > 6 months and almost 50% had extraocular disease [40].

### e) Histology findings

Majority of patients in this study were found to have extraocular disease on histology 37% vs. 26% with intraocular disease (fig 17). The survival rates were lower than those found in studies done elsewhere due to late presentation by our patients who present with advanced disease. The pattern of the survival, that is lower survival rate among those with extraocular disease, supports findings of the studies done by other authors. Chang et al found the 5-year survival rate to be 90.9% and 39% for intraocular and extraocular disease respectively[35].

Those with intraocular disease were 8 times more likely to be alive (95% CI 2.23-34.49) than those with extraocular disease $p<0.001$ (table 9). The survival rate was 56% among those with intraocular disease and 13% among those with extraocular disease. Only 6 out of 105 patients had a reporting of choroidal invasion (without involvement of the sclera and ciliary body). Of these six patients, five were dead at the end of three years and one was alive. Stannard et al found 21 of the 23 patients with choroidal involvement to be alive at the end of three-year follow-up[19]. Only 2 out of 105 were reported as having moderately differentiated retinoblastoma. Both the patients were dead at the end of three years. One patient had extrascleral spread of tumour and the other had tumor confined to the globe. No patient had a well-differentiated tumor.

Stannard et al found 91.6% of patients with well differentiated retinoblastoma to have survived 3 years, survival rate was 63% in those with moderate differentiation and 56.8% among those with poorly differentiated disease [19].

20% of the patients did not have conclusive reporting on the extent of the disease while 13% had no histology reports. This may have introduced bias in the correlation between extent of disease and survival.

**Multivariate analysis**

The following variables were analysed; age, sex, laterality, total delay, histology and clinical presentation of leucocoria only (without evidence of proptosis, recurrence or metastasis). Histological evidence of tumour confined to the globe and clinical presentation of leucocoria only were found to significantly affect the 3-year survival rate. Histological evidence of tumour confined to the globe was the most significant factor contributing to good outcome (table 10).

## HISTOLOGY vs. SURGICAL FINDINGS

### Histology

30% of the specimens examined were reported as having complete surgical excision of the tumour (table 13) Complete excision was defined as histological evidence of tumour-free optic nerve resection margin with no involvement of the sclera. This low complete excision rate may have contributed to our poor survival rate. This is very low compared to findings in study carried out in Tanzania that found complete excision to be 62% [33]. However their findings did not correlate with the outcomes in the same study where the disease free survival probability was found to be 0.23 at 30-months follow up period.

Optic nerve involvement was only involved in 24% of the specimen compared to 68% in Tanzania and 60% in Uganda [33, 41]. Retrolaminar optic nerve involvement with resection free margin was reported in 3% of the histologies while resection margin involvement was recorded in 21% which correlated with the findings in Tanzania of 29% [33]. Choroidal extension was reported in 10.4% which was low compared to the study done on Tanzania where the choroidal extension was found to be 62% [33].

We found that 21% of histology reports had inconclusive report on the extent of tumor spread while 30% of the histology reports were missing from the patients' records (table 13). This may have resulted in bias during calculation of the histological findings and even relating it to survival. Further, none of these histologies could be used in decision making on the management of the patients and therefore the clinician had to rely solely on the surgical findings about the extent of retinoblastoma to decide whether there was complete excision of the tumor and hence no further treatment was needed or whether tumor was not completely excised and the patient therefore needed secondary management.

### Correlating histology with surgical findings

In correlating the histological reports against intraoperative findings, we found the accuracy to be 69.9% (table 11). The histopathological findings were used as the gold standard against the surgeon's intraoperative findings. However there were a few cases (4) where orbital involvement was clearly noted but histology reported intraocular disease for the same specimen. Both incomplete surgical notes on the tumor extent may have introduced bias grossly and the incomplete or missing histology reports. In literature search, no study was found that had made a similar comparison between surgery and histology findings.

The other aspect of histology limitation is the delay between surgery and histology reporting. This delay also meant that the histology findings were not available immediately to aid the clinician in decision making on patient management. The delay ranged between 3 days and 4 months with a mean of 2 and half months (SD 4.2). 48% of the reporting was done within two weeks of the surgery (fig 18). These findings did not take into consideration the time it took between a pathologist reporting and the actual time when it became available to the clinician. This was difficult to retrieve from the medical records. The range of duration between 3 days and 3 months had an unacceptable upper limit that may have caused undue delay in the secondary management of patient concerned.

# 6 CONCLUSIONS

The survival rate of patients treated for retinoblastoma was found to be very low compared to findings in studies done in the developed countries and developing countries outside Africa. The main reasons were the late presentation and presentation with recurrent disease. This is contributed mainly by the fact that Kenyatta National Hospital is a referral institution admitting patients referred from other centres either after primary management or for primary management. The main factors associated with good outcome at three years were found to be age of presentation less than 12 months, early disease presentation (leucocoria without recurrences, proptosis and metastasis), intraocular disease on histology and total delay to management of less than or equal to five months. The factors associated with poor outcome were presentation with advanced or metastatic disease, extraocular disease on histology and total delay to management of more than five months. Laterality of the disease and family history of retinoblastoma were not found to significantly influence the survival and outcome of retinoblastoma.

The accuracy in correlating the intraoperative findings with histopathological findings was moderate. Only 48% of the histologies were reported within two week of the surgical intervention.

# 7 RECOMMENDATIONS

There is a great need for continued education to primary health workers on early detection of retinoblastoma and prompt and appropriate referral of the patients to an ophthalmologist. This will help to reduce delays that occur due to mis-diagnosis and poor referral system. Education to the public on retinoblastoma presentation and familial transmission so that parents are empowered with information on the course of action to take if symptoms are noted in children.

In the hospital set up, there is need for development of a questionnaire or checklist which will include all aspects of history taking, patient examination, surgical findings, histology findings, secondary management and subsequent follow up for all retinoblastoma patients admitted at the hospital. This would ensure that the patients are well managed and all the necessary examinations and investigations done and provide a good flat form for future studies on this disease. We need to develop a cancer registry at the institution, which will aid in follow up of patients and provide information for scientific studies and management audit in the future. Proper documentation and storage of patients' medical records is essential to the management and proper follow up of patients. The principle needs to be re-emphasized to the clinical staff as well as record staff.

There is need for the training of an ophthalmic-pathologist in our institution. This will improve the quality of the histology report that this will improve greatly management of retinoblastoma patients. It would also help to reduce the duration between surgery and histology report. In the meanwhile, fora should be established where ophthalmologists and pathologists can exchange ideas and update on the expectations that either specialty have that can improve the speed and quality of histology reports.

# 8 STUDY LIMITATIONS

The main challenge of the study was following up the patients in order to determine the outcome. Where no contact could be obtained, consideration was made in data analysis and interpretation.

Incomplete medical information was another challenge that may have lead to bias in data analysis. These included incomplete or missing referral notes, poor history taking, inadequate information on tumor spread intraoperatively and on histology report and missing investigations.

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## 10 APPENDIX I

**Questionnaire**

1. Patients name and Hospital Number _____
2. Date of Admission _____
3. Date of Discharge _____
4. Date of last follow up _____
5. P. O. Box _____

   Telephone Number _____

   Name of Next of Kin and contact _____

   Home district _____

   Location _____

   Village _____

   Chief _____
6. Sex Male ☐ Female ☐
7. Age at presentation to KNH (months) _____
8. Duration of symptom (months) – (1st delay) _____
9. Laterality

   Unilateral RE: ☐ _____ LE: ☐ _____

   Bilateral ☐ _____

   Trilateral ☐
10. Presenting complaint :

    a) White reflex ☐

    b) Squint ☐

    c) Orbital Swelling ☐

    d) Pain / redness ☐

    e) Others (specify) _____

11. Ocular findings on Examination

    a) Strabismus ☐

    b) Leucocoria ☐

    c) Proptosis ☐

    d) Orbital inflammation ☐

e) Recurrent mass ☐

f) Already enucleated (State where) _____

g) Others (specify) _____

12 Findings at Surgery

a) Tumour within globe grossly ☐

b) Tumor outside globe clinically ☐

c) Thickened optic nerve ☐

13 Histological findings

a) Tumor confined to eyeball ☐

b) Tumor involving optic nerve but resection margin free? ☐

c) Tumor involving optic nerve upto resection margin ☐

d) Extrascleral spread ☐

e) Cellular differentiation ☐

f) No histology report ☐

14 Time lag to treatment (2nd delay) _____

15 Investigations done:

a) U/Sound ☐

b) CT Scan ☐

c) MRI Scan ☐

e) CSF ☐

f) Others _____

16 Mode of management

a) Enucleation ☐

b) Exenteration ☐

c) Chemotherapy ☐

d) Cryotherapy ☐

e) Others (specify) _____

17 Second line of management

a) Chemotherapy ☐

b) Radiotherapy ☐

c) Exenteration ☐

| 18 | Outcome | Yr 1 | Yr 2 | Yr 3 | Yr 4 | Yr 5 |
|---|---|---|---|---|---|---|
| | a) Alive | ☐ | ☐ | ☐ | ☐ | ☐ |
| | b) Dead | ☐ | ☐ | ☐ | ☐ | ☐ |
| | c) Unknown | ☐ | | | | |

19 Cause of death where applicable _____

20 Date of last follow-up _____

21 Follow up period in months _____

## 11 APPENDIX II

**UNIVERSITY OF NAIROBI**

*COLLEGE OF HEALTH SCIENCES*

Telephone: 2728756, 2723926 or 726300 Ext. 43776
Telegrams: "Medken" Nairobi
Telex: Varsity 22095
Email: ophthalmoluon@yahoo.com

***DEPARTMENT OF OPHTHALMOLOGY***
Kenyatta National Hospital
P.O. Box 19676
NAIROBI, KENYA

Dear parent/ guardian,

Re: _____

I am a doctor currently stationed at the Eye Department at the Kenyatta National Hospital. I am following up on the progress of your child following the treatment he/she received in the hospital and would like to communicate with you concerning the same. Please text me or flash me on telephone number 0712503763 and I will get in touch with you.

Thanking you,

Dr. Nyawira Gichigo

---

Kwa mzazi,

Re: _____

Mimi ni daktari ninayehudumu katika wadi ya Macho katika hospitali kuu ya Kenyatta. Ningetaka kuwasiliana nawe juu ya mwanao aliyepata matibabu katika hospitali ya Kenyatta. Tafadhali wasiliana nami kwa njia ya sms au kuniandikia ujumbe wa `please call me' kwa simu nambari 0712503763 na nitakupigia simu.

Ahsante sana,

Dr. Nyawira Gichigo