Page 149 to 157

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# Presenting Patterns of Retinoblastoma at Sekuru Kaguvi Eye Hospital in Harare, Zimbabwe

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## Abstract

**Background:** Retinoblastoma is the most common primary intraocular malignancy of childhood world over and Zimbabwe has the third highest incidence worldwide. Despite the high incidence, published literature on retinoblastoma in Zimbabwe is limited.

**Objectives:** To characterise the presenting patterns of retinoblastoma amongst patients attending Sekuru Kaguvi Eye Hospital (SKH), determine the recurrence rate, mortality rate and factors associated with mortality amongst these patients.

**Study design:** Hospital based retrospective records review and patient recall.

**Methodology:** A retrospective cross-sectional study in which medical records of patients admitted at SKH from 1st January 2010 to 31st December 2014 with a histological diagnosis of retinoblastoma were reviewed. Those fitting the inclusion criteria were recalled back to the hospital where they had an ocular examination and computed tomography (CT) scan of the orbits and brain.

**Results:** Eighty-seven patients had a histological diagnosis and fitted the inclusion criteria. The mean age was 32.8 months (median 27 months). There was no gender predilection and two thirds (58/87) of the cases were unilateral. Proptosis was the most common presenting symptom accounting for 64.4% of cases (56/87). The mean paternal age was 31.8 years (median 29 years). Over 60% of patients (59/87) had traditional eye medications (TEM) used on them. Amongst the 68 patients that were followed up, cases of death as reported by the guardians were 61.8% (42/68). Orbital recurrence amongst survivors was 28%. Mortality in patients with retinoblastoma at SKH was significantly associated with older age at presentation, female gender, bilateral disease, presenting with proptosis and use of TEM.

**Conclusions:** Proptosis, late presentation with advanced disease, high mortality rate and unacceptably high loss to follow-up are the characteristics of RB seen among admitted patients at Sekuru Kaguvi Eye Hospital in Zimbabwe.

***Keywords:*** *Retinoblastoma; Proptosis; Leucocoria; Childhood; Cancer*

**Abbreviations:** SKH: Sekuru Kaguvi Eye Hospital; CT: Computed tomography; TEM: Traditional eye medicines; RB: Retinoblastoma; USA: United States of America; DRC: Democratic Republic of Congo

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## Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy of childhood occurring in about 1 in 17 000 live births. [1] Zimbabwe is estimated to have the third highest incidence worldwide. [2] This malignancy accounts for about 3% of all childhood cancers worldwide but in Zimbabwe this proportion is doubled. [1,3] Despite the high incidence in Zimbabwe, published literature on RB in this country is limited.

In developed countries, leukocoria is the most common presenting symptom of RB accounting for about 60% of cases followed by strabismus (20%). [1] In contrast, a pilot study carried out at SKH in 2013 reported that proptosis was the most common presenting symptom accounting for 62% of cases followed by leukocoria (29%). [4] Advanced paternal age has been reported to be associated with RB [1] however, the above mentioned pilot study at SKH reported a mean paternal age of 31 years. An audit conducted in 2013 reported that RB was the most common cause of deaths amongst paediatric admissions at SKH. [5] Although this condition is curable orbital recurrence of RB following enucleation is about 4.2% in the United States of America (USA) as reported by Kim., *et al.* [6] Unfortunately, literature on the recurrence of RB in Africa is limited [6] and the recurrence at SKH is unknown. All these observations prompted for further research into RB to be conducted at SKH.

## Materials and Methods

### Study design

This was a retrospective cross-sectional hospital based study in which medical records of patients admitted at SKH between 1 January 2010 and 31 December 2014 with a diagnosis of RB were reviewed and patients recalled for assessent.

### Study setting

This study was conducted at SKH, the largest tertiary eye institute at Parirenyatwa Group of Hospitals in Zimbabwe.

### Study population

All patients who presented and were admitted to SKH with an eye condition during the period from 1 January 2010 to 31 December 2014. This time period was selected because the country's economy was stabilising following introduction of multicurrency system making medical care more accessible to the general public.

### Inclusion criteria

- Patients admitted to SKH during the period under review with a diagnosis of RB.
- Patients whose notes were available.
- Patients who had a histological diagnosis of RB.

### Exclusion criteria

- Patients with RB who were re-admitted at SKH during the period under review.
- Patients whose notes were not available.
- Those who did not have a histological diagnosis of RB.

Those fitting the criteria were recalled back to the hospital where they had an ocular examination and computed tomography (CT) scan of the orbits and brain.

### Data processing and analysis

Data was analysed using Epi-Info version 7.1.4. The characteristics of the study subjects were evaluated using descriptive statistics. Univariate analysis was carried out to identify factors associated with mortality in RB. Results were evaluated at a 95% confidence interval and at a significance level of $p < 0.05$.

## Results

A total of 108 patients were admitted at SKH over the 5 year period with a clinical, radiological or histological diagnosis of RB. Of these, 87 fitted the inclusion criteria as shown in Figure 1 below.

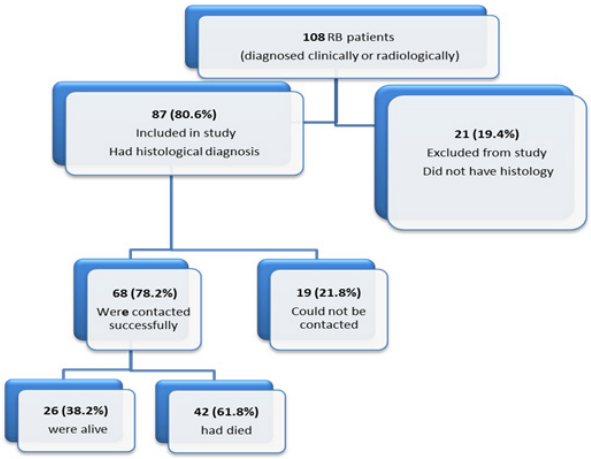


***Figure 1:*** *Flow chart of study patients.*

Patients' age at presentation ranged from 1 month to 156 months (13 years) with mean age of 32.8 months and median of 27 months. (Figure 2 below)

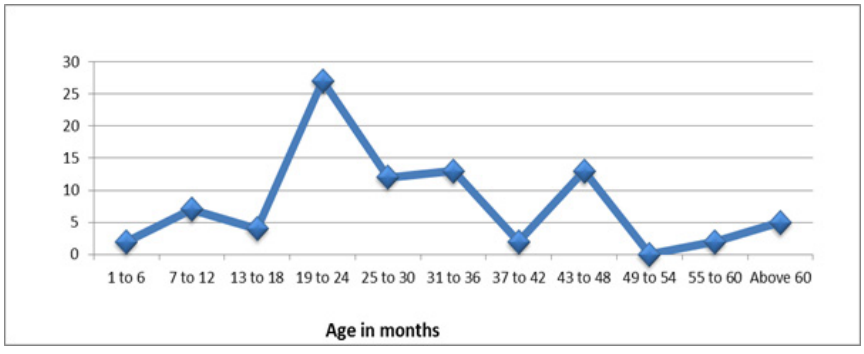


***Figure 2:*** *Age distribution at presentation.*

**Gender distribution:** There was no gender predilection. The male to female ratio was 1:1.1. $X^2$ test, p = 0.621.

**Laterality:** About two thirds (66.7%) of the study population had unilateral disease.

**Earliest symptom noticed:** Leukocoria was the earliest symptom noticed by caregivers in 90.8% of cases (79/87) as shown in Figure 3 below.

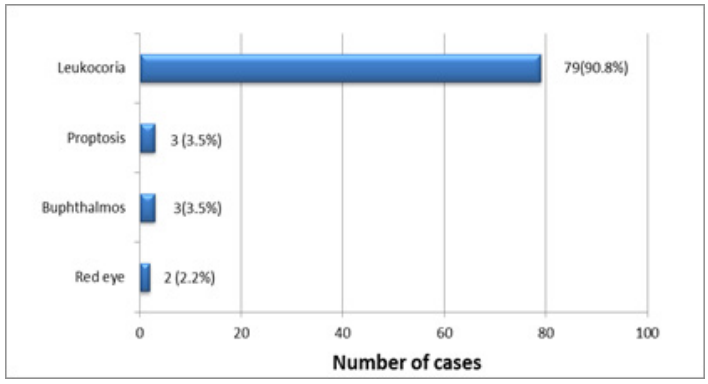


***Figure 3:*** *Frequency distribution of the earliest symptoms noticed by caregivers.*

**Presenting symptom:** The majority of patients (64.4%; 56/87) presented with proptosis as shown in figure 4 below.

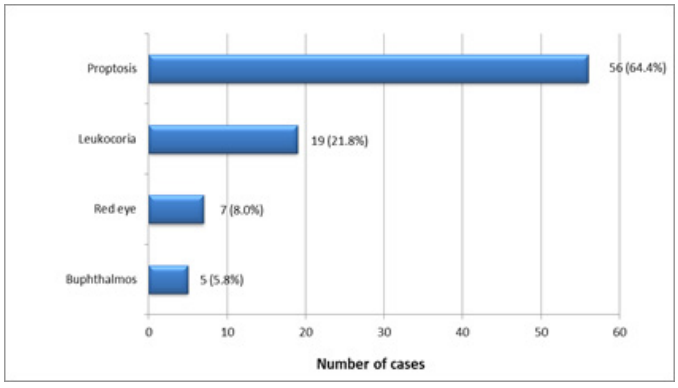


***Figure 4:*** *Frequency distribution of presenting symptom.*

**Delay in presenting to hospital:** The period of delay in presenting to hospital was that from the day the first symptom was noticed by the caregiver to the day the patient presented to SKH. Patients delayed by a period that ranged from 3 weeks to 4 years. The average period was 10 months.

**Delay in treatment:** The period from radiological diagnosis to treatment ranged from 1 day to 90 days and the average period of delay in commencing treatment was 10 days.

**Paternal Age:** Paternal age ranged from 22 years to 50 years with mean of 31.8 years and median of 29 years.

**Traditional Eye Medicine use:** Fifty-nine of the 87 cases (67.8%) had information regarding TEM use. Forty of them (67.8%) had guardians who admitted to using TEM on the child. The other 19 (32.2%) denied use.

**Recurrence of retinoblastoma:** In this study, orbital recurrence was defined as evidence of orbital tumour on CT scan amongst patients who had tumour confined to the globe on histology following enucleation. Of the 26 surviving patients, 25 of them had tumour confined to the globe on histology following enucleation and 1 had optic nerve involvement. Seven of the 25 patients (28%) with intraocular tumour had orbital recurrence.

**Mortality:** At the time of follow-up, cases of death as reported by the parent or guardian were 61.8% see figure 1.

**Factors associated with mortality**

- **Older age of patient:** Patients who died were older (median age 29 months) than those who survived (median age 24 months). $X^2$ test, p = 0.018
- **Female gender:** Females were 1.5 times less likely to survive compared to males. $X^2$ test, 95% CI = 0.92 – 2.46; RR = 1.50; p = 0.044
- **Bilateral disease:** A larger proportion of bilateral cases (90.9%) died compared to unilateral cases (56.5%). $X^2$ test, p = 0.001
- **Presenting with proptosis:** Majority of patients who presented with proptosis (72.1%) died compared to those without proptosis (44%). $X^2$ test, p = 0.010
- **TEM use:** TEM users were 1.4 times less likely to survive compared to non-users. $X^2$ test, 95% CI = 0.90 – 2.26; RR = 1.43; p = 0.045

## Discussion

**Age at presentation**

Patients with RB in developing countries are known to present to hospital much later than those in developed countries. The overall mean age at presentation in this study was 32.8 months. Comparing with a study by Dr Tumushime conducted here between 1987 and 1988 where the mean age was 30 months, the mean age at presentation of patients with RB at SKH has remained unchanged over the past 25 years. [7] Affected patients in South Africa, Kenya and DRC have a similar mean age at presentation. [8-10] In Mali, RB patients present at much older ages and has the highest mean age at presentation of 50 months. [11] Patients in the USA and the UK present much earlier and mean age at presentation is about 18 months. [12]

The age distribution in our study peaked at 24 months and 48 months. The second peak could indicate that more of the older children who were at home with the disease were beginning to present to hospital, suggesting improved awareness.

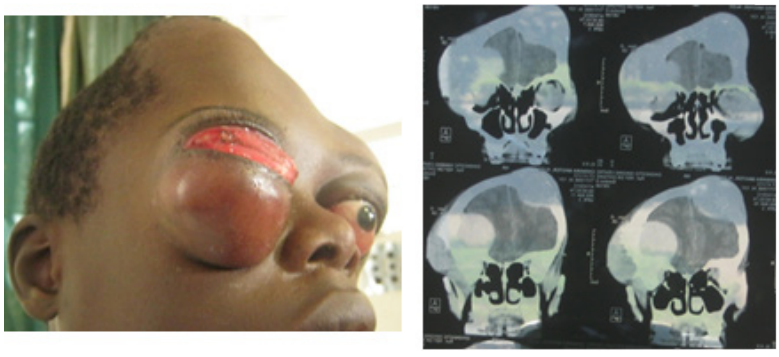

***Figure 5:*** *13 year old, late presenter with bilateral RB, skull and intracranial metastases confirmed on imaging.*

**Presenting Symptoms**

In developed countries, leukocoria is the most common presenting symptom of RB accounting for about 60% of cases followed by strabismus (20%). [1] The most common presenting symptom in our study was proptosis accounting for nearly two- thirds (64.4%) of cases followed by leukocoria which accounted for about a fifth of cases (21.8%). Other developing countries show similar results with proptosis being the commonest presenting symptom. [11, 13-15] The predominance of proptosis at presentation is due to late presentation. [16] South Africa and DRC however, are different with most of their patients presenting with leukocoria. [17,10] Twenty-five years ago, leukocoria used to be the most frequent presenting symptom of RB amongst patients in Zimbabwe [7] but now they present with proptosis. The change in pattern of presentation documented here could be attributed to economic challenges being experienced that result in limited access to medical care in Zimbabwe.

**Late Presentation**

On average, patients in this study delayed to present to hospital by a period of about 10 months. This period is shorter in South Africa (7 months), DRC (6.5 months) and Iran (7.4 months) where the majority of patients present with leukocoria. [9,10,18] Developed countries have even shorter delays ranging from 2 to 3 months. [19-21] In our study, although the majority of caregivers had noticed leukocoria in the patient, they took the child to a health facility after proptosis had appeared. Reasons for presenting late included seeking traditional medication, late referral from primary health centres, lack of finances to travel and some guardians who suspected cataract preferred to have the child operated at an older age and so delayed the hospital visit. About two thirds of the study population at SKH used TEM and they were 1.5 times more likely to present with proptosis compared to non-users. Patients delayed to present to hospital because of visiting traditional healers, using TEM and often, presented when there was no improvement. It was observed that guardians often sought medical attention for proptosis which was more disfiguring and painful than leukocoria.

In conclusion, high myopic subjects' macular thickness and ganglion cells have decreased with the increasing of myopic error. On the other hand, Females have thinner macular thickness compared to males.

**Paternal age**

An association between aging and mutations in germ line cells has been demonstrated, [22] suggesting a higher incidence of childhood malignancies (including RB) among children of older parents. [23] Matsunanga., *et al*. in Japan reported an increased risk of RB in children with fathers aged 35 years and older and Dockerty., *et al*. in the UK reported that fathers aged 45 years and older were 3 times more likely to have children with RB compared to those who were younger. [24,25] The mean paternal age in countries such as Iran, Japan, Netherlands and France ranges from 32.3 years to 34.4 years. [18,24,26,27] Literature on similar studies in Africa is limited. The mean paternal age in our study population was 31.8 years suggesting that advanced paternal age may not be a risk factor for the development of RB in patients presenting to SKH.

**Gender distribution**

There was a slight female predominance in this study with male to female ratio of 1: 1.1 however this was not statistically significant. Several studies from different parts of the world also report no gender predilection. [10,12,28,29,30] There are however other studies conducted in Mali, Kenya, DRC, and China that reported male predominance. [8,11,31] Nyamori., et al. reported that in Kenya, the male predominance suggested that caregivers preferentially sought medical treatment for the boy child over the girl child however no studies have been conducted to prove that assumption. [8]

**Laterality**

About two thirds of the RB cases in this study were unilateral. These findings are consistent with those in developed countries but differ with other populations. In Mali about 90% of cases are unilateral and studies conducted at two hospitals in Nigeria observed no bilateral cases. [11,32,33] In the Asian population of Britain, more than three quarters of RB cases are unilateral. [34]

**Recurrence of retinoblastoma**

Orbital recurrence in this study was 28%. The high orbital recurrence could have been a consequence of treatment delay, defaulting treatment and poor surgical technique. Amongst in-patients at SKH the period from diagnosis to treatment ranged from 1 day to 90 days (mean 10 days) therefore some patients could have already had microscopic extraocular spread of the tumour by the time the enucleation was performed. Patients who defaulted treatment had an even greater risk of orbital recurrence. SKH is a teaching hospital and the majority of enucleation surgeries are performed by doctors in training who could be practising poor surgical techniques that result in tumour seeding. On the other hand, the high orbital recurrence could have been an indication of chemotherapy failure especially in those that developed orbital recurrence even after completing the full treatment regimen without defaulting. Chan., *et al*. reported that failure of chemotherapy is associated with expression of the multidrug resistance protein p170 which frequently occur in RB. Perhaps some of our patients who developed recurrence expressed this protein. Cyclosporine inhibits p170 making chemotherapy failures rare [35] however cyclosporine is not routinely used in the treatment of patients who present to SKH because of availability challenges.

**Mortality in patients with retinoblastoma**

The mortality rate of RB in developing countries is estimated to be 40%. [36] Mortality rates as high as 90% have been reported in DRC. [37] In our study, cases of death as reported by the parent or guardian were 61.8%. The mortality rate could not be accurately calculated because the date of death could not be ascertained for some patients and death certificates could not be obtained. It was therefore uncertain whether RB was the cause of death.

The most important factor associated with high mortality was late presentation as suggested by Chantada., *et al*. [38] This was observed in our study as patients who presented at an older age and with more advanced disease (proptosis or bilateral disease) were less likely to survive. Developed countries have very low mortality rates due to early detection and appropriate treatment. Some of these countries perform genetic testing which can predict children at high risk of developing RB in utero. [39]

More females died compared to males and this could have been because there were slightly more females in the study or it was an indication of preferential treatment of the boy child over the girl child in the study population supporting the hypothesis by Nyamori., *et al.* in Kenya. [8]

TEM use was found to be associated with high mortality. TEM users were 1.5 times more likely to present with proptosis and were 1.4 times less likely to survive compared to non-users. Those who used TEM delayed coming to hospital and often presented when the condition had not improved with TEM. As a result, they were more likely to present with advanced disease associated with poorer prognosis.

## Conclusion

Retinoblastoma is characterised by proptosis being the leading presenting symptom, late presentation with advanced disease, high mortality rate and unacceptably high loss to follow-up rate at Sekuru Kaguvi Eye Hospital in Zimbabwe.

**Recommendations**

- Awareness campaigns and screening programs for retinoblastoma should be implemented and these could be linked to immunisation programs. Social media could be used as an awareness tool and baby photographs could be screened for the red reflex with the use of smart phone applications.
- A registry for children with retinoblastoma should be created, containing all contact details so as to improve follow-up. A loss to follow-up rate of 21.8% is too high to ignore when we expect quality service provision.
- Treatment should be made more accessible by decentralizing treatment facilities and a toll free line should be provided so that guardians with affected children get prompt expert advice over the phone.

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**Conflict of interest**

This study was not sponsored by any organization and there is no conflict of interest.

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