# Clinical presentation and management of retinoblastoma at Queen Elizabeth Central Hospital, Blantyre, Malawi

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## ABSTRACT

**Objective:** Retinoblastoma is the commonest intraocular malignancy in childhood worldwide commonly affecting children in the first 5 years of life. The primary goal of retinoblastoma treatment is to improve survival. This is achievable through early detection. We conducted this study to report the clinical presentation and management of retinoblastoma in Blantyre, Malawi.

**Methodology:** This was a retrospective case series in which all files of patients who presented with a clinical diagnosis of retinoblastoma from 1st January to 31st December 2017 were reviewed. Data extracted included clinical presentation, lag time, examination findings, investigations and treatment provided. Categorical variables were summarized as percentages and frequencies whilst continuous variables were analysed as medians.

**Results:** A total of 43 patient records were retrieved. The median age was 31 months with a median lag time of 3 months (IQR 0.1 – 48 months) with most patients (n =37, 86%) presenting to the retinoblastoma treatment unit within two weeks of being referred. There was no gender preponderance with a male to female ratio of 1:1 Most patients presented with leukocoria (n = 29, 67.4%) and almost a third had proptosis (n = 13, 30.2%).Thirty six patients (83.7%) had a unilateral presentation. Patients were clinically staged using the ICRB staging. There was limited availability of facilities for thorough patient evaluation with 21 (48.8%) patients being examined under anaesthesia, B-scan being performed in 14 (32.6%) patients and only 6 (13.9%) patients undergoing Magnetic Resonance Imaging (MRI). Enucleation and chemotherapy were the only treatment options available with chemotherapy being given to 40 (93%) of the patients and 28 (65.1%) children underwent enucleation apart from chemotherapy over the study period.

**Conclusions:** The median lag time to presentation was 3 months and most of the delay in presentation was at the level of the patient before the first contact with the health system. There is a need to improve treatment options for retinoblastoma at Queen Elizabeth Central Hospital whilst also improving community awareness and early case detection at the primary level of health care.

**Key words:** Presentation, Lag time, Examination, Investigations, Treatment

## INTRODUCTION

Retinoblastoma is an intra-ocular cancer that occurs due to a mutation of the RB1 gene[1]. It is the most common intraocular malignancy in children, with an incidence of 1 in 15,000 to 1 in 18,000 live births worldwide[1,2].This tumour arises from the primitive photoreceptor cells in the developing retina that contain predisposing mutations in both copies of the RB1 gene. It can be unilateral or bilateral, growing as a solitary or multifocal tumour[3].The mean age at diagnosis is 12 months for bilateral tumours and 24 months for unilateral tumours[4].

Leukocoria is the most common presenting sign of retinoblastoma[4]. Abramson *et al*[5] reported that some children with retinoblastoma develop a squint[4]. This was further noted to be the second most common presentation in the developed world. Advanced intraocular tumours present with pain, glaucoma or buphthalmos[5]. A study done by Goddard *et al*[6] indicated that patients may present with orbital or metastatic disease as the tumour progressed and metastases occur most commonly in the central nervous system, bones, bone marrow and liver. This shows that most children with retinoblastoma are likely to be systemically well. Poor visual tracking, glaucoma, and inflammation were also seen as other presenting signs[6]. A study conducted in the Democratic Republic of Congo (DRC) showed similar results with leukocoria being the most common presenting factor followed by strabismus[7].

Clinical examination includes imaging and examination under anaesthesia to stage the tumour and

rule out other causes of leukocoria[4]. Delay in diagnosis can be divided into parental associated delay and health care associated delay[8]. The duration between when a parent recognized a symptom and when they presented to the hospital is known as lag time. Lag time is a prognostic indicator that often determines the treatment that a patient will receive. Those with a long lag time are likely to undergo eye removal surgery compared with patients with a low lag time who would likely receive globe-salvaging or sight-salvaging treatments.

Lag time is used as an indicator that is associated with possible poor outcomes and mortality[8]. A high lag time is reported to be associated with high-risk retinoblastoma that includes choroidal and optic nerve invasion.

Classification of retinoblastoma has gone through many changes as treatment strategies have evolved. In the 1960s, Reese and Ellsworth developed the Reese-Ellsworth classification which showed to predict globe-salvage[9]. This was a time where external beam radiation was the primary form of treatment[9]. However, the Reese-Ellsworth classification failed to incorporate vitreous and subretinal seeding, and a more modified classification was developed to predict success. Eventually, the International Classification of Retinoblastoma (ICRB) was developed, placing an emphasis on focal and diffuse vitreous and subretinal seed[10]. This is the classification that is widely used to date.

Community awareness of retinoblastoma is important in early diagnosis of retinoblastoma. This consists of regular teaching programs for paediatricians and general physicians, including the key symptoms of retinoblastoma. The timely diagnosis of retinoblastoma increases the chance of treatment success[11].

Currently, the retinoblastoma therapy aims to prevent blindness and serious side effects that can reduce life expectancy and quality life of the patients. Conservative therapy includes photocoagulation, cryotherapy, chemotherapy and radiotherapy[12]. Surgical practice includes enucleation and exenteration[11]. However, exenterations are now highly discouraged. In Indonesia, about 20% of children that come with intraocular retinoblastoma are treated with enucleation[14]. This study also showed that mortality rates were high if parents refused the indicated surgical therapy. Meel *et al*[13] also reported that death was caused by tumour metastasis. This shows us that there is a need of community action to promoting early diagnosis and treatment for child with retinoblastoma, especially in a developing country.

Malawi's child eye health tertiary facility is located in the Southern region of the country and an average of 45 patients with retinoblastoma are managed annually at the facility. We conducted a descriptive case series at the hospital to report the clinical presentation and management of patients with retinoblastoma.

## MATERIALS AND METHODS

*Setting:* This descriptive case series study was undertaken in the Ophthalmology Department at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi, which is the country's paediatric ophthalmology referral facility. The center treats at least four new patients with a diagnosis of retinoblastoma each month. The treatment is provided in collaboration with the Paediatric Oncology Department at QECH.

*Study participants:* All files of children who presented with a clinical diagnosis of retinoblastoma from 1st January to 31st December 2017 were included in the study.

*Data collection:* All data collected was paper-based and documented onto a structured data collection tool. This included socio demographic features, pre-referral pathway, and family history. The lag time was defined as the duration between when the parent first noticed ophthalmic symptoms and the first presentation to QECH.

Data was collected on whether there was use of investigations such as B-scan and MRI and also on how the retinoblastoma was graded (International Classification for Retinoblastoma). Those with proptosis were documented as extra-ocular retinoblastoma. The findings of examination were documented whether they underwent examination under general anaesthesia or not. Data was also collected on the treatment modality given to patients. No pathological results were documented as this service was not readily available at the time of the study.

*Data analysis:* Data was coded, entered and managed using Microsoft Word Excel and analysed using STATA version 15. Categorical variables were summarized as percentages and frequencies whilst continuous variables were analysed as medians.

*Ethical clearance:* The College of Medicine Research and Ethics Committee (COMREC) approved the study protocol (P.07/18/2445). To maintain the confidentiality and anonymity of patients, the data was extracted without identifiers and names were replaced with unique identification numbers.

## RESULTS

The study population (n=43) had a median age of 31 months (inter-quartile range 3 – 82 months) with a male-to-female ratio of 1:1 and most (n = 20, 46.5%) were referred from a secondary level health facility followed by tertiary hospital referrals (n = 18, 41.9%) with only 11.6% (n = 5) being referred from the primary level of health care. Most patients (n = 37, 86%) arrived to QECH within two weeks of being referred.

**Table 1:** Patient characteristics and social demographics of those with retinoblastoma at QECH (n=43)

| | No. | (%) |
|---|---|---|
| Age (months) | 31 (3-82)* | |
| 0-6 | 9 | 20.9 |
| 7-12 | 9 | 20.9 |
| 13-18 | 4 | 9.3 |
| Above 18 | 21 | 48.9 |
| Sex | | |
| Male | 21 | 48.8 |
| Female | 22 | 51.2 |
| Referral facility | | |
| Primary | 5 | 11.6 |
| Secondary | 20 | 46.5 |
| Tertiary | 18 | 41.9 |
| Pre-referral treatment | | |
| Yes | 8 | 18.4 |
| No | 35 | 81.4 |
| Arrival time following referral (weeks) | | |
| Less than 2 | 37 | 86 |
| More than 2 | 6 | 14 |

*Median (inter-quartile range)

*Presenting features:* The majority of the population noticed the symptoms after 18 months of age (n=22, 51.1%) and eye involvement was mostly unilateral (n=36, 83.7%). Most of the patients presented with a white lesion (n=29, 67.4%) in the eye followed by eye swelling (n= 19, 44.2%). There were no children that presented with strabismus or buphthalmos. None of the children presented with metastatic disease. The median lag time to presentation was 3 months (inter-quartile range 0.1 – 48 months) with the majority of the children (n=24, 55.8%) presenting within the first 3 months of noticing the symptoms (Table 2).

**Table 2:** Presenting features of children with retinoblastoma at QECH (n=43)

| | No. | (%) |
|---|---|---|
| Age symptoms were first noticed (months) | | |
| 0-6 | 7 | 16.3 |
| 7-12 | 11 | 25.6 |
| 13-18 | 3 | 7 |
| >18 | 22 | 51.1 |
| Involvement | | |
| Unilateral | 36 | 83.7 |
| Bilateral | 7 | 16.3 |
| White lesion | | |
| Yes | 29 | 67.4 |
| No | 14 | 32.6 |
| Swelling | | |
| Yes | 19 | 44.2 |
| No | 24 | 55.8 |
| Poor vision | | |
| Yes | 7 | 16.3 |
| Not documented | 36 | 83.7 |
| Pain | | |
| Yes | 2 | 4.7 |
| No | 41 | 95.3 |
| Redness | | |
| Yes | 4 | 9.5 |
| No | 39 | 90.5 |
| Lag time (months) | 3*(0.1-48) | |
| 0-3 | 24 | 55.8 |
| 3-6 | 4 | 9.3 |
| 6-12 | 9 | 20.9 |
| >12 | 6 | 13.9 |

*Median

*Examination findings and investigations done:* The most common examination feature noted was leukocoria (n=32, 74.4%) whilst pseudohypopyon was the least common examination finding (n = 2, 4.6%). A third (32.6%) of the patients had a B-scan done as part of their assessment whilst Magnetic Resonance Imaging (MRI) was performed in only 6 children. Just over half of the study population (n=22, 51.2%) were examined without utilizing anaesthesia (Table 3).

**Table 3:** Patient evaluation of children with retinoblastoma at QECH (n=43)

| | No. | (%) |
|---|---|---|
| Leukocoria | | |
| Yes | 32 | 74.4 |
| No | 11 | 25.6 |
| Proptosis | | |
| Yes | 13 | 30.2 |
| Not documented | 30 | 69.8 |
| Pseudohypopyon | | |
| Yes | 2 | 4.6 |
| No | 41 | 95.4 |
| Staging (ICRB) | | |
| Group D | 30 | 69.8 |
| Group E | 13 | 30.2 |
| B-Scan | | |
| Yes | 14 | 32.6 |
| No | 29 | 67.4 |
| MRI | | |
| Yes | 6 | 13.9 |
| No | 37 | 86.1 |
| EUA | | |
| Yes | 21 | 48.8 |
| No | 22 | 51.2 |

*Treatment modalities:* Almost two-thirds of the patients had undergone an enucleation surgery as treatment for retinoblastoma (n=28, 65.1%) and a third (n=15, 24.9%) were awaiting surgery. The majority of the population had received pre-surgical or post-surgical chemotherapy (n=40, 93%). Radiotherapy treatment was not available at the facility (Table 4).

**Table 4:** Treatment given to children with retinoblastoma at QECH (n=43)

| | No. | (%) |
|---|---|---|
| Enucleation | | |
| Done | 28 | 65.1 |
| Pending | 15 | 34.9 |
| Chemotherapy | | |
| Administered | 40 | 93 |
| Pending | 3 | 7 |

## DISCUSSION

This study reports a median age of 31 months at the time of diagnosis of retinoblastoma. This is similar to findings from other African countries such as Zambia and Kenya [14,15].The male to female ratio of our study population is also similar to the findings from the majority of studies on retinoblastoma where the sex ratio has been reported as 1:1[1,2,6,14]. The majority of the patients were referred from secondary health facilities followed by from tertiary health facilities. 41.9% of the patients being referred from tertiary facilities highlights the need to equip other tertiary facilities in Malawi with human resources and facilities for treating retinoblastoma patients. At the same time, a small percentage of referrals from the primary level (11.6%) points to the need for strengthening

primary eye care to facilitate early detection and referral of retinoblastoma cases from the primary level.

The median lag time of 3 months before presentation was long compared to reports from high income countries where lag times are as short as three days[5,15,16]. However, the lag time was shorter compared to previous findings from DRC, Cote d'Ivoire, Zambia and Kenya where the median lag time ranged from 6.8 months to 9.27 months[6,14,16]. It is important to note that it took less than two weeks for 86% of the patients to present for treatment at QECH Blantyre following referral. This implies that the delay in presentation can be attributed to delays by patients in making contact with the health system and not to delays with referrals within the health system. Some of the patient-related barriers to seeking eye health care in general in low income countries include lack of awareness, long distances to the nearest health facility and high transportation costs[18]. It is thus important to conduct studies to investigate the main barriers to accessing eye care for retinoblastoma patients in Malawi to guide community-level interventions to improve timely detection.

Almost three-quarters of the patients from our study had presented with leukocoria. This is in line with most reports on the commonest presentation of retinoblastoma from Western countries such as United States of America and France where at least half of the cases present with leukocoria[19-21]. This is also comparable to reports from other countries in Sub-Saharan Africa such as Republic of Cote d'Ivoire, the Democratic Republic of the Congo and Kenya, where 70 to 90% of patients with retinoblastoma present with leukocoria.

Leukocoria was followed by orbital cellulitis (37.2%). This is over double (13.2%) what Nyaka reported in 2010[3]. Orbital cellulitis is a rare presenting feature in the developed world. Mullaney *et al*[22] reported 4.8% in Saudi Arabia. In the United States and other developed nations cellulitis is noted in 10% of patients that are diagnosed with retinoblastoma[23].

In our study 44% of patients presented with swelling of one eye. Proptosis is a feature of extra-ocular retinoblastoma and was found in this study to be 30% with an additional 10% reported to have an orbital mass. These findings are similar to Nyaka[3] who reported 44.1% of the patients with swelling of the eye in 2010. It is known, that proptosis is seen frequently in low and middle income countries. A study done in Zambia noted that proptosis occurred in 47% of their patients and was the most common presenting sign[15]. Other developing countries such as Nigeria and Zimbabwe reported 85% and 65% respectively[16]. This was in sharp contrast to what was seen in the developed countries such as USA (0.5%) and Korea (1.4%)[22].

According to the International Classification of Retinoblastoma (ICRB), proptosis is a feature of advanced retinoblastoma which signifies extraocular involvement of the tumour and in our study, about a third of the patients had proptosis. A high percentage of retinoblastoma patients with proptosis has also been reported from other countries in Sub-Saharan Africa such as Zambia, Nigeria and Zimbabwe where 47% to 85% of the patients had proptosis[22]. First-time presentation with extraocular retinoblastoma in low income countries is attributed to delayed presentation[22]. This is in contrast to reports from developed countries such as USA and Korea where only 0.5% to 1.4% of patients with retinoblastoma present with proptosis[22].

The patients that were staged in our study had group D & group E tumours. Due to the advancement of the tumours at presentation, other treatment modalities such as brachytherapy or eye salvaging interventions such as intraocular chemotherapy cannot be offered. Besides lack of their availability.

Due to limited access to facilities for anaesthesia for small children at the time of the study, most patients (51.2%) underwent dilated fundoscopy without anaesthesia. The B-scan ultrasound machine was also not functional at the time and only 32.6% underwent ultrasonography as part of evaluation. In addition, the MRI machine was not functional for most of the study period and only 13.9% underwent MRI imaging. All these three facilities that were of limited availability are important for accurate patient evaluation, tumour grading and monitoring response to treatment[2]. It is important for retinoblastoma centres to have these facilities available to optimise patient management.

Enucleation was performed in 65.1% of the patients. All patients with retinoblastoma at QECH receive the same standard treatment regardless of lag time and staging. This constitutes three cycles of chemotherapy followed by enucleation which is subsequently followed by another three cycles of post-operative chemotherapy (vincristine, etoposide and cyclophosphamide). Although cryotherapy is available, the treatment is not normally given due to advanced disease at the time of presentation. Other treatment modalities such as brachytherapy, radiotherapy and intra-ocular chemotherapy are not available. This is in contrast to western countries where patients have access to more treatment options and that enable globe-salvaging therapeutic approaches[23]. Pathological staging was not done due to the unavailability of a pathologist at the public hospital at the time of the study. A collaboration with the paediatric oncology team has enabled tissue samples to be sent to a paying facility for histological confirmation and staging. Those that present to hospital with metastatic disease and given palliative chemotherapy which consists of 6 cycles of chemotherapy followed by enucleation. Then another 3 cycles of chemotherapy is given. Radiation therapy is still not available in the country.

As Malawi plans to develop retinoblastoma services in the country, collaboration with local experts in other disciplines such as paediatric oncology, radiology and pathology is paramount. At the same time, international multidisciplinary collaborations such as with the

retinoblastoma network offer an opportunity for training in newly introduced treatment options, strengthening referral pathways and research on interventions that can improve treatment outcomes[21].

From our study findings, it is however not enough to improve the diagnostic and therapeutic facilities for retinoblastoma at tertiary level without effective interventions to promote early detection at primary level. There is thus a need for studies on the most effective models for health promotion at community level to increase community awareness on the signs of retinoblastoma and promote earlier presentation. At the same time, there is need for research into the primary eye care interventions that would improve detection at primary level in Malawi.

A major limitation of our study is the retrospective nature of the study where some medical records had incomplete details to enable accurate reporting on clinical features such as tumour staging. However, we were able to demonstrate the long lag time to presentation for retinoblastoma patients and areas that can be improved in the health system to improve retinoblastoma outcomes.

## CONCLUSIONS

The median lag time between detection of the first symptom and visiting the retinoblastoma treatment center was 3 months. Most of the delay in presentation was at the level of the patient before the first contact with the health system. There is a need to improve treatment options for retinoblastoma whilst also improving community awareness and early case detection at the primary level of health care.

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*Competing interests:* The authors declare that they have no competing interests.

## REFERENCES

1. Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol.* 2009; **93**:1129–31.
2. Pandey AN. Retinoblastoma: An overview. *Saudi J Ophthalmol.* 2014; **28**:310–315.
3. Nyaka A. The pattern of retinoblastoma at Queen Elizabeth Central Hospital [Post Graduate]. University of Nairobi; 2010.
4. Abramson DH, Beaverson K, Sangani P, *et al.* Screening for retinoblastoma: presenting signs as prognosticators of patient and ocular survival. *Pediatrics.* 2003; **112**(6 Pt. 1):1248–55.
5. Goddard AG, Kingston JE, Hungerford JL. Delay in diagnosis of retinoblastoma: risk factors and treatment outcome. *Br J Ophthalmol.* 1999; **83**:1320-23.
6. Nyaywa M, Chipalo-Mutati G, Chintu C; Modes of presentation, management and outcome of retinoblastoma treatment at University Teaching Hospital. *Med J Zambia.* 2016; **43**(4): 216-223.
7. Stephan C, Bray F, Ferlay J, Liu B, Parkin D. Cancer of childhood in sub Saharan African. *Ecancer Med Sci.* 2017; **11**:345-355
8. Posner M, Jaulim A, Vasalaki M. Lag time for Retinoblastoma in the UK revisited: a retrospective analysis. *BMJ Open.* 2017; **7**:e015625.
9. Dimaras H, White A, Gallie B. The Kenyan National Retinoblastoma Strategy: Building local capacity in the diagnosis and management of pediatric eye cancer in Kenya. 2008 (accessed Dec 13, 2011).
10. Shah, Nandish. Access to Imaging Technology in the Developing World. Radiology in Global Health: Strategies, Implementation and Applications. 2013: 13-17. 10.1007/978-1-4614-0604-4_3
11. Skuta GL, Cantor LB, Weiss JS. Retinoblastoma. In: Ophthalmic pathology and intraocular tumor. *Amer Academy Ophthalmol San Francisco.* 2012: **178**-181.
12. Gunguz K, Yanik O, Yavuz K, Tacyldnz N and Unal E Chemotherapy in retinoblastoma: Current approaches. *Tuk J Ophthalmol.* 2015; **45**(6):259-267.
13. Meel R, Radhankrisan V, Bakhshi S. Current therapy and recent advances in management of retinoblastoma. *Indian J Med PaediatOncol: Official Journal of Indian Medical of Indian Society of Medical and Paediatric Oncology.* 2012; **33**(2):80-88.
14. Lukamba R, Yao J, Kabesha T; Retinoblastoma in Sub-Saharan Africa. *J Glob Oncol.* 2018; **4**: JGO.17.00056
15. RibeiroKC, Antoneli CB. Trends in eye cancer mortality among children in Brazil, 1980-2002. *Pediatr Blood Cancer.* 2007; **48**:296–305.
16. Chang CY, Chiou TJ, Hwang B, *et al.* Retinoblastoma in Taiwan: survival rate and prognostic factors. *Jpn J Ophthalmol.* 2006; **50**:242–249.
17. Nyamori J, Kimani K, Njuguna M. Retinoblastoma referral pattern in Kenya. *Middle East Afr J Ophthalmol.* 2014; **21**(4):321-327.
18. Lewallen S, Courtright P. Recognising and reducing barriers to cataract surgery. *Community Eye Health.* 2020;**13**(34):20–21.
19. Abramson DH. Retinoblastoma incidence in the United States. *Arch Ophthalmol.* 1990; **108**:1514.
20. Balmer A, Munier F. Leukocoria in a child; emergency and challenge. *Klin Monbl Augenheilkd.* 1999; **214**(5):332-335.

21. Global Retinoblastoma Study Group: Global retinoblastoma presentation and analysis by national income level. *JAMA Oncol.* 2020; **6**:1–12.
22. Mullaney PB, Karcioglu ZA, Huaman AM, Mesfer SAL. Retinoblastoma associated orbital cellulitis. *Br J Ophthalmol.* 1998; **82**:517-521.
23. Lucile's Packard Children's Hospital; Stanford School of Medicine. Retinoblastoma in children, 2021. Stanford (USA): Stanford University; 2021.