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ABSTRACT: BACKGROUND: Retinoblastoma is a malignant tumour that develops from the immature cells of the retina. It is the most frequent type of paediatric intraocular cancer and is curable. Clinical and histological findings after enucleation of the affected eye dictate not only the patient's secondary care but also their prognosis. We assessed the clinical and histopathologic predictors of survival among children with retinoblastoma from two tertiary health facilities in Uganda. **METHODS**: This retrospective research utilized archived formalin fixed & paraffin embedded blocks of eye specimens enucleated between 2014 to 2016 at Mbarara University, pathology department and Ruharo Eye Centre. The specimens were then processed and stained with haematoxylin and eosin. The confirmation of retinoblastoma was made to include histologic stage and features of the tumor. Biographic data of the patients and the clinical features such as leukocoria, proptosis, phthisis, staphyloma, buphthalmos were retrieved from the records. **RESULTS:** Males (55.1%) dominated the study population (N=78). The median age was 31 months. The commonest clinical sign was leukocoria (69.2%) and the most abundant histopathological stage was stage 1 (41%). Optic nerve invasion 39.5%, choroidal invasion 29.5%, scleral invasion 7.7% and orbital extension 16.7% were seen. Flexner-Wintersteiner rosettes were seen in 24.6%. Necrosis was a prominent feature (71.2%). The two-year survival was estimated to be 62%. Leukocoria (RR 1.1), female gender (RR 1.4), intralaminar optic nerve invasion (RR 7.6) and a lack of orbital extension (RR- 7) were significant predictors of survival. **CONCLUSION**: Leukocoria and proptosis are noticeable clinical signs of retinoblastoma. Most patients present while in stage one although stage four presentation is also common. Leukocoria, optic nerve invasion, orbital extension, and gender are significant factors predictive of survival in patients with retinoblastoma.

Keywords: clinical features; histopathologic features; retinoblastoma; survival; children

Introduction

Retinoblastoma (RB) is a malignant tumour that develops from the immature cells of the retina [1]. It is the most common intraocular cancer of childhood affecting approximately 1 in 15,000 – 20,000 births, for an incidence of 7000 – 8000 new cases annually worldwide and 4000 deaths annually [2, 3]. It is an important cause of blindness, morbidity and mortality particularly in the underdeveloped countries of sub-Saharan Africa [4]. The greatest disease burden is recorded in large populations that have high birth rates, such as in Asia and Africa [5] [6]. Regions with greatest prevalence have the

highest mortality with up to 70% mortality in Asia and Africa, compared with 3–5% in Europe, Canada, and the USA [6]. In Uganda, retinoblastoma is the 5th commonest cancer after lymphomas, Kaposi sarcoma, leukemia and nephroblastoma [7].

The survival of retinoblastoma patients in Africa, Uganda in particular is low largely because of delayed presentation [8]. The advanced stage of disease is found to be associated with very poor outcome. Survival majorly depends on severity of disease at presentation. Survival rates in the UK and US approach 100% [9] with survival in other continents, primarily developing nations, much lower. Survival rates in developed Latin America countries has been reported to be 80–89%, 48% in India, and as low as 20–46% in Africa [10]. In Uganda, survival rose from 45% in the pre-chemotherapy era to 65% in the post chemotherapy era [8].

A worldwide issue is poor access to comprehensive retinoblastoma pathology   [6]. Histological examination of the enucleated globes in the region has also been inconsistent as shown in studies done in Uganda and in Kenya [11, 12]. Retinoblastoma management not informed by histological examination could impede development of a rational management plan and lead to unsatisfactory clinical outcomes.

There is paucity of data on the association between clinical and histopathological features and survival so as to guide appropriate retinoblastoma management and ultimately improve survival, this study intended to address this gap.

Methods

Study design and site

This was a retrospective study carried out at two health facilities in south western Uganda. Mbarara Regional Referral Hospital (MRRH) is a tertiary hospital with a 350-bed capacity, located along Kampala-Kabale highway, 286kms from Kampala the capital city.   The facility serves as a general referral hospital with pathology, surgical, medical, obstetrical and gynaecological, Pediatric services, and ear, nose, and throat (ENT), dental, orthopaedic, and other specialized units also on site. It is government funded through the Ministry of Health intended to provide free service and covers the districts of Mbarara, Isingiro, Sheema, Bushenyi, Ibanda, Kiruhura, Lyantonde and Ntungamo. It also receives patients from the neighbouring nations of Democratic Republic of Congo (DRC), Rwanda and Tanzania. It is a teaching hospital for Mbarara University of Science and Technology (MUST) and other health training institutions in the region.

Another study site was Ruharo Eye Center (REC). The patients with suspected retinoblastoma are referred to Ruharo Eye Center, a mission owned Ophthalmology centre for specialised care where the patients are managed. REC is one of the referral centres for retinoblastoma cases in the country and receives over 90 cases of retinoblastoma annually.

The enucleated specimens were taken to MUST histopathology laboratory in the MUST pathology department, which is the only government aided histopathology laboratory in the southern and western part of Uganda. The MUST pathology department is a referral unit for cases which require histologic diagnosis in the region.

Study variables

Clinical features were retrieved from archived records. These included leukocoria, strabismus, proptosis, uveitis, cataract, staphyloma, phthisis, laterality and treatment. Clinical outcome data was recorded as either alive or dead.   The Staging was by the AJCC TNM8 staging system as pT1, PT2, pT3 and pT4.

The following histologic features were noted: Growth patterns as exophytic, endophytic and mixed; Invasion of lens, conjunctiva and corneal epithelium; Invasion of anterior segment structures as present or absent (iris, ciliary body and trabecular meshwork); Necrosis as none, mild (involving less than 25%), moderate (25-50%) and extensive (more than 50%); Calcification as none, mild

(involving less than 25%), moderate (25-50%) and extensive (more than 50%); Flexner-Wintersteiner rosettes as mild (0-25%), moderate (25- 50%) and many (more than 50%).

The well differentiated tumours were those with more than 50%, moderately differentiated as those less than 50% and poorly differentiated as those without any rosettes; Homer-Wright rosettes as absent or present; Mitosis as present or absent; Presence of inflammation as chronic (lymphohistiocytic) or acute inflammation.

Data analysis

Stata Version 13 was used for analysis. Baseline participants' characteristics were described using appropriate summary statistics, which is, mean or median for continuous variables and proportions for categorical variables. The histopathological stages of retinoblastoma among children were presented as proportions in a bar graph. The Survival after 2 years in care was computed as a cumulative measure and expressed as a proportion of all children still alive by two years out of all that were admitted with retinoblastoma at REC. The corresponding 95% confidence interval (CI) was also reported.

Independent variables included sociodemographic factors like age, gender and geographical region of residence, in-hospital care, histopathologic features of the tumor and clinical presentation of the children. Unadjusted risk-ratios were reported together with their corresponding 95% CI. A significance level of 5% was used. All independent variables with p<0.1 were included in the multivariate model building using a manual backward-stepwise selection method. Variables that lost their association with survival at 2-years were excluded from the final multivariate model. Also, variables that could not allow for convergence of the model were excluded. For all variables in the final model, adjusted risk-ratios were presented with their corresponding 95% Confidence Intervals.

Results

We included 78 eye specimens in the study. As shown in *Table 1*, the median age of diagnosis was 31 months and most of the participants were between 12-59 months (78.4%). Majority were males (55.1%) while most of them originated from western Uganda (33.3%). In most cases, only one eye was affected at the time of diagnosis (70.5%).

Table 1. Baseline characteristics of sample source patients.

Characteristic	n(%)
Age in months, median (IQR)	31 (18-39)
Age categories (months)	
<12	10 (12.8)
12-59	58 (78.4)
≥60	10 (12.8)
Gender	
Male	43 (55.1)
Female	35 (44.9)
Region	
Western	26 (33.3)
Eastern	21 (26.9)
Central	22 (28.2)
Northern	5 (6.4)
International	4 (5.1)

Laterality	
Unilateral	55 (70.5)
Bilateral	23 (29.5)
Chemoreduction therapy	
Given	63 (80.8)
Not given	15 (19.2)

The commonest clinical sign was leukocoria (69.2%) which was followed by proptosis (32.1%). See Figure 1 below.
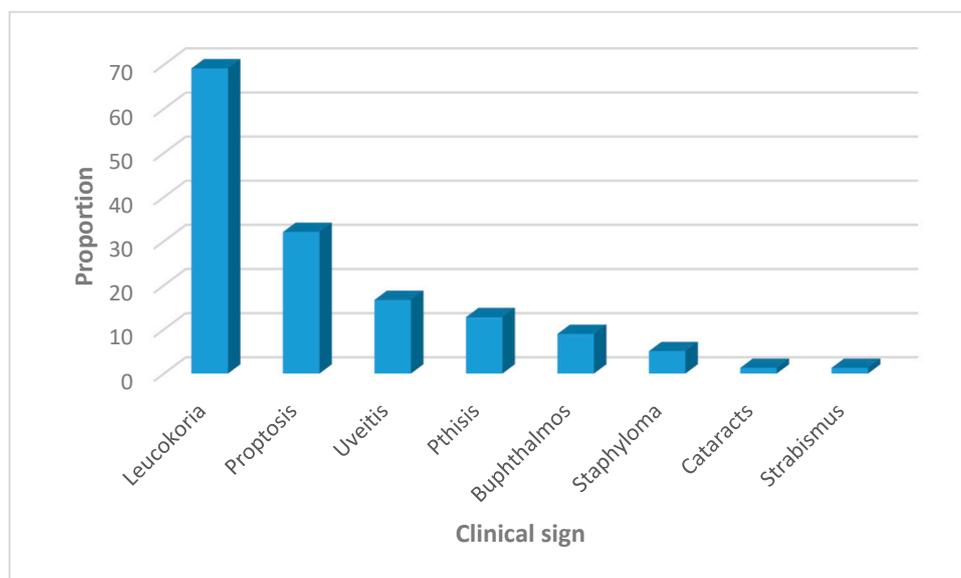

Figure 1. Bar graph showing clinical characteristics of the specimen participants.

The commonest pathologic stage was stage 1 (41.0%) followed by 4 (26.9%), then 2 (26.9%) and then 3 (5.1%). Stage 2 was further classified as 2A (24.4) and 2B (2.6) while stage 3 would be further classified as 3A (1.3), B (2.6), C (1.3), D (0). See Figure 2 below.
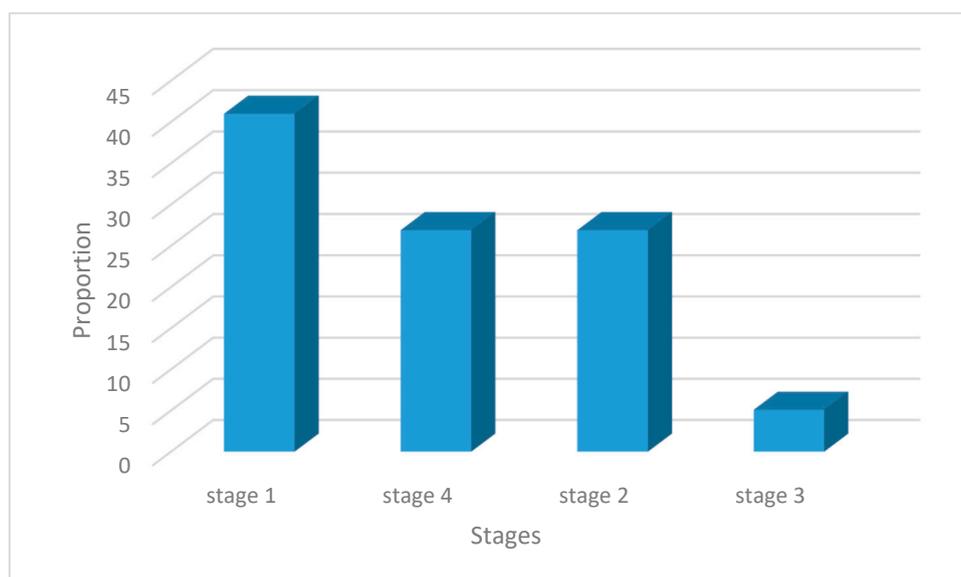
Figure 2. Bar graph showing histopathologic stages of the specimens.

Choroidal invasion was seen in 29.5% (23) of the specimens, more than half of these were massive. Optic nerve invasion was seen in 31.5% (30) cases with almost half of these having invasion to the surgical end/margin. Orbital extension was seen in 16.7 % (13) cases while scleral invasion seen in a paltry 7.7%. Iris, trabecular meshwork and ciliary body invasion accounted for 16.7% (13) each. Lens, corneal, conjunctival and vascular invasion accounted for a combined paltry 7.8% (6). Endophytic tumor was seen in 71.8% (56) cases. Flexner-Wintersteiner rosettes were seen in 34.6% (27) cases while Homer-Wright rosettes in only 6.4% (5) cases. Necrosis was seen in 71.8% cases while calcification was seen in 41% cases while mitoses were seen in only 9% cases. See Table 2 below.

Table 2. Histopathologic features of the samples.

Characteristic	n(%)
Choroidal invasion	
Absent	55 (70.5)
Focal	13 (16.7)
Massive	10(12.8)
Optic nerve invasion	
Absent	48 (61.5)
Prelaminar	10 (12.8)
Intra-laminar	4 (5.1)
Retrolaminar	3 (3.9)
Surgical margin/cut end	13 (16.7)
Scleral invasion	
Absent	72 (92.3)
Partial thickness	1 (1.3)
Full thickness	5 (6.4)
Orbital extension	13 (16.7)
Iris	13 (16.7)
Trabecular meshwork	13 (16.7)
Growth pattern	
Endophytic	56 (71.8)
Exophytic	14 (17.9)
Mixed	8 (10.3)
Lens Invasion	1 (1.3)
Ciliary body invasion	13 (16.7)
Corneal epithelium invasion	2(2.6)
Conjunctival invasion	1 (1.3)
Vascular invasion	2(2.6)
Flexner-Wintersteiner rosettes	
None	51 (65.4)

	Mild	12 (15.4)
	Moderate	7 (9.0)
	Many	8 (10.2)
Homer-Wright rosettes		
	None	73 (93.6)
	Present	5 (6.4)
Necrosis		
	None	22 (28.2)
	Mild	18 (23.1)
	Moderate	12 (15.4)
	Massive	26 (33.3)
Calcification		
	None	46 (59.0)
	Mild	13 (16.6)
	Moderate	12 (15.4)
	Massive	7 (9.0)

The 2-year survival was estimated to be 62% as shown in Table 3 below.

Table 3. Estimation of survival at 2 years.

Status at 2 years	n (%)	Proportion (CI)
Dead	30 (38.5)	38 (28- 50)
Alive	48 (61.5)	62 (50- 72)

At univariate analysis, gender, region of origin, leukocoria, proptosis, cataract, choroidal invasion, orbital invasion and necrosis were significant factors in predicting survival. Age, laterality, chemoreduction, buphthalmos, growth pattern, calcification, vascularity, mitosis, differentiation were not significant. Scleral invasion and anterior segment invasion were not able to produce a risk ratio because the alive category had zeroes. See Table 4 below.

Table 4. Results of univariate analysis showing predictors of 2year survival.

Characteristic	Dead n (%)	Alive n (%)	Unadjusted RR (95% CI)	p value
Gender				
Female	7 (20)	28 (80)	1.7 (1.20- 2.47)	0.003
Male	23 (53.5)	20 (46.5)	1.0	

Region				
Eastern	11 (52.4)	10 (47.6)	0.8 (0.45- 1.33)	0.354
Central	7 (61.8)	15 (38.2)	1.1 (0.73- 1.68)	0.630
Southern	0 (0)	5 (100)	1.7 (1.26- 2.30)	0.001
International	2 (50)	2 (50)	0.8 (0.29- 2.27)	0.692
Western	10 (38.5)	16 (61.5)	1.0	
Leukocoria				
Present	15 (27.8)	39 (72.2)	1.9 (1.12- 3.31)	0.018
Absent	15 (62.5)	9 (37.5)	1.0	
Proptosis				
Present	20 (80)	5 (20)	4.1 (1.83- 8.98)	0.001
Absent	10 (18.9)	43 (81.1)	1.0	
Cataract				
Present	0 (0)	1 (100)	1.7(1.43- 2.05)	0.000
Absent	30 (38)	47 (61)	1.0	
Choroidal invasion				
Absent	17 (30.9)	38 (69.1)	6.9 (1.07- 44.72)	0.043
Focal	4 (30.8)	9 (69.2)	6.9 (1.04- 46.03)	0.045
Massive	9 (90)	1 (10)	1.0	
Optic nerve invasion				
Absent	14 (29.2)	34 (70.8)	9.2 (1.39- 61.06)	0.021
Prelaminar	2 (20)	8 (80)	10.4 (1.4- 70.12)	0.016
Intralaminar	0 (0)	4 (100)	13.6 (2.07- 89.4)	0.007
retrolaminar	2 (66.7)	1 (33.3)	4.3 (0.37- 51.29)	0.245
Surgical margin/ cut end	12 (92.3)	1 (7.7)	1.0	
Orbital extension				
Absent	18 (27.7)	47 (72.3)	9.4 (1.42- 62.16)	0.020
Present	12 (92.3)	1 (7.7)	1.0	
Necrosis				
None	3 (13.6)	19 (83.4)	2.3 (1.34- 2.75)	0.002
Mild	8 (44.4)	10 (55.6)	1.4 (0.76- 2.73)	0.259
Moderate	3 (25)	9 (75)	1.95 (1.08- 3.50)	0.025
Severe	16 (61.5)	10 (38.5)	1.0	

Female gender, leukocoria, proptosis, choroidal invasion, optic nerve invasion orbital invasion, region, cataract and necrosis were run in the final model however region, cataract, choroidal invasion, proptosis and necrosis would not bring convergence so they were eliminated from the final model.

Female gender, leukocoria, orbital extension, optic nerve invasion were significant predictors of survival with female being able to survival 1.4 times, better than males, patients without leukocoria being able to survive 1.1 times better than those without.

Patients without optic nerve invasion will survive better than those with optic nerve invasion depending on the degree of invasion and patients without orbital extension will be able to survive 7 times better than those with orbital extension. See Table 5 below.

Table 5. Shows predictors of 2- year survival at multivariate analysis.

Variable	Adjusted RR (95% CI)	P value
Gender		
Female	1.4 (1.07- 1.70)	0.009
Male	1.0	
Leukocoria		
Present	1.1 (1.10- 1.11)	0.000
Absent	1.0	
Optic nerve (ON) invasion		
Absent	6.0 (0.85- 42.3)	0.072
Prelaminar ON invasion	7.0 (0.99- 49.27)	0.052
Intralaminar ON	7.6 (1.08- 53.98)	0.042
Retrolaminar ON	2.4 (0.18- 31.04)	0.504
Surgical margin ON	1.0	
Orbital extension		
Absent	7.0 (1.00- 49.25)	0.002
Present	1.0	

Discussion

The median age of the patients at presentation was 31 months which is comparable to a study at a tertiary centre in Kinshasa, Democratic Republic of Congo who found the median age at 32 months and 29 in months in an Indian population. However, this is not comparable to studies done in developed countries who report a median age of 12 months such as in the UK. This is attributed to the late presentation and delayed diagnosis of these cases in our setting and other developing countries [9, 13, 14].

The prevalence of males and females vary widely from studies. Male were 55.1% which was comparable to a Kenyan study at 54% as well as other studies in both developed and developing countries such as Turkey and Pakistan [12] [15, 16]. However, studies done in Malaysia and Nigeria have reported a higher prevalence of females. This could be attributed to the genetic differences in the different populations and referral selection due to differences in cultural beliefs [17, 18].

The commonest age groups involved was the 12-59 months (78.4%), Delayed diagnosis is commonly encountered in developing countries with 90% of cases diagnosed before the age of 5 years as evidenced by a study done in Cameroon which is consistent with our study at 91.2% and 85% in Nigeria [4, 17]. Those less than 12 months were 12.8% which is comparable to a study in Kenya [19]. On the contrary most children diagnosed with RB in developed countries are less than 24 months because of the early presentation and diagnosis [1].

Unilateral cases were 70.5% and this is comparable to many studies which reported unilateral cases to be 72%, 74% 71.2% in Kenya, Uganda and Pakistan respectively [11, 12, 20]. Sub-Saharan

Africa studies have found 11% to 33% of patients with retinoblastoma to have bilateral disease as seen in a study done in Republic of Côte d'Ivoire and the Democratic Republic of the Congo which is in keeping with our study [13, 21].

Leukocoria (69.2%) and proptosis (37.2%) were the commonest presenting symptoms. This was comparable to a study done at Kenyatta Hospital in Kenya at 71% and 37% respectively [12]. Also, leukocoria was the commonest presenting sign Republic of Côte d'Ivoire and the Democratic Republic of the Congo [13, 21]. However, this is different from data in middle income to upper income countries who present with leukocoria and strabismus as the commonest signs, such as in Egypt and in the UK [9, 22]. This is because symptoms such as proptosis symptoms are signs of advanced RB and present when there is most likely orbital extension. The frequency of other less common symptoms such as buphthalmos, phthisis, cataracts and staphyloma were similar to a study done in India[23].

Intraocular tumours (stages pT1-3) constituted 73.1% while extraocular tumours (stage pT4) were 26.9%. This was comparable to a study done in India which found intraocular tumours and extraocular tumours to be 72.3% and 27.7% respectively [14]. PT4 was our second most common stage which was consistent with findings of a study done in India that showed pT1 of 48.1% and pT4 in 26% [24]. However, this is lower than the percentage found in a study done at Ruharo Eye Centre, Uganda that showed that almost half the tumours were extraocular (46%). This is due to the introduction of an effective safe chemotherapy regimen in Uganda which presumably reduced the progression of disease to advanced stages [8].

Endophytic pattern was seen in 71.8% while exophytic pattern 17.9% and mixed pattern in 10.3%. The incidence of growth patterns varies widely with the endophytic and mixed types being more predominant. This difference could be attributed to a difference in the biologic nature of these tumors [24, 25].

Choroidal invasion was seen in 29.5% which is comparable to that of Shields *et al.,* (1993) of 23% [26]. Though the incidence of choroidal invasion varies greatly in various reported series, ranging from 15.2% to 62%, it is lower than of findings in other developing countries such as in India of 47.4% [23]. This has been attributed to the limited peripheral calottes that were taken during the sectioning. However massive choroidal invasion was seen in 12.8% cases which is comparable to the 18% seen in Jordan, but was still lower than that from other studies such as in India at 24.6% because of the limited sectioning [15, 23].

Reports indicate that 24% to 45% of eyes have any degree of optic nerve invasion. Optic nerve invasion was seen in 39.5% which was comparable with the study in America of 38.7% and at 32% in India [25, 27]. However, it was higher than that a much earlier study in the USA, probably reflecting to the advanced stage of the tumours in our study [28]. Retrolaminar ON invasion was seen in 3.9 % cases which is comparable to Shields *et al.,* (1994) of 5.5%, however studies from developing countries have shown a higher percentage such as Gupta *et al.,* (2009) with 17% and Ralph Eagle (2009) with 10.4%[27-29]. Invasion of resected margin of optic nerve was seen in 16.7% cases. This was comparable to other studies in the developing world, however this is higher than for developed countries such as in USA of 1% [28].

Scleral invasion was seen in 7.7% cases which was in keeping with other studies such as that of Argentina at 8.8%, and 7% of Pakistan [30, 31]. Orbital extension was seen in 16.7% which is comparable to 18% in Indian study [32]. This is due to the advanced stages of the tumours in developing countries. Invasion of the iris was seen in 16.7% which is in keeping with a study done in India of 10.7% [23]. The higher incidence of these risk factors in developing world might be related to later presentation (more advanced stage) in relation to the lower socioeconomic status and the delay in seeking and getting treatment [11].

Tumour differentiation is highly variable between different reports from the developing world. Many tumours showed higher incidence of poorly differentiated (up to 80%) compared to well differentiated tumours which was comparable to our study of 65% probably reflecting the late age of presentation of the undifferentiated tumours [23].

Generally, necrosis was seen in 71.2% cases which was higher than in most studies because of the fact that most cases had undergone chemoreduction before enucleation in our study as compared to other studies who examined primarily enucleated eyes, however, extensive necrosis seen is 33.3% was comparable to 31% of an Indian study[23].

Calcification in retinoblastoma is a frequent histologic finding with a reported frequency between 40% and 95%, although the subject has not been studied in depth. Our study found calcification in 41%of the cases, which is similar to the 48% in Malaysia but this is lower than seen in Israel at 84% [18, 33].

Two- year survival was estimated to be 62 % and this was comparable to a study done Taiwan at 64.4% [34]. This is higher than those of surrounding countries such as Kenya of 22.6% and 23% in Tanzania and this difference is assumed to be due to the development of an effective safe chemotherapy regimen in Uganda[8, 12, 35]. However, this is lower than for the developed countries such as UK where survival is estimated at 95% [9]. The poorer survival in LMIC is attributed to a combination of many factors including diagnostic delays resulting in advanced stage of disease at presentation, lack of availability of chemotherapeutic agents, cost of treatment leading to abandonment of care and limited access to surgery and radiotherapy[12, 35].

Age was not found to be a predictor in our study as it is in many studies, however studies in India and in Singapore have shown that age less than 24 months a significant predictor with these children being able to survive most likely because children who present at a younger age may have tumours diagnosed at earlier stages of the disease [23, 36].

Our study showed that sex had significant influence on survival (RR 1.4) with females having a 1.4-fold chance of survival compared to males. Though most studies have not shown any difference in survival between males and females with RB, many studies have shown that females have a better cancer survival than males [37, 38]. Though environmental and hormonal factors have been implicated in adulthood cancer, genetics have been thought to be the commonest cause for this difference in childhood cancers as evidenced in some studies [39].

Most studies have shown that people with leukocoria have a better survival (RR 1.1) with our study showing that these people are almost 1.1 times more likely to be alive at 2 years than those without leukocoria. This is because leukocoria can easily be seen as an abnormal sign and hence patients will present when tumour is less advanced [12, 40]. Most studies from developing countries such as in Kenya have shown that proptosis is associated with a poor survival as it is a sign of more advanced disease, and this was consistent with this study which showed a significant association, however this was not included in final model as it would not achieve convergency.at multivariate analysis[12].

Cataract was a significant predictor at univariate analysis but lost significance at multivariate analysis. Cataract was a significant factor on univariate analysis and is this is in keeping with some studies in India and USA which show that orbital cellulitis, phthisis bulbi, staphyloma, and cataract are clinical predictors of high risk pathology [23, 41].

The rate of survival in patients with ON invasion depends on degree of ON invasion. Survival rates increase as the degree of invasion reduces and this was evidenced at univariate analysis where absent ON invasion, prelaminar ON and intralaminar ON invasion was significant [24]. However, at multivariate analysis, there was statistical significance for only intralaminar ON probably due to fewer numbers.

Scleral invasion has been shown to be an independent factor of survival in most studies however, this study did not provide a risk ratio as there was no one in the alive group [24, 30]. Choroidal invasion was seen to be significant in univariate analysis but could not be included it in the multivariate model because it could not allow for convergence, though mortality is higher in those with massive choroidal invasion.

Survival in patients with anterior segment invasion has been shown to be low, however our analysis couldn't produce risk ratios as there was no one in the exposure group, though mortality associated with these patients was very high.

Our study showed that orbital extension was significantly predictive of survival. Patients without orbital extension being able to survive 7 times better than those with orbital extension. Orbital extension is a major cause of death in children with retinoblastoma in the developing countries with mortalities of up to 100%. The presence of orbital invasion was associated with a 10–27 times higher risk of systemic metastasis as compared to cases without orbital invasion. This is in agreement with studies done in USA and in India [32, 42].

Necrosis was a significant factor at univariate analysis though it lost significance at multivariate analysis. Most studies including ours have not found necrosis to be associated with survival however, a study done in USA showed that patients with extensive necrosis are associated with high risk pathology and mortality [43]. Our study did not show that differentiation is a predictive factor as it is in many other studies, however a study in Jordan has shown that poorly differentiated tumours are associated with more advanced tumor pathology [15]. Growth type has not been associated with survival though a study in Jordan illustrated that the mixed type independently affects survival as it would be found in advanced tumours[44]. Calcification was not shown be a significant factor of survival, nevertheless no studies have been done to see its impact on survival.

Conclusion

Leukocoria and proptosis are the most common clinical signs of Retinoblastoma. The dominant pathologic stage is stage 1 though late presentation (stage 4) is also observed. Survival is still low though generally higher than neighbouring countries. Leukocoria, optic nerve invasion, orbital extension, and gender were the significant factors predictive of survival in patients at Mbarara Regional Referral Hospital. Sensitisation of health workers and community on identification and referral of any child with leukocoria to improve histopathology reporting in order as well as to identify patients at risk is highly recommended.

Author Contributions: Conceptualization, RA, DL and KW.; methodology, RA and AB.; software, RA.; validation, DL and KW; formal analysis, RA.; investigation, RA, AB and RK.; resources, RK.; data curation, RA and RK.; writing—original draft preparation, RA and AB.; writing—review and editing, RA and RK; visualization, RA.; supervision, DL and KW.; project administration, RA. All authors have read and agreed to the publication of this manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the declaration of Helsinki. Ethical review and approval were obtained from the Faculty of Medicine Research Committee (FRC) and Research Ethics Committee of Mbarara University of Science and Technology (MUST-REC Number: 07/06-17).

Informed Consent Statement: Individual patient consent was waived because we reviewed records and obtained archived block eye specimen. There was no real time involvement with the patients.

Data Availability Statement: Data used in this study is available from the corresponding author upon request.

Conflicts of Interest: The authors and funders declare no conflict of interest in this study.

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