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Radiological patterns and predictors of survival among retinoblastoma patients with optic nerve involvement attending the oncology department at KCMC.

Vailet A. Mteta[1,2*], Furahini Godfrey[3,1], Alex Mremi[4], Blandina T. Mmbaga[5], Yotham Gwanika[6], Innocent H.P. Uggh[7], Adnan Sadiq[6]

[1]Kilimanjaro Christian Medical University College, Moshi, Tanzania
[2]Department of Radiology Kilimanjaro Christian Medical Centre, Moshi, Tanzania
[3]Department of ophthalmology Kilimanjaro Christian Medical Centre, Moshi, Tanzania
[4]Department of Pathology Kilimanjaro Christian Medical Centre, Moshi, Tanzania
[5]Department of Clinical Research, Kilimanjaro Clinical Research Institute, Moshi, Tanzania
[6]Department of oncology Kilimanjaro Christian Medical Centre, Moshi, Tanzania

ABSTRACT

Background: Retinoblastoma is the most common pediatric ocular malignancy, yet data on optic nerve involvement (ONI) in resource-limited settings remain scarce.
Objective: To evaluate the clinical and radiological characteristics of pediatric retinoblastoma with ONI and assess survival outcomes.
Methods: This retrospective cohort study included 141 patients diagnosed between January 2018 and January 2023 at Kilimanjaro Christian Medical Centre. ONI was classified anatomically as intraocular, intraorbital, intracanalicular, or intracranial, based on the most posterior extent of involvement. Survival analysis was performed using Cox regression.
Results: Of the 141 patients, ONI was detected in 82 (58.2%): intraocular in 20 (14.2%), intraorbital 9 (6.4%), intracanalicular 25 (17.7%), and intracranial 28 (19.9%). Patients without ONI had the highest survival, whereas intracranial ONI was associated with the poorest outcomes. Cox regression showed that advanced ONI and delayed presentation significantly increased mortality risk, while chemotherapy improved survival.
Conclusion: Classification of ONI based on anatomical extent provides a reproducible framework for assessing disease severity. Delayed presentation and advanced ONI were associated with poorer survival outcomes.

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Retinoblastoma; radiological features; optic nerve involvement; predictors of survival

Introduction

Retinoblastoma is the most common intraocular malignancy in children, typically diagnosed before the age of five. Clinical presentation varies, but leukocoria and strabismus are the most frequent early signs [1–3].

Radiological imaging plays a central role in diagnosis and staging. MRI is the preferred modality for evaluating intraocular tumors and detecting optic nerve involvement (ONI), while CT is used when MRI is unavailable or contraindicated. Histopathological grading remains the gold standard for ONI assessment; however, in resource-limited settings, radiological classification offers a practical alternative [1,2,4].

ONI is a critical prognostic factor, as posterior extension of the tumor along the optic nerve increases the risk of extraocular spread, intracranial involvement, and death. However, most existing studies on ONI and survival outcomes are from high-income countries, where early detection and multimodal therapy are more accessible. Data from sub-Saharan Africa remain scarce, despite the region's high burden of delayed presentation and limited access to advanced care

Contact Vailet A Mteta ✉ va.mteta@gmail.com Kilimanjaro Christian Medical University College, Moshi, Tanzania.

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[2,4,5]. Identifying reliable radiological predictors of survival is therefore essential for guiding treatment decisions and improving outcomes, particularly in regions where delayed presentation is common.

This study aimed to describe radiological patterns of ONI and evaluate predictors of survival among retinoblastoma patients treated at Kilimanjaro Christian Medical Centre (KCMC), Tanzania. By focusing on radiological assessment, we sought to provide reproducible prognostic insights in a resource-limited setting and highlight opportunities for earlier detection and improved outcomes.

Materials and Methods

Study design and period

This was a retrospective cohort study conducted at Kilimanjaro Christian Medical Centre (KCMC), Moshi, Tanzania, between January 2018 and January 2023.

Study population and eligibility criteria

Inclusion criteria: Patients with histologically confirmed retinoblastoma and available MRI and/or CT imaging data.

Exclusion criteria: Patients with incomplete or missing medical records.

Ethical considerations and consent for publication

Ethical approval for this study was obtained from the Kilimanjaro Christian Medical Centre Research Ethics Committee in May 2023, reference number No. PG 54/2023.

A formal waiver of consent was granted for the retrospective review of patient records, as the study involved the analysis of existing data without direct patient contact.

For patients contacted during follow-up, verbal consent was obtained by telephone solely for the purpose of clarifying survival status. This verbal consent did not extend to the retrospective data analysis.

Consent for publication was explicitly addressed, and no identifiable patient data are included in this manuscript.

Patient flow

A total of 146 patients were identified. One patient abandoned treatment, and four were lost to follow-up, leaving 141 patients with complete imaging and follow-up data included in the final analysis.

Data collection

Eligible patients were identified from the oncology registry system. Medical records were reviewed to extract demographic information, clinical presentation, radiological findings, treatment modalities, and survival outcomes. All data were anonymized before analysis to ensure confidentiality.

Handling of missing data and follow-up

Patients with incomplete records were excluded. For survival status, telephone follow-up was conducted when necessary. Patients who were alive at last contact were censored. Median follow-up duration was 24 months (range 3–84).

Imaging protocols

MRI was the primary modality; CT was used when MRI was unavailable or contraindicated. MRI was performed in 112 patients (79.4%), CT in 25 patients (17.7%), and 4 patients (2.8%) underwent both modalities.

MRI (1.5 Tesla, KCMC radiology department)

Patients underwent orbital and brain MRI using axial and coronal T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. Diffusion-weighted imaging (DWI) was performed to assess tumor cellularity. A susceptibility-weighted sequence (SWI) was used to detect hemorrhage and calcifications. Post-contrast T1-weighted sequences were obtained after intravenous gadolinium administration to evaluate optic nerve enhancement and intracranial extension. Slice thickness ranged from 3 to 5 mm, with high-resolution orbital views.

CT (Siemens SOMATOM definition AS, 128-slice)

CT was performed when MRI was unavailable or contraindicated. Thin-section axial and coronal images were acquired with a slice thickness of 1–2 mm. Non-contrast CT was used to detect intraocular calcification, while contrast-enhanced CT was performed to assess optic nerve and orbital extension.

Radiological assessment

Optic nerve involvement (ONI) was categorized anatomically into intraocular, intraorbital, intracanalicular, and intracranial groups. ONI was classified based on the most posterior extent of tumor

involvement. Intraocular involvement was defined as a tumor confined within the globe. Intraorbital involvement was defined by extension into orbital soft tissues beyond the sclera. Intracanalicular involvement was identified when the tumor extended into the optic canal, while intracranial involvement was defined by extension beyond the canal into the cranial cavity. Classification was based on MRI or CT findings. Patients were assigned to a single ONI category based on the most posterior extent of involvement; categories were mutually exclusive. All imaging studies were reviewed by two board-certified radiologists. Images were interpreted independently, and discrepancies were resolved through consensus discussion. Interobserver agreement was assessed qualitatively, and concordance was >90% for ONI classification categories. Histopathological confirmation of ONI was available in a subset of patients who underwent enucleation. In these cases, radiological findings were compared with pathology reports, which confirmed ONI in 85% of cases. However, due to limited pathology resources, radiological classification was the primary method of ONI assessment.

Treatment modalities

Treatment strategies included chemotherapy, chemoradiotherapy, radiotherapy, cryotherapy, enucleation, and palliation. Patients could receive more than one modality; therefore, percentages are overlapping. Post-management ocular outcomes (e.g., phthisis bulbi and tumor in the anterior chamber) were also documented.

Outcome measures

The primary outcome was two-year survival, measured from the date of diagnosis to death or the last contact. Patients alive at last contact were censored. Secondary outcomes included associations between ONI categories, clinical features, and survival.

Statistical analysis

Data were analyzed using SPSS version 23. Descriptive statistics summarized demographic and clinical characteristics. Kaplan–Meier survival curves were generated for ONI categories, with differences tested using the log-rank test. Patients alive at last contact were censored at their last known follow-update. The proportional hazards assumption was verified graphically and statistically before applying the Cox proportional hazards regression model, which estimated hazard ratios (HRs) and 95% confidence intervals (CIs) with death as the modeled event. Statistical significance was set at $p < 0.05$.

Results

Background characteristics of study participants

Of the 141 patients, 83 (58.9%) were male and 58 (41.1%) female. The mean age at onset was 11.5 months (±8.7). Most patients (81.6%) developed the disease before 12 months, but 60.3% presented to the hospital after 12 months. Clinical features included leukocoria (87.2%), proptosis (46.1%), and eye pain (20.6%). Unilateral disease was more common (68.1%) than bilateral (29.8%). The majority presented at the advanced stage (IIRC Group E, 36.2 %). Table 1 summarizes the sociodemographic and clinical characteristics of the study participants ($N = 141$).

Table 1. Sociodemographic and clinical characteristics of the participants ($N = 141$).

Variable	*n*	%
Sex		
Male	83	58.9
Female	58	41.1
Age at onset in months		
Mean (±SD) 11.5 (±8.7)		
≤12	115	81.6
>12	26	18.4
Survival duration with disease in months		
Mean (±SD) 24.6 (±9.9)		
≤12	35	24.8

Continued

Variable	*n*	%
13–24	70	49.6
>24	36	25.6
Age at presentation in months		
Median (Range) 14.0 (3–84)		
≤12	56	39.7
>12	85	60.3
Residence		
Kilimanjaro	26	18.4
Outside-Kilimanjaro	115	81.6
Family history of RB		
Yes	16	11.3
No	125	88.7
Clinical presentation		
Leukocoria	123	87.2
Proptosis	65	46.1
Eye pain	29	20.6
Different colored eyes	5	3.5
Others (Enlarged pupil, Swollen eye, Strabismus)	3	2.1
Tumor laterality		
Unilateral	96	68.1
Bilateral	42	29.8
Trilateral	3	2.1
IIRC*		
Group A	7	5
Group B	22	15.6
Group C	30	21.3
Group D	31	22
Group E	51	36.1

**Tumor staging and classification: International intraocular retinoblastoma classification*
Percentages were calculated using N = 141 unless otherwise stated.

Radiological patterns of optic nerve involvement in retinoblastoma patients

A mass with calcification was observed in 131 patients (92.9%). Extraocular disease was present in 68 (48.2%). Optic nerve involvement (ONI) was detected in 82 patients (58.2%). Radiological features of retinoblastoma patients are shown in Figure 1. ONI categories were mutually exclusive and were based on the most posterior extent of involvement: intraocular (20, 14.2%), intraorbital (9, 6.4%), intracanalicular (25, 17.7%), and intracranial (28, 19.9%). Radiological features such as mass, calcification, and extraocular disease were overlapping and not mutually exclusive (Figs. 2–3).

Optic nerve involvement (ONI) distribution

Figure 3 displays evidence of optic nerve involvement (ONI) in patients. Of the 141 patients, 82 (58.2%) had ONI, while 59 (41.8%) did not.

Figure 4 outlines the distribution of ONI. 82 patients (58.2%) had ONI, while 59 (41.8%) did not. Categories were intraocular 20 (14.2%), intraorbital 9 (6.4%), intracanalicular 25 (17.7%), intracranial 28 (19.9%)

Survival rates of retinoblastoma patients with different degrees of optic nerve involvement

Figure 5 depicts Kaplan–Meier survival estimates by optic nerve involvement (ONI), showing that children with intracranial ONI had nearly three times

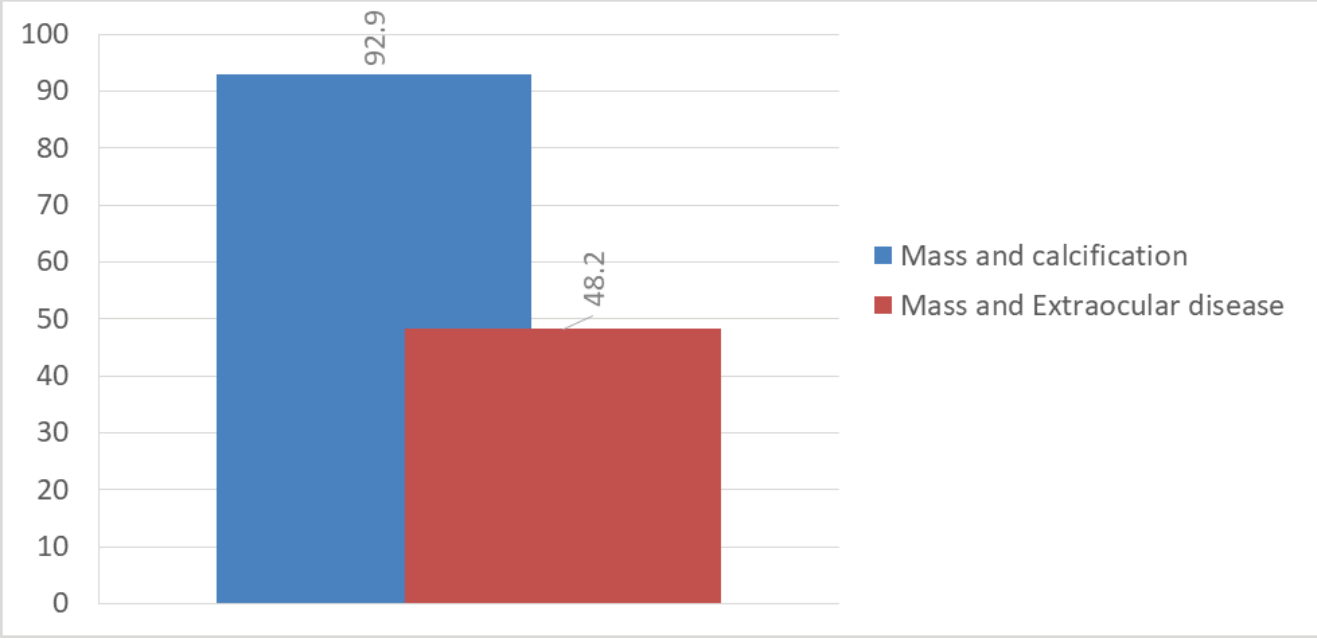


Figure 1. Radiological features (*N* = 141).

the risk of death compared with those without ONI (HR = 2.87, 95% CI: 1.92–4.29). Delayed presentation (>12 months) increased the risk of death (AHR = 1.54, 95% CI: 1.20–2.10). Chemotherapy was protective (AHR = 0.30, 95% CI: 0.14–0.96).

Treatment modalities were overlapping, as many patients received more than one form of therapy. For example, patients who underwent enucleation also received adjuvant chemotherapy, and some additionally received radiotherapy. Therefore, the distribution of treatment modalities should not be interpreted as mutually exclusive categories. Treatment strategies included chemotherapy (80, 56.7%), chemoradiotherapy (46, 32.6%), radiotherapy (15, 10.6%), cryotherapy (4, 2.8%), enucleation (113, 80.1%), and palliation (25, 17.7%). Patients could receive more than one modality; therefore, percentages are overlapping (Fig. 6).

Post-management findings

Post-treatment pathological findings were analyzed across the entire cohort (*N* = 141), as all patients underwent enucleation. These included tumor in the anterior chamber (117, 83%), tumor touching the lens (28, 19.9%), phthisis bulbi (24, 17%), and opaque media due to vitreous hemorrhage (4, 2.8%) (Fig. 7).

Cox proportional hazards models of survival among retinoblastoma patients

Survival analysis using Cox regression demonstrated that advanced optic nerve involvement was associated with an increased risk of mortality. Patients with intracranial ONI had the highest risk (HR = 2.87, 95% CI: 1.92–4.29). Intracanalicular involvement was also associated with poorer survival (HR = 2.13, 95% CI: 1.45–3.12). Delayed presentation (>12 months) was associated with increased risk of death (AHR = 1.54, 95% CI: 1.20–2.10), and the use of adjuvant chemotherapy was associated with improved survival (HR = 0.72, 95% CI: 0.51–0.98), consistent with the values presented in Table 2. Hazard ratios above 1 indicate increased risk, while values below 1 indicate protective associations. Wide or infinite confidence intervals in some subgroups (e.g., unilateral versus bilateral disease, palliation) were acknowledged as reflecting small sample sizes.

Discussion

This study assessed radiological patterns and predictors of survival among retinoblastoma patients with ONI at KCMC. Intraocular mass with calcification was the most frequent radiological feature observed in over 90% of patients. ONI was present in more than half of the cohort, with intracranial extension representing the most adverse category.

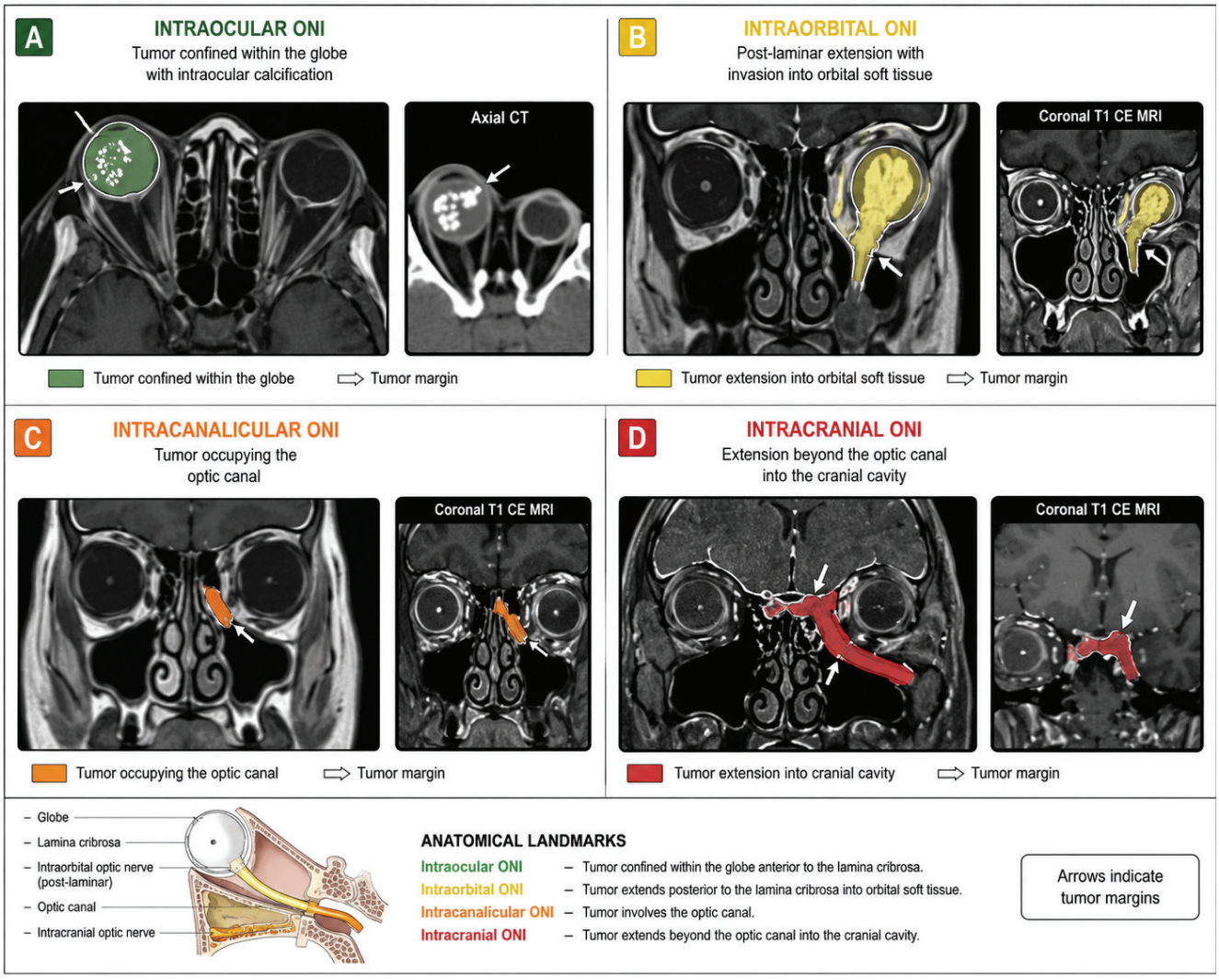


Figure 2. Representative schematic radiological illustration of optic nerve involvement (ONI) in retinoblastoma. (A) Intraocular ONI demonstrating a tumor confined within the globe, with associated intraocular calcification and no extension beyond the lamina cribrosa. (B) Intraorbital ONI demonstrates post-laminar optic nerve invasion with extension into the orbital soft tissues beyond the globe. (C) Intracanalicular ONI demonstrating tumor extension into and occupying of the optic canal. (D) Intracranial ONI demonstrates tumor progression beyond the optic canal into the intracranial compartment. White arrows indicate the tumor margins and the most posterior extent of optic nerve involvement. The lower schematic illustrates the anatomical relationship among the globe, lamina cribrosa, intraorbital optic nerve, optic canal, and intracranial optic nerve corresponding to the four stages of disease progression. This schematic was created for illustrative purposes and does not represent images from an individual patient.

Consistent with prior literature, intraocular mass with calcification was the most frequent radiological feature observed in over 90% of patients. Optic nerve involvement (ONI) was present in more than half of the cohort, with intracranial extension representing the most adverse category. These findings reinforce the central role of MRI in detecting ONI and staging disease in resource-limited settings. They are consistent with a study by Razek et al. which showed an enhancing mass on MRI and calcific foci common in retinoblastoma [1].

Another study done by Jansen et al. showed a mass with a blooming artifact on SWI, suggestive of calcifications with the addition of post-laminar thickening of the optic nerve signifying optic nerve involvement [6]. While histopathology remains the gold standard for ONI assessment, reliance on radiology in this study reflects the realities of resource-limited settings. Radiological classification provided timely and reproducible prognostic information, although misclassification bias cannot be excluded. Future studies should integrate

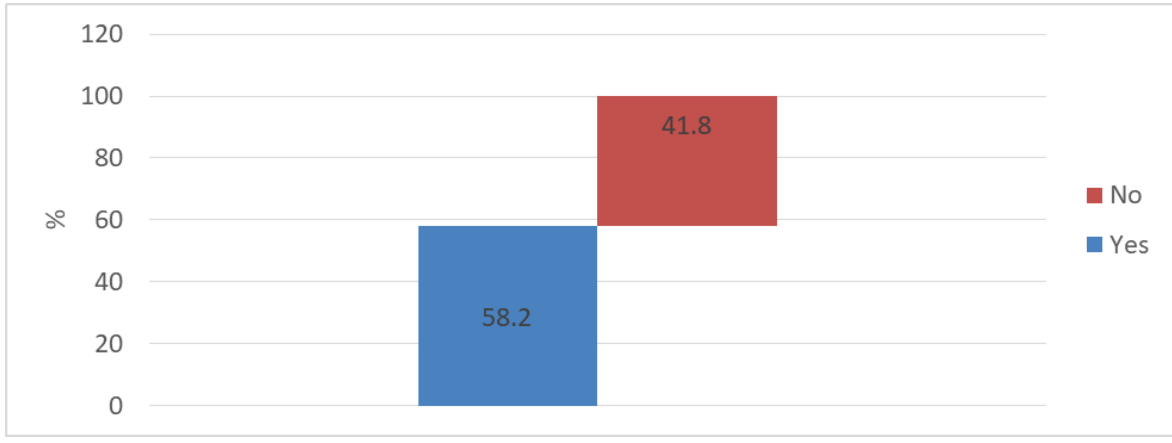


Figure 3. Evidence of optic nerve involvement (N = 141).

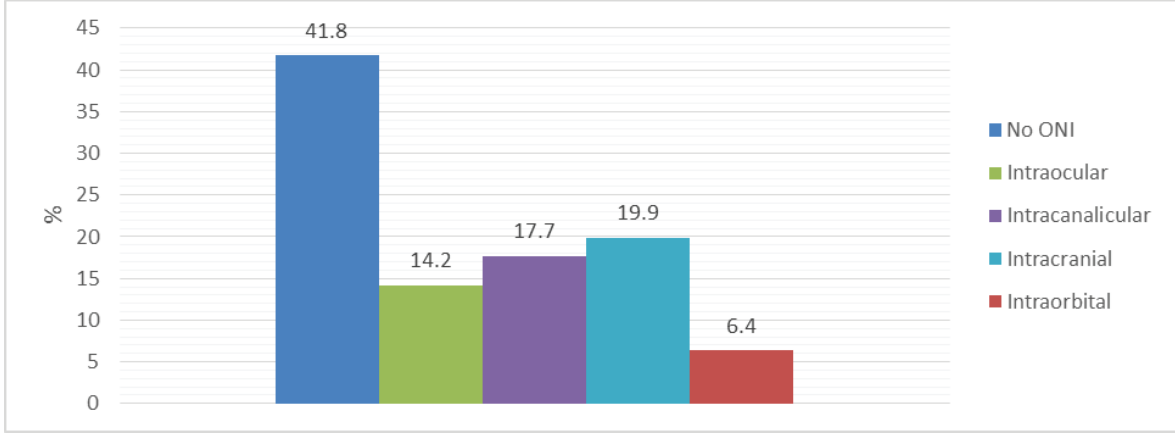


Figure 4. Optic nerve involvement (ONI) distribution (N = 141).

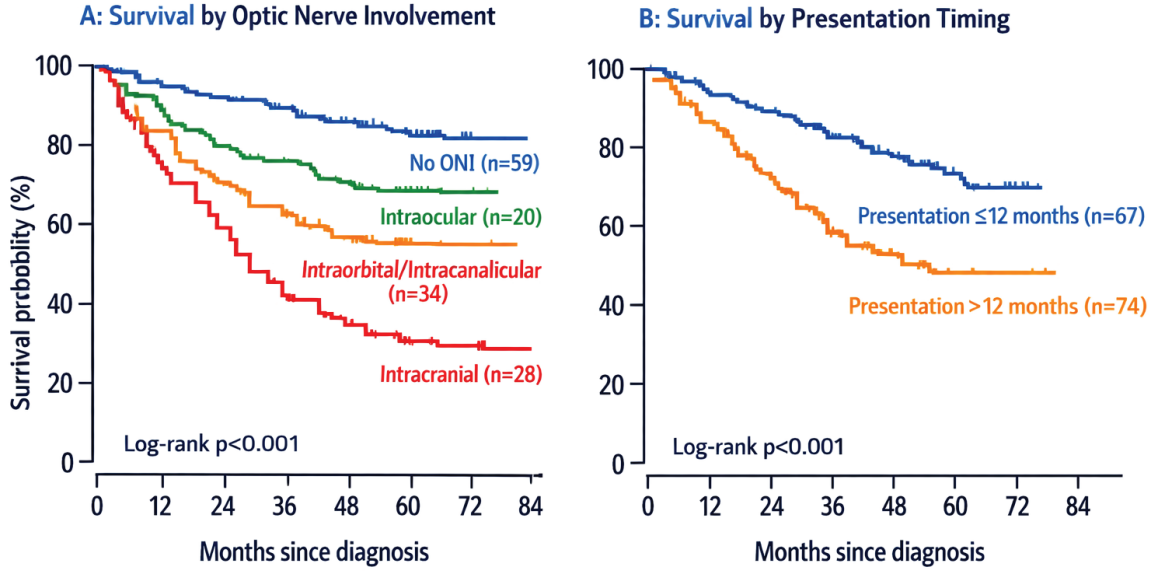


Figure 5. Kaplan–Meier survival estimates of the patients with varying degrees of ONI, showing survival by optic nerve involvement (A) and survival by presentation timing (B). Percentages were calculated using N = 141 unless otherwise stated. Log-rank $p < 0.001$.

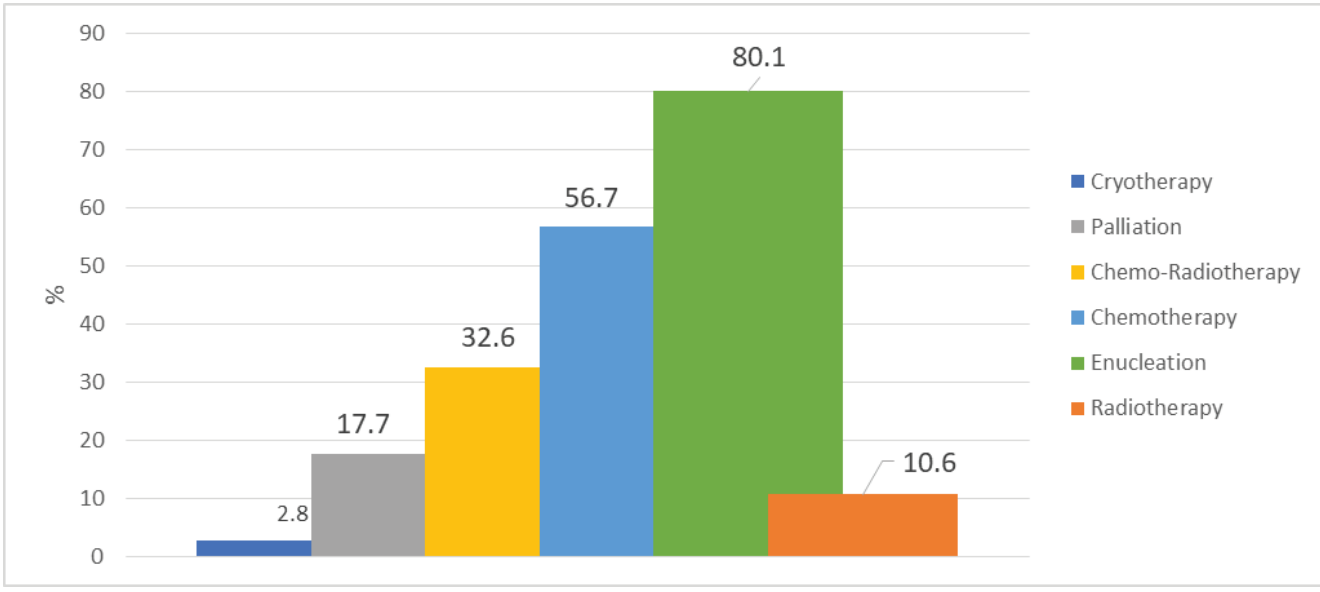


Figure 6. Treatment modalities among the study cohort (N = 141). Categories are overlapping; patients may have received more than one treatment modality.

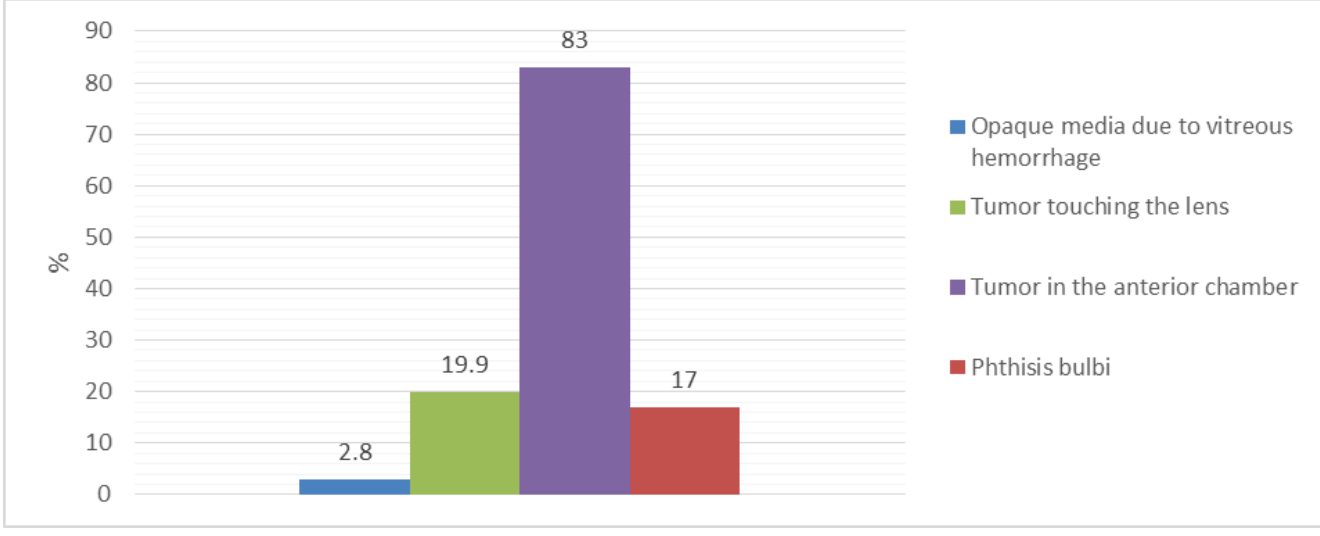


Figure 7. Post-management findings (N=141).

systematic histopathological correlation to validate radiological predictors.

The multivariable Cox proportional hazards model identified several independent predictors of survival. An increasing extent of optic nerve involvement was consistently associated with worse survival. Compared with patients without ONI, those with intraorbital (AHR = 1.23, p = 0.03), intraocular (AHR = 1.47, p = 0.02), intracanalicular (AHR = 1.54, p < 0.001), and intracranial involvement (AHR = 1.69, p < 0.001) demonstrated progressively higher hazards of mortality. Our findings demonstrate that advanced ONI is associated with poorer survival outcomes. Patients presenting with intracranial extension had the highest risk of mortality, while those with intraorbital or intracanalicular involvement also showed reduced survival compared with patients with disease confined to the globe.

Age at presentation emerged as another significant determinant. Children presenting after 12 months had a higher risk of mortality (AHR = 1.54, p = 0.02) than those presenting earlier. Delayed presentation was linked to more advanced disease at diagnosis, suggesting that time to presentation may influence the stage at which patients are first evaluated.

Table 2. Cox proportional hazards models of survival among retinoblastoma patients

Variable	Survival HR (95% CI)	*p*-value	*AHR (95% CI)	*p*-value
ONI				
No ONI	Ref		Ref	
Intraorbital	1.20(1.02, 1.78)	0.002	1.23(1.05, 1.89)	0.03
Intraocular	1.92 (1.34, 3.46)	<0.001	1.47 (1.14, 2.45)	0.02
Intracanalicular	1.43 (1.18, 2.05)	0.002	1.54 (1.21, 2.21)	<0.001
Intracranial	2.71 (1.51, 3.76)	0.004	1.69 (1.22, 2.43)	<0.001
Age at presentation				
Up to 12 months	Ref		Ref	
More than 12 months	1.34 (1.05, 1.72)	<0.001	1.54 (1.20, 2.10)	0.02
Sex				
Male	Ref		Ref	
Female	1.32 (0.87, 2.02)	0.197	1.22 (0.67, 1.99)	0.123
Residence				
Kilimanjaro	Ref			
Outside Kilimanjaro	0.84 (0.50, 1.42)	0.525		
Leukocoria				
No	Ref		Ref	
Yes	2.56 (1.23, 5.35)	0.012	3.18 (1.75, 5.34)	0.023
Proptosis				
No	Ref		Ref	
Yes	0.33 (0.21, 0.53)	<0.001	1.09 (0.56, 2.12)	0.80
Unilateral				
No	Ref			
Yes	4.25 (2.30, 7.87)	<0.001		
Bilateral				
No	Ref		Ref	
Yes	1.25 (1.05, 1.80)	<0.001	1.26 (1.08, 1.96)	0.003
Evidence of optic nerve involvement				
No	Ref		Ref	
Yes	4.45 (2.78, 7.11)	<0.001	5.2 (2.23, 9.45)	<0.001
Chemotherapy				
No	Ref		Ref	
Yes	0.27 (0.03, 0.69)	0.021	0.30 (0.14, 0.96)	0.011
Palliation				
No	Ref		Ref	
Yes	0.30 (0.06, 0.95)	0.005	0.28 (0.11, 0.73)	<0.001
IIRC				
Grade A	Ref		Ref	
Grade B	1.38 (1.11, 2.05)	0.019	1.39 (1.10, 1.58)	0.019
Grade C	1.30 (1.05, 1.97)	0.005	1.51 (1.11, 2.34)	0.038
Grade D	1.32 (1.09, 1.99)	<0.001	1.50 (1.10, 2.23)	0.039
Grade E	1.46 (1.06, 2.12)	<0.001	1.61 (1.05, 2.04)	0.022
Calcification				
No	Ref			
Yes	1.21 (0.71, 2.05)	0.485		
Extraocular disease				
No	Ref			
Yes	0.99 (0.64, 1.52)	0.967		
Enucleation				
No	Ref			
Yes	1.44 (0.94, 2.20)	0.221		

*AHR - Adjusted Hazard Ratio

While this pattern is consistent with progression over time, the retrospective design does not allow us to infer causality. Similar observations have been reported in regional studies, where delayed healthcare access contributes to advanced disease at diagnosis.

Leukocoria, while traditionally considered an early warning sign, was paradoxically associated with an increased mortality risk in this cohort, likely reflecting late recognition despite symptom presence. Regarding tumor laterality, bilateral disease independently predicted poorer survival (AHR = 1.26, $p = 0.003$), indicating a more aggressive or genetically driven disease phenotype. Unilateral disease was significant in the unadjusted analysis but did not retain significance after adjustment, suggesting confounding by other disease severity markers.

In contrast, sex, residence, calcification, extraocular disease, and enucleation were not independently associated with survival after adjustment, suggesting that tumor biology and extent of spread outweigh these factors in determining prognosis. Notably, proptosis, although significant in unadjusted analysis, lost significance in the multivariable model (AHR = 1.09, $p = 0.80$), indicating confounding by disease stage. Our findings align with previous studies that reported delayed presentation as a major contributor to poor survival in sub-Saharan Africa [7, 8].

Our findings are consistent with recent African and Asian studies. Reports from Nigeria and Kenya highlight delayed presentation as a major contributor to advanced optic nerve involvement (ONI) and poor survival, with intracranial extension strongly associated with mortality [9,10]. Similarly, a multicenter study from India demonstrated that children presenting after 12 months of age had significantly worse outcomes, particularly when ONI extended intracranially. A systematic review in South Asia further confirmed wide disparities in survival compared with high-income countries, attributing poor outcomes to late diagnosis and limited access to multimodal therapy. These parallels underscore that ONI is a reproducible prognostic marker across diverse low-resource settings, reinforcing the urgent need for earlier detection and timely intervention [11,12].

Survival analysis demonstrated clear stratification based on the degree of ONI. Patients without ONI had the most favorable outcomes, while survival progressively declined with increasing anatomical extension. Intracranial involvement was associated with the worst prognosis. This pattern reflects the biological progression of retinoblastoma from a localized intraocular tumor to a disseminated disease involving the central nervous system. Once the tumor extends beyond the lamina cribrosa into the optic nerve and toward intracranial structures, the risk of metastasis and treatment failure increases substantially.

The overall two-year survival rate was 49.6%, substantially lower than rates reported in high-income countries, where early detection and multimodal therapy are more accessible. Patients without ONI maintained high survival probabilities, while those with intracranial ONI experienced a rapid decline within 20 months. These results underscore ONI as a critical prognostic marker and highlight the urgent need for interventions that promote earlier presentation.

These findings are consistent with earlier reports [13], which demonstrated that advanced optic nerve invasion is a critical determinant of poor survival. The similarity likely reflects comparable delays in diagnosis and healthcare access across sub-Saharan African settings.

Study strengths and limitations

This multidisciplinary study integrated radiological, pathological, and clinical data from patients, providing ample data for research analysis. The inclusion of all patients with retinoblastoma in a hospital that has a large catchment area provides enough data on the state of well-being of these individuals. This will help in policy-making and the betterment of healthcare systems. This study had several limitations. First, as a retrospective cohort, it relied on existing medical records, which occasionally contained incomplete data. Second, ONI was classified radiologically rather than pathologically, which may introduce misclassification bias. Third, some hazard ratio estimates were unstable, with wide confidence intervals, reflecting small subgroup sizes due to the small sample size. Fourth, inconsistencies in denominators across tables and figures were corrected, but residual data limitations may affect precision. Finally, the single-center design limits generalizability, and survival estimates may not fully represent outcomes in other regions of Tanzania or sub-Saharan Africa.

Conclusion

Overall, this study demonstrates that survival in retinoblastoma is primarily driven by the extent of optic nerve involvement, delayed presentation, bilateral disease, and tumor stage. Chemotherapy use was associated with improved survival in our cohort. This observation highlights the potential benefit of systemic therapy, although the study design precludes definitive conclusions about treatment efficacy. The findings emphasize the urgent need for early detection strategies, improved public awareness, and timely referral systems to reduce advanced disease presentation and improve survival outcomes.

Recommendations

A larger prospective cohort study should be conducted to allow greater patient enrollment and more effective follow-up over a longer period. The follow-up study should be conducted in a multicenter setting where there is availability of all treatment options, to avoid patient loss to follow-up and increase the generalizability of the findings.

Public health education campaigns should be strengthened to ensure that patients are brought to the hospital in a timely manner without delay to avoid extraocular disease on presentation.

There should be reinforcement of the cancer registry database for good data recording to avoid missing data.

Acknowledgment

We acknowledge the KCMC for the permission to conduct this study; it would not be easy to use these data without the permission.

Conflict of interest

The author declares no competing interests.

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Author contributions

VAM: Initiated and developed the core concept of the study, conducted the formal data analysis and interpretation, drafted the initial manuscript, and reviewed the manuscript. FG, BTM, YG, and AS provided oversight and guidance throughout the research project, reviewed the manuscript, significantly contributed to assuring its factual correctness, and overall quality of the manuscript.

Availability of ss and materials

The anonymized datasets used and analyzed during the current study are available from the corresponding author upon reasonable request, subject to institutional approval and ethical restrictions.

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