ACCSCIENCE PUBLISHING

Tumor Discovery

ORIGINAL RESEARCH ARTICLE

A 12-year analysis of presentation, histopathological features, high-risk factors, and survival in retinoblastoma patients undergoing primary enucleation at a tertiary eye care center in Bangladesh

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Abstract

Retinoblastoma is the most common primary intraocular malignancy in children, with approximately 100% survival rates in higher-income countries. The outcomes of retinoblastoma depend on factors such as disease presentation, treatment access, histopathological high-risk factors, and national income level. This retrospective study analyzed 12-year data (2012 – 2023), including presentation, histopathological features, histopathological high-risk factors, and survival outcomes, of 78 retinoblastoma patients who had undergone primary enucleation at a tertiary eye center in Bangladesh. The overall median age was 33 months, with a slightly older median age among females (35 months) and a mild male predominance. The mean symptom duration was 5.68 ± 3.56 months, with earlier presentation in male patients. The most common presenting sign was leukocoria (70.5%), followed by red eye (20.5%). Combined endophytic and exophytic tumor growth (36%) and poor differentiation (44.9%) were prevalent. High-risk factors were present in 84.6% of patients, with massive choroidal invasion (41%) and retrolaminar optic nerve invasion (38.5%) being the most frequent. Approximately 57.7% of patients solely underwent enucleation, and 27% of children died, yielding an overall survival rate of 69.23%. The findings of this study suggest that multiple high-risk factors are often present in advanced tumors, posing challenges in management and increasing the risk for metastasis. Efforts to improve outcomes should focus on raising awareness, promoting early presentation, enhancing histopathological reporting, and developing specialized human resources.

Keywords: Primary enucleation; Delayed presentation; Advanced tumor; Histopathological high-risk factor; Massive choroidal invasion; Retrolaminar invasion

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1. Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy in children, accounting for approximately 11% of cancers diagnosed in the first year of life globally.[1]

The incidence rate is 1 in 16,000 – 18,000 live births,[1] with approximately 9,000 new cases added each year worldwide.[2] In the United States, the number of new cases detected annually has remained steady at 200 – 300 over the past 40 years. In contrast, higher incidence rates have been reported in Europe.[3,4] The median age at diagnosis is 18 months globally, although it is 14 months in high-income countries and 30.5 months in low-income countries.[5] In unilateral retinoblastoma, the median age of diagnosis was 35 and 19.7 months in low- and high-income countries, respectively, where's 22.9 and 8.1 months, respectively, in bilateral cases.[5]

RB presentation and outcomes vary by age at diagnosis and national income level. Leukocoria is the most common presenting sign, followed by strabismus; these early presentations are more typical in high-income countries. In contrast, advanced presentations, such as proptosis, orbital cellulitis, and red eye, are more frequent in low-income countries.[5]

The tumor is typically confined to the globe at early stages, supporting both ocular salvage and higher survival rates. Treatment modalities include enucleation, chemotherapy (various routes), radiotherapy, and local therapy. A multidisciplinary team approach, involving ophthalmologists (ocular oncologists, retina specialists, pediatric ophthalmologists, and/or oculoplastic surgeons), pediatric oncologists, radiation oncologists, anesthesiologists, histopathologists, ocularists, counselors, and social support groups, is the current standard for RB treatment. In early cases, treatment may be limited to local therapy and chemotherapy. However, in delayed cases, treatment options include enucleation or neoadjuvant chemotherapy, followed by secondary enucleation of the worse eye, with or without radiotherapy. Some patients may require adjuvant chemotherapy with or without radiotherapy following primary enucleation. For all enucleated cases, histopathology plays a crucial role in guiding the management plan, making histopathological examination of enucleated eyes mandatory. The presence of histopathological high-risk factors (HRFs) can provide early indications of local recurrence, distant metastases, tumor progression, and overall prognosis. Key HRFs associated with metastases include invasion of the choroid, sclera, extrascleral space, and optic nerve (beyond the lamina cribrosa, total optic nerve, or cut end).[6] Expert histopathologists are thus integral to the multidisciplinary management team for RB.

In high-income and upper-middle–income countries, the 3-year survival rates are approximately 99% and 91%, respectively, with high ocular salvage rates and fewer reported HRFs.[7,8] In contrast, lower-middle-income and low-income countries report survival rates of 77% and 40%, respectively, with significantly higher rates of mortality and metastasis.[7] Most of these low- and lower-middle-income countries are underdeveloped or developing countries in Asia and Africa, where delayed presentation complicates the management of RB cases. Factors such as delayed presentation, inadequate treatment facilities, lack of trained ocular oncologists and histopathologists, and financial challenges contribute to higher child mortality rates in these regions.

This study aimed to describe the pattern of HRFs following primary enucleation in patients with RB as well as the presentation, histopathological features, and survival outcomes of these patients in a lower-middle-income country in Southeast Asia.

2. Methods

2.1. Study design

This hospital-based retrospective study analyzed patients with RB who had undergone primary enucleation. Data were collected from the Orbit, Oculoplasty, and Ocular Oncology Department of Chittagong Eye Infirmary, a tertiary eye care and retinoblastoma center in Bangladesh. Data from January 2012 to December 2023 were included, covering a 12-year period. A total of 96 children with RB who had undergone primary enucleation were classified as Groups D and E. Among these, 78 patients were included in the study.

2.2. Tumor grading, staging, and HRFs

Tumors were classified according to the International Intraocular Retinoblastoma Classification (IIRC) for intraocular tumors and the International Retinoblastoma Staging System (IRSS) for extraocular tumors based on data obtained from medical records, evaluation under anesthesia (EUA), imaging, and histopathology reports.[9,10] The IIRC categorizes tumors as follows:

- Group A: Tumor ≤3 mm, ≥3 mm from the fovea, and ≥1.5 mm from the optic disc, with no seeding.
- Group B: Tumor of any size or location (except Group A criteria), without vitreous or subretinal seeding, and with subretinal fluid ≤5 mm from the tumor margin.
- Group C: Discrete tumor of any size or site with focal vitreous or subretinal seeding and subretinal fluid up to one quadrant.
- Group D: Diffuse vitreous or subretinal seeding and/or extensive endophytic (tumor spread toward vitreous cavity) or exophytic disease (subretinal tumor spread), with seeding exceeding Group C criteria and retinal detachment of more than one quadrant.

- Group E: Massive tumor causing anatomical or functional eye destruction, with neovascular glaucoma, intraocular tumor (Figure 1), aseptic orbital cellulitis, tumor touching the lens, tumor anterior to the anterior vitreous face, diffuse infiltrating tumor, and phthisis or pre-phthisis.

The IRSS categorizes patients with RB into five stages (Stages 0 – IV). Stage 0 includes patients treated conservatively, whereas Stage I includes cases with enucleated eyes in which resection is histologically complete. Stage II indicates a microscopic residual tumor in an enucleated eye. Stage III includes regional extension, subdivided into overt orbital disease and pre-auricular or cervical lymph node involvement. Stage IV involves distant metastatic disease and is further divided into two subgroups: (a) Hematogenous metastasis, with a single lesion or multiple lesions, and (b) central nervous system (CNS) extension, with pre-chiasmatic lesions, CNS mass, or leptomeningeal disease.

Data were collected about age, sex, laterality of the tumor, presenting symptoms, duration of symptoms, tumor grading and staging, tumor growth pattern, tumor differentiation, histopathological HRFs, adjuvant treatments received, follow-up period, and survival. Of the 96 patients, data from 78 patients were completed and included in the study. Patients who had undergone secondary enucleation or had incomplete data were excluded from the study.

The criteria for histopathological HRFs were selected based on various global studies conducted to identify and evaluate HRFs, including anterior chamber, iris, trabecular meshwork, Schlemm's canal, ciliary body, choroid (massive, defined as >3 mm choroidal invasion in thickness or width),

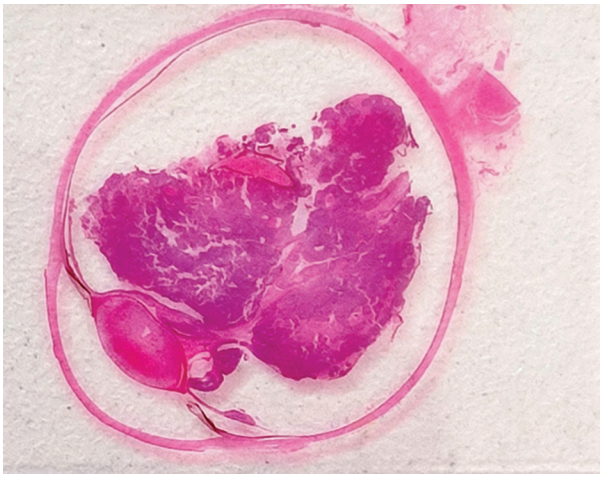


Figure 1. Cross-sectional view of the eyeball through pupil-optic nerve section, showing intraocular retinoblastoma stained with eosin and hematoxylin (H&E) stain, occupying >50% of the globe

sclera, extraocular structures, and retrolaminar optic nerve (including the cut end).[11,12] Tumor differentiation was classified according to rosette formation into well-differentiated (presence of Homer–Wright, Flexner–Wintersteiner, and/or fleurettes), moderately differentiated (presence of Homer–Wright and/or Flexner–Wintersteiner rosettes), poorly differentiated (presence of only Homer–Wright rosettes), and undifferentiated (absence of rosettes/fleurettes).[13]

This retrospective study posed no risk to individual patient identification; therefore, institutional review board (IRB) approval was obtained. The study was approved by the local IRB and conducted in accordance with the principles of the 2013 Declaration of Helsinki.

2.3. Statistical analysis

Statistical analyses were conducted using SPSS 16, with a $P < 0.05$ considered statistically significant. Differences between the male and female symptom duration were analyzed using an independent t-test. Survival rates were calculated using Kaplan–Meier survival analysis.

3. Results

3.1. Demographic profile

The mean age of the patients was 34.56 ± 19.90 months, ranging from 3 months to 90 months. Males had a mean age of 35.90 ± 20.95 months, whereas females had a mean age of 32.91 ± 19.68 months. The overall median age was 33 months (30 months for males and 35 months for females). The lowest and highest presenting ages in males were 3 months and 90 months, respectively, whereas those in females were 4 months and 84 months, respectively. Approximately 62% of the children were older than 24 months, with 31% aged 13–24 months and 8% being younger than 12 months. The most frequent presenting age was 24 months.

Male patients accounted for 55.1% (n = 43) of the included patients, whereas females accounted for 44.9% (n = 35) of the total patients, yielding a male-to-female ratio of 1.4:1 (Table 1). Approximately 90% of cases were unilateral RB. Among bilaterally presenting cases (10.3%, n = 8), only one child underwent bilateral enucleation (1.3%). Left-eye involvement was more common (53.6%). Only 2.6% (n = 2) had a family history of RB, presenting as unilateral cases.

3.2. Lag time with clinical presentation

The mean duration from symptom onset to diagnosis was 5.89 ± 4.30 months (5.68 ± 3.56 months for males and 5.94 ± 5.09 months for females), with a p-value of 0.9, indicating no statistical significance (Table 2). Symptom durations

Table 1. Demographic profile of patients (*n*=78)

Characteristics	Number of patients (n, %)
Age	Months
Median	33
Mean	34.56±19.90
Range	3–90
Male median age	30
Male mean age	35.90±20.95
Female median age	35
Female mean age	32.91±19.68
Presentation (months)	Number
0 – 12	06 (7.69%)
13 – 24	24 (30.77%)
>24	48 (61.54%)
Most frequent presenting age	24 months
Gender	
Male	43 (55.1%)
Female	35 (44.9%)
Laterality of presentation (*n*=78)	
Unilateral	70 (89.7%)
Bilateral	08 (10.25%)
Enucleation (*n*=78, eye=79)	
Right	36 (46.2%)
Left	41 (52.6%)
Both	01 (1.3%)
Positive family history	
Yes	02 (2.6%)
No	76 (97.4%)

Table 2. Presentation of the patients

Clinical feature[a]	Number
Leukocoria	55 (70.5%)
Red eye	16 (20.5%)
Squint	10 (12.8%)
Proptosis	05 (6.4%)
Painful blind eye	03 (3.8%)
Decreased vision	03 (3.8%)
Phthisis bulbi	01 (1.3%)
Duration of the symptom	**Months**
Range of duration	0.5 – 24
Mean	5.89±4.30
Mean duration for males	5.68±3.56
Mean duration for females	5.94±5.09
P value	0.966
IIRC underwent enucleation (*n*=78; eye=79)	
Group D	06 (7.7%)
Group E	73 (93.6%)

[a]A single child may present with multiple signs. One patient required bilateral enucleation, initially presenting with Group E in one eye and Group C in the other. After the first enucleation, the patient was lost to follow-up and later returned with recurrence.

ranged from 15 days to 14 months in males and 30 days to 24 months in females. The most common presenting symptom was leukocoria (70.5%, n = 55), followed by red eye (20.5%, n = 16) and squint (12.8%, n = 10; Table 2). One patient (1.3%) presented with phthisis bulbi, an atypical presentation.

Most cases of primary enucleation were classified as Group E RB (93.6%), with 8% as Group D RB (Table 2). Among the eight bilateral cases, six were classified as Groups E and B, and two cases as Groups D and C. The distribution of stages was as follows: 58% (n = 45) in Stage I, 33% (n = 26) in Stage II, and 5% (n = 4) in Stage III.

3.3. Histopathological features and HRFs

Most patients (36%, n = 28) exhibited both endophytic and exophytic growth patterns, followed by exophytic growth patterns (30.8%, n = 24). Approximately 26% (n = 20) of cases were endophytic tumors, while diffuse infiltrating patterns were the least common at 7.7% (n = 6). Poor differentiation (44.9%, n = 35) was the most prevalent tumor differentiation. Well-differentiated tumors were observed in approximately 26% (n = 20) of cases, followed by moderately differentiated tumors in 24% (n = 19) of cases (Figure 2). Undifferentiated tumors were the least frequent, occurring in only 5% (n = 4; Table 3). Among 78 patients, 84.6% (n = 66) were HRF-positive, while 15.4% (n = 12) had tumors confined to the retina. Tumor invasion was more prevalent in the posterior segment than in the anterior segment. In cases of anterior segment invasion, the anterior chamber was the most commonly infiltrated (19.2%, n = 15), followed by the ciliary body (16.7%, n = 13) and iris (15.4%, n = 12). Both the trabecular meshwork and Schlemm's canal were infiltrated in 11.5% (n = 9) of cases each. Regarding posterior segment involvement, massive choroidal invasion occurred in 41% (n = 32) of cases, which was higher than optic nerve invasion at 38.5% (n = 30), and 26.9% (n = 21) of cases showed retrolaminar invasion without optic nerve transection. Choroidal (focal) and optic nerve (pre-laminar and laminar) invasion were observed in 20.6% (n = 16) of cases. Among cases with scleral invasion (15.4%, n = 12), 10.2% (n = 8) showed inner-third invasion, while 5.1% (n = 4) had a full-thickness invasion. Beyond intraocular invasion, extrascleral invasion was found in 6.4% (n = 5) of cases, and orbital invasion was identified in 3.8% (n = 3; Table 3).

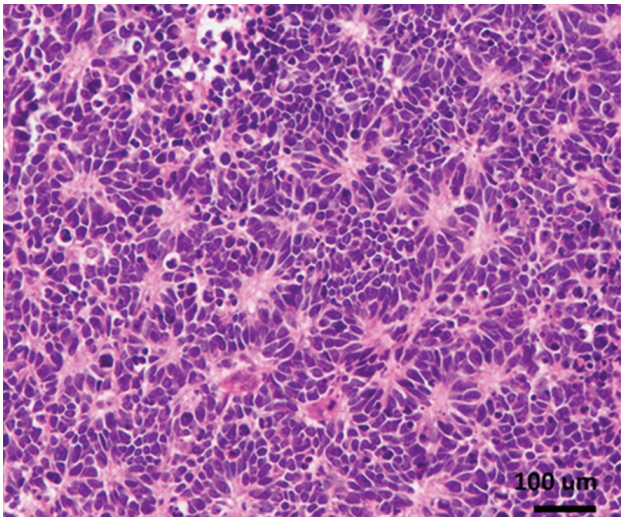


Figure 2. Slide of well-differentiated retinoblastoma showing rosettes in eosin and hematoxylin (H&E) at 20× magnification. Scale bar: 100 µm

Table 3. Histopathological characteristics

	Number (%)
Growth pattern (*n*=78)	
Endophytic	20 (25.6)
Exophytic	24 (30.8)
Both	28 (36)
Diffuse infiltrating	06 (7.7)
Tumor differentiation (*n*=78)	
Well-differentiated	20 (25.6)
Moderate differentiated	19 (24.4)
Poorly differentiated	35 (44.9)
Undifferentiated	04 (5.1)
Histopathological high-risk factor present (*n*=78, HRF=66)	
Anterior chamber infiltration	15 (19.2)
Iris infiltration	12 (15.4)
Trabecular meshwork	09 (11.5)
Schlemm's canal	09 (11.5)
Ciliary body	13 (16.7)
Choroid (massive)	32 (41)
Optic nerve (retrolaminar)	
Post-laminar optic nerve invasion (PLONI)	21 (26.9)
Transection of the optic nerve	09 (11.5)
Combined choroid (focal) and optic nerve (pre-laminar and laminar)	16 (20.6)
Sclera	12 (15.4)
Extra scleral	05 (6.4)
Orbital	03 (3.9)

Note: More than one histopathological feature was present in one enucleated eye.

3.4. Treatment and outcomes

In addition to primary enucleation, 33.3% (n = 26) of patients received adjuvant chemotherapy only and 5.1% (n = 4) received both adjuvant chemotherapy and external beam radiotherapy (EBRT). A total of 57.7% (n = 45) of patients underwent primary enucleation without additional chemotherapy due to the absence of histopathological HRFs and 3.8% (n = 3) refused further treatment. Approximately 27% (n = 21) of children died and 3.8% (n = 3) were lost to follow-up (presumed deceased). Approximately 23.07% (n = 18) of patients died due to metastasis and 3.8% (n = 3) died suddenly of unknown causes. The overall survival rate was 69.23%. The follow-up period after enucleation ranged from 6 months to 12 years.

4. Discussion

RB is a rare but deadly malignant tumor, accounting for 2%–3% of all childhood cancers.[14] Intraocular malignant tumors are most commonly malignant melanomas, with RB as the second most prevalent tumor. Approximately 200 years ago, this tumor was recognized as a distinct disease from fungal infection by James Wardrop of Scotland in 1809.[1] Since then, various diagnostic methods and treatments have been developed. Recently, a multidisciplinary team management approach has been initiated in several centers to treat this tumor and ensure comprehensive care under one umbrella. Due to advancements in diagnosis and management in higher-income countries, survival and globe salvage rates are nearly 100%.[7] Prognoses and survival rates are less favorable in low- and middle-income countries.

Literature indicates that approximately 90% of RB cases are from underdeveloped countries, where patients typically present with advanced intraocular RB or even more severe disease.[15] In these cases, life-saving measures often take priority over globe-salvaging treatments. Many institutions lack the resources and trained personnel required for chemotherapy, radiotherapy, and imaging. In addition, families of patients with RB may lack access to information, face financial challenges, and hold traditional beliefs that complicate timely treatment, leading to high rates of enucleation. A global study by the Retinoblastoma Outcome Study Group, which included 260 centers from 149 countries, reported that enucleation was the only available treatment in all centers, with intravenous chemotherapy available in 254 centers, while low-income countries had access to intra-arterial chemotherapy.[7]

In the present study, the median age of presentation was 33 months, with female patients presenting at an older age than male patients (35 vs. 30 months). According to

the Global Retinoblastoma Presentation Study, the median age of presentation in unilateral cases was 27.1 months, whereas that in bilateral cases was 12.3 months.[5] The median age of unilateral RB presentation in lower-middle-income countries in the same study was 29.1 months. Our country, a lower-middle-income country in Southeast Asia, demonstrated a higher median age of presentation than that mentioned in the above study. The age of presentation may vary based on geographical location.[5] A recent study on RB presentation across Asia reported a median age of 25 months, although it did not differentiate between unilateral and bilateral cases.[16] This study also found that the mean age was higher in South Asian countries than in other Asian regions. In the present study, the mean age of presentation was 34.56 ± 19.90 months, whereas in Southeast Asia, the median age was 30 months.[17] A study from India showed a mean age range of 29 to 33 months,[18] whereas two separate studies from Pakistan reported means of 36 ± 28 months and 42 ± 20 months. In the present study, 8% of children were under 1 year of age, 30% were between 1 and 2 years, and 61% were above 2 years; this distribution was similar to an Indian study where 38% of children were under 2 years and 62% were above 2 years of age.[19]

Leukocoria was the most common presenting symptom in our study (70.5%), followed by red eye (20.5%). However, global studies and most other studies have reported squint as the second most common presentation.[5,15] In a Chinese study, leukocoria was reported in 67% of cases, followed by red eye in 13%.[17] An Eastern Indian study noted proptosis as the second most common sign after leukocoria, whereas squint was most frequent in other parts of India.[15,20] In the present study, late-stage symptoms, such as proptosis, were observed in 6.4% of cases, and a painful blind eye was observed in 3.8% of cases. High-income countries, such as the United States and South Korea, have much lower rates of proptosis (0.5% and 1.4%, respectively), whereas this rate is significantly higher in lower-middle-income countries, such as Nigeria (44.2%), Pakistan (52.8%), and Thailand (26.7%).[18]

Our study observed a male predominance in sex distribution (55.1% male, n = 43; 44.9% female, n = 35), with a male-to-female ratio of 1.4:1,[1]; this finding was in line with the 1.52:1 ratio observed in India and 1.8:1 noted in Asian children by the Global Retinoblastoma Study Group.[21]

In this study, 10.25% (n = 8) of patients presented with bilateral RB, with only 2.6% (n = 2) of patients reporting a family history. While heritable RB often presents bilaterally, approximately 12%–15% of unilateral cases may also have a heritable basis and can later manifest bilaterally.[1] One of our patients required bilateral enucleation after initially presenting unilaterally, subsequently returning after a year with advanced RB in the previously healthy eye. The family refused neoadjuvant chemotherapy, and enucleation was performed to save the child's life.

The time from symptom onset to diagnosis is critical for RB outcomes. A symptom duration of 6 months or more correlates with poorer outcomes. In the present study, the mean symptom duration was 5.89 ± 4.30 months. A recent study reported an average lag time of 5 months for Asian children, 8 months in Southeast Asia, and 15 months in Central Asia.[16] In sub-Saharan Africa, this period is 8.5 months.[22] A prolonged lag time results in more advanced tumors, increasing enucleation rates.[16] Lag time exceeding 1 year is associated with a higher risk of extraocular invasion and increased mortality.[23] Factors contributing to longer lag times include poverty, reliance on traditional medicine, limited awareness of treatment options, lack of awareness among local pediatricians and physicians, and geographic distance from treatment facilities. In our study, we identified poverty, belief in traditional medicine, and lack of treatment facilities and physician awareness as the main factors causing delays.

In the present study, 93.7% (n = 73) of patients presented with advanced RB in Group E whereas only 7% presented with advanced RB in Group D. A review of 2,697 Indian patients with RB showed that 73 – 78% presented with advanced RB (Groups D and E).[19,20,24] Another study on 700 Chinese children undergoing primary enucleation showed that 60% of patients in Group E and 32% in Group D presented with advanced RB.[17] Among 78 study patients, 58% were in Stage I, 33% in Stage II, and 5% in Stage III. Accurate diagnosis and treatment planning for RB necessitate grouping and staging, which requires EUA before initiating treatment. Although RB is primarily diagnosed clinically, additional imaging such as ultrasonography (B-scan), computed tomography (CT), and magnetic resonance (MRI) may be necessary for unclear cases and to assess tumor extension. In this study, all patients underwent EUA and B-scans; most had CT scans, while only a few had MRIs, primarily due to constraints. As CT scans present a risk of radiation exposure, which is particularly concerning for hereditary RB cases, MRI is generally preferred. However, the high cost of MRI made it inaccessible for most of our patients. The Global Retinoblastoma Presentation Study demonstrated a preference for imaging based on income level: lower-income countries performed CT scans in 69% of cases, MRIs in 16.5%, and both modalities in 17.1%. In contrast, high-income countries performed CT scans in only 0.6% of cases, MRIs in 34.7%, and both imaging types in 64.7%.[7]

For unilateral RB, enucleation is often the preferred treatment in many underdeveloped and developing countries across Africa, Asia, and Latin America, where alternative treatment options are limited. According to the Global Retinoblastoma Outcome Study, enucleation rates are high, with 73.6% in low-income countries and 67.1% in lower-middle-income countries.[7] This study also indicated that this rate in higher-income countries is 59.7%. Reddy *et al.*[25] reported that in Southeast Asia, enucleation is the primary treatment for Group D and E unilateral RB. Following enucleation, it is essential to send the enucleated eye for histopathological evaluation, and the optic nerve length should be >10 mm. Research suggests that a 10 – 15-mm long section of the optic nerve is curative in 85 – 90% of non-heritable unilateral cases without extraocular involvement.[26]

Histopathological analysis plays a crucial role in identifying HRFs, as the subsequent treatment plan, metastasis risk, and survival outcomes depend on HRF presence. Older presentation age (>24 months) is associated with HRFs.[8,26,27] In the present study, the median age at presentation was 33 months, with 62% (n = 48) of patients above 24 months. Among 78 patients who underwent primary enucleation, 84.61% (n = 66) patients were HRF-positive, supporting findings from previous studies.[8,26,27] In the present study, a mixed endophytic and exophytic growth pattern was observed in 36% of cases, followed by an exophytic pattern in 30%. Tumor differentiation revealed a higher prevalence of poorly differentiated tumors (44.9%, n = 35). Asian studies also indicate a trend toward poorly differentiated tumors in older patients (over 24 months).[8,28]

Delayed presentation contributed to multiple HRFs in 37.6% (n = 27) of our patients, aligning with rates reported by Kaliki *et al.* (38%) and Yaqoob *et al.* (35.2%).[8,29] Most patients had massive choroidal invasion (41%, n = 32; Figure 3), which is documented in the literature with prevalence ranging from 15.2% to 62%.[26] Recent studies have suggested that focal choroidal invasion if associated with optic nerve invasion (pre-laminar and laminar), is also a risk factor. Cases involving both choroidal and optic nerve invasion have a poorer prognosis and higher recurrence risk, necessitating careful adjuvant therapy.[30] In our study, 20.6% (n = 16) of patients exhibited both focal choroidal and pre-laminar or laminar optic nerve invasion.

Survival and metastasis risk are significantly impacted by optic nerve invasion, especially post-laminar optic nerve invasion (PLONI) and optic nerve transection involvement. Metastasis rates for PLONI range from 12% to 42% and those for optic nerve transection involvement range from 41% to 78%.[31,32] In this study, retrolaminar optic nerve invasion (38.4%, n = 30) was the second most common HRF (Figure 4A and B). PLONI without transection occurred in 26.9% (n = 21) of cases, and PLONI with transection occurred in 11.5% (n = 9). Higher rates than ours have been reported in middle-income countries, ranging from 39.6% to 49%.[8,33]

A comparative study of 331 Indian and 193 American children showed that Indian children had a five-fold greater risk of optic nerve invasion and a three-fold greater risk of massive choroidal invasion

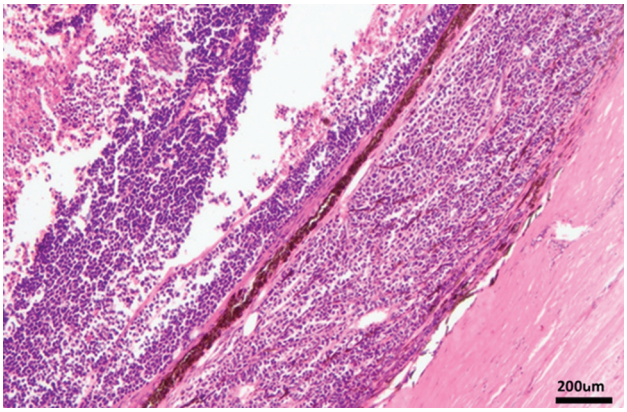


Figure 3. Massive choroidal invasion >3 mm, observed in eosin and hematoxylin (H&E) stain at 20× magnification. Scale bar: 200 µm

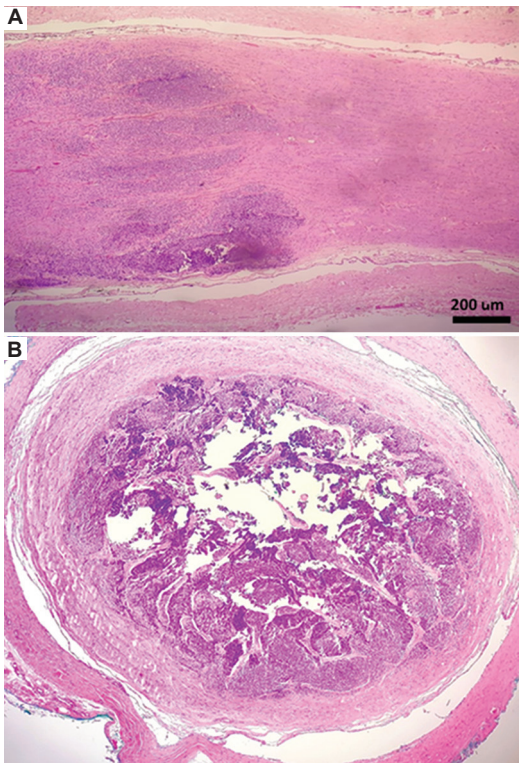


Figure 4. Optic nerve invasion by tumor. (A) Post-laminar invasion, Scale bar: 200 µm; (B) Optic nerve transection involved with tumor

than American children.[31] In the present study, HRFs of the anterior segment included the involvement of the anterior chamber (19.2%), iris (15.4%), trabecular meshwork (11.5%), Schlemm's canal (11.5%), and ciliary body (16.7%). Ciliary body and iris involvement in our study was higher than that reported by Kaliki *et al.* and Yaqoob *et al.* (3.7% each and 4.7% each, respectively) but lower than the rates observed by Yahaya *et al.* (28% and 21.5%).[8,33,34] These studies did not mention about the invasion of the anterior chamber, trabecular meshwork, or Schlemm's canal. In addition, we observed scleral invasion in 15.4% of cases, extrascleral invasion in 6.4%, and orbital invasion in 3.9%. Studies from the Indian subcontinent reported scleral invasion rates between 4.9% and 14% and extrascleral invasion from 1.6% to 11.8%, whereas a study from Uganda found a scleral invasion rate of 22.7%.[8,35] In comparison studies with American and Indian RB patients, these rates were 1% and 2%, respectively.[31] Of the 78 patients, 38.4% (n = 30) received adjuvant treatment; approximately 33% received vincristine, etoposide, and carboplatin chemotherapy, and 5.1% received both chemotherapy and external beam radiotherapy (EBRT). In 3.8% of cases, the parents refused any treatment.

A significant global burden (43%) of RB cases exists in six Asia-Pacific countries: China, India, Indonesia, Pakistan, Philippines, and Bangladesh.[15] Mortality rates for this cancer vary by continent: the highest rates are observed in Africa (70%) and Asia (40%) compared with North America (3%) and Europe (5%).[23] Increased mortality in Africa and Asia is attributed to factors such as economic challenges, illiteracy, lack of awareness, shortages of trained medical personnel, limited treatment facilities, and cultural beliefs. Survival rates also correlate with a country's income level, as socioeconomic conditions affect the likelihood of seeking medical attention. Early presentation and improved treatment facilities have notably increased survival rates in higher-income countries. For example, a 2002 study reported a 5-year survival rate of 87% in the United States, and a 2021 study found a 4- – 8-year survival rate of 99%. In Europe, the 5-year survival rate was 95% in a 2002 study and 100% in a 2017 study, while Japan reported a 10-year survival rate of 95%.[7] These high rates apply to only 10% of patients with RB worldwide, primarily those in high-income countries. However, 80% of patients with RB worldwide live in low- and middle-income countries in Asia, Africa, and Latin America.[5] In Asia, 5-year survival rates vary by income level: 89% in Taiwan (high income), 86% in China (upper-middle-income), and 37% in Indonesia (middle-income). Lower-middle-income Asian countries have similarly variable rates, with Uzbekistan at 66.6%, India at 48%, and Nepal (10-year survival) at 24%.[7,23] In Africa, 5-year survival rates are 60% in Uganda (low-income), 53% in Senegal (lower-middle-income), and 46% in Namibia (upper-middle-income).[7,23] The overall survival rate in our study was 69.23%, based on a follow-up period of 6 months to 12 years. According to the Global Retinoblastoma Outcome Study, the survival rate in low-income countries is 40% compared with 77% in lower-middleincome and 79% in upper-middle-income countries.[7]

Bangladesh, a lower-middle-income country, has a survival rate of 69.3%, which is below the estimated rate of 77% for similar-income countries. Approximately 27% of study children died, with 23% due to metastasis, possibly linked to delayed presentation, multiple HRFs, and treatment refusal. The Global Retinoblastoma Outcome Study reported metastasis rates by economic status: 24% in low-income, 51.4% in lower-middle-income, 16.9% in upper-middle–income, and 2.1% in high-income countries. Authors attributed lower metastasis rates in low-income countries to underreporting and higher rates in lower-middle-income countries to delayed presentation and numerous histopathological HRFs.[8] In this study, the mortality rate due to RB alone was 23.07%, with additional deaths (3.8%) due to other causes. In a 3-year study of RB outcomes, mortality rates were reported as 29.7% in low-income, 52.3% in lower-middle-income, 16.9% in upper-middle–income, and only 1.1% in high-income countries.[8]

In this retrospective analysis, 21 patients died, 3 were lost to follow-up, and the remaining patients were either in regular or irregular follow-up, with periods ranging from 6 months to 12 years. Counseling on the disease's nature proved effective for tumor recurrence detection, initiating prompt treatment, sibling screening, and raising awareness among patients' families and neighbors.

This study was conducted at a tertiary eye care center in Bangladesh, which is a lower-middle-income country with a high population density. Limited healthcare infrastructure and personnel hinder the availability of ophthalmic services nationwide. Complete RB treatment is available at only two tertiary eye care centers, with some secondary hospitals offering only enucleation services. Most healthcare centers lack trained personnel for histopathological assessment and RB treatment, potentially contributing to the underreporting of metastasis and survival rates. This study mainly focused on the presence of a high HRF (84.6%), underscoring the need for early case detection and lag time reduction. Recently, multidisciplinary management for RB has been recommended to preserve life and vision, although such a model is challenging in low- and lower-

middle-income countries. In such contexts, awareness programs, training of specialized ophthalmologists through fellowships, professional collaboration, and effective referrals can promote early detection and reduce the advanced presentation of RB.

This retrospective study may have biases in some data, and it only reports the overall survival rate.

5. Conclusion

Enucleation marks the beginning, not the end, of treatment in advanced RB cases. Detailed histopathology reports specifying HRFs are crucial for further management. Delayed presentation complicates treatment and is a poor prognostic factor due to higher metastasis risks. To improve outcomes, we should prioritize awareness, early presentation, accurate histopathological reporting, and human resource development alongside appropriate treatment.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Soma Rani Roy
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Ethics approval and consent to participate

This study was approved by the local IRB of the Chittagong Eye Infirmary and Institute of Community Ophthalmology. Informed consent written and verbally were obtained from the parents or legal guardians of the patients before their participation.

Consent for publication

Consent was taken from the parents or legal guardians of the patients to use their data and images in this study.

Availability of data

Not applicable.

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