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# Diagnostic Challenges and Therapeutic Response in Retinoblastoma

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## Abstract

***Background:*** Retinoblastoma is a common malignant intraocular tumor of early childhood that is potentially vision- and life-threatening, with outcomes strongly influenced by timeliness of diagnosis and access to appropriate multimodal treatment. The purpose of the study is to evaluate the clinical presentation, diagnostic challenges, treatment modalities, and therapeutic outcomes in pediatric patients with retinoblastoma. ***Methods:*** This hospital-based descriptive study was conducted at the Department of Ophthalmology, National Institute of Ophthalmology and Hospital, Dhaka, Bangladesh, from April 2011 to March 2013, and included 46 pediatric patients with retinoblastoma. Clinical presentation, diagnostic features, disease staging, treatment modalities, therapeutic response, and complications were evaluated using comprehensive ophthalmic examination and imaging. Treatment was individualized according to disease severity, and patients were followed to assess outcomes. Data were analyzed using descriptive statistics. ***Results:*** Among 46 children, most were ≤3 years at diagnosis (73.9%; mean age 2.5 ± 1.6 years), with male predominance (56.5%). Unilateral disease occurred in 71.7%, and leukocoria was the commonest presentation (69.6%). Nearly half had delayed presentation (45.7%). Most presented with Stage II disease (60.9%). Enucleation with radiotherapy was the most frequent treatment (26.1%). Disease control was achieved in 89.1%, with metastasis in 6.5% and mortality in 4.3%. Neutropenia was the commonest complication (17.4%). ***Conclusion:*** Early recognition and timely, multimodal treatment of pediatric retinoblastoma are crucial for effective disease control and favorable therapeutic outcomes.

**Keywords:** Retinoblastoma, Diagnostic Challenges, Therapeutic Response.



## INTRODUCTION

Retinoblastoma (RB) is one of the most common malignant intraocular tumors of childhood, accounting for approximately 4% of all pediatric cancers. It predominantly affects children under five years of age, with an estimated incidence of 1 in 15,000 live births [1–3]. Globally, nearly 8,000 new cases are diagnosed each year, and the majority present before the age of five, representing about 3% of all childhood malignancies. Although survival rates in developed countries approach 95%, untreated retinoblastoma can result in severe visual impairment and may be life-threatening [4]. The hereditary form of RB is associated with mutations in the RB1 gene, predisposing affected children to bilateral disease and an increased risk of secondary malignancies [5].

Diagnosis of retinoblastoma remains challenging due to its variable clinical presentation [6]. Early signs commonly include leukocoria, strabismus, or an abnormal red reflex, detectable through fundoscopy, ocular ultrasonography, and magnetic resonance imaging. In resource-limited settings, restricted access to diagnostic facilities and limited awareness frequently contribute to delayed diagnosis [7,8]. Social and cultural factors, including reluctance toward enucleation, may further impede timely management [9]. These challenges emphasize the importance of a multidisciplinary approach incorporating ophthalmic assessment, imaging, and genetic counseling, particularly for early detection among at-risk family members [10].

Delayed diagnosis or misdiagnosis has serious implications for both visual prognosis and survival. In low-income regions, retinoblastoma often progresses to advanced intraocular, orbital, or metastatic stages before treatment is initiated, with nearly 90% of cases presenting late [11]. Marked global disparities in survival exist, with outcomes exceeding 95% in developed countries compared to survival rates as low as 50% in underdeveloped regions, largely attributable to delayed presentation and limited healthcare access [3]. Economic, infrastructural, and social barriers further aggravate these delays and negatively affect outcomes.

Management of retinoblastoma has evolved considerably since the introduction of chemotherapy in the 1960s. Contemporary treatment strategies typically involve primary chemoreduction combined with focal therapies, while external beam radiotherapy is reserved for refractory cases [12–15]. Advances such as intra-arterial and intravitreal chemotherapy have been increasingly adopted worldwide [16–19]. Therapeutic outcomes are closely related to disease stage at diagnosis, with early-stage tumors achieving cure rates of up to 90–100%, although globe salvage rates vary among institutions due to differences in treatment protocols [20–22]. Optimal outcomes require coordinated multidisciplinary care involving ophthalmologists, oncologists, and radiologists to achieve tumor control, preserve vision when feasible, and improve long-term survival [23].

Despite these advances, substantial challenges persist in low- and middle-income settings, where delayed presentation, misdiagnosis, and limited access to specialized services continue to compromise outcomes. Heterogeneity in clinical presentation and resource-dependent diagnostic pathways often results in advanced disease at diagnosis, necessitating more aggressive treatment and reducing the likelihood of eye preservation. Moreover, variability in treatment availability and therapeutic response highlights the need for context-specific data to better understand real-world practices and outcomes. The purpose of the study is to evaluate the clinical presentation, diagnostic challenges, treatment modalities, and therapeutic outcomes in pediatric patients with retinoblastoma.

## OBJECTIVE

- To evaluate the clinical presentation, diagnostic challenges, treatment modalities, and therapeutic outcomes in pediatric patients with retinoblastoma.

## METHODOLOGY & MATERIALS

This hospital-based descriptive study was conducted at the Department of Ophthalmology, National Institute of Ophthalmology and Hospital, Dhaka, Bangladesh, from April 2011 to March 2013. A total of 46 pediatric patients clinically diagnosed with retinoblastoma were included in the study based on predefined inclusion and exclusion criteria. Both newly diagnosed cases and patients referred from other healthcare facilities were evaluated to assess clinical presentation, diagnostic challenges, treatment modalities, and therapeutic outcomes.

**Inclusion Criteria:**

- Pediatric patients clinically diagnosed with retinoblastoma.
- Newly diagnosed patients as well as those referred from other healthcare facilities.
- Patients with complete medical records and available follow-up information.

**Exclusion Criteria:**

- Patients with ocular conditions other than retinoblastoma.
- Patients with incomplete or missing medical records.

Demographic data, including age at diagnosis and sex, were recorded, and a detailed clinical history was obtained focusing on presenting symptoms such as leukocoria, proptosis, pseudohypopyon, hyphema, and symptom duration. Information on laterality, delay in presentation, and initial misdiagnosis was documented. All patients underwent comprehensive ophthalmic evaluation, including assessment of visual behavior where feasible, pupillary reactions, anterior and posterior segment examination, and intraocular pressure measurement. Diagnostic investigations included B-scan ultrasonography and computed tomography (CT) of the orbit and brain to evaluate intraocular tumor extent and extraocular spread, with disease staging determined from clinical and radiological findings. Treatment was individualized based on tumor stage, laterality, and severity, including enucleation, radiotherapy, chemotherapy, cryotherapy, or combinations, with enucleated specimens examined histopathologically. Patients were followed up regularly to monitor therapeutic response, treatment-related complications, disease control, metastasis, and survival, and loss to follow-up was noted. Therapeutic outcomes were categorized as complete tumor regression, partial or poor response, or requirement for secondary enucleation, while both systemic and ocular treatment-related complications were recorded. Data were analyzed using Microsoft Excel, with descriptive statistics expressed as frequencies, percentages, mean, and standard deviation.

# RESULTS

**Table 1: Demographic Characteristics of Patients (n = 46)**

| Variable | | Frequency (n) | Percentage (%) |
|---|---|---|---|
| **Age at diagnosis** | ≤ 3 years | 34 | 73.9 |
| | > 3 years | 12 | 26.1 |
| **Age group (years)** | < 1 year | 8 | 17.4 |
| | 1–3 years | 26 | 56.5 |
| | 3–5 years | 7 | 15.2 |
| | > 5 years | 5 | 10.9 |
| | Mean age ± SD (years) | 2.5 ± 1.6 | |
| **Sex** | Male | 26 | 56.5 |
| | Female | 20 | 43.5 |

The majority of patients (73.9%) were diagnosed at or before 3 years of age. The most common age group at presentation was 1–3 years (56.5%), followed by <1 year (17.4%), 3–5 years (15.2%), and >5 years (10.9%). The mean age was 2.5 ± 1.6 years. There was a slight male predominance, with 26 males (56.5%) and 20 females (43.5%).

**Table 2: Clinical Characteristics and Diagnostic Features of Patients with Retinoblastoma (n = 46)**

| Variable | | Frequency (n) | Percentage (%) |
|---|---|---|---|
| **Laterality** | Unilateral | 33 | 71.7 |
| | Bilateral | 13 | 28.3 |
| **Presenting symptoms** | White reflex in the pupil (leukocoria) | 32 | 69.6 |
| | White reflex with proptosis | 7 | 15.2 |
| | Pseudohypopyon | 5 | 10.9 |
| | Hyphema | 2 | 4.3 |
| **Other diagnostic features** | Delay in presentation (>3 months) | 21 | 45.7 |
| | Initial misdiagnosis | 11 | 23.9 |

Unilateral involvement was observed in 33 patients (71.7%), while bilateral disease occurred in 13 patients (28.3%). The most common presenting symptom was white reflex in the pupil (leukocoria, 69.6%), followed by white reflex with proptosis (15.2%). Less frequent features included pseudohypopyon (10.9%) and hyphema (4.3%). A delay in presentation exceeding 3 months was noted in 21 patients (45.7%), and initial misdiagnosis occurred in 11 patients (23.9%).

**Table 3: Clinical Stage of Retinoblastoma at Presentation (n = 46)**

| Stage | Number of Patients | Percentage (%) |
|---|---|---|
| Stage I | 9 | 19.6 |
| Stage II | 28 | 60.9 |
| Stage III | 9 | 19.6 |
| Stage IV | 0 | 0.0 |
| **Total** | **46** | **100.0** |

The majority of patients presented with Stage II disease (60.9%), indicating locally advanced intraocular involvement. Stage I and Stage III disease were observed in 9 patients each (19.6%), while no patients had Stage IV disease at presentation.

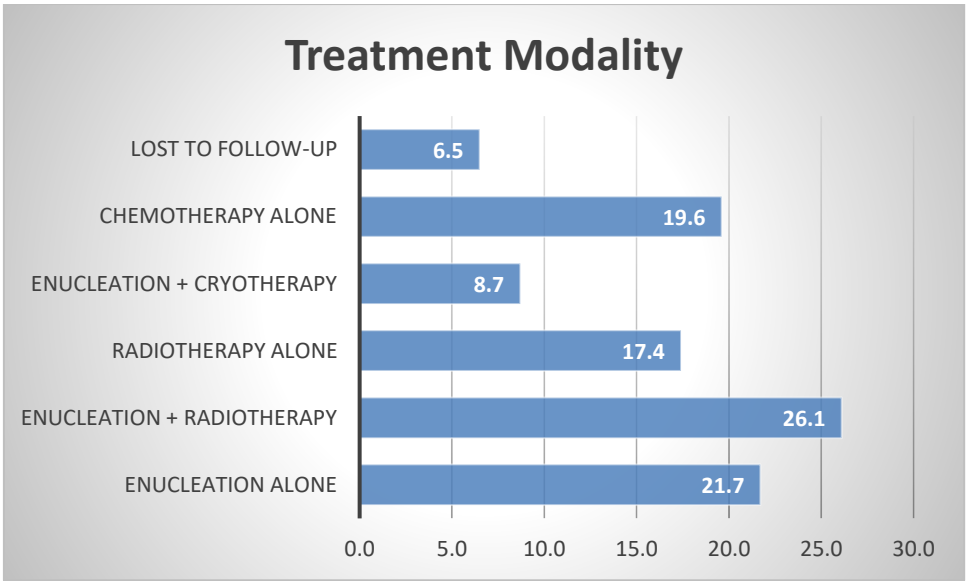


**Figure 1: Treatment Modalities Applied to Patients with Retinoblastoma (n = 46)**

The most frequently used treatment was enucleation combined with radiotherapy (26.1%), followed by enucleation alone (21.7%) and chemotherapy alone (19.6%). Radiotherapy alone was administered in 8 patients (17.4%), while enucleation combined with cryotherapy was used in 4 patients (8.7%). Three patients (6.5%) were lost to follow-up during the course of treatment.

**Table 4: Therapeutic Response and Outcomes of Patients with Retinoblastoma (n = 46)**

| Variable | Frequency (n) | Percentage (%) |
|---|---|---|
| Complete tumor regression | 20 | 43.5 |
| Partial / poor response | 5 | 10.9 |
| Secondary enucleation | 5 | 10.9 |
| Disease controlled | 41 | 89.1 |
| Metastasis | 3 | 6.5 |
| Mortality | 2 | 4.3 |

Complete tumor regression was achieved in 20 patients (43.5%), while partial or poor response occurred in 5 patients (10.9%), necessitating secondary enucleation in another 5 patients (10.9%). Overall, disease control was achieved in 41 patients (89.1%). Metastatic disease developed in 3 patients (6.5%), and mortality was recorded in 2 patients (4.3%).

**Table 5: Treatment-Related Complications in Patients with Retinoblastoma (n = 46)**

| Complication | Frequency (n) | Percentage (%) |
|---|---|---|
| Neutropenia | 8 | 17.4 |
| Cataract | 4 | 8.7 |
| Secondary glaucoma | 3 | 6.5 |

Neutropenia was the most common complication, occurring in 8 patients (17.4%). Ocular complications included cataract in 4 patients (8.7%) and secondary glaucoma in 3 patients (6.5%).

## DISCUSSION

Retinoblastoma is a common malignant intraocular tumor in children that can threaten both vision and life if not diagnosed and managed promptly. Clinical features such as leukocoria, proptosis, pseudohypopyon, and hyphema serve as important indicators of tumor presence and disease severity. The findings of this study demonstrate that delayed presentation, atypical clinical signs, and initial misdiagnosis are associated with more advanced intraocular disease, necessitating aggressive treatment modalities such as enucleation, chemotherapy, and radiotherapy. These results highlight the critical importance of early recognition, accurate diagnosis, and timely intervention in pediatric retinoblastoma to optimize therapeutic outcomes and improve the likelihood of eye and vision preservation.

The demographic profile of the 46 pediatric patients in this study demonstrates a clear predominance of early childhood presentation, with 73.9% diagnosed at or before 3 years of age and a mean age of 2.5 ± 1.6 years.

This closely aligns with previous reports describing retinoblastoma as a disease of early childhood. The most common age group at diagnosis was 1–3 years (56.5%), closely mirroring the findings of Kabre *et al*.[24], who reported 57.5% of cases within this age range. A slight male predominance was observed in our cohort (56.5%), again comparable to Kabre *et al*.'s reported male proportion of 57.5% [34]. The relatively smaller proportions of patients diagnosed before 1 year of age (17.4%) or after 3 years (26.1%) further support the established epidemiological trend that retinoblastoma predominantly presents within the first few years of life, with modest male predominance.

The clinical characteristics of our patients were also consistent with patterns reported in earlier studies. Unilateral disease predominated, accounting for 71.7% of cases, similar to the observations of Soliman *et al*.[25] (52%) and Nabie *et al*.[26] (57.7%). Leukocoria was the most common presenting feature in our cohort (69.6%), followed by proptosis (15.2%), paralleling findings from both studies, where leukocoria was the dominant presenting sign. A substantial proportion of patients experienced delayed presentation exceeding three months (45.7%), reflecting challenges in early recognition of the disease. Additionally, initial misdiagnosis was documented in nearly one-quarter of patients (23.9%), underscoring diagnostic difficulties that have been similarly highlighted in previous cohorts. Collectively, these findings emphasize that retinoblastoma often presents with unilateral leukocoria and remains susceptible to diagnostic delay and misclassification, particularly in resource-limited settings.

With regard to disease stage at presentation, the majority of patients in our cohort presented with Stage II disease (60.9%), while Stage I and Stage III each accounted for 19.6% of cases; importantly, no patients presented with Stage IV disease. This distribution is in agreement with findings reported by El *et al*.[27], whose hospital-based registry demonstrated considerable variability in stage at diagnosis, with a substantial proportion of children presenting with symptomatic and locally advanced disease rather than at the earliest stage. The predominance of intermediate-stage disease in our study highlights the persistent challenge of achieving early detection, reinforcing the need for increased awareness and prompt referral to improve stage-specific outcomes.

Treatment patterns in this cohort reflect the multimodal management strategies commonly reported in the literature. Enucleation combined with radiotherapy was the most frequently employed modality (26.1%), followed by enucleation alone (21.7%) and chemotherapy alone (19.6%), while radiotherapy alone and enucleation with cryotherapy were used less frequently. This treatment distribution is consistent with the observations of Singh *et al*.[28], who reported that pediatric retinoblastoma management often involves enucleation and systemic chemotherapy, frequently complemented by radiotherapy or focal therapies. The use of multiple treatment modalities in our study underscores the individualized nature of retinoblastoma management, where therapeutic decisions are guided by disease stage, laterality, and the potential for globe preservation.

Therapeutic outcomes in this cohort were generally favorable. Complete tumor regression was achieved in 43.5% of patients, while partial or poor response occurred in 10.9%, leading to secondary enucleation in a similar proportion. Overall disease control was attained in 89.1% of cases, with relatively low rates of metastasis (6.5%) and mortality (4.3%). These outcomes are comparable to the single-center experience reported by Kim *et al*.[29], in which chemotherapy-based multimodal treatment resulted in high long-term survival and substantial rates of ocular salvage. The similarity between these findings highlights the effectiveness of multimodal therapeutic approaches in achieving tumor control while limiting metastatic spread and mortality.

Treatment-related complications in our cohort reflected known adverse effects associated with multimodal retinoblastoma therapy. Neutropenia was the most common complication (17.4%), consistent with the hematologic toxicity associated with systemic chemotherapy. Ocular complications were less frequent but clinically significant, with secondary cataract occurring in 8.7% and secondary glaucoma in 6.5% of patients. These findings are comparable to those reported by Anteby *et al*.[30], who documented cataract formation and other radiation-related ocular changes during follow-up. The comparatively lower frequency of ocular complications in our cohort may be attributable to differences in treatment protocols or duration of follow-up. Overall, these results highlight that while modern multimodal therapy achieves effective disease control, careful long-term monitoring for both systemic and ocular complications remain essential in the management of pediatric retinoblastoma.

**Limitations of the study**

The study had a few limitations:

- The study was hospital-based and conducted at a single tertiary care center, which may limit the generalizability of the findings.
- The sample size was relatively small, reducing statistical power.
- Advanced genetic testing and newer imaging or treatment modalities were not routinely available during the study period.
- Long-term visual and survival outcomes could not be fully assessed due to loss to follow-up in some patients.

Despite these limitations, the study provides valuable insights into the clinical presentation, staging, laterality, and management of retinoblastoma in a resource-limited setting.

## CONCLUSION

Pediatric retinoblastoma is a vision- and life-threatening intraocular malignancy that typically presents in early childhood. In this study, the majority of patients presented with unilateral disease and leukocoria as the most common clinical feature, while delayed presentation and initial misdiagnosis posed notable diagnostic challenges. Stage II disease was the most prevalent at presentation. Multimodal treatment, particularly enucleation combined with radiotherapy, achieved high rates of disease control and tumor regression, with relatively low rates of metastasis, mortality, and treatment-related complications, emphasizing the importance of early recognition and timely, individualized therapy.

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