

# Epidemiological profile of retinoblastoma in North India: Implications for primary care and family physicians

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## ABSTRACT

**Background:** Retinoblastoma is the most common primary intraocular malignancy among children. Despite being curable in early stages, majority of the cases in India present in late stages, when outcomes are very poor. **Objectives:** The aim of this study was to assess the epidemiological profile, clinical characteristics, and treatment practices among retinoblastoma patients in north India. **Materials and Methods:** Data on all patients with retinoblastoma, over a 10-year-time period from 2009 to 2018, who were treated in a tertiary care hospital in north India, were assessed. Data were analyzed to describe the demographic characteristics, clinical features in terms of stage at presentation, and management practices in terms of diagnostic investigations and treatment. The statistical significance for difference in percentages was assessed using Fischer's exact test at a 5% significance level. **Results:** A total of 25 retinoblastoma patients were enlisted, of whom one was excluded as it was adult onset retinoblastoma. The median age at presentation was 3 years, with a male to female ratio of 1:1.4. Bilateral presentation was seen in 16.6% cases. Majority (66.6%) of the patients underwent magnetic resonance imaging of brain and orbit as a part of the diagnostic workup. Intraocular disease was seen in 58.3% patients, whereas 41.6% patients had extraocular disease. Local therapy with vision preservation could be used only in 8.3% patients, whereas 87.5% patients were referred for enucleation. Chemotherapy with combination of vincristine, etoposide, and carboplatin was used extensively both, in neoadjuvant setting (83.3%) and in the adjuvant setting. **Conclusion:** Despite availability of treatment for eye preservation, its utility is limited due to the advanced stage at presentation. Awareness about the disease and its symptoms for early diagnosis, especially with the Mid-Level Health Provider at Health and Wellness Centers, is likely to improve early reporting and treatment and meeting the Vision 2020 goals.

**Keywords:** Advanced stage, developing countries, retinoblastoma, treatment modalities

## Introduction

Retinoblastoma is the most common primary intraocular malignancy in children, although it is a rare disease.<sup>[1]</sup> It is not distributed equally around the world. Higher incidence is seen in Africa, India, and native America.<sup>[2]</sup> In the United States, the reported incidence is 11 per million in children less than 4 years

of age.<sup>[3]</sup> The reported incidence of retinoblastoma in Delhi is 28 per million under 5-year children.<sup>[4]</sup> Similarly, variations are also seen in stage at presentation, survival and prognosis. Although countries such as USA, Europe, Australia, Japan and New Zealand have survival rates which are as high as 95%, studies from Asia, Africa and South America have reported as high as 20%–60% mortality.<sup>[5]</sup>

Retinoblastoma may present as a bilateral or multifocal disease, which is hereditary in about 25% of the patients characterized by the presence of germ-line mutations of the RB1 gene. Majority of the unilateral or unifocal form are non-hereditary.<sup>[5]</sup> The

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World Health Organization (WHO) reports that 66% of children are diagnosed before their second year and 95% are diagnosed before the age of five. The most common presenting feature of Retinoblastoma is leukocoria (white pupillary reflex) which may be accompanied by strabismus. In the advanced stage, children may present with buphthalmos (eyeball enlargement), orbital involvement, or metastasis.<sup>[6]</sup>

The disease if diagnosed early is curable and vision preservation can be attempted with effective systemic agents and newer local treatment modalities such as laser photocoagulation, cryotherapy, brachytherapy, thermotherapy, and intravitreal chemotherapy.<sup>[7]</sup> Intraarterial chemotherapy (IAC) has also recently been incorporated in the management of retinoblastoma. IAC is used alone or with intravenous chemotherapy in patients with intraocular retinoblastoma.<sup>[8]</sup> With the incorporation of the above treatment modalities, there has not only been an attempt at preserving the life of the child but also the preservation of the eye and vision. However, majority of patients in developing countries such as India present in advanced stages when enucleation remains the only treatment of choice. Extra orbital metastatic disease when present has a dismal outcome.<sup>[9]</sup> Treatment for each patient needs to be individualized depending on the stage at presentation and the likely objectives of the treatment.

There is limited published evidence on the clinical profile of retinoblastoma in India. This is essential to frame any guidelines for primary care physicians and health workers, for both early detection and community-based management of such cases after primary treatment from specialists. To bridge this evidence gap, this study aimed to assess the demographic characteristics, clinical characteristics, and treatment practices among retinoblastoma patients in north India.

## Materials and Methods

This is a hospital-based study conducted in the department of Radiation Oncology of a tertiary care teaching hospital in north India. A hospital-based cancer registry (HBCR) is maintained in the department. This registry is part of the Indian Council of Medical Research Cancer Registry program with the overall aim of determining evidence on burden of cancer, its distribution, time trends and other epidemiological evidence which can be used for developing evidence-informed cancer care policies. The HBCR maintains data on all cancer patients who are treated in this health facility, and provides information on sociodemographic profile of patients, clinical features, disease staging, treatment and outcomes recorded during follow-up visits.

The HBCR data on all retinoblastoma patients who were treated were retrieved for a period of 10 years from 2009 to 2018. A total of 25 patients of retinoblastoma were identified from the retrospective records. Twenty-four of these were pediatric cases, and one of them was a rare presentation of an “adult onset retinoblastoma.”

Only patients who were diagnosed on the basis of clinical and radiological investigations were included. Magnetic resonance imaging (MRI), computed tomography (CT) of the orbits and brain and B-scan ultrasonography were used for diagnostic workup. Data were collected from the patient records for age and gender. In addition clinical data for the TNM staging system used for staging the extraocular tumors was collected.<sup>[10]</sup> For the intraocular tumors, subclassification was done based on the International Classification of Intraocular Retinoblastoma (ICIR).<sup>[11]</sup>

We analyzed the records for the age at presentation, sex of the child, family history, symptoms, laterality, bilateral presentation if any, diagnostic workup, the extent of disease at presentation and the treatment patterns followed. The details of chemotherapy delivered in terms of dose, schedule, the number of cycles, toxicity, and timing with respect to surgery were also analyzed.

To test for statistical significance, we used the Fischer’s exact test at a 5% significance level.

Administrative approval to use the secondary data from the HBCR in the Department of Radiation Oncology, at Government Medical College and Hospital, Chandigarh, was obtained from the Principal Investigator of the HBCR.

## Results

A total of 25 patients were identified, of which 24 were pediatric cases. The rare case of adult-onset retinoblastoma presented at an age of 32 years. The patient was diagnosed as right phacolytic glaucoma and received extensive management for the same with no response. The patient underwent enucleation of the right eye and the histopathology revealed adult onset retinoblastoma with tumor deposits in the optic nerve. Postoperatively the patient received six cycles of chemotherapy followed by external beam radiation (45 gray delivered in 25 fractions over 5 weeks) to the eye.

The remaining 24 cases were of pediatric retinoblastoma. Table 1 shows the clinical symptoms at presentation, laterality of the tumors, gender and age distribution. Approximately 83% patients were under 5 years, most common age group of presentation being between 2 and 5 years. The median age at presentation was 3 years. The male to female ratio was 1:1.4, which was statistically insignificant. None of the patients had a positive family history of retinoblastoma in the family. Bilateral presentation was seen in 4 (16.6%) patients. Among the two eyes right eye presentation was more than two times (12) more frequent than the left (6). The most common presenting symptom was leukocoria (87.5%) followed by squint (70.8%) and proptosis of the eye ball (58.3%).

Majority of the patients (66.6%) underwent MRI evaluation, whereas the rest (25%) underwent either CT evaluation or USG evaluation (8.3%) of the eye. Based on the clinical and radiology assessment, 14 (58.3%) patients had intraocular disease, whereas

the rest (41.6%) had an extraocular disease [Table 2]. Within the patients with extraocular disease, 8 (33.3%) had involvement of the optic nerve, whereas 1 (4.1%) patient each had lymph node and intracranial involvement. The patients with only intraocular involvement had 5 (35.7%) patients in IIRS Group E, 6 (42.8%) patients in Group D, 2 (14%) patients in Group C and 1 (7%) patient of Group B. For patients with bilateral presentation the eye with the higher stage was accounted for.

Treatment decisions were taken as per the stage at presentation. In view of locally advanced disease only 2 (8.3%) patients were eligible for vision sparing local therapy by laser, whereas the majority 21 (87.5%) were referred for enucleation as shown in Table 2. Two patients received local radiation to the orbit, one patient for locally recurrent disease and the other patient with bilateral disease underwent enucleation of one eye and external beam radiation to the contralateral eye. Three other patients with bilateral disease refused treatment for the contralateral eye.

Chemotherapy was used in the neoadjuvant setting in 20 patients. All patients received the standard chemotherapy with carboplatin 560 mg/m<sup>2</sup> (D1), etoposide 150 mg/m<sup>2</sup> (D1, D2), and vincristine 1.5 mg/m<sup>2</sup> (D1), repeated every 4 weeks. For patients less than 36 months of age the dose was calculated according to the body weight instead of body surface area. Chemotherapy was well tolerated with four patients requiring blood transfusion and two patients presenting with chest infections on chemotherapy which were managed conservatively. Three patients received postoperative adjuvant chemotherapy in view of optic nerve involvement on postoperative histopathology.

## Discussion

This retrospective analysis was done to evaluate the epidemiological profile, clinical features, stage at presentation, and treatment modalities offered to the patients. Although the corresponding figures may vary for developed countries where patient present in early stages, our data were similar to the literature reported for other developing countries.

Retinoblastoma is a malignant tumor of the eye arising from immature retinal cells, most commonly affecting children under 5 years of age.<sup>[12]</sup> The disease when diagnosed early enables us to save the vision, eye, and the life of the child. With newer focal therapies more children can be offered vision preserving procedures.<sup>[13]</sup> Unfortunately, majority of patients in our country present in advanced stage when vision preservation is not possible. Saving the life of the child remains the paramount goal. Lack of awareness about the disease and symptoms leads to patient presenting late in advanced stages.<sup>[14]</sup>

In a recent study by Padma *et al.*<sup>[15]</sup> from India only 54.7% of retinoblastoma patients agreed for treatment and only 39.6% of patients completed the scheduled therapy. Lack of awareness was one of the main reasons why parents did not seek medical

**Table 1: Demographic and clinical characteristics of retinoblastoma patients**

Characteristics	Number of patients (%)
Age (years)	
1-2	9 (37.5%)
2-5	11 (45.8%)
>5	4 (16.6%)
Sex	
Male	14 (58.3%)
Female	10 (41.7%)
Site	
Right eye	14 (58.3%)
Left Eye	6 (25%)
Bilateral	4 (16.6%)
Clinical features	
Leucocoria	21 (87.5%)
Proptosis	14 (58.3%)
Squint	17 (70.8%)
Diagnostic investigation	
MRI	16 (66.6%)
CT scan	6 (25%)
USG eye	2 (8.3%)

**Table 2: Staging and Treatment of the Retinoblastoma patients**

Characteristic	Number of patient (%)
Clinical staging	
Intraocular disease (Stage 1)	14 (58.3%)
Stage B	1
Stage C	2
Stage D	6
Stage E	5
Optic nerve involvement (stage II)	8 (33.3%)
Lymph node involvement (stage III)	1 (4.1%)
Intracranial spread (stage IV)	1 (4.1%)
Treatment	
Surgery	
Enucleation	21 (87.5%)
Laser therapy	2 (8.3%)
EBRT	2
Chemotherapy	
6 cycles	14
2-4 cycles	7
Adjuvant chemotherapy	3

assistance early. Outcomes of treatment in terms of loss of eye and therapy related complications lead to refusal of treatment.

The Government of India has recently expanded the scope of comprehensive primary care from a set of five services within the domain of reproductive, and maternal and child health care, to a set of 13 services which include non-communicable diseases. Screening of common cancers including head and neck cancer, cervical cancer, and breast cancer is also being carried out by health workers, with linkage for treatment at higher centers. Health and Wellness Centers (HWC) are being created with addition of a new cadre of health workforce—Mid-Level Health

Provider (MLHP). The MLHP is either a nurse or a doctor of AYUSH stream. There is a need to train the MLHP on such conditions as retinoblastoma which can be detected easily, and where timely referral can not only save the vision by restoring the eye, but also increases overall survival.

As per literature 70%–75% of retinoblastoma cases are unilateral,<sup>[16]</sup> 83.3% of our cases were unilateral too. In our study, median age at presentation was 3 years. As per literature 90% cases are diagnosed before the age of 5,<sup>[17]</sup> in our study 83.3% patients were diagnosed before the age of 5 years. Retinoblastoma does not have a sex predilection as shown in various studies,<sup>[18,19]</sup> the same was also seen in our study with a male to female ratio of 1:1.4, which was statistically insignificant. The most common clinical presentation as reported in literature is leukocoria followed by strabismus,<sup>[20]</sup> which was true in our study also. The primary care health workers should be familiar with this most common presentation. Leucocoria can be picked up even in a photograph. The identification of leucocoria or the white eye reflex in children less than 5 years of age should immediately prompt the primary health-care workers to refer the child to an eye care specialist. With the increasing use of digital technology, and telemedicine, it is also possible for the peripheral health worker to consult a doctor using the image clicked on a mobile phone. Any child presenting with new onset squint should also be evaluated for a possibility of underlying retinoblastoma. The children can be screened during the routine vaccination visits. Another common presentation seen in our study was proptosis which is not common in the developed countries. This presentation is common because the advanced disease presents as enlarged eye. MRI of the brain and orbit is the most sensitive investigation to evaluate the disease extent for ocular, extraocular and brain involvement.<sup>[21]</sup> The same was performed in the majority of our patients; however, some patients because of the financial limitations could not afford this investigation.

Approximately, 90%–95% patients in developed countries present with intraocular disease, whereas only 60%–70% patients present with intraocular disease in developing countries.<sup>[22]</sup> Patients in our study had advanced disease with only 58.3% patients having intraocular disease at presentation with majority having advanced group D or E IRSS stages. Amongst the remaining, majority patients had extraocular disease, whereas lymph node metastases and intracranial spread was also seen. In a study of retinoblastoma patients from India and the United States of America, it was noted that Asian Indians had a fivefold greater risk of having optic nerve invasion and threefold greater risk of massive choroidal invasion compared with Americans.<sup>[23]</sup> In our study approximately 33% patients had optic nerve involvement.

Globe preservation in retinoblastoma depends on the stage at presentation. In view of advanced disease at presentation, enucleation was the most common treatment offered to our patients. Role of neoadjuvant chemotherapy in advanced retinoblastoma patients for downstaging or improving survival

is not proven in literature.<sup>[24,25]</sup> In a study by Kaliki *et al.*<sup>[26]</sup> from India, systemic chemotherapy was the most commonly used primary treatment modality in view of advanced disease. In an attempt to salvage the eye and improve results for advanced disease neoadjuvant chemotherapy was offered to 87.5% patients in our analysis but it failed to help in preservation of the eye. Conservative vision preserving procedures could be done in only two patients. The high rate of enucleation for retinoblastoma raises the need to create awareness at the level of primary healthcare providers and the general population for early identification of the disease. The most common presentation for retinoblastoma is leukocoria which is easy to recognize at the level of the primary health-care workers. Referrals to tertiary level centers at an early stage may help in its management with conservative measures and may not necessitate globe removal.

External beam radiotherapy as a primary treatment for retinoblastoma has become less popular over time due to increased risk of secondary tumors, optic neuropathy, retinopathy and subsequent growth malformations.<sup>[27]</sup> In our Institute, role of external beam radiation was limited to patients with recurrent disease or patients with bilateral disease for the contralateral less involved eye. Literature does mention the role of adjuvant chemotherapy in patients with postoperative optic nerve involvement.<sup>[25,28]</sup> We used adjuvant chemotherapy for patients with optic nerve involvement in postop histopathology.

The ultimate aim in successful treatment of retinoblastoma patients besides providing survival and vision preservation is improved quality of life. These patients require a lifelong follow-up as they are susceptible to contralateral eye tumors, second primary tumors and late effects of treatment. Late side effects of treatment may include intellectual disability, diminished vision, contracted socket etc., Orbital growth after enucleation is diminished, however this impact may be reduced by the timely placement of the implant.<sup>[27]</sup> In a study on the retinoblastoma patients in India it was seen that the prosthesis was used in less than 41% of patients who underwent enucleation. Families of these patients are reluctant for prosthesis placement and do not understand the implications of its timely placement.<sup>[15]</sup> These patients require regular counselling to maintain enhanced self-esteem and healthy lifestyle. In the inherited form of retinoblastoma, even the siblings are at an increased risk of developing retinoblastoma and the need for timely referral for treatment. Primary care physicians can greatly assist in achieving all these goals.

There are certain drawbacks of our study, major being that it was a retrospective analysis of a very small patient number. Nevertheless, our study truly represents the epidemiology and clinical profile of the patients of retinoblastoma typically presenting in developing countries. Majority of them harboring an advanced disease at presentation and challenging the treating multidisciplinary team for integrating the available treatment modalities for best available results in term of vision, globe, and life preservation.

## Conclusion

To conclude, the findings of our study show that retinoblastoma occurs most frequently (83%) among children under 5 years of age, with no sex predisposition. It presents most commonly with leukocoria followed by strabismus. Approximately 88% patients underwent enucleation in view of advanced stage at presentation. At this stage, saving the life of the child becomes the primary goal and preservation of vision becomes difficult. Awareness among the health-care workers, especially towards recognition of symptoms during early stages is required to save the vision and life of these children with potentially curable disease. The primary care physicians should be trained for management of treatment related side effects among children during follow-up. The Government of India should also include placing greater emphasis to address the unmet need for management of retinoblastoma within the health programs such as Rastriya Bal Suraksha Karyakram (RBSK), and the National Blindness Control Program. Newer chemotherapy drugs and advanced local procedures such as laser, brachytherapy, and cryotherapy can only be put to use if patients present at early stages.

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## Conflicts of interest

There are no conflicts of interest.

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