

## Pediatric Cancer

# Clinicoepidemiological Profile and Treatment Outcomes in Children with Retinoblastoma: Experience from a Cancer Care Center in Northeast India

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## Abstract



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## Keywords

- ▶ advanced stages
- ▶ chemotherapy
- ▶ childhood malignancy
- ▶ retinoblastoma
- ▶ survival
- ▶ treatment refusal

**Background** Retinoblastoma (RB) is the most common primary intraocular malignancy in children. We sought to provide a comprehensive assessment of epidemiological profile and treatment outcomes of children with RB.

**Methods** In this retrospective study, we analyzed 189 children diagnosed with RB at our center between 2004 and 2017. Survival was analyzed with the Kaplan–Meier method and log-rank test.

**Results** Median age at presentation was 14 months with male: female ratio 1.2:1. Mean duration between onset of symptoms and presentation was 49 days (standard deviation  $\pm$  79). Most common presenting symptom was white pupillary reflex in 60% of children. Family history of RB and other cancers was found in one (0.5%) and seven (4%) children, respectively. Primary mode of diagnosis and staging was ocular ultrasonography (bone scan) in 87% of patients. Computed tomographic scan and magnetic resonance imaging were done in 124 (66%) and 30 (16%) patients, respectively. International staging system grade E disease was found in 144 (76%), extraocular disease in 55 (29%), bilateral disease in 49 (26%), and trilateral disease in 3 (1.5%) children. Out of 189 children with RB, 33 (18%) refused treatment and 156 children received treatment (24 children [15%] abandoned treatment midway and 132 [85%] completed treatment). One hundred children (64%) received systemic therapy as neoadjuvant or adjuvant chemotherapy and 20 (13%) received local therapy. Eyeball and vision salvage rate with chemotherapy were 20 (13%) and 9 (6%), respectively. Cryotherapy was the most common modality of local treatment used in 11 (55%) children. Five-year survival for patients who received treatment was 76% (median survival not reached). In the treatment refusal group, median survival was 9 months.

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**Conclusion** In developing countries, RB is mostly detected in advanced stages resulting in poor outcomes. Increased awareness and accessibility to dedicated centers for treating childhood malignancy can lead to early diagnosis, better prognosis, and increased vision salvage.

## Introduction

Retinoblastoma (Rb) is a rare tumor and is also the most common intraocular malignancy of childhood. The reported incidence worldwide is ~1 in 18,000 live births.<sup>1,2</sup> In India, RB constitutes 3.1% of all childhood cancers in boys and 4.1% in girls from 0 to 14 years of age group.<sup>3</sup>

RB most commonly presents with leukocoria followed by other symptoms including poor vision, redness, squint, or proptosis.<sup>2</sup> The average age of diagnosis is 18 months, and unilateral cases are diagnosed later than bilateral ones with average age of 24 months for unilateral versus 12 months for bilateral cases.<sup>4</sup> The disease may be unilateral or bilateral; bilateral involvement is seen in 25 to 35% of cases.<sup>4</sup>

RB was associated with near certain death just over a century ago. Over the recent years, treatment of RB has significantly improved. In the early stages, the main aim is to preserve the globe as well as vision, with minimum treatment-related adverse effects. This has been made feasible with the frequent use of intravenous chemotherapy and focal treatment methods. Of the recent advancements, the use of targeted delivery of chemotherapy to the eye in the form of intraarterial and intravitreal chemotherapy has shown promising results.<sup>5</sup> Radiotherapy is beneficial in selected cases, either in the form of external beam radiotherapy and stereotactic radiotherapy or plaque brachytherapy.<sup>6,7</sup> In cases of advanced orbital disease, a multimodal treatment protocol in the form of systemic chemotherapy followed by either focal therapy or enucleation has improved survival as well as globe and vision preservation to some extent. The disease being potentially curable requires a multidisciplinary approach for appropriate treatment and thus the prognosis is dependent on early diagnosis. Goals of therapy are life salvage, followed by globe salvage, and vision preservation in decreasing priority. However, challenges remain, especially for the developing world where most of the cases are diagnosed in advance stages.

## Methods

This study was designed as a retrospective study. Children who presented and underwent treatment at the medical and pediatric oncology department of our center between 2004 and 2017 were recruited and analyzed retrospectively. The study received the institutional ethics committee approval.

### Objectives of the Study

The aim of this study was to analyze clinical and epidemiological profile and treatment outcomes with special reference to eye and vision salvation in children presenting with RB.

### Inclusion Criteria

All children from 0 to 14 years of age group diagnosed by radiological and/or ophthalmological examination are included for the study.

### Exclusion Criteria

Children with relapsed RB at presentation, patient not received any treatment after confirmation of the diagnosis, and patients who failed to undergo complete diagnostic workup were excluded from the analysis. Clinicoepidemiological and treatment-related data were collected from case files of the patients and health records available in our hospital database and in collaboration with the Ophthalmology Center, Guwahati, Assam, India.

After the diagnosis with the help of ophthalmologic examination under anesthesia and ocular ultrasonography (bone scan), children underwent complete staging evaluation using contrast enhanced magnetic resonance imaging (MRI) brain and orbits, chest X-ray posteroanterior view and bone marrow aspiration and biopsy, lumbar puncture and radionuclide bone scan in patients with extraorbital involvement along with complete hemogram, liver and kidney function test, serum lactate dehydrogenase, viral serology as per institution protocol. Children, thereafter, underwent staging using International Classification of Intraocular Retinoblastoma.<sup>8-10</sup>

### Statistical Analysis

The results are presented as descriptive statistics using methods of calculating central deviation. Disease and patient characteristics were calculated in percentage and presented in the form of pie chart. Association between use of chemotherapy and compliance to treatment was analyzed using chi-squared test and presented in form of bar diagram. Survival was analyzed with the Kaplan–Meier method and log-rank test. Calculations were done using IBM SPSS version 16.0.

## Results

A total of 206 patients of RB were registered at our institute during the study period between April 1, 2004 to March 31, 2017. Out of 206 cases, 189 children were found to be eligible for the study. Most of the ineligible patients were those who failed to undergo complete diagnostic workup and lost to follow-up after first visit.

Median age of presentation for the study group was 14 months with slightly male preponderance (1.2:1) (**Table 1**). Median duration from symptom onset to presentation at healthcare facility was found to be of 49 days. Family history of RB and of other malignancies was elicited in 0.5 and 4% of children, respectively.

**Table 1** Baseline demographic profile

Median age (mo)	14
Male:female	1.2:1
Median duration from symptom (d)	49 (SD ± 79)
Family history of RB (%)	0.5
Family history of other cancers (%)	4

Abbreviations: RB, retinoblastoma; SD, standard deviation.

**Table 3** Treatment characteristics

Refusal to treatment	33 (18%)	
Chemotherapy (n = 156)	100 (64%)	
Focal therapy (n = 156)	33 (21%)	
External beam RT (n = 33)	13 (39%)	
Cryotherapy (n = 33)	11 (33%)	
Globe salvation (n = 156)	20 (13%)	
Vision salvation (n = 156)	19 (12%)	
Overall survival (mo)	40	
Median survival without CT (mo)	27 NR	p = 0.02
Median survival with CT (mo)		

Abbreviations: CT, computed tomography; RT, radiotherapy.

In this study, three-fourth of all children had unilateral disease (→ **Table 2**), and the most common presenting symptom was leukocoria (60%) followed by red eye (5%). Of all children included in this study, 87% were diagnosed based on ultrasound. Staging workup included computed tomography (CT) and MRI scan, which were performed in 66 and 16% of the children, respectively. Most of the children included in the study presented with an advanced disease (stage D—21% and stage E—76%) with evidence of extraocular disease spread present in 29% of children.

Regarding treatment characteristics (→ **Table 3**), of all children found to be eligible for the study, 33(18%) of them refused to take any form of treatment and were lost to follow-up. Of remaining 156 children who underwent treatment at our institute, 100 (64%) received some form of chemotherapy (including neoadjuvant and/or adjuvant). Out of these 100 children who received chemotherapy, 68 (68%) underwent neoadjuvant chemotherapy and remaining received only adjuvant chemotherapy. Since most of the children presented in an advanced stage, in spite of using neoadjuvant chemotherapy, only 33 (21%) children were eligible for and underwent focal therapy. Most common mode of focal therapy used was external beam radiotherapy in 13 (39%) children followed by cryotherapy in 11 (33%) children. Of 156 children who received treatment, eyeball salvation was achieved in 20 (13%) children and vision salvation in 19 (12%) children. In this study, chemotherapy was found to be associated with improved survival in children with advance disease. Median survival in children who received some form

**Table 2** Baseline disease characteristics

Unilateral vs. bilateral (%)	73 vs. 27
Presentation with leukocoria	113 (60%)
Ultrasound-based diagnosis (%)	87
CT scan	124 (66%)
MRI	30 (16%)
Stage E	144 (76%)
Stage D	39 (21%)
Extraocular disease	55 (29%)

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

of chemotherapy was not reached as compared with 27 months in children who did not receive any form of chemotherapy (p = 0.02).

## Discussion

RB is the most thoroughly studied example of heritable cancers and is also the most common intraocular tumor in the children. Most of these malignancies are sporadic and unilateral, in nearly 60% of the cases. The remaining 40% are inherited, with bilateral presentation seen in 25% of the cases.<sup>11</sup> The median age at presentation in our study was found to be 14 months, which is lower than 3.5 years reported by the study from Sahu et al<sup>12</sup> and 30 months reported in the study from Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.<sup>13</sup> and is similar to the study by Padma et al.<sup>14</sup> Our study found slightly male predominance with a male to female ratio of 1.2:1, which was similar to that reported from other Indian studies.<sup>12,14</sup> The median duration of illness in our study group is 1.5 months, with a family history of RB and of other malignancy found is 0.5 and 4%, respectively. Study from Tata Memorial Hospital, Mumbai, Maharashtra, India, reported a longer duration of illness (i.e., 8 months) before presentation and similar family history of malignancy, as compared with our study.<sup>12</sup> This may be due to complete ignorance of symptoms for longer duration by the parents. In our study cohort, 27% of the children had bilateral disease, similar to the study by Chawla et al and Naik et al, which reported 25% of cases with bilateral tumors.<sup>11,15</sup> The most common mode of presentation was leukocoria in 60% of children followed by red eye in 5%, which is similar to other reported Indian studies. Further staging workup in form of contrast-enhanced CT scan and MRI of brain and orbit was performed in 66 and 16% of children. Most of the children in our study presented at an advance stage (stage D—21% and stage E—76%) as compared with 78% reported in study from PGIMER, Chandigarh, India.<sup>13</sup> Extraocular disease at presentation was found in 29% of children similar to 27% reported from PGIMER, Chandigarh, India<sup>13</sup> but was found to be less than as compared with 57 to 58% reported in study by Sahu et al and Padma et al.<sup>12–14</sup> However, these figures are in contrast

to the Western world,<sup>16</sup> where the incidence of extraocular disease has been reported to be less than 5%. Therefore, a major challenge in our country is the implementation of an early detection program to minimize the progression of RB to advanced stages and allow for the treatment at earlier stages of disease and have better treatment outcomes.

In our study, 33(18%) children after registration did not receive any form of treatment and were lost to follow-up. Lost to follow-up rate in our study is found to be lower than the report from PGIMER, Chandigarh, India (25.6%).<sup>13</sup> This further explains the lack of awareness among parents regarding this curable disease. As compared with study by Padma et al, where only 55% children agreed to and underwent treatment, in our study 82% children underwent treatment.<sup>14</sup> One more possible reason of declining treatment by parents is the counseling regarding enucleation for advanced disease. A study from Malaysia<sup>17</sup> reported that most families refuse treatment upon counseling in favor of enucleation. In our study population, 97% of children had advanced disease at presentation of which 64% received systemic chemotherapy either in neoadjuvant or adjuvant setting. Of these children, 68% received neoadjuvant and remaining 32% received adjuvant systemic chemotherapy. Most commonly employed regimen for chemotherapy was vincristine, etoposide, carboplatin regimen.

In spite of using systemic therapy, only 21 and 39% of children were found to be suitable for focal therapy and external beam radiotherapy, respectively. This resulted in eyeball salvation rate of 13% and vision salvation rate of 12% in our study population. In our study, we found significantly lower rates of eyeball salvation and vision salvation as compared with the study from other developing countries like Thailand, which found globe salvation rates of 52%<sup>18</sup> and globe salvation rate of 100% in studies from developed countries.<sup>9,19,20</sup> Similar to our study, rate of globe salvation reported in the study from PGIMER, Chandigarh, India, was only 17%.<sup>13</sup> Median overall survival of the entire study group was found to be 40 months. In cohort of children who received systemic chemotherapy median overall survival was significantly higher than those who did not receive any form of systemic chemotherapy. This finding highlights the importance of systemic chemotherapy in treatment of RB and more so in cohort of children with advanced disease at presentation.

## Conclusion

In developing countries, RB is mostly detected in advanced stages resulting in poor outcomes. Increased awareness and accessibility to dedicated centers for treating childhood malignancy can lead to early diagnosis, better prognosis, and increased vision salvage. Fortunately, an early diagnosis<sup>21</sup> will lead to many eyes that can be treated safely and support a lifetime of good vision, thus pointing to the key elements for national and global focus: awareness, collaboration, and affordable expert care. Initiative for screening like Photo Red India, an innovative study that trained healthcare professionals to use flash photography and to identify childhood eye diseases, including RB, is much warranted.<sup>22</sup>

## Ethics Approval and Consent to Participate

Institutional ethics committee (BCCI Medical Ethics Committee) approval was obtained for the study before reviewing the patient records and the study conformed to the Declaration of Helsinki.

## Availability of Data and Material

Obtained from hospital-based case records and hospital information services.

## Funding

None.

## Conflicts of Interest

None declared.

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