

## ORIGINAL ARTICLE

**FACTORS THAT INFLUENCE SURVIVAL RATE IN  
EXTRAOCULAR RETINOBLASTOMA PATIENTS  
AT CIPTO MANGUNKUSUMO HOSPITAL 2018****Dwie Aprina<sup>1</sup>, Julie Dewi Barliana<sup>2</sup>, Dian Estu Yulia<sup>2</sup>, Rita Sita Sitorus<sup>2</sup>**<sup>1</sup>*Department of Ophthalmology, Faculty of Medicine Universitas Indonesia, Kirana Cipto Mangunkusumo Hospital, Jakarta, Indonesia*<sup>2</sup>*Pediatric Ophthalmology Division, Department of Ophthalmology, Faculty of Medicine Universitas Indonesia, Kirana Cipto Mangunkusumo Hospital, Jakarta, Indonesia  
Email: dwiap88@gmail.com***ABSTRACT**

**Introduction:** Optimal therapeutic approach for extraocular retinoblastoma has not been determined. The prognosis of extraocular retinoblastoma compared with intraocular retinoblastoma remains relatively poor. The aim of our study is to describe the factors that influence the survival rate of extraocular retinoblastoma.

**Methods:** A retrospective study. Patients diagnosed with extraocular retinoblastoma in Cipto Mangunkusumo Hospital, within 1 January to 31 December 2018 were reviewed for patient and tumor characteristic, ocular management, and patient survival.

**Result:** During the study period, a total of 80 patients were diagnosed with retinoblastoma in our center, 41.2% had an extra-ocular extension. The mean age at diagnosis was 25.57 months, with 56.7% being males. Leukocoria is the initial sign most often noticed by parents. The median lag period was 12 months. Neoadjuvant chemotherapy was performed in 96.7% of cases, that carried out an average of 3-4 cycles before enucleation/exenteration. At the end of September 2019, there were 17 deaths in our study. Overall survival was 19.82 months with a mean age of 27.6 months, whereas extraocular death time ranged from 4 months to 55 months.

**Conclusion:** Death was more common in patients with age at first symptom less than 24 months, bilateral retinoblastoma, lag period more than 12 months, advanced stage (IVB) and delayed therapy after proptosis more than 3 months.

**Keywords:** retinoblastoma, prognosis, survival

**INTRODUCTION**

Retinoblastoma is the most common primary intraocular malignancy in children with an approximately incidence of 1/15000-20000 birth in the world.<sup>1</sup> In Kirana Cipto Mangunkusumo hospital, the incidence of retinoblastoma is 74 cases were found in 2007–2008.<sup>2</sup> In developed countries, retinoblastoma is usually diagnosed in its early intraocular stages leading to high chances for preservation of vision, globe and disease-free survival of the patient. However, in developing countries, retinoblastoma is often diagnosed at a later stage with extraocular dissemination, thus leading to much lower rates of ocular salvage and patient survival.<sup>3</sup>

Advanced retinoblastoma can directly invade the orbit, spread via the optic nerve to the central nervous system, or metastasize hematogenously to bone marrow, and later to visceral organs.<sup>1</sup>

The main therapeutic priority for retinoblastoma is to first save the child's life through early tumor detection and prevention of metastatic spread. Secondary goals are globe salvage and maximizing visual potential. The optimal therapeutic approach for extraocular retinoblastoma has not been determined, but several previous studies stated that the combination of surgery, radiotherapy, and chemotherapy shows a longer survival compared to chemotherapy alone.<sup>4</sup> The prognosis for extraocular retinoblastoma compared with intraocular retinoblastoma patients remains relatively poor, especially in patient whose disease disseminates into the central nervous system (CNS) and those with distant metastatic disease.

Sitorus et al.<sup>5</sup> in 2009 found that a total of 87 patients over 7 years presented with extraocular retinoblastoma with varying survival rates. Our study aims to describe the factors that influence the survival rate of extraocular retinoblastoma.

## **METHODS**

### *Study design and population*

We retrospectively analysed the medical records of 30 children who were diagnosed histologically or clinically in the Cipto Mangunkusumo Hospital with the inclusion criteria being those who presented with bulging eyes and were diagnosed with extraocular retinoblastoma via orbital ultrasound in the Pediatric Ophthalmology Department, Cipto Mangunkusumo Hospital, within 1 January to 31 December 2018. We excluded patients with residual and recurrent extraocular retinoblastoma.

The data collected included gender, laterality, age at first diagnosis, baseline symptoms before diagnosis, lumbar and bone marrow puncture features, length of follow-up, management, chemotherapy cycle before enucleation, treatment results, patient's latest condition were all obtained from medical records.

The lag period was defined as the period from the first symptoms recognized by the parent and initiation of treatment. Overall survival (OS) is the time interval from first diagnosis to death. Extraocular death time (EOD) is the time interval from extraocular manifestation (proptosis) to death. At the end of September 2019, 13 patients were alive, while 17 patients died prior to the cut-off date.

Statistical analysis was performed using software Statistical Package for the Social Science version 20.0. Data are represented as means when the distribution was normal and median with range when distribution was not normal.

### *Staging of Extraocular retinoblastoma*

The staging system used in this study, known as the International Retinoblastoma Staging System (IRSS) can be categorized into four stages : Stage 1 involves complete histological resection after eye enucleation; Stage 2 involves microscopic residual tumor post-enucleation; Stage 3 comprises regional extension, which is further divided into overt orbital disease (Stage 3a) and extension to preauricular and cervical lymph nodes (Stage 3b); Stage 4 includes metastatic disease, further divided into hematogenous metastasis (Stage 4a) and central nervous system extension (Stage 4b).

## **RESULTS**

During the study period, a total of 80 patients were diagnosed with retinoblastoma in our center, with 33 patients had an extra-ocular extension(41.2%). About 3 patients were excluded because they had residual or recurrent retinoblastoma. In total, 30 medical records were being processed and analyzed.

Table 1 described basic characteristic data regarding the included cases, with the proportion of males is more than females. The average age of diagnosis was 25.57 months (range: 1 to 68 months). Unilateral and bilateral cases have the same percentage. The initial mode of presentation was varied, there was leukocoria (63.4%), proptosis (26.7%), strabismus (6.7%) and buphthalmos (3.3%). Leukocoria is the initial sign most often noticed by parents but parents bring the patient to the hospital if proptosis is seen.

Lag period from detection of the first sign to consultation ranging from 3 to 39 months (median of 12 months). Delay in diagnosis is due to ignorance of the seriousness of the disease (13.3%), fear of enucleation (16.7%), limited costs for treatment and travel during therapy (10%), a misdiagnosis by health workers (13.3%), and desire for seeking traditional treatment (10%), and 36.7% had no known reason.

Patients with bilateral retinoblastoma were more likely to be found when the lag period was less than 12 months. In a more advanced stage (stage IV) Extraocular retinoblastoma was treated more quickly (lag period <12 months) as shown in Table 2.

Results of investigations made for the confirmation of diagnosis and for staging are shown at Table 3, and revealed involvement of optic nerve, extrascleral, and central nervous

system in 21.4%. The mean age at diagnosis of proptosis was 27.53 months (range 4 - 68 months). There were 14 cases received therapy more than 3 months after the appearance of proptosis.

**Table 1.** Basic Characteristic Data (n=30)

Variable	Number of Subjects (%)
<b>Gender</b>	
Male	17 (56,7%)
Female	13 (43,3%)
<b>Family History</b>	
Yes	0 (0%)
No	19 (63,3%)
N/A	11 (36,7%)
<b>Laterality</b>	
Unilateral	15 (50%)
Bilateral	15 (50%)
<b>Age at diagnosis</b>	
0-2 years old	16 (53,3%)
2-4 years old	14 (46,7%)
<b>Initial presentation</b>	
Leukocoria	19 (63,4%)
Proptosis	8 (26,7%)
Strabismus	2 (6,7%)
Buphthalmos	1 (3,3%)
<b>Staging</b>	
IIIA	16 (53,3%)
IIIB	1 (3,3%)
IVA	7 (23,3%)
IVB	6 (20%)

N/A: Not Available

**Table 2.** Lag Period (n=30)

Lag Period	< 12 months (%)	> 12 months (%)
<b>Laterality</b>		
Unilateral	12 (80)	3 (20)
Bilateral	15 (60)	10 (40)
<b>Age at diagnosis</b>		
< 2 years	14 (82.3)	3 (17.6)
> 2 years	13 (100)	0
<b>Stage</b>		
III	7 (41.1)	10 (58.8)
IV	9 (69.2)	4 (30.7)

Neoadjuvant chemotherapy was performed in 96.7% of cases, that carried out an average of 3-4 cycles before enucleation/exenteration. Tumor mass regression was seen in all patients after the third cycle of neoadjuvant chemotherapy. There were 2 cases required up to

7-8 cycles of neoadjuvant chemotherapy because there no regression. Both patients were dead before enucleation/exenteration.

**Table 3.** Imaging Feature of Extraocular Retinoblastoma (n=28)

<b>Imaging Feature</b>	<b>Number of Subject (%)</b>
Isolated extrascleral involvement	6 (21.4)
Isolated optic nerve involvement	6 (21.4)
Involvement of optic nerve and extrascleral	2 (7.14)
Involvement of orbital muscel and optic nerve	6 (21.4)
Isolated involvement of the orbital muscles	2 (7.14)
Involvement of the central nervous system	6 (21.4)

All patients received chemotherapy after surgery, but four cases were also treated with external beam radiation. At the end of September 2019, there were 17 deaths in our study. Overall survival was 19.82 months with a mean age of 27.6 months (median 19 months), whereas extraocular death time ranged from 4 months to 55 months (mean 18.64 months).

**Table 4.** Factors Assessed for Survival in Extraocular Retinoblastoma

	<b>Category</b>	<b>Death (%)</b>
Onset of symptoms	< 24 months	16 (59.3)
	> 24 months	1 (33.3)
Laterality	Unilateral	8 (53.3)
	Bilateral	9 (60)
Lag period between first diagnosis and therapy	< 12 months	9 (52.9)
	> 12 months	8 (57.1)
Interval between first proptosis to therapy	< 3 months	9 (47.3)
	> 3 months	7 (63.6)
Interval between first diagnosis EORB to therapy	< 5 weeks	10 (58.8)
	> 5 weeks	6 (50)
Staging	III A	9 (56.2)
	III B	1 (100)
	IV A	3 (42.8)
	IV B	4 (66.7)

Table 4 shows the factors assessed for survival in extraocular retinoblastoma. Death was more common in patients with age at first symptom more than 24 months, bilateral retinoblastoma, lag period more than 12 months, advanced stage (IV B) and delayed therapy after proptosis more than 3 months.

## DISCUSSION

In developed countries, retinoblastoma is usually diagnosed in its early intraocular stages leading to high chances for preservation of vision, globe and disease-free survival of the patient. However, in developing countries, retinoblastoma is often diagnosed at a later stage

with extraocular dissemination, thus leading to much lower rates of ocular salvage and patient survival.<sup>6,7</sup>

We retrospectively studied 30 children diagnosed with extra-ocular retinoblastoma presenting 37.5 % of all retinoblastoma diagnosed in our center. The proportion of patients with extraocular retinoblastoma in this study is almost the same as that of other studies from India which is around 27-37%.<sup>8</sup> Retinoblastoma has no sex predilection. In this literature, there was not much difference in the occurrence of retinoblastoma in boys (56.7%) and girls (43.3%). It can also be found in several studies in India.<sup>9</sup>

In this study, the age of our patients ranged from 1 months to 6 years and averaged 25.57 months. This rate was lower when compared to the study in Ghana, averaging a diagnosis at 36 months of age.<sup>10</sup> The age at diagnosis of retinoblastoma in developing countries varies from 24 months to 3 years. Patients with bilateral tumors has the same number as unilateral cases. This is different from several studies conducted in Asia and America, where bilateral numbers were more numerous.<sup>11</sup>

Leucocoria (63.4%) is the most common presenting sign of retinoblastoma. The frequency of common modes of presentation of retinoblastoma in our study is consistent with many studies from different parts of the world. However, proptosis was present in 26.7 % of cases in our study; it was reported in high frequency from some of the developing countries like India (25.3%).<sup>12</sup> Study from Menon et al.<sup>13</sup> in Malaysia. stated that proptosis (83%) was a symptom that most often caused parents to bring their children to the doctor for treatment.

In this study, it was found that most of the subjects were included in stage III A based on the IRSS classification. This is similar to the results from studies by Chawla et al.<sup>8</sup> and Pant et al.<sup>10</sup> In staging, imaging is needed to detect extraocular invasion. In this study, 21.42% of patients had tumor expansion into the central nervous system (involvement of the preciasma and suprasella) on imaging. The results of these imaging are also not much different from previous studies conducted in India, where as many as 28% of cases of extraocular retinoblastoma on imaging obtained intracranial extension.<sup>14</sup> In addition to imaging, staging by performing bone marrow aspiration and lumbar puncture was also performed. Histopathological examination after enucleation is difficult to use to determine extraocular invasion in this study, this is due to the unreliable histopathological results after chemotherapy or chemoreduction before enucleation.

The mean lag period in our patients was 13 months, These results are longer than other studies.<sup>15</sup> Other studies from the developing world have also described a long lag period and have analyzed various reasons.<sup>14,16</sup> Erwenne and Franco et al.<sup>6</sup> concluded that delayed

presentation with extra-ocular invasion is strongly associated with age at diagnosis and lateness of referral. Antoneli et al.<sup>17</sup> analyzed the lag time and concluded that longer lag time is associated with disseminated disease and this period, if shortened may lead to decrease in number of cases with extra-ocular dissemination. Another study concluded that it is not only longer lag time but also denial of management by parents that are responsible for the delayed diagnosis. It is likely that parents with a poorer educational background have limited information regarding signs and symptoms of retinoblastoma. Parents often stated that even though they noted an abnormality in the eye, often leukocoria, they did not relate this to the possibility of having cancer. In our study, the various reasons of delayed consultation reported by parents are limited access to ophthalmologist, financial constraints, lack of health insurance, denial of enucleation, and the use of self-treatments or traditional healers before seeking hospital care.

The therapy for extraocular retinoblastoma is unclear. Until now, developed countries are still trying to maintain the eyeball in patients with intraocular retinoblastoma at an advanced stage, while in developing countries, enucleation is the main choice to prevent tumor spread and reduce mortality. Chemoreduction using neoadjuvant chemotherapy has been used in several studies to reduce tumor volume and thus allow enucleation.<sup>18</sup> There are no proven definitive therapy or management protocols for extraocular retinoblastoma. They continue to remain a challenging disease to treat because of its complex nature and usually various combination therapies are needed to achieve reasonable results. A treatment protocol comprising an initial triple drug high-dose chemotherapy (3-6 cycles) followed by appropriate surgery, orbital radiotherapy and an additional 12 cycle standard-dose chemotherapy have been suggested. In this study, the standard therapy for extraocular retinoblastoma was the administration of neoadjuvant chemotherapy given before enucleation to reduce tumor mass and to prevent further metastases. After administration of neoadjuvant chemotherapy, mass enucleation/exenteration was performed. Adjuvant chemotherapy that is given after enucleation is additional chemotherapy that aims to remove tumor cells and prevent metastases/recurrences. Some patients also receive adjuvant external radiotherapy if there are still tumor remnants at the incision margin. In this study, there was one patient who immediately received radiation due to active bleeding from the tumor after refusing to give neoadjuvant chemotherapy.

Five of the 29 patients received only neoadjuvant chemotherapy without enucleation/exenteration due to worsening of the condition and died before surgery. This is in accordance with the study of Radhakrishnan et al.<sup>19</sup> which stated that although neoadjuvant chemotherapy can significantly reduce the size of the tumor mass, it is not associated with

pathological responses, because 95% of extraocular retinoblastoma specimens after neoadjuvant chemotherapy show tumor cells still active. The study also concluded that neoadjuvant chemotherapy alone was not sufficient to control tumor growth and replace exenteration/enucleation in eradicating tumor cells. Shields et al.<sup>20</sup> stated that chemoreduction alone was satisfactory for Reese-Ellsworth (RE) group I-IV retinoblastoma but in group V RE required EBRT in 47% of cases.

Several previous studies in high- and middle-income countries in Latin America have reported survival rates for extraocular retinoblastoma. Chantada et al.<sup>21</sup> reported a 70% overall survival for stages II and III extraocular retinoblastoma. Antonelli et al.<sup>17</sup> in Brazil showed a high figure compared to Chantada et al. where, the overall survival in patients with extraocular retinoblastoma for 3 years was about 58.3% whereas in this study, it was found that 56.7% of patients with extraocular retinoblastoma were dead. Most of the patients in this study died within 1.5 years of proptosis, indicating the aggressiveness of the tumor cells. Tumor spread to the central nervous system was the most common cause of death for patients in this study. Prevention of spread to the central nervous system with adjuvant chemotherapy has not been proven to help reduce metastases because the survival rate and recurrence rates after administration still varied.

In this study, the variables selected to assess the factors that influence survival rates in extraocular retinoblastoma are age at diagnosis, laterality, lag period, the interval from proptosis to therapy and stadium. Rubin et al. stated that laterality determines prognosis and influences survival rates for extraocular retinoblastoma patients. This is different from the study conducted by Erwenne et al.<sup>6</sup> where there was no significant difference in survival rates for extraocular retinoblastoma with laterality. In that study, age at diagnosis and delay in diagnosis and therapy were two factors that have statistically significant results on the survival rate of extraocular retinoblastoma. Leander et al.<sup>22</sup> in Honduras found that good education by giving a flyer and posters increasing the initial diagnosis and survival rate in retinoblastoma patients. In our hospital, leaflets and brochures related to retinoblastoma have been provided to diagnose patients early. However, there are no further studies related to the effectiveness of leaflets and brochures on the survival rate of extraocular retinoblastoma patients.

This study has several limitations, including its retrospective study design, incomplete information on medical records, variable length of follow-up, and small sample size. Prospective studies with fairly long and uniform follow-up times and larger sample sizes are needed to delineate survival rates and assess factors that influence more representative survival rates.

## CONCLUSION

Delay in diagnosis and therapy for extraocular retinoblastoma are caused by several reasons including fear of enucleation, ignorance about the seriousness or danger of the disease, limited costs for treatment, the desire to seek alternative treatment first, and misdiagnosis by health personnel. In conclusion, factors that are considered to affect the survival rate are age at first symptom, laterality, lag period, first time proptosis interval to therapy, and stage.

## REFERENCES

1. Ali MJ, Honavar SG, Reddy VAP. Orbital retinoblastoma: Present status and future challenges – A review. *Saudi Journal of Ophthalmology*. 2011;25(2):159–67.
2. Yusran M. Angka kesintasan pasien retinoblastoma [Penelitian Deskriptif]. universitas indonesia; 2012.
3. Ravindranath Y. Childhood Leukemia and Cancer, An Issue of Pediatric Clinics, E-Book. Elsevier Health Sciences; 2014. 353 p.
4. AlAli A, Kletke S, Gallie B, Lam W-C. Retinoblastoma for Pediatric Ophthalmologists. *Asia Pac J Ophthalmol (Phila)*. 2018;7(3):160–8.
5. Sitorus RS, Moll AC, Suhardjono S, Simangunsong LS, Riono P, Imhof S, et al. The effect of therapy refusal against medical advice in retinoblastoma patients in a setting where treatment delays are common. *Ophthalmic Genet*. 2009;30(1):31–6.
6. Erwenne CM, Franco EL. Age and lateness of referral as determinants of extra-ocular retinoblastoma. *Ophthalmic Paediatr Genet*. 1989;10(3):179–84.
7. Finger PT, Harbour JW, Karcioğlu ZA. Risk Factors for Metastasis in Retinoblastoma. *Surv Ophthalmol*. 2002;47(1):1–16.
8. Chawla B, Hasan F, Azad R, Seth R, Upadhyay AD, Pathy S, et al. Clinical presentation and survival of retinoblastoma in Indian children. *Br J Ophthalmol*. 2016;100(2):172–8.
9. Pant G, Verma N, Kumar A, Pooniya V, Gupta SK. Outcome of extraocular retinoblastoma in a resource limited center from low middle income country. *Pediatr Hematol Oncol*. 2017;34(8):419–24.
10. Essuman V, Ntim-amponsah CT, Akafo S, Renner L. Presentation of retinoblastoma at a paediatric eye clinic in Ghana. - PubMed - NCBI. 2019.
11. Chantada G, Fandiño A, Casak S, Manzitti J, Raslawski E, Schwartzman E. Treatment of overt extraocular retinoblastoma. - PubMed - NCBI. 2019.
12. Jenkinson H. Retinoblastoma: diagnosis and management—the UK perspective. *Arch Dis Child*. 2015;100(11):1070–5.
13. Menon BS, Reddy SC, Maziah WM, Ham A, Rosline H. Extraocular retinoblastoma. *Med Pediatr Oncol*. 2000;35(1):75–6.
14. Sethi S, Pushker N, Kashyap S, Sharma S, Mehta M, Bakhshi S, et al. Extraocular retinoblastoma in Indian children: clinical, imaging and histopathological features. *Int J Ophthalmol*. 2013;6(4):481–6.
15. Gao J, Zeng J, Guo B, He W, Chen J, Lu F, et al. Clinical presentation and treatment outcome of retinoblastoma in children of South Western China. *Medicine (Baltimore)*. 2016;95(42):e5204.
16. Menon BS, Alagaratnam J, Juraida E, Mohamed M, Ibrahim H, Naing NN. Late presentation of retinoblastoma in Malaysia. *Pediatr Blood Cancer*. 2009;52(2):215–7.
17. Antoneli CBG, Ribeiro KB, Rodriguez-Galindo C, Soares FA, Arias VA, Novaes PERS, et al. The addition of ifosfamide/etoposide to cisplatin/teniposide improves the survival of children with retinoblastoma and orbital involvement. *J Pediatr Hematol Oncol*. 2007;29(10):700–4.
18. Shields CL, Shields JA. Recent Developments in the Management of Retinoblastoma. 2019.
19. Radhakrishnan V, Kashyap S, Pushker neelam, Sharma S, Pathy S, mohanti bidhu, et al. Outcome, pathologic findings, and compliance in orbital retinoblastoma (International Retinoblastoma Staging System stage III) treated with neoadju... - PubMed - NCBI. 2019.
20. Shields CL, Honavar SG, Meadows AT. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. - PubMed - NCBI. 2019.
21. Chantada GL, Gutter MR, Fandiño AC, Raslawski EC, de Davila MTG, Vaiani E, et al. Treatment results in patients with retinoblastoma and invasion to the cut end of the optic nerve. *Pediatr Blood Cancer*. 2009;52(2):218–22.
22. Leander C, Ligia F, Pena A, C Howard S, Galindo CR, A Willimas J, et al. Impact of an education program on late diagnosis of retinoblastoma in Honduras. - PubMed - NCBI. 2019.