The survival outcomes of unilateral retinoblastoma in Malaysia

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ABSTRACT

Retinoblastoma (RB) is the most common malignant intraocular tumour in children and can present as unilateral or bilateral disease. Unilateral RB represents 60% of all cases and tend to present at a relatively advanced stage of RB. Unilateral RB in Malaysia has a one-year survival rate of 99.0% and five-year survival of 93.0%. Shorter lag time, longer duration of follow-up and compliance with follow-up are good prognostic factors for the survival of unilateral RB patients. It is essential to report the prognostic factors associated with unilateral RB in our population. This information will assist healthcare professionals in understanding the factors that influence outcomes and support the development of long-term treatment guideline.

KEYWORDS:
Unilateral, retinoblastoma, survival outcomes, prognostic factors, Malaysia, paediatric

INTRODUCTION

Retinoblastoma (RB) is the most common malignant intraocular tumour in children and can present as unilateral or bilateral disease.[1] Globally, it is estimated to occur in approximately one out of every 16,000-18,000 live births.[2] The incidence of RB in Asia is about 1 in 16,642 live births, and India has the highest incidence of RB, with 1500 new cases per year, accounting for 33.0% of the global burden.[3] Malaysia reports between 27 to 36 cases annually.[4]

Unilateral RB represents 60% of all cases, with a mean age at diagnosis of 24 months.[5] Unilateral cases tend to present at a relatively advanced stage of RB, when compared with bilateral cases.[6] The reported mean ocular survival time is 20.67 months, and the overall survival rate is 96%. Initial chemotherapy, along with enucleation, is reported to reduce mortality in cases of advanced unilateral disease.[5,7]

There are limited data on the incidence, survival rates and prognostic factors for unilateral RB in Southeast Asia, including Malaysia. Identification of previously unreported evidence-based prognostic factors for survival of unilateral RB and its survival rate specific to our population will help to educate healthcare professionals and the community regarding the importance of recognising factors affecting the survival of unilateral RB and facilitating the development of integrated long-term clinical management guidelines for RB survivors.

Survival of unilateral retinoblastoma in Malaysia

The Malaysian National Eye Database's Retinoblastoma Registry has a collection of data on RB cases throughout Malaysia in all main tertiary hospitals with paediatric ophthalmology services. Analysing data of 114 patients from 2001 to 2020 that met the criteria of being diagnosed with unilateral RB with the age of less than 17 years old, 65 (57%) were from Hospital Kuala Lumpur, 27 (24%) were from Hospital Pakar Universiti Sains Malaysia and 22 (19%) were from Hospital Wanita Kanak-Kanak Sabah (Table I).

The mean age at diagnosis was 29 (18.9) months. This is a slightly younger age group, compared to unilateral RB patients in a Pakistani study, which was 37 months, and older than patients in the United States (US), which was 25 months.[8,9] The mean age at diagnosis in Malaysian children is similar to that from other South East Asian countries, as the mean age at diagnosis in the Philippines ranged from 24-33 months, with a significantly older age at presentation in unilateral disease, which was attributed to financial constraints and misdiagnoses.[10,11] Malaysian children showed fairly similar involvement in both genders in unilateral RB; boys accounted for 57.0% of cases, and girls made up the remaining 43.0%.

The white reflex (90.4%) was the most common first symptom of disease parents noticed, followed by strabismus (22.8%). This is consistent with the global RB presentation reported by Fabian et al.[12] Leukocoria (96.5%) was the most common sign observed in Malaysian children and is consistent with global data. Proptosis, which represents advanced disease, is reported to be higher in other Asian countries, such as Pakistan (22.0%) and Indonesia (66.0%).[13,14] Most (57.1%) of the non-surviving patients presented with proptosis, and all non-surviving patients were extraocular and diagnosed with International Retinoblastoma Staging System stage IV disease at presentation. This is the most advanced stage of disease and is linked to high mortality and a grave prognosis.[15] This stage

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Table I: Demographic and clinical data of Malaysian children with unilateral retinoblastoma

Variables	Frequency, n (%)		
	Death (n=7)	Censored (n=107)	Total (N=114)
Age at diagnosis (months)			
Less than 24 months	2 (28.6)	18 (16.8)	20 (17.5)
24 - 48 months	3 (42.9)	31 (29.0)	34 (29.8)
More than 48 months	2 (28.6)	58 (54.2)	60 (52.6)
Mean (SD)	23 (16.9)	29 (19.1)	29 (18.9)
Range	6 - 48	2 - 106	2 - 106
Gender			
Male	4 (57.1)	61 (57.0)	65 (57.0)
Female	3 (42.9)	46 (43.0)	49 (43.0)
Race			
Malay	6 (85.7)	70 (65.4)	76 (66.7)
Chinese	0	10 (9.3)	10 (8.8)
Indian	0	6 (5.6)	6 (5.3)
Others	1 (14.3)	21 (19.6)	22 (19.3)
Lag time			
Less than 6 months	1 (14.3)	79 (73.8)	80 (70.2)
More than 6 months	6 (85.7)	28 (26.2)	34 (29.8)
Mean (SD)	12 (11.0)	6 (10.7)	6 (10.8)
Range	2 - 36	0 - 96	0 - 96
Clinical features			
Leukocoria	7 (100.0)	103 (96.3)	110 (96.5)
Retinal detachment	3 (42.9)	31 (29.0)	34 (29.8)
Secondary glaucoma	3 (42.9)	17 (15.9)	20 (17.5)
Proptosis	4 (57.1)	9 (8.4)	13 (11.4)
Strabismus	0	11 (10.3)	11 (9.6)
Tumour extension			
Intraocular	0	98 (91.6)	98 (86.0)
Extraocular	7 (100.0)	9 (8.4)	16 (14.0)
Staging			
Intraocular A - B	0	2 (1.9)	2 (1.8)
Intraocular C - D	0	31 (29.0)	31 (27.2)
Intraocular E	0	65 (60.7)	65 (57.0)
Extraocular 0 - II	0	3 (2.8)	3 (2.6)
Extraocular III	0	1 (0.9)	1 (0.9)
Extraocular IV	7 (100.0)	5 (4.7)	12 (10.5)
Second neoplasm	1 (14.3)	0	1 (0.9)
Treatment received			
Enucleation	4 (57.1)	102 (95.3)	106 (93.0)
Chemotherapy	7 (100.0)	63 (58.9)	70 (61.4)
Focal therapy	0	8 (7.5)	8 (7.0)
EBRT	0	4 (3.7)	4 (3.5)
Non-compliance to follow-up			
Yes	5 (71.4)	10 (9.3)	15 (13.2)
No	2 (28.6)	97 (90.7)	99 (86.8)
Age at death (months)			
Mean (SD)	56 (26.2)	NA	NA
Range	23 - 97	NA	NA
Cause of death			
Disease progression	4 (3.5)	NA	NA
Severe sepsis	3 (2.6)	NA	NA

Abbreviations: EBRT, external beam radiotherapy; NA, not applicable. Censored : survived patients beyond the end of study period

of disease is seen at a high frequency in developing countries.[12] Similarly, Jain et al. reported that most of their study's non-surviving patients had advanced disease at presentation; 58.8-92.3% had extraocular disease.[16]

The hereditary form of unilateral RB, which were based on clinical assumption were present in only two patients, who were sisters. The low incidence of the hereditary form is likely because the incidence of the hereditary form is higher in bilateral cases.[17] Hereditary RB also includes a higher risk of developing a second primary neoplasm, which is 20% in those who have not received radiotherapy and 40-50% of those who have been irradiated.[18] However, data from the Malaysian National Eye Database's Retinoblastoma Registry showed only one (0.9%) patient who developed second neoplasm, and it was a paraganglioma. This patient had a sporadic form of RB and received systemic chemotherapy without any radiotherapy.

Enucleation (93.0%) and systemic chemotherapy (70.0%) were the most common treatment modalities given (Table II). This is because the majority of cases were diagnosed with International Classification for Retinoblastoma group E disease (57.0%), which warrants treatment with systemic

Table II: Treatment modalities received by Malaysian children with unilateral retinoblastoma

Variables	Frequency, n (%)			
	Enucleation	Chemotherapy	EBRT	Focal Therapy
Tumour extension				
Intraocular (n=98)	93 (94.9)	54 (55.1)	2 (2.0)	8 (8.2)
Extraocular (n=16)	13 (81.3)	16 (100.0)	2 (12.5)	0
Staging				
Intraocular A - B (n=2)	1 (50.0)	1 (50.0)	0	0
Intraocular C - D (n=31)	28 (90.3)	12 (38.7)	0	8 (25.8)
Intraocular E (n=65)	64 (98.5)	41 (63.1)	2 (3.1)	0
Extraocular 0 - II (n=3)	3 (100.0)	3 (100.0)	1 (33.3)	0
Extraocular III (n=1)	1 (100.0)	1 (100.0)	0	0
Extraocular IV (n=12)	9 (75.0)	12 (100.0)	1 (8.3)	0

Abbreviations: EBRT, external beam radiotherapy.

Table III: Overall unilateral retinoblastoma survival in Malaysia

	1-year survival		3-year survival		5-year survival	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Unilateral retinoblastoma	113 (99)	97,100	111 (97)	94,100	107 (93)	88,98

Abbreviations: CI; Confidence interval.

Table IV: The associated prognostic factors for survival of children with unilateral retinoblastoma in Malaysia

Variables	Crude HR	(95% CI)	p-Value[a]	Adjusted HR	(95% CI)	p-Value[b]
Age at diagnosis (months)						
Less than 24 months	-	-				
24 - 48 months	0.81	0.14, 4.87	0.82			
More than 48 months	0.31	0.04, 2.20	0.24			
Gender						
Male	-	-				
Female	0.98	0.22, 4.38	0.98			
Lag time						
Less than 6 months	-	-				
More than 6 months	14.26	1.71,118.48	0.014	102.04	1.58,6583.95	0.030
Enucleation						
Yes	-	-				
No	0.08	0.02,0.36	0.001	0.04	0.01,1.08	0.055
Duration of follow up	0.90	0.86,0.95	0.000	0.02	0.89,0.99	0.026
History of default						
Yes	0.05	0.01, 0.27	0.000	0.03	0.01,0.86	0.041
No	-	-				

[a]simple Cox Hazard Regression, [b]multiple Cox Hazard Regression
Abbreviations: HR; hazard ratio, CI; confidence interval, p<0.05 significant

Table V: Summary of literature of factors affecting survival rate of children with retinoblastoma in Asia

Country	Author / Year	Older age at	on-compliance diagnosis	Extraocular to follow-up	Lag time extension	Duration of follow-up
India	Chaw et al. / 2016	✓	NA	✓	✓	NA
Thailand	Rojanaporn et al. / 2020	✓	NA	✓	✓	NA
Singapore	Aung et al. / 2009	✓	NA	NA	✓	NA
Taiwan	Chang et al. / 2006	X	NA	✓	✓	NA
Korea	Kim et al. / 2020	X	NA	NA	NA	NA
Malaysia	Our study / 2025	X	✓	X	✓	✓

✓; Significant factors with 95% Confidence Interval or p < 0.05. X; not significant, NA; not available.

chemotherapy and enucleation.[19] Chemotherapy in intraocular disease were given to reduce tumour size and reduce risk of metastases. Focal therapy (7.0%) was not given as often, as it is recommended for earlier stages of disease, which had lower incidence levels in Malaysian children. External beam radiotherapy (3.5%) was the least treatment modality given as it is usually reserved for cases not responding well to chemotherapy. Another reason for the lack of these treatment modalities could be because these treatments are not available in most tertiary centres in Malaysia. In a study conducted in Egypt, enucleation (53.7%) was the main treatment given, followed by chemotherapy (46.3%), and most of their cases were groups D (41.9%) and E (33.5%).[5] Globally, enucleation remains an important treatment option, despite advancements in globe-salvage therapy.[12]

The overall survival rates of Malaysian children with unilateral RB were 99.0% (after one year), 97.0% (after three years) and 93.0% (after five years) as shown in Table III. This is slightly lower than the five-year survival rates for unilateral RB in Great Britain (97.0%) and China (95.5%).[20,21] A country's income level (low vs. high) has been reported as a risk factor of poor survival.[12] This is because patients in lower income countries presented with more aggressive disease, and these countries often lack sophisticated treatment and investigation facilities such as MRI, radiotherapy and focal treatments. This leads to limited disease management options. Better survival was attributed to the earlier diagnosis and treatment common in higher income countries, which is consistent with shorter lag time as a significant good prognostic factor in our data.

There are limited data on the survival rates specific to unilateral RB in other countries. The reported one-, three- and five-year survival rates of RB in India are 83.0-94.0%, 73.0-91.0% and 68.0-90.0%, respectively.[22,23] Survival rates in other Asian countries, such as Taiwan, Nepal, Indonesia and Thailand, are 64.4%, 26.6%, 20.0% and 73.0%, respectively.[24-27] The poor survival rate in Indonesia is attributed to high rates of treatment refusal (16.0%), treatment abandonment (40.0%) and a preference for less expensive alternative medicine.[24] In Malaysia, 2.6% of the patients refused treatment, but there were no patients who abandoned treatment once treatment commenced. Among these patients, 15 (13.2%) had a history of default prior to starting treatment, but they were compliant throughout the course of treatment.

Lag time less than six months, longer duration of follow-up and compliance with follow-up were the significant good prognostic factors in Malaysian children with unilateral RB, based on a multivariate analysis (Table IV). Shorter lag time has also been reported as a significant prognostic factor in India, Thailand and Singapore.[22,28,29] A global RB study also reported that early detection is the most important prerequisite for a better outcome.[1] Here, longer lag times were due to the lack of awareness by parents, parents' dilemma, parents' preferences for alternative medicine, financial constraints and a refusal to seek an earlier medical consultation. Roland et al. reported that the cause of delay in South Asian countries is also attributable to a lack of knowledge on the severity of the disease, a lack of access to healthcare and resorting to alternative medicine.[15]

Limited data are available on the impact of follow-up duration and compliance as prognostic factors for the survival of unilateral RB patients. Fabian et al. reported that higher income countries with better survival rates had a longer follow-up time, of 37 months, compared to low-income countries (14.7 months).[12] A longer duration of follow-up allows managing doctors to identify patients who develop complications or respond poorly to treatment. Therefore, necessary interventions to avoid further complications could be administered, hence preventing unwanted complications and ensuring better survival. The reason for defaulting on follow-up after a diagnosis in Malaysia was due to poor insight on the severity of the disease and resorting to alternative medicine, as in other South Asian countries.[15] Those who defaulted ultimately presented again to managing institutions, once the disease had progressed and parents realised that alternative medicine had no effect on their children.

Extraocular extension was an insignificant prognostic factor, although studies in India and Thailand reported that rates of extraocular extension were significant.[22,28] More than half (56.0%) of Malaysian patients with extraocular extension survived, and a majority of them had shorter lag times (56.3%) with good compliance with follow-up (66.7%). By contrast, a majority of the non-surviving patients had longer lag times (85.7%) and were non-compliant with follow-up (71.4%). Therefore, even if patients had extraocular extension at presentation, a shorter lag time and compliance with follow-up led to better survival outcomes for these patients ($p < 0.05$). This is because they were able to receive appropriate and adequate treatment as early as possible, compared to patients who experienced a delay in beginning treatment. Although the non-surviving patients did receive treatment, the progression of disease and complications of severe sepsis affected the efficacy and adequacy of treatment, hence their poor outcomes.

An older age at diagnosis was not identified as a significant prognostic factor in our data, despite previously reported studies claiming that age at diagnosis was significant.25,28-30 Among the survivors, 54.2% had an older age at diagnosis (48 months), compared to the non-surviving patients (23 months). In short, early onset RB does not indicate a poor survival prognosis in Malaysian children with unilateral RB. Similarly, studies in Taiwan and Korean did not find age at diagnosis to be a significant prognostic factor.[31,32] Table V summarises the factors affecting the survival rate in Asia.

CONCLUSION

The outcomes of this study highlight an urgent need to improve RB awareness among parents, healthcare workers and the community for earlier detection, better access to treatment and ensuring compliance with follow-up. The survival rate of unilateral RB in Malaysia can be improved to make it a zero-death cancer, but prognostic factors for survival must be managed promptly to ensure better survival. A national-level initiative should be proposed to achieve this goal which includes continuous education on RB awareness for primary healthcare providers, parents and the community.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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