Clinical characteristics and prognosis of patients with retinoblastoma: 8-year follow-up

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Background/aim: The aim of this study was to investigate the potential correlation between clinical characteristics and prognosis of patients with retinoblastoma (Rb).

Materials and methods: This retrospective study included 314 Rb patients. Clinical data including laterality of eyes, sex, age, presenting signs, lag time, and survival were recorded and analyzed.

Results: Leukocoria is the most common clinical presentation of Rb. Patients with isolated leukocoria had shorter lag time and exhibited a high survival rate (85%, 5 years). Patients with strabismus and blurred vision, and who were older and had longer lag time, exhibited an excellent survival rate (100% and 92.3%, respectively, 5 years). Patients with exophthalmos had the longest lag time and the lowest survival rate (17.8%, 5 years). The 5-year survival rate of patients with a lag time of ≤6 months was 84.7%, which was significantly higher than that of patients with a lag time of >6 months (64.7%).

Conclusion: Leukocoria, strabismus, and blurred vision are mild clinical manifestations of Rb that are associated with better disease prognosis, whereas exophthalmos is an indicator of poor prognosis. Long lag time is a risk factor for the survival of Rb, which can be avoided. Early detection and treatment can greatly improve the survival of Rb patients.

Key words: Retinoblastoma, diagnosis, prognosis

1. Introduction

Retinoblastoma (Rb) is the most common intraocular malignant tumor in children, accounting for approximately 3%–4% of all malignant tumors in children aged 0–14 years (1,2). Currently, in developed countries with advanced tools for medical diagnosis, Rb can be detected early, thus leading to an improved survival rate of more than 95% for this high-mortality disease. However, the survival rate from this disease is still as low as approximately 50% worldwide (3). This may be due to the poor diagnostic and therapeutic capacity, as well as generally poor health conditions, experienced in low-income countries. This leads to late diagnosis of the disease and thus a high incidence of extraocular complications and a high risk of distant metastasis (4). Rb can be cured if the disease is diagnosed early, if disease severity is appropriately assessed, and if proper treatments are applied (5). Therefore, this study aimed to identify clinical characteristics of Rb patients, to find the potential relationship between clinical manifestations and survival rates from Rb, and to provide

a clinical basis for prediction of disease outcomes and treatment options.

2. Materials and methods

2.1. Clinical data

This retrospective study with complete follow-up data included 314 patients who were diagnosed as having Rb at the Zhongshan Ophthalmic Center at Sun Yat-sen University from January 2003 to February 2011. Clinical data, including laterality of eyes, sex, age at diagnosis, presenting signs, lag time before treatment, survival conditions, and survival time, were recorded. Patients were followed until death or the cutoff date (February 2013), whichever occurred first. The mean follow-up time was 41.4 ± 27.9 months (median, 33 months; range, 1–110 months).

Patients' clinical presentations at diagnosis were categorized into 6 groups based on the description given by the patients or their families: 1) leukocoria (white reflection from the pupil); 2) strabismus; 3) inflammation

with symptoms and signs such as red eye, eye pain, photophobia, lacrimation, hyphema, hypopyon, and/or orbital cellulitis; 4) blurred vision (vision loss or blindness); 5) exophthalmos (eyeball protrusion as a result of the eye being pushed forward by orbitally invaded Rb); and 6) others, including relatively rare symptoms such as narrow eyes (atrophy of eyeball) and ptosis or Rb without obvious symptoms diagnosed by eye examination or photograph accidentally. If the patients presented with more than one type of symptom, they were classified into each appropriate symptom group. Lag time before treatment was defined as the interval between the occurrence of the first symptom and treatment.

2.2. Treatment

Patients with intraocular retinoblastoma were classified into group A, group B, group C, group D, or group E according to the International Intraocular Retinoblastoma Classification (IIRC) (6). Patients with extraocular retinoblastoma were grouped into stage 1, stage 2, stage 3, or stage 4 according to the International Retinoblastoma Staging System (IRSS) (7).

In the present study, for unilateral retinoblastoma, eyes in groups A, B, and C and some eyes in group D, which were identified using local measures (cryotherapy, transpupillary thermotherapy, and laser) with or without chemoreduction, were used. All group E, stage 1, and advanced D eyes were enucleated. Chemoreduction was performed with standard doses of VEC protocol: intravenous vincristine (0.05 mg/kg, day 1), etoposide (5 mg/kg, days 1 and 2), and carboplatin (18.6 mg/kg, day 1). Chemoreduction cycles were executed every 3–4 weeks for a total of 6 cycles. For bilateral retinoblastoma, chemoreduction is used in most cases. Enucleation was performed on stage E retinoblastomas after failure to control the tumor by other modalities. Periorbital carboplatin injection (20 mg/2 mL) was given in advanced retinoblastoma cases in both eyes, in the only remaining eye, or in those eyes in stages 2 and 3. In addition, for retinoblastoma cases stage 2, 3, and 4, the treatment consisted of enucleation, high-dose chemotherapy of VEC protocol (intravenous vincristine (0.25 mg/kg, day 1), etoposide (12 mg/kg, days 1 and 2),

and carboplatin (28 mg/kg, day 1)), and external beam radiotherapy to the orbit and metastatic sites.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 17.0. The Kaplan–Meier method was used to calculate the 5-year probability event-free survival (5-PEF). The log-rank test was used to compare the difference in survival rates. The Cox proportional hazards model was used to analyze the effects of multiple risk factors on survival situations. Nonparametric tests were used to compare the differences in sex, lag time before treatment, and age between unilateral and bilateral cases. Spearman correlation analysis was used to analyze the relationship between age and lag time before treatment. $P < 0.05$ (two-tailed test) was considered statistically significant.

3. Results

3.1. Clinical data

Table 1 summarizes the clinical characteristics of patients with Rb. A total of 314 patients (399 eyes) were included in the study. In the cohort, 197 (62.7%) patients were male and 117 patients (37.3%) were female. Of the patients, 229 (72.9%) had unilateral cases and 85 (27.1%) had bilateral cases. Of the 399 eyes, 199 (49.9%) were left eyes and 200 (50.1%) were right eyes.

3.2. Age at diagnosis and lag time before treatment

The mean age at diagnosis was 24.5 ± 18.2 months, and the average lag time before treatment was 3.6 ± 5.6 months (range, 0–4 years). There was a positive correlation between age at diagnosis and lag time before treatment (r = 0.16, P = 0.04), indicating that the older the patients were at diagnosis, the more prolonged their lag time was before treatment. Age at diagnosis was significantly lower in bilateral cases than in unilateral cases (Table 1).

3.3. Clinical manifestations

Leukocoria (n = 242, 77.1%) was the most common clinical manifestation of Rb in patients. Patients with leukocoria were significantly older than those without leukocoria. The lag time before treatment was significantly lower in patients with isolated leukocoria than in patients with leukocoria in combination with other symptoms.

Table 1. Patients' characteristics and outcomes according to sex and laterality.

	Sex			Laterality		
	Male n = 197	Female n = 197	P	Unilateral n = 229	Bilateral n = 85	P
Mean lag time before treatment (months)	3.6 ± 5.3	3.6 ± 6.1	0.67	3.5 ± 5.4	4.3 ± 6.4	0.66
Mean age (months)	24.7 ± 17.7	24.1 ± 19.1	0.64	28.3 ± 19.0	14.1 ± 10.0	0.00
5-PEF (%)	82.7	77.5	0.27	82.6	75.5	0.34

Of 43 patients with inflammation (13.7%), 8 patients had leukocoria and 3 patients had exophthalmos.

Of the 13 patients with strabismus (4.1%), none of them presented other clinical symptoms. The lag time before treatment in patients with strabismus was significantly longer than in those without. Patients with strabismus tended to be older than those without (P = 0.05).

Of 13 patients with blurred vision (4.1%), one patient had red eye and one patient had leukocoria. The age at diagnosis was significantly older in patients with leukocoria than in those without.

Of 15 patients with exophthalmos (4.8%), 9 patients had leukocoria for a period of time ranging from 7 days to 2 years before the occurrence of exophthalmos. The lag time before treatment was significantly longer in patients with exophthalmos than in those without. Patients with exophthalmos exhibited a tendency towards being older than those without.

Of the 10 patients with other symptoms (3.2%), 4 patients were discovered accidentally. Of these 4 cases, 2 patients had a family history of Rb and 2 patients were found to show abnormal pupillary reflection during photo acquisition. Ptosis, narrow eyes (atrophy of eyeball), and corneal opacity occurred in 3 cases, 2 cases, and 1 case, respectively.

3.4. Disease stage
There were 159 eyes from group E, 66 from group D, 52 from group C, 136 from group B, and 9 from group A. A total of 44 patients had stage 1 disease, 12 patients had stage 2 disease, 18 patients had stage 3 disease, and 3 patients had stage 4 disease.

3.5. General survival analysis
The 5-year survival rate of all 314 patients was 80.9%. The survival rate did not change after 38 months (Figure 1). There was no significant difference in the survival rate between male and female patients or between unilateral and bilateral cases (Table 1).

3.6. Lag time before treatment and survival analysis
The 5-year survival rate was 84.5% for patients with lag time before treatment of ≤6 months and 64.7% for those with lag time before treatment of >6 months. There was a significant difference in the survival rate between these 2 groups (P < 0.01).

3.7. Survival analysis of patients with different clinical manifestations
In regard to clinical manifestations, strabismus had the highest 5-year survival rate (100%), followed by blurred vision (92.3%), isolated leukocoria (85.0%), leukocoria (81.5%), inflammation (70.4%), and exophthalmos (17.8%) (Figure 2).

There was no significant difference in the survival rate between patients with leukocoria and those without. However, the 5-year survival rate in patients with isolated leukocoria (85.0%) was significantly higher than in those with leukocoria combined with other symptoms (40.1%) (Table 2).

The 5-year survival rate in patients with exophthalmos (17.8%) was significantly lower than that in patients without (84.1%). Patients with inflammation (70.4%) tended to have a lower 5-year survival rate compared
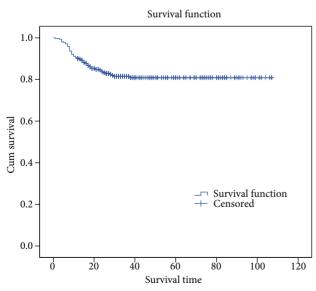

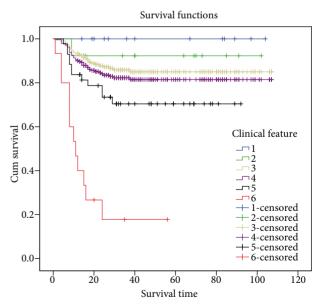**Figure 1**. Five-year survival rate of 314 patients with Rb.

Figure 2. Five-year survival rate of Rb patients with different clinical manifestations. 1, Strabismus; 2, blurred vision; 3, isolated leukocoria; 4, leukocoria; 5, inflammation; 6, exophthalmos.

Table 2. Differences in age, lag time, and 5-PEF in patients with different clinical manifestations.

Group	Eyes (n)	Age (months)		Lag time before treatment (months)		5-PEF (%)	P
		Mean ± SD	P	Mean ± SD	P		
Leukocoria	242	22.8 ± 15.3	0.02	3.8 ± 5.6	0.36	81.5	0.68
Nonleukocoria	72	30.4 ± 24.7		3.1 ± 5.8		79.1	
Leukocoria (simple)	223	22.4 ± 15.6	0.15	3.2 ± 4.8	0.00	85.0	0.00
Leukocoria (combined)	19	27.6 ± 10.6		10.6 ± 9.2		40.1	
Inflammation	43	24.9 ± 20.5	0.87	2.7 ± 5.3	0.23	70.4	0.06
Noninflammation	271	24.5 ± 17.8		3.8 ± 5.7		82.6	
Strabismus	13	34.1 ± 22.1	0.05	8.3 ± 9.8	0.02	100	0.11
Nonstrabismus	311	24.1 ± 17.9		3.4 ± 5.3		80.1	
Blurred vision	13	53.9 ± 31.2	0.00	4.4 ± 6.5	0.60	92.3	0.34
Nonblurred vision	311	23.3 ± 16.3		3.6 ± 5.6		80.4	
Exophthalmos	15	29.1 ± 9.4	0.08	10.1 ± 9.7	0.02	17.8	0.00
Nonexophthalmos	299	24.3 ± 18.5		3.3 ± 5.2		84.1	

to those without (82.6%), but the difference was not statistically significant (P = 0.06) (Table 2).

3.8. Multiple factor survival analysis

The Cox proportional hazards model was used to analyze the effect of multiple factors on the survival rate of the 314 Rb patients, including factors such as the presence of leukocoria, strabismus, inflammation, exophthalmos, or blurred vision; sex; age; laterality; and lag time before treatment. Exophthalmos and lag time before treatment were found to be significant as independent risk factors (Table 3).

4. Discussion

In the past few decades, the survival rate of Rb has significantly improved, especially in developed countries. The 5-year survival rate has increased to 95% and 87% in Europe and the United States, respectively (8). Our data showed that the 5-year survival rate was 80.9%, which was comparable to that in other developing countries and regions: 80.9% in Taiwan (9), 83.1% in Iran (10), and 81% in other developing countries (Argentina, Brazil, Turkey, Jordan, and Venezuela) (11). The survival rate reported in our study was significantly higher than that reported for less developed countries, such as in East Africa (30%) (12) and Central America (48%) (13).

In the present study, we found that leukocoria was the most common clinical manifestation of Rb in patients (77.1%), which was comparable to findings from Turkey (64.8%–82%) (14,15). Leukocoria is usually indicative

of large intraocular tumors that fill the eyeball without extraocular invasion (16). Therefore, patients with leukocoria exhibit a relatively high 5-year survival rate. Abramson et al. reported that patients with leukocoria had a survival rate of 86% (17). In our study, we found that patients with isolated leukocoria who were younger and had a shorter lag time before treatment exhibited a relatively higher survival rate (85%). The survival rate decreased to 40.1% if patients with leukocoria also exhibited other symptoms. These findings suggest that leukocoria is a mild early clinical presentation, so if patients are treated before other symptoms occur, the survival rate can be significantly improved.

In our study, patients with inflammation were younger and had shorter lag times before treatment compared to those with other clinical manifestations except leukocoria. However, the 5-year survival rate of patients with inflammation was only 70.4%, and patients with inflammation exhibited a lower survival tendency compared to patients without inflammation (82.6%) (P = 0.06). These findings suggest that inflammation is more likely to occur in younger children and that its easy detection by parents leads to earlier diagnosis. However, patients with inflammation typically experience more severe conditions and poor prognosis. Therefore, more attention should be paid to those Rb patients with manifest signs of inflammation.

In developed countries, strabismus is the second most common clinical manifestation in Rb patients, followed

Table 3. Risk factors for overall survival based on clinical characteristics determined by Cox regression analysis.

Clinical characteristics	β	SE(β)	95% CI	EXP(β)	P
Leukocoria	−0.20	0.39	0.38–1.74	0.82	0.60
Strabismus	−6.06	138.37	0.00–1.40	0.002	0.97
Inflammation	0.11	0.13	0.86–1.45	1.12	0.40
Exophthalmos	0.55	0.08	1.47–2.04	1.73	0.00
Blurred vision	−0.15	0.18	0.61–1.22	0.86	0.40
Sex	0.27	0.27	0.77 - 2.24	1.31	0.31
Age	0.00	0.01	0.98–1.02	1.00	0.97
Laterality	0.25	0.31	0.69–2.36	1.27	0.44
Lag time	0.00	0.00	1.00–1.00	1.00	0.02

by leukocoria (17,18). However, in our study, we found that strabismus occurred in only 4.1% of Rb patients. Strabismus is commonly associated with the occurrence of macular tumors or macular retinal detachment (19). Navo et al. (20) speculated that strabismus is the earliest clinical presentation of Rb and is associated with good prognosis, and that Rb patients with strabismus tend to be younger and to experience shorter disease duration, effectively yielding a higher survival rate (as high as 90%) compared to patients with leukocoria. In our study, the survival rate of patients with strabismus was 100%. However, the occurrence of strabismus was not associated with age, and patients with strabismus had the longest lag time before treatment, suggesting that strabismus may not raise parents' attention, thus leading to a delay in seeking treatment.

Blurred vision is the only clinical manifestation that the patients can verbalize, thus being typically detected in older patients. Rb is generally considered to be less likely to occur in older children (>5 years) and thus may be neglected by the examining physician (21). This may explain why these Rb patients had the longest lag time before treatment in our study. Although patients with strabismus and blurred vision exhibited significantly longer lag times before treatment compared with other clinical presentations, the 5-year survival rate was higher. Several factors may contribute to this high survival rate. First, the tumor site and growth rate may be an important factor in determining the survival of Rb patients. Tumors in the macula can cause an early occurrence of strabismus and blurred vision, but they grow slowly. Therefore, even though patients with strabismus and blurred vision typically have a longer disease course, they tend to have a better prognosis. Second, pathological differentiation of the tumor may be another factor in determining the

survival rate of Rb patients. However, further studies are required to demonstrate the role of tumor differentiation on the survival rate of patients with strabismus and blurred vision.

Orbital invasion rarely occurs in Rb patients in developed and developing countries (11,18), but it is the most common symptom of Rb patients in less developed countries (22–24). Although patients with orbital invasion accounted for only 4.8% of all Rb patients in our study, their death rate accounted for 21.1% of Rb patients, with a survival rate of only 17.8%. Approximately 50% of patients with exophthalmos exhibited leukocoria during the disease course before the occurrence of exophthalmos, but they unfortunately were not hospitalized until after the occurrence of exophthalmos. Orbital invasion is generally thought to be a clinical manifestation associated with poor Rb prognosis. Even when patients with orbital invasion are treated aggressively, the survival rate of these patients is still very low. Therefore, reducing the occurrence of orbital invasion and its associated high mortality rate is a critical goal for ophthalmologists.

In the present study, the mean age at diagnosis of Rb was 24.5 months, which was similar to that reported in other developing countries and regions (24–28.5 months) (9–11,20) and in between the mean age in developed countries (19.7 months) (17) and less developed countries (36.5 months) [23]. Navo et al. (20) found that death could be maximally avoided in younger Rb patients with less lag time before treatment if the patients were diagnosed early. Erwenne and Franco (25) reported that Rb with lag time before treatment of >6 months was associated with extraocular invasion and poor prognosis. Our study also found that lag time before treatment was a risk factor for death in Rb patients. The survival rate of patients with lag time before treatment of ≤6 months was significantly

higher than that of patients with lag time of >6 months. In some countries, screening for early diagnosis of Rb has improved the early detection rate of Rb. The American Academy of Pediatrics recommends that the red reflex test should be performed in infants and children from birth to 2 years of age in order to screen for abnormalities of the posterior segment of the eye and opacities in the visual axis; this would help identify the common early clinical signs of leukocoria and strabismus in Rb patients (26). In Honduras, the extraocular incidence of Rb has dropped from 73% to 35% following efforts to educate parents with vaccinated children about leukocoria (27).

In summary, leukocoria, strabismus, and blurred vision are early mild clinical manifestations of Rb that are associated with better disease prognosis. Long lag time before treatment is a major risk factor in determining survival from Rb and can be significantly attenuated by educating parents about the disease. It is therefore of critical importance to introduce Rb via various media outlets in order to raise public awareness, thereby increasing the chances of early detection and the probability of survival of patients with Rb.

References

1. Parkin DM, Stiller CA, Draper GJ. International Incidence of Childhood Cancer. IARC Scientific Publications Number 87. Lyon, France: International Agency for Research on Cancer; 1988.

2. Parkin DM, Kramarova E, Draper GJ. International Incidence of Childhood Cancer Volume 2. IARC Scientific Publications Number 144. Lyon, France: International Agency for Research on Cancer; 1998.

3. Shields JA, Shields CL, Meadows AT. Chemoreduction in the management of retinoblastoma. Am J Ophthalmol 2005; 140: 505–506.

4. Chantada G, Fandiño A, Manzitti J, Urrutia L, Schvartzman E. Late diagnosis of retinoblastoma in a developing country. Arch Dis Child 1999; 80:171–174.

5. Rodriguez-Galindo C, Wilson M, Chantada G, Fu L, Qaddoumi I, Antoneli C, Leal-Leal C, Sharma T, Barnoya M, Epelman S et al. Retinoblastoma: one world, one vision. Pediatrics 2008; 122: e763–770.

6. Murphree AL. Intraocular retinoblastoma: the case for a new group classification. Ophthalmol Clin North Am 2005; 18: 41–53.

7. Chantada G, Doz F, Antoneli CB, Grundy R, Clare Stannard FF, Dunkel IJ, Grabowski E, Leal-Leal C, Rodríguez-Galindo C, Schvartzman E et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer 2006; 47: 801–805.

8. Gatta G, Capocaccia R, Coleman MP, Ries LA, Berrino F. Childhood cancer survival in Europe and the United States. Cancer 2002; 95: 1767–1772.

9. Chang CY, Ghiou TJ, Hwang B, Bai LY, Hsu WM, Hsieh YL. Retinoblastoma in Taiwan: survival rate and prognostic factors. Jpn J Ophthalmol 2006; 50: 242–249.

10. Naseripour M, Nazari H, Bakhtiari P, Modarres-Zadeh M, Vosough P, Ausari M. Retinoblastoma in Iran: outcomes in terms of patients' survival and globe survival. Br J Ophthalmol 2009; 93: 28–32.

11. Chantada GL, Dunkel IJ, Qaddoumi I, Antoneli CB, Totah A, Canturk S, Nawaiseh I, Fandiño A, Pífano I, Peksayar G et al. Familial retinoblastoma in developing countries. Pediatr Blood Cancer 2009; 53: 338–342.

12. Bowman RJ, Mafwiri M, Luthert P, Luande J, Wood M. Outcome of retinoblastoma in east Africa. Pediatr Blood Cancer 2008; 50: 160–162.

13. Luna-Fineman S, Barnoya M, Bonilla M, Fu L, Baez F, Rodríguez-Galindo C. Retinoblastoma in Central America: Report from the Central American Association of Pediatric Hematology Oncology (AHOPCA). Pediatr Blood Cancer 2011; 58: 545–550.

14. Ozkan A, Pazarli H, Celkan T, Karaman S, Apak H, Kaner G, Uzel O, Yildiz I. Retinoblastoma in Turkey: survival and clinical characteristics 1981–2004. Pediatr Int 2006; 48: 369–373.

15. Ozdemir H, Tacyildiz N, Unal E, Yavuz G, Ugur H, Gunduz K. Clinical and epidemiological characteristics of retinoblastoma: correlation with prognosis in a Turkish pediatric oncology center. Pediatr Hematol Oncol 2007; 24: 221–231.

16. Augsburger JJ, Bornfeld N, Giblin M. Malignant intraocular tumors-retinoblastoma. In: Yanoff M, editor. Ophthalmology. 1st ed. St. Louis, MO, USA: Mosby International; 1999. pp. 921–928.

17. Abramson DH, Beaverson K, Sangani P, Vora RA, Lee TC, Hochberg HM, Kirszrot J, Ranjithan M. Screening for retinoblastoma: presenting signs as prognosticators of patient and ocular survival. Pediatrics 2003; 112: 1248–1255.

18. Butros LJ, Abramson DH, Dunkel IJ. Delayed diagnosis of retinoblastoma: analysis of degree, cause, and potential consequences. Pediatrics 2002; 109: e45.

19. Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW 3rd. Presenting signs of retinoblastoma. J Pediatr 1998; 132: 505–508.

20. Navo E, Teplisky D, Albero R, Fandino AC, Demirdjian G, Chantada GL. Clinical presentation of retinoblastoma in a middle-income country. J Pediatr Hematol Oncol 2012; 34: e97–101.

21. Aguirre Neto JC, Antoneli CB, Ribeiro KB, Castilho MS, Novaes PE, Chojniak MM, Arias V. Retinoblastoma in children older than 5 years of age. Pediatr Blood Cancer 2007; 48: 292–295.

22. Abdu L, Malami S. Clinicopathological pattern and management of retinoblastoma in Kano, Nigeria. Ann Afr Med 2011; 10: 214–218.

23. Badthu B, Sah SP, Thakur SK, Dulal S, Kumar S, Sood A, Das H, Sah RP. Clinical presentation of retinoblastoma in Eastern Nepal. Clin Experiment Ophthalmol 2005; 33: 386–389.

24. Bhurgri Y, Muzaffar S, Ahmed R, Ahmed N, Bhurgri H, Usman A, Faridi N, Malik J, Kazi LA, Bashir I et al. Retinoblastoma in Karachi, Pakistan. Asian Pac J Cancer Prev 2004; 5: 159–163.

25. Erwenne CM, Franco EL. Age and lateness of referral as determinants of extra-ocular retinoblastoma. Ophthalmic Paediatr Genet 1989; 10: 179–184.

26. Mahoney DH. Retinoblastoma. In: McMillan JA, editor. Oski's Pediatrics: Principles and Practice. New York, NY, USA: Lippincott Williams & Wilkins; 1999. pp. 1525–1527.

27. Leander C, Fu LC, Peña A, Howard SC, Rodriguez-Galindo C, Wilimas JA, Ribeiro RC, Haik B. Impact of an education program on late diagnosis of retinoblastoma in Honduras. Pediatr Blood Cancer 2007; 49: 817–819.