RESEARCH ARTICLE

Presentation of Retinoblastoma Patients in Malaysia

Shridevi Subramaniam[1], Jamalia Rahmat[2]*, Norazah Abdul Rahman[2], Sunder Ramasamy[2], Nirmala Bhoo-Pathy[1,3], Goh Pik Pin[1], Joseph Alagaratnam[2]

Abstract

Background: Retinoblastoma is a rare type of cancer that usually develops in early childhood. If left untreated it can cause blindness and even death. The aim of this study is to determine sociodemographic and clinical features of retinoblastoma patients and also to determine the treatment pattern and outcome in Malaysia. Materials and Methods: Data for this study were retrieved from the Retinoblastoma Registry of the National Eye Database (NED) in Malaysia. Hospital Kuala Lumpur, Hospital Umum Kuching, Sarawak and Hospital Queen Elizabeth, Kota Kinabalu were the major source data providers for this study. Data collected in the registry cover demography, clinical presentation, modes of treatment, outcomes and complications. Results: The study group consisted of 119 patients (162 eyes) diagnosed with retinoblastoma between 2004 and 2012. There were 68 male (57.1%) and 51 (42.9%) female. The median age at presentation was 22 months. A majority of patients were Malays (54.6%), followed by Chinese (18, 5%), Indians (8.4%), and indigenous races (15.9%). Seventy six (63.8%) patients had unilateral involvement whereas 43 patients had bilateral disease (36.1%). It was found that most children presented with leukocoria (110 patients), followed by strabismus (19), and protopsis (12). Among the 76 with unilateral involvement (76 eyes), enucleation was performed for a majority (79%). More than half of these patients had extraocular extension. Of the 40 who received chemotherapy, 95% were given drugs systemically. Furthermore, in 43 patients with bilateral involvement (86 eyes), 35 (41%) eyes were enucleated and 17 (49%) showed extraocular extension. Seventy-two percent of these patients received systemic chemotherapy. The patients were followed up 1 year after diagnosis, whereby 66 were found to be alive and 4 dead. Sixteen patients defaulted treatment and were lost to follow-up, whereas follow-up data were not available in 33 patients. Conclusions: Patients with retinoblastoma in this middle-income Asian setting are presenting at late stages. As a result, a high proportion of patients warrant aggressive management such as enucleation. We also showed that a high number of patients default follow-up. Therefore, reduction in refusal or delay to initial treatment, and follow-up should be emphasized in order to improve the survival rates of retinoblastoma in this part of the world.

Keywords: Childhood cancer - clinical presentation - treatment - Malaysia

Asian Pac J Cancer Prev, **15 (18)**, 7863-7867

Introduction

Retinoblastoma is a rare type of eye cancer but is the most common primary intraocular tumour that usually develops in early childhood (Wallach et al., 2006). If left untreated it can cause blindness and even death (Sitorus et al., 2009). Therefore early recognition of the symptoms is important as early diagnosis and treatment are necessary to improve the outcomes in patients with retinoblastoma (Carter, 2009).

While, survival rates has improved to more than 90% in developed countries (Sitorus et al., 2009; Bukhari et al., 2011), a majority of patients in developing countries present with advanced disease, with extraocular dissemination (Sitorus et al., 2009). Hence, the survival rates retinoblastoma patients in these settings are dismal (Essuman et al., 2010; Bukhari et al., 2011).

Relatively few studies have studied retinoblastoma in Asian settings. We carried out this study to determine the characteristics, clinical presentation, treatment patterns and outcome of patients' with retinoblastoma in a multiethnic Asian country.

Materials and Methods

Data for this study was retrieved from the Retinoblastoma Registry of the National Eye Database (NED). The NED is a prospective clinical database with ongoing systematic online data collection pertaining to specific visual threatening eye diseases. Further details of the database have been described elsewhere (Goh et al., 2008).

*[1]National Clinical Research Centre, Dermatology Block, [2]Department of Ophthalmology, Hospital Kuala Lumpur, Jalan Pahang, [3]Julius Centre University of Malaya, Dept of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia *For correspondence: jamalia.rahmat@gmail.com*

Hospital Kuala Lumpur, Hospital Umum Kuching, Sarawak and Hospital Queen Elizabeth, Kota Kinabalu and are the major data providers for this study. Data collected in the registry comprise demography, clinical presentation, modes of treatment, outcome (remissions and recurrences) and complication. Patients also were monitored via scheduled appointments in the ophthalmology clinics. Data on mortality were obtained from the hospitals' medical record as well as active follow up through the next of kin of patients.

The current study encompassed 119 patients (79 from Hospital Kuala Lumpur, 13 from Hospital Umum Kuching, Sarawak and 7 from Hospital Queen Elizabeth, Kota Kinabalu) diagnosed between January 2004 and April 2012. Data was analysed for distribution of demographic profile, clinical presentation, treatment, management and outcome of retinoblastoma patients. All the patients were diagnosed with indirect ophthalmoscopy, fundus imaging (Retcam), ultrasonography and imaging (CT scan or MRI). Tumours were characterised using the International Intraocular Retinoblastoma Classification (IIRC) by a team of paediatric ophthalmologists.

In all the above hospitals, advanced tumours classified as Group E and some Group D were enucleated. Patients with tumors requiring shrinkage (Group B to D) were treated with systemic chemotherapy and focal consolidation using laser and cryotherapy. Systemic chemotherapy was given by the paediatric oncology team. Small tumors (Group A) received local laser or cryotherapy.

Enucleated eyes were sent for histopathological examination. Eyes with extraocular infiltration were given adjuvant systemic chemotherapy. Patients with extraocular retinoblastoma were treated with chemoreduction, enucleation and external beam radiotherapy. Radiotherapy was also delivered to tumors which failed or resistant to other treatments (Jamalia et al., 2010).

Descriptive statistics for each variable were obtained. All statistical analyses were performed using IBM SPSS Statistics 20.

Results

This study consists of 119 patients (162 eyes) diagnosed with retinoblastoma between January 2004 and April 2012. Seventy six (63.8%) patients had unilateral and 43 patients (36.1%) had bilateral disease. There were 68 male (57.1%) and 51 (42.9%) females. Majority of the patients were of Malay ethnicity (55.6%), followed by Chinese (18.8%), and Indians (8.5%), whereas the remainder (17.3%) include other races.

The median age at presentation was 22 months (1-123 months). Eight patients presented at above 5 years of age. However, the age at presentation was higher in unilateral cases (median age 29 months, range 2-123 months) than in bilateral cases (mean age 14 months, range 1-60 months) (Table 1).

Only one patient reported family history of retinoblastoma. The commonest presentations are leukocoria (110 patients), followed by strabismus (19 patients) and protopsis (12 patients). Some patients also had relatively rare presentations which include bloody eye discharge (n=1), eye redness (n=5), hyphema (n=2), preseptal cellulitis (n=3), tearing (n=3), secondary glaucoma (n=1) and incidental finding following cataract surgery, (n=2).

Median duration of symptoms was 5 months. A great majority of patients (82.1%) presented within 6 months from the onset of symptoms occurrence. Only fourteen patients presented to hospital within a year and 6 patients had the symptom for more than 1 year before being seen at a referral centre.

There were 102 patients (137 eyes) who underwent CT

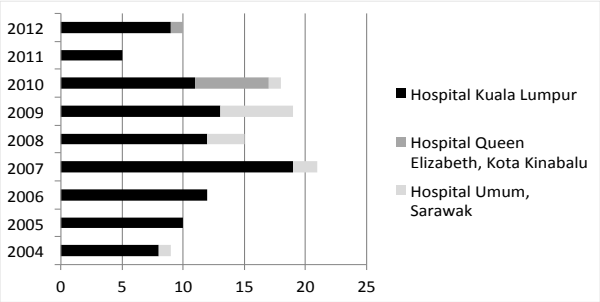

Figure 1. Number of Retinoblastoma Cases Registered from January 2004-April 2012

Table 1. Age at Presentation in Retinoblastoma Patients

Age(months)	Unilateral	Bilateral	n(%)
<12	10	18	28 (23.5)
13-24	20	15	35 (29.4)
25-36	21	7	28 (23.5)
37-48	13	2	15 (12.6)
49-60	4	1	15 (04.2)
>60	8	0	18 (06.7)
Total patients	76	43	119(100)

Table 2. Staging of Retinoblastoma at Diagnosis (IIRC)

	Unilateral n(%)	Bilateral n(%)
Group A	00 (00.0)	08 (09.3)
Group B	01 (02.3)	08 (09.3)
Group C	01 (02.3)	09 (10.5)
Group D	10 (13.2)	13 (15.1)
Group E	56 (73.7)	43 (50.0)
Not available	08 (10.5)	05 (05.8)
Total eyes	76	86

Table 3. Enucleation and Level of Tumour Extension on HPE

	Group	
	Unilateral (n=76) n(%)	Bilateral (n=86) n(%)
Enucleation	60 (78.9)	35 (40.7)
Intraocular	21 (35.0)	13 (37.1)
Extraocular extension	33 (55.0)	17 (48.6)
Optic Nerve End	05 (15.2)	02 (11.8)
Sclera	03 (09.1)	02 (11.8)
Deep Choroids	12 (36.4)	07 (41.2)
Superficial choroids	20 (60.1)	12 (70.6)
Bruch's Membrane	18 (54.5)	07 (41.2)
Lamina Cibrosa	11 (33.3)	04 (23.5)
Missing	06 (07.9)	05 (14.3)

scan investigation whereby presence of mass on CT scan was found in 97%. MRI was performed in 19 patients (29 eyes) with 89.5% showing presence of mass.

Staging of the disease at diagnosis is presented in Table 2. From total of 162 eyes, 99 eyes (61%) are in group E (based on International Intraocular Retinoblastoma Classification-IIRC). The different treatment strategies in 119 patients (162 eyes) with unilateral and bilateral disease were evaluated. Summary of enucleation performed is shown in v 3. Enucleated eyes were sent for histopathology examination (HPE) to determine the level of tumour extension. Among 76 patients with unilateral involvement (76 eyes), enucleation was done for 60 (79%) of the eyes while 55% showed histopathological evidence of extraocular extension. Meanwhile focal therapy been administered in 5 (7%) eyes and only 1 (1%) eye was treated with EBRT. Of 40 patients who received chemotherapy, 95% received systemic chemotherapy (mean, 6.5 cycles; minimum, 2; maximum, 13 cycles).

In 43 patients with bilateral involvement (86 eyes), 35 (41%) eyes were enucleated and out of those, 17 eyes (49%) showed histopathological extraocular extension. Focal therapy was performed in 35 (41%) eyes. Radiotherapy treatment was offered in 5 (6%) eyes. Thirty one (72%) patients were given chemotherapy and all of them received systemic chemotherapy (mean, 8.2 cycles; minimum, 2 cycles; maximum, 13 cycles). The patients were followed up after 1 year and complete follow up data were obtained for 86 (72.3%) of the 119 patients. Sixty six patients are alive and death was reported in 4 patients. Sixteen patients were defaulted treatment and were lost to follow-up, whereas follow-up data was not available for 33 patients.

Discussion

Retinoblastoma is the most common primary malignant intraocular tumor. The incidence varies around the world with approximately 1 of in 15,000 live births affected in the United States of America compared to 1 in 18,000 live births in Asia (Abiose et al., 1985; Klauss et al., 1990; Ajaiyeoba et al., 1992; Owoeye et al., 2006).

This study showed that the majority of patients (64%) presented with unilateral retinoblastoma and the remaining (36%) are bilateral. This figure is similar with findings from several Asian countries (Sahul et al., 1998; Patikulsila et al., 2001). In this study, there was not much difference in the number of retinoblastoma between male and female; male to female ratio of 1.3:1. The gender ratio of retinoblastoma fluctuates in most of the population (Parkin et al., 1988), and corroborates the findings of other studies in both developed and developing countries (Sanders, 1988; Ellsworth, 1969; O'Brien, 2001). Our patients appear to present very late as the average age at diagnosis was 22 months. This result complements the findings of most previous studies which were conducted in other Asian countries (Parkin et al., 1998; Chantada et al., 1999; Wiangnon et al., 2003). A relatively low number of children under one year of age are diagnosed due to lack of awareness, poor education background, low socioeconomic status, and probably due to denial of the child's disease by parents (Bukhari et al., 2011). Therefore there is delay in treatment administration and some parents refused further management. However this finding is contrast with the findings reported by Western countries where most of the patients tend to present at early stage of diagnosis, at an age of less than 20 months (Bakshi et al., 2010). It seems that the presenting symptoms of retinoblastoma in our study are similar with both Western settings (Sang and Albert, 1982; Canzano and Handa, 1999; Abramson et al., 2003; Nafiani, 2006; Arif et al., 2009; Bukhari et al., 2011), and Asian settings (Handa, 1999; Canzano and; Abramson et al., 2003; Arif et al., 2009; Bukhari et al., 2011) where leukocoria is the commonest presentation, followed by strabismus. Protopsis, which is a late sign of retinoblastoma, is still common in developing countries compared with developed countries (Sang and Albert, 1982; Klauss and Chana, 1983; Kaimbo et al., 2002; Balasubramanya et al., 2004). In addition, glaucoma and hyphema which are known signs of advanced disease (Klauss and Chana, 1983; Balasubramanya et al., 2004; Arif et al., 2009; Bukhari et al., 2011) were also observed. Hence, early detection by recognition before the point of leukocoria is required to save the eyes and the vision.

We found that a vast majority of the patients in this study are categorized in Group E based on International Intraocular Retinoblastoma Classification (IIRC) which represents advanced disease (Reddy and Anusya, 2010). For unilateral disease, eyes falling under category D and E have neither potential for visual improvement nor conservative treatment options. Hence, enucleation remains the mainstay of treatment in most Southeast Asian settings (Aung et al., 2009, Bonanomi et al., 2009; Reddy and Anusya, 2010), as was observed in the current study. Chemotherapy was administered post-enucleation in eyes with invasion into deep choroid and beyond.

In this study, a majority of eyes received systemic chemotherapy either as chemoreduction or as adjuvant therapy. Focal therapies consisting of cryotherapy and laser therapy are applied during chemoreduction and repeated at each chemo cycles to stabilize the response (Dudgeon, 1995; Chan et al., 2005). In fact, a study conducted in United States of America found that in recent years, physicians treating retinoblastoma are more likely to aim for chemoreduction via laser and cryotherapy (O' Brien, 2001). External Beam Radiotherapy administration was found to be very low in this study, and this may probably be due to its higher complications (O' Brien, 2001), for instance second neoplasms (Abramson et al., 1984; Zelter et al., 1988), especially in the area of radiation.

In our study at 1-year after diagnosis, complete follow up data were obtained for 86 (72.3%) of the 119 patients. Sixty six patients are alive and death was reported in 4 patients. Sixteen patients defaulted treatment and were lost to follow-up whereas follow-up data was not available for 33 patients. A previous study done in Malaysia reported that most patients refuse treatment and further management at the point when they are counseled to undergo enucleation (Jamalia et al., 2010). Similarly in Thailand and Indonesia, most patients refuse further

treatment especially enucleation (Hathirat et al., 1993; Sitorus et al., 2009).

Although data for this study were only from 3 treatment centers, these are the main tertiary referral centers in Malaysia, which see approximately 80% of all retinoblastoma patients in the country. We do however acknowledge that our study sample is rather small, and the follow up period of 1 year was too short to evaluate post treatment outcomes. Besides that, an adequate and complete follow-up data is a prerequisite to conduct a survival analysis but in this study we are unable to perform meaningful survival study as most of follow-up data was not available.

Nevertheless, this study underscores the need to educate the public, and health personnel on importance of early recognition and diagnosis of retinoblastoma. Emphasis should also be given on the potentially high cure rates when disease is detected and treated at an earlier stage, hence enabling preservation of the globe. Increased patients' and parents' awareness may aid in reducing treatment refusal and further delay related to initiation of treatment.

In conclusion, patients with retinoblastoma in this middle-income Asian setting are presenting at late stages. As a result, a high proportion of patients warrant aggressive management such as enucleation. The results of our study also showed that the number of patients who were lost to follow up is still high. Therefore, the reduction in the number of refusal and delay related to the initial treatment, as well as lack of adherence to follow-up should be emphasized in order to improve the survival rates of retinoblastoma

Acknowledgements

We would like to thank the Director-General of Health Malaysia for giving us the permission to publish this paper. We are really appreciate and grateful to National Eye Database Registry who helped in diverse ways with the data compilation.

References

Abiose A, Adido J, Agarwal SC (1985). Childhood malignancies of the eye and orbit in Northern Nigeria. *Cancer*, **55**, 2889-93.

Abramson DH, Beaverson K, Sangani P, et al (2003). Screening for retinoblastoma: presenting signs as prognosticators of patients and ocular survival. *Pediatr*, **112**, 1248-55.

Abramson DH, Ellsworth RM, Kitchin FD, Tung G (1984). Second non-ocular tumours in retinoblastoma surviviors: Are they radiation induced? *Opthalmology*, **91**, 1351-5.

Ajaiyeoba IA, Pindiga HU, Akang EE (1992). Tumours of the eye and orbit in ibadan. *East Afr Med J*, **69**, 487-9.

Arif M, Iqbal Z, Zia-ul-Islam (2009). Retinoblastoma in NWFP, Pakistan. *J Ayub Med Coll Abbottabad*, **21**, 60-2.

Aung L, Chan YH, Yeoh EJ, Tan PL, Quah TC (2009). Retinoblastoma: a recent experience at the national university hospital, Singapore. *Ann Acad Med Singapore*, **38**, 693-8.

Bakshi S, Gupta S, Gogia V, Ravindranath Y (2010). Compliance of retinoblastoma. *Indian J Pediatr*, **77**, 535-40.

Balasubramanya R, Pushker N, Bajaj MS, et al (2004). Atypical presentations of retinoblastoma. *J Pediatr Ophthalmol Strabismus*, **41**, 18-24.

Bonanomi MT, Almeida MT, Cristofani LM, Odone Filho V (2009). Retinoblastoma: A three-year-study at a Brazilian medical school hospital. *Clinic*, **64**, 427-34.

Bukhari S, Rehman A, Bhutto IA, Qidwai U (2011). Presentation pattern of retinoblastoma. *Pak J Opthalmol*, **27**, 142-5.

Canzano JC, Handa JT (1999). Utility of pupillary dilation for detecting leukocoria in patients with retinoblastoma. *Pediatric*, **104**, 44.

Chan HS, Gallie BL, Munier FL, Beck Popovic M (2005). Chemotherapy for retinoblastoma. *Ophthalmol Clin North Am*, **18**, 55-63.

Chantada G, Fandino A, Manzitti J, Urrutia L, Schvartzman E (1999). Late diagnosis in a developing country. *Arch Dis Child*, **80**, 171-4.

Carter J (2009). Recognizing the signs of retinoblastoma. *Practice Nursing*, **20**, 394-7.

Dudgeon J (1995). Retinoblastoma-trends in conservative management. *Br J Opthalmol*, **79**, 104.

Ellsworth RM (1969). The practical management of retinoblastoma. *Trans Am Ophthalmol Soc*, **67**, 462-34.

Essuman V, Ntim-Amponsah CT, Akafo SK, Renner L, Edusei L (2010). Presentation of retinoblastoma at a paediatric eye clinic in Ghana. *Ghana Med J*, **44**, 10-5.

Hathirat P, Kunavisarut S, Chuansumrit A, et al (1993). Chemotherapy in patients with retinoblastoma. *J Med Assoc Thai*, **76**, 85-91.

Jamalia R, Sunder R, Alagaratnam J, PP Goh (2010). Retinoblastoma registry report-Hospital Kuala Lumpur Experience. *Med J Malaysia*, **65**, 128-30.

Kaimbo WK, Mvitu MM, Missotten L (2002).Presenting signs of retinoblastoma in Congolese patients. *Bull Soc Belge Ophthalmol*, **283**, 37-41.

Klauss V (1990). Retinoblastoma in Developing Countries. *Community Eye Health*, **5**, 1-2.

Klauss V, Chana HS (1983). Ocular tumours in Africa. *Soc Sci Med*, **17**, 1743-50.

Nafianti S (2006). Retinoblastoma in children in Haji Adam Malik hospital Medan. *Majalah Kedokteran Nusantara*, **39**, 147-50.

Owoeye JF, Afolayan EA, Ademola-Popoola DS (2006). Retinoblastoma-a clinic-pathological study in Ilorin, Nigeria. *Afr J Health Sci*, **13**, 117-23.

O'Brien JM (2001). Retinoblastoma: clinical presentation and the role of neuroimaging. *AJNR Am J Neuroradiol*, **22**,427-9.

Parkin DM, Kramarova E, Draper GJ, et al., editors (1998). International incidence of childhood cancer: volume 2. IARC Scientific Publications No 144. Lyon: IARC.

Parkin DM, Stiller CA, Draper GJ, Bieber CA (1988). The international incidence of childhood cancer. *Int J Cancer*, **42**, 511-20.

Patikulsila P, Patikulsila D (2001). Retinoblastoma at Maharaj Nakorn Chang Mai Hospital; a 7 year study. *Changmai Med Bull*, **40**, 167-72.

PP Goh, Elias H, NorFariza N, Mariam I (2008). A Web Based Surveillance System. *Med J Malaysia*, **63**, 20-23.

Reddy SC, Anusya S (2010). Clinical presentation of retinoblastoma in Malaysia: a review of 64 patients. *Int J Ophthalmol*, **3**, 64-8

Sahul S, Banavali SD, Pai SK, et al (1998). Retinoblastoma: Problems and Perspectives from India. *Pediat Haema Oncology*, **15**, 501-8.

Sanders BM, Draper GJ, Kingston JE (1988). Retinoblastoma in Great Britain 1969-80: incidence, treatment, and survival. *Br J Ophthalmol*, **72**, 576-83.

Sang DN, Albert DM (1982). Retinoblastoma: clinical and

histopathologic features. *Human Pathol*, **13**, 133-47.
Sitorus RS, Moll AC, Suhardjono S, et al (2009). The effects of therapy refusal against medical advice in retinoblastoma patients in a setting where treatment delays are common. *Ophthalmic Genet*, **30**, 31-6.
Wallach M, Balmer A, Munier F, et al (2006). Shorter time to diagnosis and improved stage at presentation in Swiss patients with retinoblastoma treated from 1963 to 2004. *Pediatrics*, **118**, 1493-8.
Wiangnon S, Kamsa-ard S, Jetsrisuparb A, et al (2003). Childhood cancer in Thailand 1995-1997. *Asian Pac J Cancer Prev*, **4**, 337-43.
Zelter M, Gonzalez G, Schwartz L, et al (1988). Treatment of retinoblastoma. *Cancer*, **61**, 153-60.