Original Article

Retinoblastoma: A Recent Experience at the National University Hospital, Singapore

LeLe Aung,[1] *MD*, Yiong Huak Chan,[2] *PhD*, Eng Juh Yeoh,[1] *MBBS, MMed*, Poh Lin Tan,[1] *MBBS, MMed*, Thuan Chong Quah,[1] *MBBS, MMed*

Abstract

Introduction: Retinoblastoma is a very rare disease. There were 30 cases of retinoblastoma diagnosed and treated at National University Hospital (NUH). Materials and Methods: A retrospective chart review was performed on the medical records of 30 patients who were diagnosed with retinoblastoma between 1995 and 2008 at the Department of Paediatrics, National University Hospital, Singapore. Results: The median age at diagnosis was 1.6 years (range, 0-5.9) with a median follow-up of 1.8 years (range, 0.1 to 11.6). The median time from presenting signs to the time of diagnosis was 5.2 months (range, 0-25.2). Common presenting signs of retinoblastoma were identified; the most common of which were leukocoria (50.0%), squinting (13.3%), poor vision (10.0%), strabismus (6.6%) and unknown (33.3%). Of the 30 patients, 10 were from Singapore whilst the other 20 patients were from the surrounding countries. Twelve patients had bilateral disease at the time of diagnosis, while 18 had unilateral disease. Staging information was available in 27 patients. Enucleation was performed in 25 of 30 patients. Radiation therapy was given in 3 patients in 1995 (bilateral disease), 2001 (bilateral disease) and 2003 (unilateral disease). At the time of analysis, 19 patients were alive with no evidence of disease. Overall 5-year survival for the cohort was 88.1% [95% confidence interval (CI), 88.0-100] and event-free survival for the whole cohort was 74.2% (95% CI, 55.8-92.6). Conclusion: In our limited experience, the importance of collaboration and standardisation of the staging system, raising awareness and education of primary healthcare providers and parents are strongly stressed.

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Key words: Asian experience, Outcome, Staging, Survival

Introduction

Retinoblastoma is the most common primary intraocular malignancy in infants and children.[1] Worldwide, the incidence is 1 in 18,000 to 34,000 live births with an estimation of 5000 to 8000 new cases.[2,3] The Singapore Childhood Cancer Registry (SCCR), a hospital based cancer registry that includes all children less than 15 years of age, which was initiated by the Paediatric Oncology Group-Singapore (POGS), reported their first monograph in 2007. They noted 21 cases of retinoblastoma diagnosed at National University Hospital (NUH) between 1997 and 2005.[4] However, there is limited information regarding the presentation of symptoms, treatment and outcome of retinoblastoma in children in Singapore.

Paediatric ophthalmologists and paediatric oncologists have made enormous strides in the field of retinoblastoma throughout the world. At present, less than 5% of these children succumb to the disease in industrialised nations with advanced medical care, such as in the United States. However, elsewhere in the developing world, a majority of the children present with advanced and malignant stage and more than 50% die from disease.[5] Many authors attributed poor survival from the disease to a result of late referral and diagnosis leading to an advanced stage of the disease at the time of presentation. This is particularly true in the developing countries, where there is significant delay from the time of onset of symptoms to initial presentation and diagnosis leading to lower survival and cure rates.[3] At least 50% of these cases present with sign and symptoms of advanced extra ocular disease making the unusually excellent prognosis of retinoblastoma poor with survivals ranging from 0% to 50% at best.[3,5-9] The late referral has been attributed to account for the delay in diagnosis leading to advanced stage disease being more frequently diagnosed in these regions.[10] Various authors have also postulated that there may be a higher incidence of retinoblastoma in some

[1] Division of Paediatric Haematology/Oncology, Children's Medical Institute and Department of Paediatrics, National University Hospital, Singapore
[2] Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Address for Correspondence: Dr LeLe Aung, Department of Paediatrics, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.
Email: paev2@nus.edu.sg

developing countries such as Africa and India.[6,7]

Adjuvant chemotherapy is recommended for patients and in some reports, high dose chemotherapy with stem cell rescue for patients with advanced extra ocular disease.[11-15] However, the best regimen for this sub-set of patients has yet to be established. The treatment of these patients in the developing countries, complete with its own set of various cultural beliefs and practices, with limited resources, financial limitations, availability of chemotherapeutic agents and supportive care are also a great challenge. There is a dire need to identify the best regimen with lower toxicity and affordability whilst increasing survival. We report here our recent single institution experience in Singapore on children diagnosed with retinoblastoma.

Materials and Methods

The division of Paediatric Haematology/Oncology at NUH is a main referral centre for new and relapsed paediatric oncology cases locally within the island state and from the Southeast Asia region such as Malaysia, Indonesia, Brunei, Vietnam, Myanmar, Philippines, India and Sri Lanka. Approximately 120 new cases of childhood cancer are diagnosed and treated in Singapore each year. More than 50% of them are referred and treated at NUH each year. From 1997 to 2006, according to the SCCR, there were 197 cases of childhood cancer seen and treated at NUH with the most common diagnosis being childhood leukaemia. A retrospective chart review was performed on 30 patients who were diagnosed with retinoblastoma between January 1995 and June 2008 at the Department of Paediatrics, NUH. January 1995 was selected as this was the beginning of when a comprehensive list of all paediatric cancer cases was recorded at NUH. The study end date of June 2008 was chosen so as to allow ample time for the follow-up of patients. Details of the date of initial presentation, initial presenting signs and symptoms, stage of the disease, the treatment received and the status of the patient at the time of the analysis were all recorded. A Kaplan-Meier analysis was performed for event-free and overall survivals for the cohort.[16]

Results

Out of a total of 32 patients seen at our centre during the study period, 2 patients did not continue with their follow-up and thus were excluded from the analysis. The median age at diagnosis was 1.6 years (range, 0.1-5.9) with a median follow-up of 1.8 years (range, 0.1-11.6). The majority [16 (53.3%)] were girls. Geographically, of the 30 patients, 10 were from Singapore while the other 20 patients were from the surrounding countries (Malaysia = 4, Indonesia = 7, Brunei = 3, Sri Lanka = 2, Vietnam = 2, other = 2). Eleven (36.7%) patients were of Chinese ethnicity, 12 (40%) were of Malay ethnicity and the rest (23.3%) were of other ethnicity. There was a higher representation of Malay ethnicity in our patients despite the predominantly Chinese population in Singapore.

Table 1. Patient Characteristics

Gender	
Male: Female	14:16
Laterality	
Unilateral	18
Bilateral	12
Positive family history	2
Signs/symptoms of presentation	
Leukocoria	15
Strabismus/squinting	6
Other	4
Unknown	10
Age at diagnosis (mo)	
0 to 3	3
>3 to <48 months	25
≥ 8 months	2
Time from symptoms to diagnosis (mo)	
≤1	3
≥1.1 to <3	2
>3 to < 12	9
≥ 12	6
Unknown	10

Common presenting signs of retinoblastoma were then identified from the histories in the medical records of each patient. The most common of which was leukocoria (50.0%), followed by squinting (13.3%), poor vision (10.0%), strabismus (6.6%), and unknown symptom (33.3%), (Table 1). The median time from presenting signs to the time of diagnosis was 5.2 months (range, 1-25.2). The median time of presentation of symptoms to time of diagnosis for Singaporeans was 11.3 months (range, 0-25.2) while for foreign patients, it was 5.5 months (range, 0.4-18.8). Of the 20 patients for whom this information was available, only 3 patients presented within 1 month from recognition of symptoms to time of diagnosis. The remaining 17 patients presented with a delay in diagnosis of 2 or more months, duration from initial symptoms to the time of diagnosis. The time interval was not known in 10 patients. Eighteen patients had unilateral disease at the time of diagnosis, 12 had bilateral disease (Table 1). Every attempt was made to locate the staging information of each patient. There were 18 whose staging was recorded in the medical records. The

Table 2. Patient and Tumor Characteristics

Pt no.	Age (y)/ Sex	Symptom to Dx (mo)	Laterality	Stage	Enucleation	Adjuvant therapy	Dx-FU (y)	Status
1.	3.2/ F	NA	Unilateral	NA	Yes	None	0	DOD
2.	0.4/ F	NA	Bilateral	5	Yes	Carbo/VP16, CRYO	0.1	Alive
3.	1.6/ F	1.2	Unilateral	5	Yes	VETOPEC	0.1	ANED
4.	0.2/ F	5.5	Unilateral	NA	Yes	None	0.1	LTF
5.	0.3/ M	0	Unilateral	1	No	VCR-Carbo	0.3	Alive
6.	2.5/ M	18.8	Unilateral	4	Yes	VETOPEC	0.3	DOD
7.	2.7/ F	16.9	Unilateral	1	Yes	None	0.8	Alive
8.	0.8/ M	NA	Bilateral	4	Yes	COGARET 0231	0.8	Alive
9.	2.0/ M	12.0	Bilateral	4	Yes	XRT/CRYO/ VETOPEC	0.9	DOD
10.	5.9/ F	1.0	Unilateral	NA	Yes	None	0.9	ANED
11.	2.0/ M	4.8	Unilateral	5	Yes	XRT/CRYO	1.0	ANED
12.	1.4/ F	14.5	Unilateral	4	Yes	CRYO	1.1	ANED
13.	2.5/ M	NA	Unilateral	NA	Yes	Other	1.6	Alive
14.	2.1/ M	NA	Bilateral	1	Yes	TORONTO	1.6	ANED
15.	0.4/ M	1.8	Bilateral	NA	Yes	TORONTO	1.8	ANED
16.	0.2/ F	4.4	Bilateral	5	Yes	TORONTO	1.9	ANED
17.	1.3/ F	11.6	Bilateral	NA	Yes	TORONTO/LASER/CRYO	2	ANED
18.	3.5/ F	3.4	Unilateral	4	Yes	None	2.4	ANED
19.	0.3/ M	2.0	Bilateral	NA	Yes	CSA/LASER/CRYO	2.9	ANED
20.	2.1/ M	NA	Bilateral	NA	Yes	OTHER CHEMO	2.9	Alive
21.	2.4/ M	NA	Unilateral	NA	Yes	None	5.1	ANED
22.	2.3/ F	4.7	Unilateral	5	Yes	VETOPEC	5.1	ANED
23.	0.1/ F	0.4	Unilateral	4	Yes	None	5.1	ANED
24.	2.4/ M	25.2	Bilateral	4	No	VETOPEC	5.3	ANED
25.	1.4/ M	NA	Bilateral	NA	No	TORONTO	5.4	ANED
26.	1.4/ F	NA	Unilateral	5	Yes	None	7.7	Alive
27.	1.6/ F	3.0	Unilateral	1	Yes	None	8.3	ANED
28.	4.6/ F	NA	Unilateral	NA	No	None	8.6	ANED
29.	0.8/ M	4.9	Bilateral	5	Yes	TORONTO/CRYO	8.8	ANED
30.	1.5/ F	17.8	Unilateral	NA	Yes	TORONTO/CRYO	11.6	ANED

Pt: patient; Yr: year; mo: months; Dx: diagnosis; Dx-FU: time diagnosis to follow up; F: female; M: male; NA: not applicable; XRT: radiation therapy; LTF: lost to follow-up; ANED: alive with no evidence of disease; DOD: dead of disease; AWD: alive with disease; VETOPEC: vincristine, etoposide; cyclophosphamide; TORONTO: Toronto protocol

staging system varied depending on the ophthalmologist and was as per the tumour, node, metastasis (TNM) staging or Reese-Ellsworth staging systems. Seven patients were each classified as either stage 4 or stage 5. For the remaining 12 patients, there was no standardised staging information available. Positive family history was noted in 2 cases and genetic testing of retinoblastoma was noted in 2 patients. The remaining patients' medical records, however, did not contain any family history or genetic testing for retinoblastoma.

With regard to the treatment for retinoblastoma, enucleation was performed in 25 of 30 patients; 15 (60.0% of those enucleated) of these patients had unilateral eye disease at the time of initial diagnosis. Radiation therapy was given in 2 patients in the year 1995 (bilateral) and 2003 (unilateral disease). Cryotherapy was given in 8 patients

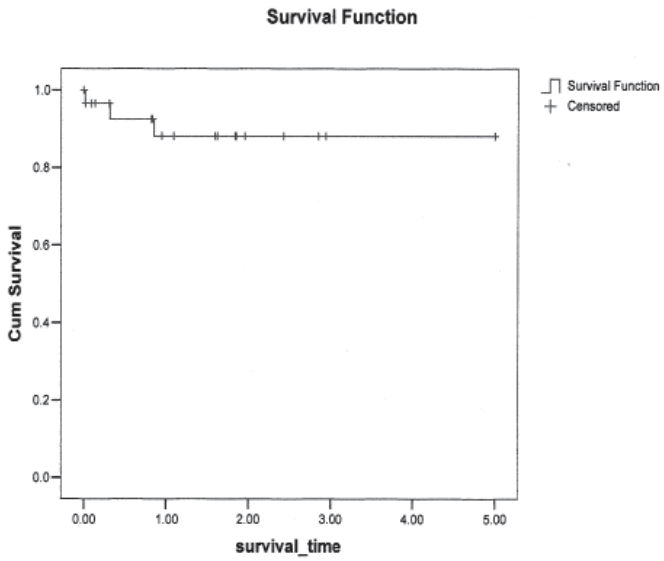

Fig. 1. 5-year overall survival of cohort (n = 30).

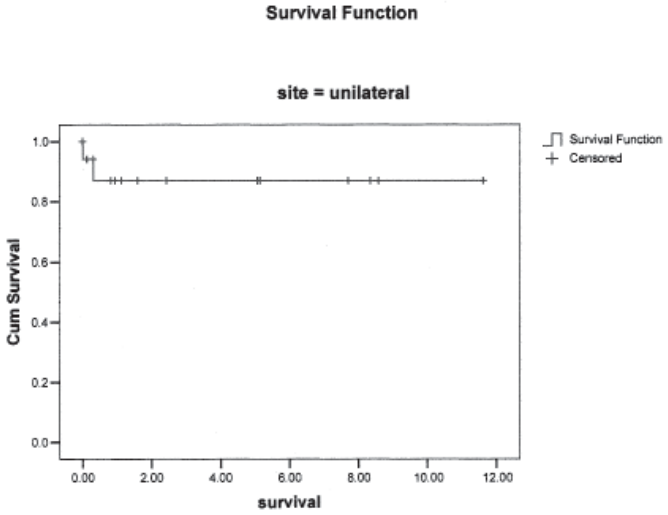

Fig. 1a. 5-year overall survival of those with Unilateral disease (n = 18)

and laser therapy was given in 2 patients. Chemotherapy consisted of Toronto protocol (n = 7), vincristine, etoposide, cyclophosphamide (VETOPEC) (n = 5) and other chemotherapy (n = 5)[17,18] (Table 2).

At the time of analysis, with a median follow-up of 1.8 years (range, 0.1-11.6), 19 patients were alive with no evidence of disease, 7 were alive, 3 were dead from the disease and 1 lost to follow-up. The 5-year overall survival (OS) for the cohort by Kaplan-Meier survival analysis revealed 88.1% [95% confidence interval (CI), 75.1-100.0] (Fig. 1). The 5-year overall survival for those with unilateral disease was 86.9% (95% CI, 95.5-100) (Fig. 1a). The 5-year overall survival for those with bilateral disease was 90.0% (95% CI, 71.0-100), no survival plot available as there was only 1 event.

The 5-year event free survival (EFS) for the cohort by Kaplan-Meier survival analysis revealed 74.2% (95% CI, 55.8-92.6) (Fig. 2). The 5-year event-free survival for those with unilateral and bilateral disease was 69.7 (95% CI, 43.5-95.9) and 80.0% (95 CI, 54.8-100.0), respectively (Figure 2a, 2b).

Discussion

Retinoblastoma is not a common problem among various childhood cancer being diagnosed in paediatrics and in Singapore with the crude incidence rate of 3.75 per million according to the first monograph of the SCCR.[4] Timely diagnosis of childhood cancer is extremely important as many paediatric malignancies are highly curable. As such it has been reported widely that the prognosis of this disease is very much dependent on prompt diagnosis.[19] In our small experience, the median time from recognition of symptoms to the time of diagnosis was 2 weeks difference amongst local Singaporeans and foreign patients, 11.3 months and 5.5 months, respectively. One local patient took 25.2 months and another 17.8 months from the time of initial recognition of symptoms of leukocoria to the time of diagnosis. The circumstances which led to this major difference are unclear. Of the 20 patients for whom this information was available, only 3 patients presented within 1 month from recognition of symptoms to the time of diagnosis. Seventeen out of the 20 patients (85%) presented with a delay in diagnosis, with duration from initial symptoms to the time of diagnosis at 2 or more months. The delay in diagnosis in our series did not greatly affect the outcome, as even the patient who presented at 25.2 months from symptoms was alive and remain disease-free at 5.3 years from the initial diagnosis. However, it is important to note that our sample size is rather small to make a definitive conclusion. Prompt recognition of symptoms and referral is still the key in children seen with leukocoria, strabismus or similar eye symptoms in general paediatrics and polyclinics.

The most common symptom from which patients sought further treatment in our cohort was leukocoria (50.0 %), followed by squinting (13.3%), poor vision (10.0%), strabismus (6.6%) and unknown symptoms (33.3%). In an earlier report by Tan et al from 1976 to 1995, in their experience of 98 patients (56 local, 42 foreign), 41 patients were studied, of which 82.9% presented with leukocoria.[20] A study from Taiwan also revealed that leukocoria was the most common presenting sign.[21,22] This is consistent with the finding in our study. Consistent recording and application of a standardised staging system appears to be lacking. Of the 3 published series available via a PubMed search on retinoblastoma in Singapore, none mentions the use of a consistent or any staging system classification for

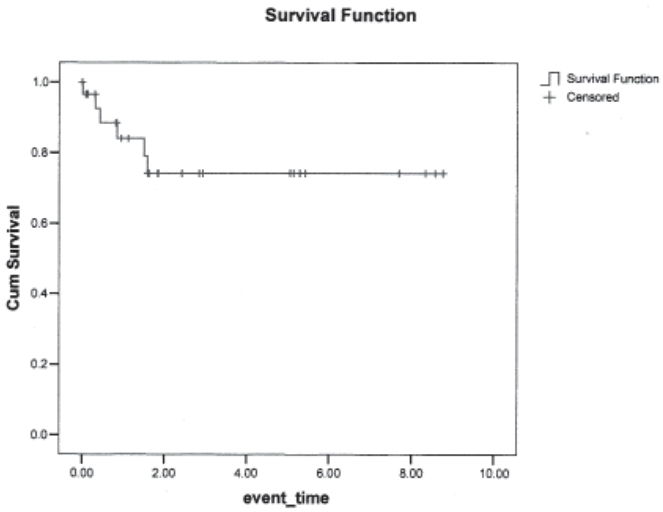

Fig. 2. 5-year event free survival of cohort (n = 30).

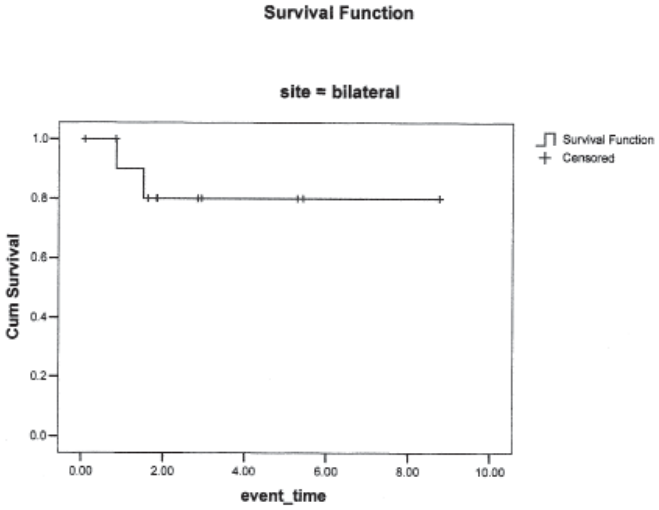

Fig. 2b. 5-year event-free survival of those with bilateral disease (n = 12).

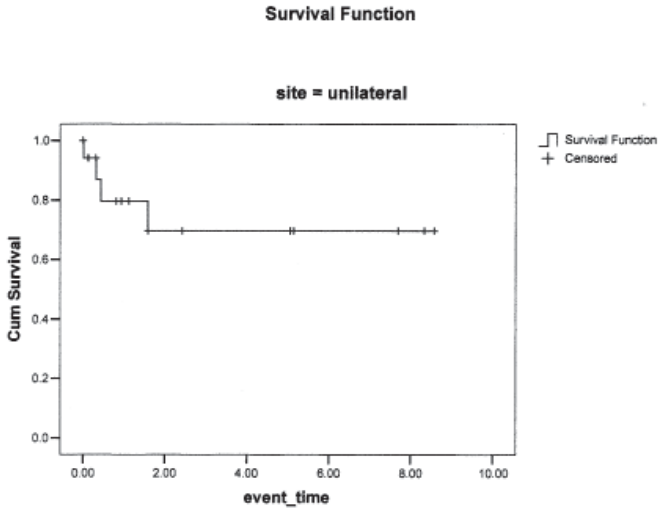

Fig. 2a. 5-year event-free survival of those with unilateral disease (n = 18).

the patients.[20,23,24] Similarly, in our review, there were 18 patients whose medical records contained some staging information. The staging system used, however, was dependent on the decision of the primary ophthalmologist examining the child's eye. This confirms the notion that, at least during the study period, there is no standardised and widely accepted classification system for retinoblastoma. Recent publications have proposed an International Retinoblastoma Staging System for simplification.[25] Since then, in our own institution, all retinoblastoma patients are seen and treated by a common primary team of paediatric ophthalmologists, oncologists, and radiation doctors who apply the same staging system.

It is of interest to note that even in one of the most advanced industrialised nations in Southeast Asia, enucleating is still the most frequent form of treatment modality employed. Various authors have indicated that earlier detection may allow a more widespread use of vision and eye sparring treatments which may in turn lead to lower morbidity, which in turn could lead to a presumed higher quality of life and physical perception.[26,27] Perhaps the reason for the high incidence of enucleation in our study can be explained by a delay in diagnosis with presentation after more than 1 month between the detection of symptoms and diagnosis in the majority of patients. However, we cannot be certain whether there were a multitude of factors involved such as various cultural roles and beliefs, a higher volume of foreign patients leading to a provider fear of lost to follow-up/default rate thus choosing enucleation as treatment of choice, the financial burden and high cost of therapy, and lastly the rarity of the disease resulting in a lack of expertise in the multi-disciplinary team. It is difficult to ascertain outcome based on adjuvant chemotherapy. Similar to staging, there has been no standardised and consistent adjuvant chemotherapy regimen employed for these children at our centre in the past. Various chemotherapy regimens such as VETOPEC[18] and Toronto protocol[17] were used. Radiation therapy was given for 2 patients; 1 of whom had unilateral eye disease at the age of 2.0 years at the time of diagnosis; stage status was classified as stage 5, who is alive with no evidence of disease (ANED). The second patient was diagnosed with bilateral disease at the age of 2.0 years but subsequently succumbed to the disease at 0.9 years from initial diagnosis. Local control with cryotherapy was used in 7 patients. Thus, it is difficult to analyse survival outcomes based on a specific therapy.

We have since made tremendous strides in our own institution. We have started a working group consisting of paediatric oncologists, paediatric ophthalmologists, geneticists, and radiation oncologists with a particular

interest in retinoblastoma, a retinoblastoma regional collaboration has also been initiated, and the first regional retinoblastoma meeting was held in Singapore recently with expert speakers from around the Asian region.

Conclusion

In conclusion, the incidence and diagnosis of retinoblastoma is still rare in Singapore. Prompt diagnosis, early referral by general practitioners and local and regional collaboration are all an integral component for continued high cure rates for these children.

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