

Retinoblastoma in Singapore: 1976 to 1995

N W H Tan,* V Balakrishnan,***M Med (Ophth), FRCSE, FRCOphth*, Y L F Ling,***FAMS, FRCS, FRCOphth*

Abstract

There were at least 56 local and 42 foreign patients seen in Singapore between 1976 and 1995 inclusively. The local incidence rate is 1 in 15 789 live-births, and there appears to be no predilection for sex and race. Ninety-eight per cent presented before the age of five with the average age at diagnosis being 18 months. Bilateral cases were diagnosed earlier than unilateral cases. At least 17% are hereditary, with only 2 of these with positive family histories. Of the 41 patients studied for presenting complaints, 82.9% had leukocoria, 19.5% had strabismus and 12.2% had decreased visual acuity. The main mode of treatment was enucleation alone in unilateral disease; in bilateral cases, the main mode was enucleation of the more badly affected eye together with radiotherapy and cryotherapy of the fellow eye. Ninety per cent of all patients who underwent treatment have had enucleation done. Four patients defaulted treatment-with counselling of the parents of these patients, this number could be reduced or at least kept low. Patients with early diagnosis and treatment are more likely to survive. Eight of the 56 patients died. However, with better treatment modalities, the prognosis for both life and vision have, in recent years, improved significantly.

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Introduction

Retinoblastoma (RB) makes up about 3% of all childhood tumours in Western countries,* and is the commonest intraocular tumour of childhood² there as well as in Southeast Asia.³ It is the consequence of a point mutation, deletion or rearrangement of the normal tumour-suppressing RB gene at the RB locus on the long arm of chromosome 13 (13q14). The inheritance is autosomal dominant, with a high penetrance of 90%.⁴ Lately, it has been of particular interest because of the isolation and sequencing of the RB gene. As such, there is now hope of identification of gene carriers in RB families,⁷ and for more specific genetic counselling.² Figure 1 shows the mechanism of development of hereditary and non-hereditary retinoblastomas.

Apart from the development of this malignant intraocular tumour, children suffering from hereditary RB are also at higher risk of developing second non-ocular malignancies.^{5,6} Studies in this area have led to the recognition of the role of tumour-suppressor genes in the tumorigenesis of RB as well as a surprising range of other malignancies, for example osteosarcoma, leukaemia and pinealoblastoma,⁵⁻⁷ with osteosarcoma being the commonest second tumour.^{7,8} It has been reported that a child with hereditary retinoblastoma has approximately 5% chance of another malignancy in the

next 10 years; 18% within the first 20 years and 26% within 30 years. Those who received radiotherapy have an additional risk compared to those who did not.^{6,9,10}

Without treatment, it is almost always fatal;² but with treatment, the 3-year survival rate is generally more than 90%.^{5,11-14} Spontaneous regression has been known to occur in about 1%.^{8,11} This high survival rate, however, is counter-balanced by an appalling morbidity, as many of these children undergo enucleation usually as primary treatment in unilateral disease or in the more affected eye in bilateral disease.¹⁰ It is not unknown that when faced with the choice of having a blind child or losing the child to the disease, some parents have decided, no doubt with much soul-searching, against the former. It is only in very recent years that improvement in other treatment modalities, especially chemotherapy, is offering hope for the preservation of sight in some of these children.

This trend towards more conservative treatment,¹⁰ that is, radiotherapy, cryotherapy, photocoagulation, chemotherapy (including intravitreal chemotherapy¹⁵) and brachytherapy, will result in fewer enucleations as primary treatment.¹⁶ However, the choice of treatment still depends on the stage of the disease,^{6,9} and preference of the centre concerned.⁶

Numerous studies have been done in Western coun-

* Medical Student

National University of Singapore

** Consultant

Singapore National Eye Centre

Address for Reprints: Dr Yvonne Ling, Singapore National Eye Centre, 11 Third Avenue, Singapore 168751.

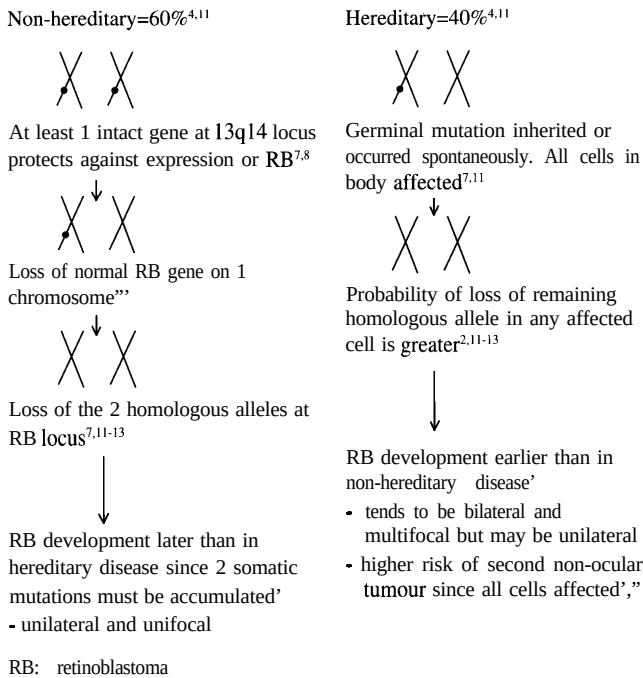


Fig. 1. Mechanism of development of hereditary and non-hereditary retinoblastoma.

tries like the United States of America and the United Kingdom. Regretfully, there has been little study done on the epidemiology and outcome of our local population-this study aims to be a primer for later studies.

This is a retrospective study of all retinoblastoma cases diagnosed in Singapore from 1976 to 1995 (20 years). The aims of this study were:

- to determine the epidemiology;
- to study the treatment given, and
- to study the outcome of the disease *vis a vis* the treatment given.

Patients and Methods

The Singapore Cancer Registry was able to provide a list of hospitals in which the RB cases diagnosed from 1976 to 1995 have been seen.

Some cases were treated by private practitioners. Selected practitioners with an interest in paediatric ophthalmology, whose names appeared very often in referral letters to or from the hospitals, were approached.

An attempt was made to retrieve all the case files. Unfortunately, some could not be found. For these patients, the Singapore Cancer Registry was able to provide limited information, which include age at diagnosis, sex, race, and in some cases, death.

To supplement the information provided by the Cancer Registry on the age and cause of death, the Registry of Births and Deaths was contacted so that deaths that had not yet been notified at the Cancer Registry were not missed.

The Pathology Department was able to provide histological reports that were missing from the case files, as well as reports of some patients whose case files were not available.

Notification of cancers is not mandatory. Notification is also not carried out if enucleation is not performed for histological confirmation of the diagnosis of retinoblastoma. Hence, where possible, operating theatre records were checked to capture the retinoblastoma cases that underwent examination-under-anaesthesia but not enucleation. In addition, 3 hospitals were able to trace, from records on computer, a list of patients diagnosed with retinoblastoma.

Population numbers used in deriving the results of this study were based on figures given in the Report on the Registration of Births and Deaths and the Singapore Demographic Bulletins.

Data entry was done on a prepared data form.

Results

From the above sources, a total of 98 patients were diagnosed with retinoblastoma from 1976 to 1995 inclusively. Fifty-six were Singapore residents. The other 42 were foreigners who came from Indonesia (17 cases), Malaysia (12 cases), the Seychelles (1 case) and unspecified countries (12 cases). Only residents were included in the study.

Of these 56 resident cases, 41 had available medical records for more detailed analysis. This study will therefore concentrate on these 41 resident cases.

Demographic Characteristics

Table I shows the demographic characteristics of the

TABLE I: DEMOGRAPHIC CHARACTERISTICS OF THE CASE SERIES SEEN FROM 1976 TO 1995

Demographic characteristics	Results	
Total number	56	
Incidence rate	1 in 15 789 live births	
Sex		
• Males	31 (55.4%)	
Race	Study population	General population
• Chinese	46 (81.2%)	71.1%
• Malays	6 (10.7%)	17.8%
• Indians	2 (3.6%)	7.3%
• Others	2 (3.6%)	3.8%
Age at diagnosis for all cases		
• range	1 to 74 months	
• mean	20 months	
Mean age at diagnosis		
• unilateral disease	2 1.8 months	
• bilateral disease	9 months	

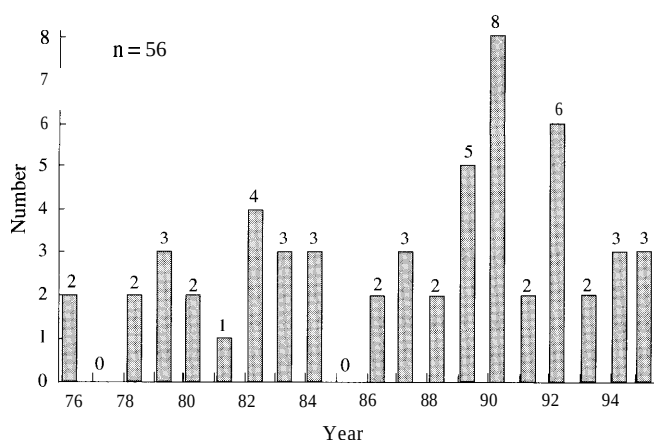


Fig. 2. Distribution of cases by year from 1976 to 1995.

TABLE II: PRESENTING SYMPTOMS AND SIGNS OF 41 RETINOBLASTOMA PATIENTS DIAGNOSED FROM 1976 TO 1995

Presentation	Number	% of total
Leukocoria	34	82.9
Strabismus	8	19.5
Decreased visual acuity	5	12.2
Buphthalmus	3	7.3
Others†	6	14.6

† 1 hypopyon,²⁷ 1 redness, 1 pain, 2 non-specific, and 1 no information

case series. The distribution of the cases by year is shown in Figure 2. Number of cases diagnosed each year within the study period ranged from 0 to 8, with an average of 3 per year.

Table I also shows the distribution of the cases by sex and race. There does not appear to be any predilection for sex and race.

Range and average age at diagnosis are shown in Table I. Figure 3 shows the frequency of age at diagnosis for all 56 cases. The graph shows a positive skew, with 51 of the 56 cases (91%) presenting at age less than 3 years. For the purpose of comparison with figures quoted from other studies, it was also calculated that 55 of the 56 cases (98%) were younger than 5 years of age.

Laterality and Family History

Useful information was available for 41 cases.

There were 7 bilateral cases (17%) and 34 unilateral cases (83%). Of the 34 unilateral cases, 20 had left-sided diseases (59%) and 14 had right-sided diseases (41%).

Only 2 of the 41 patients (4.8%) had positive family history, a positive family history being one in which at least one other relative has been diagnosed with retinoblastoma. Both these patients had bilateral disease. Thus, at least 17% (7 bilateral cases) were hereditary with only 2 of these having a positive family history.

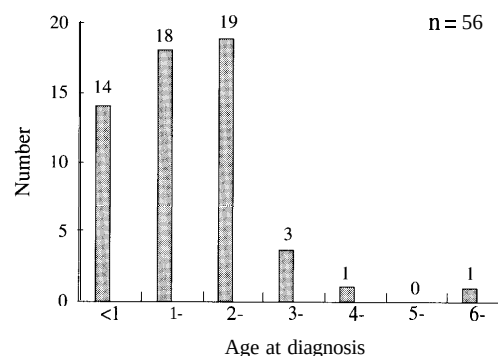


Fig. 3. Age at diagnosis of retinoblastoma cases diagnosed from 1976 to 1995.

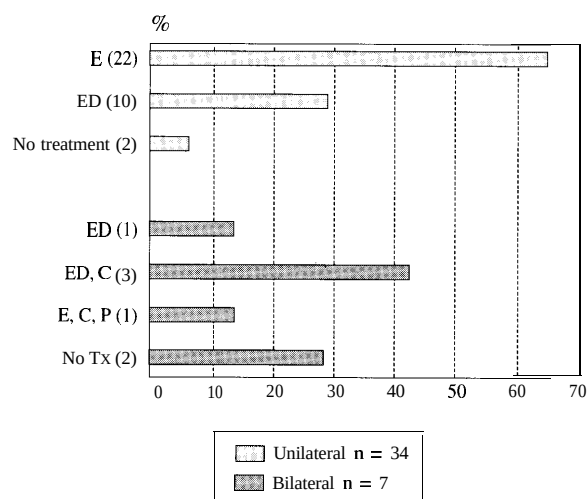


Fig. 4. Treatment modalities for unilateral disease.

E : enucleation

ED : enucleation and external beam irradiation

C : cryotherapy

P : photocoagulation

Presenting Symptoms and Signs

Table II shows the distribution of symptoms and signs in the 41 cases where records were available. The commonest presenting complaints were leukocoria (82.9%), followed by strabismus (19.5%), then decreased visual acuity (12.2%).

Eleven patients presented with 2 complaints and 2 presented with 3 complaints.

Treatment Modalities

Figure 4 shows enucleation only, to be the main mode of treatment in unilateral disease. Of the 32 cases of unilateral disease enucleated, 10 underwent further radiotherapy.

The main mode of treatment in bilateral disease is enucleation of the more severely affected eye together with radiotherapy and cryotherapy to the fellow eye. The patient who had enucleation, cryotherapy and photocoagulation done with no radiotherapy at all in

the course of treatment has a positive family history. It is likely that radiotherapy was deliberately avoided in this patient because it is associated with an increased incidence of second non-ocular neoplasms especially in patients with the inherited form of the disease.⁶

Thirty-seven of the 41 patients (90%) with both unilateral and bilateral diseases underwent enucleation.

Two patients with unilateral disease refused treatment. Two cases of bilateral disease declined any sort of primary intervention.

Chemotherapy was not used at all as primary treatment.

Extent of the Disease at Enucleation, Primary Treatment and Outcome

Table III shows the extent of the disease at enucleation and outcome, with and without treatment.

Cases with *no primary treatment*: Of the 4 cases without treatment, 2 were unilateral, 1 died 23 months after diagnosis, while the other, whose tumour was thought

to have undergone regression, was still alive 21 months after diagnosis.

The 2 remaining cases were bilateral. One patient died 16 months after diagnosis, the other was alive at the time of this study (18 months after diagnosis) and undergoing palliative radiotherapy.

Cases with primary treatment: Of the 37 cases who underwent treatment, 24 had disease confined to the globe at enucleation. One patient from this group died from osteosarcoma of the maxilla and skull which was diagnosed at the age of 4 years 4 months (4 years and 1 month after the diagnosis of retinoblastoma). This particular patient had bilateral disease but no family history. It is noted that radiotherapy was previously given for treatment of the retinoblastoma. Death occurred 5 years 2 months after diagnosis of the retinoblastoma.

Where the optic nerve was involved but not beyond the resection margin, all 6 patients survived.

In the 3 cases where the optic nerve was involved beyond the resection margin, 1 patient died of metastasis to the bone marrow 15 months after diagnosis, despite radiotherapy.

The 2 cases with extraocular extension (where disease has broken out of the globe and invaded the orbit) that were treated both had unilateral disease. One underwent enucleation 2 weeks after diagnosis while the other initially declined treatment but 9 months later, consented and underwent enucleation. Both died 19 and 16 months respectively after diagnosis.

Cases with no detailed information: In the 15 cases where useful detailed information were not available, it was known that 2 had died. One of them had extraocular disease which was diagnosed at 3 years old and he died 4 months after diagnosis. The extent of the disease in the other patient was unknown but he died 10 months after diagnosis.

TABLE III: EXTENT OF DISEASE AND OUTCOME, WITH OR WITHOUT TREATMENT

Extent of enucleation	No.	Treatment	No. died
<i>Unilateral disease</i>			
- no extension beyond nerve head	21	E ED	16 5 0
- optic nerve involved excluding resection margin	5	E ED	2 3 0
- resection margin of optic nerve involved	2	ED	2 0
- extraocular†	2	E	2 2
- unknown	4	E No treatment	2 2 0 1
Total	34	—	3
<i>Bilateral disease</i>			
- no extension beyond nerve head	3	ED, C E, C, P	2 1 1 0
- optic nerve involved excluding resection margin	1	ED, C	1 0
- resection margin of optic nerve involved	1	ED	1 1
- extraocular	0	—	—
- unknown	2	No treatment	2 1
Total	7	—	3

† cases in which the disease has broken out of the globe, with orbital invasion

E : enucleation only

ED : enucleation and external beam irradiation

C : cryotherapy

P : photocoagulation

Discussion

At least 56 resident cases were diagnosed in the 20 years from 1976 to 1995 inclusively. Although the data were captured from a variety of sources, it is still possible that a small number was missing because of under-reporting and loss of information as a result of patients refusing treatment.

Incidence

The reported figures for worldwide incidence of RB range from 1 in 15 000 to 1 in 30 000 live births.⁷ Others have found the incidence rate to range from 1 in 15 000 to 1 in 28 000 live births.¹⁷

The incidence rate of 1 in 15 789 live births in this study falls within the reported range. Figures given in other studies were as follows:

Great Britain ¹³	1 in 28 000 live births
United States of America (Ohio) ¹⁸	1 in 23 287 live births
New Zealand ¹⁷	1 in 17 500 live births

In this study, there was a general increase in the number of cases diagnosed from 1976 to 1995. This increase may be due to better diagnosis and more complete notification in the later years.

Sex and Race

Tests of significance have not been used in the determination of sex and race predilection since the numbers concerned were small. However, there appears to be no predilection for sex and race, as is generally accepted. This has also been quoted in a study done in the United States of America.⁴

Studies done in Indonesia and Malaysia have found no predilection for sex and ethnic groups.^{19,20} A study done in New Zealand¹⁷ is quoted as saying that previous studies have shown that the incidence in Japanese population does not differ from that in European and American populations, although there is evidence to show that frequency may be higher in the Indian sub-continent and Africa.

Age at Diagnosis

Retinoblastoma is classically a disease of infancy and the very young, although it can occasionally occur in older children and adults.⁶ Ninety-five per cent of cases present by the age of 4 or 5 years.^{2,16}

It is found in this study that 91% were younger than 3 years old and 98% were younger than 5 years old. This is comparable to an American study in which 95% were diagnosed before the age of 5 years.⁴ In a study done in Indonesia, however, only 76.08% of patients were in the age group of 0 to 5 years¹⁹—this probably reflects later diagnosis.

Average age at diagnosis is generally accepted to be 18 months, with bilateral cases diagnosed earlier at 12 months and unilateral cases at 23 months.⁸ In this study, the mean age at diagnosis was 20 months, with bilateral cases diagnosed at 9 months and unilateral cases at 22 months. This is consistent with the knowledge that bilateral cases presented earlier than unilateral ones since only one further somatic mutation is required at the RB locus for the tumour to develop.^{2,11,12}

Laterality and Family History

In this study, the 7 bilateral cases made up 17%. This is closer to the reported figure of 25% seen in a study in the United States of America⁴ rather than the figure given in a study done in the United Kingdom of 40%.¹

Some cases of unilateral disease may be hereditary,

although this has not been confirmed by genetic studies. Hence, it may only be said that at least 17% are hereditary.

Presenting Complaints

Leukocoria and strabismus are the top two commonest presenting signs in most studies.^{2,8,11} It has been found so in this study. Leukocoria was seen in 82.9% of local patients, as compared to 44%, 56% and 76% reported by Hopping et al, Ellsworth, and Lennox et al, respectively."

Smaller tumours tend not to produce leukocoria but rather, strabismus.⁸ Unfortunately, strabismus seldom leads to early diagnosis since it is so common. By the time the mass produces leukocoria, it is usually already moderately advanced.⁸

Treatment Modalities

Treatment may require combined modalities. Enucleation is performed less frequently today due to earlier diagnosis and better alternative methods of treatment.^{21,22} Abramson et al¹⁶ did a study of 1253 retinoblastoma patients seen at the New York Hospital between 1951 and 1980. Comparing the periods 1951-1965 and 1966-1980, there was a steady reduction in the proportion of patients undergoing primary enucleation, from 97% to 87% for unilateral cases and from 97% to 91% for bilateral cases.

Having said that, enucleation is nonetheless an important and safe method²² and is generally the treatment of choice, especially in cases of advanced disease, where hope of retaining useful vision in the eye is small.⁶

In this study, 90% of patients who underwent treatment have had enucleation done. This was because the majority of patients presented with fairly advanced disease.

Two out of the 34 unilateral patients (5.9%) refused treatment. This was low compared to the 2 out of 7 (28.9%) bilateral cases who declined treatment.

Chemotherapy was not used at all as a form of primary treatment. Prevailing regimes had not proved effective. It has only been used in this study, in patients with distant metastasis. However, new chemotherapy regimes which have recently been developed promise better cure rates even as a primary modality²³ and there are indications that intraocular chemotherapy may be beneficial in selected cases.¹⁵

Extent of the Disease at Enucleation, Treatment and Outcome

The local practice for unilateral disease is for patients to further undergo a course of radiotherapy after enucleation when the disease is found to extend beyond the globe. However, 5 patients with involvement up to only the nerve head underwent radiotherapy in addition to enucleation. It is likely doctors of these patients

have opted to have radiotherapy done so that the possibility of any tumour cell having been left behind is further reduced. However, it is now known that this significantly increases the risk of developing a second non-ocular tumour, especially osteosarcoma of the orbit, if they carry the RB gene. The 30-year cumulative incidence rate is approximately 35% for hereditary cases who received external beam irradiation compared with 6% for those who did not.⁶

The patient who had bilateral retinoblastoma and later died of osteosarcoma had, in the course of treatment, received radiotherapy. It is now recommended that radiotherapy be avoided in patients with bilateral diseases and in those with positive family histories because of the higher risk of triggering the development of a second, non-ocular tumour.⁶

In both unilateral and bilateral diseases, the more advanced forms have a lower survival rate.²⁴ This was seen in this study, where both patients with extraocular disease, and 1 out of the 3 with involvement of the resection margins have died. However, only 1 out of 30 with no involvement of the optic nerve or no involvement beyond the resection margin has died. This illustrates the importance of early diagnosis.

Conclusion

Fifty-six resident and 42 non-resident patients were captured in this retrospective 10-year study. There appears to be a gradual increase in numbers over the years. The local incidence rate is 1 in 15 789 live births. However, it should not be forgotten that these numbers might be underestimated due to under-reporting and loss of information through patients refusing treatment. The actual numbers for both resident and non-resident cases could be higher.

Based on the detailed study of 41 resident patients, 98% presented before the age of five. Bilateral cases were diagnosed earlier than the unilateral ones. It was found that at least 17% were hereditary, that is, bilateral, but only 2 of these patients had a positive family history.

The patients mostly presented with leukocoria, but a number of them had seemingly benign complaints like strabismus and decreased visual acuity. It is therefore important for doctors to have a high index of suspicion even in patients with common complaints such as poor vision, strabismus and persistent eye redness. In such instances, direct ophthalmoscopy should be done to detect a white pupillary reflex or a mass in the posterior retina.

Enucleation was, on the whole, performed on 90% of patients. The main mode of treatment for unilateral disease was enucleation alone. In bilateral disease, the more badly affected eye was enucleated while the other eye was treated conservatively. It is noted that chemo-

therapy was not used at all as a form of primary treatment. However, a recent study done by Gallie et al²⁵ in Toronto suggests that chemotherapy with focal therapy is effective in curing most retinoblastomas. In Singapore, the "Toronto" protocol (vincristine, teniposide, carboplatin and cyclosporine) has been adopted to treat recurrent retinoblastoma. There are also plans to embark on the use of chemotherapy in combination with focal therapy as a primary line of management in cases where the eye may be salvaged and especially in bilateral cases where 1 eye is often less affected. This will hopefully allow more eyes to be salvaged without increasing the risks involved.

This study also illustrates the importance of early diagnosis and prompt institution of appropriate treatment in improving prognosis. In both bilateral and unilateral diseases, the more advanced forms have lower survival rates. In the period of study, 8 out of the total of 56 patients died.

Genetic diagnosis may be used in early detection. Determination of mutant gene carrier status in individuals with positive family history is now possible,²⁶ although it is technically still a laborious process. In Singapore, a combination of techniques is used to identify probable areas of defect in the RB gene. However, locally, the feasibility of using genetic diagnosis as a tool in early detection is still under evaluation.

There is no doubt that the prime objective in management of patients with retinoblastoma is the survival of these patients. However, the second objective, which is to preserve as much vision as possible in 1 or both eyes,²⁶ should not be neglected. Therefore, even though enucleation is a safe and effective way of managing this disease, with better chemotherapeutic regimes and new treatment modalities the management strategy is changing to follow the general shift towards individualisation of treatment and employment of more conservative measures as the primary mode of treatment.^{10,26} With early detection and improved treatment modalities, one can hope to preserve sight without compromising the survival rates.

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