RETINOBLASTOMA IN SOUTH AFRICA

A 20-year retrospective study at two tertiary academic hospitals in Johannesburg

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A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Medicine in Ophthalmology

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DECLARATION

I, Saadiah Goolam declare that this dissertation is my own work. It is being submitted for the degree of Master of Medicine in the branch of Ophthalmology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed S GOOLAM

This 16 day of June 2014

The work reported in this dissertation was carried out in the Departments of Ophthalmology and Paediatric Oncology at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

The project was approved by the Ethics Committee, University of the Witwatersrand (Appendix A).

DEDICATION

To the memory of

Thokozani Masombuka

19/03/05 to 17/06/12

& to all our retinoblastoma children..

ABSTRACT

Retinoblastoma is the most frequent malignant intraocular tumour of childhood, and in Africa it is the commonest and most important life threatening ocular neoplasm. In resource-rich countries such as the United States and Canada, survival rates for patients with retinoblastoma approach 100%. This is in stark contrast to developing countries where survival rates may be less that 20%. Despite the vast majority of affected patients living in less developed countries, there is little attention and published literature on disease characteristics in these populations.

OBJECTIVES: To characterise retinoblastoma in the South African population through a 20-year retrospective analysis of patient records at two tertiary academic hospitals in Johannesburg.

DESIGN AND METHOD: Retrospective clinical case series analysis of medical records of patients with retinoblastoma presenting to Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital between 01 January 1992 and 31 December 2011.

RESULTS: The total number of retinoblastoma cases identified was 282, with 245 of these meeting the study inclusion criteria. Retinoblastoma comprised 6.9% of total paediatric oncology presentations. 65.3% were unilateral, 34.3% bilateral and 0.4% trilateral. The overall male to female ratio was 1.08. Mean age at presentation overall was 32.6 months (median 28.0 months), for unilateral 39.4 months (median 33.0 months) and for bilateral 19.7 months (median 17.0 months). The mean delay to presentation overall was 7.0

months (median 4.0 months), for unilateral 8.5 months (median 5.0 months) and for bilateral 4.4 months (median 3.0 months). The most frequent presenting symptoms were leukocoria (37.1%) and proptosis (34.7%). Distribution of disease stage at presentation (using the International Retinoblastoma Staging System) was 1.6% with Stage 0, 24.1% with Stage I, 27.8% Stage II, 16.3% Stage III and 25.3% Stage IV (data not available in 4.9%). 26.5% of patients defaulted care. The five-year survival rate was 57.7% in the overall study population, and according to disease stage at presentation: 95.3% - Stage I, 84.8% - Stage II, 49.7% - Stage III and 5.7% - Stage IV.

CONCLUSION: The five-year survival rate for Stage I disease is similar to the overall five-year survival rates reported in the developed world. This suggests that treatment standards at the study hospitals are comparable with those of developed countries and that similar overall survival rates may be achieved if patients were to present as early. Delay to presentation, disease stage at presentation and defaulting care were identified as key factors contributing to the poor overall survival rate. This study provides information regarding patient demographics, social challenges in management, and patient outcomes in comparison to developed countries and to reports from other African populations. It also highlights the need for educational campaigns and screening initiatives to address poor survival outcomes as a result of late presentation and high rates of patients defaulting care. Finally, this report serves as a platform for comparison with future research in this area.

ACKNOWLEDGMENTS

It is with deep appreciation that the following persons are acknowledged:

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3. Dr Petra Gaylard for patiently and meticulously reviewing every aspect of the statistical analysis involved in this study.
4. Dr Linda Wainwright for her knowledge and interest in this project, and for facilitating the data collection process.
5. The staff at the paediatric oncology units at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital for their assistance in accessing patient medical records.

PERSONAL CONTRIBUTIONS

All aspects of data collection were performed by the primary researcher (myself) at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital.

All statistical analysis, including data preparation, was performed entirely by myself using Stata 12 (statistical software program) and Microsoft Excel and Word for Mac 2011. Statistical advice was received from Dr Petra Gaylard who reviewed all the statistical analysis included in this study.

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LIST OF ABBREVIATIONS

RB1	Retinoblastoma gene
ICRB	International Classification of Retinoblastoma
IRSS	International Retinoblastoma Staging System
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CHBAH	Chris Hani Baragwanath Academic Hospital
DXT	Deep X-ray therapy

CHAPTER 1

1.1 INTRODUCTION AND LITERATURE REVIEW

Retinoblastoma is the most frequent malignant intraocular tumor of childhood, and in Africa it is the commonest and most important life threatening ocular neoplasm.[1,2,3]

In Europe, North America and Australia, retinoblastomas account for 2 to 4% of total neoplasms in children, with similar relative frequencies in Asia, while in African populations retinoblastoma is reported to account for 10-15% of childhood cancers.[4]

Epidemiological studies suggest an incidence of approximately 1 in 16,000 to 18,000 births annually worldwide.[5]

Retinoblastoma is a cancer with a genetic aetiology, and arises from mutations in both alleles of the Retinoblastoma gene (RB1). The disease may occur in a heritable (germline mutation) and non-heritable form (somatic mutation). In germline mutations the mutation is present in all cells of the body and is transmitted to the affected individual's offspring. In somatic mutations, only the tissue of concern has the mutation, and there is no chance of transmitting the disease to offspring.[3,6] The heritable form includes all cases of bilateral and familial retinoblastoma, as well as a few cases of unilateral tumour – a mutation in the RB1 gene is either inherited from an affected parent or arises spontaneously in one chromosome, and a spontaneous mutation occurs in the remaining copy of the gene which results in the

disease.[3,6] While unilateral sporadic retinoblastoma is usually not heritable, approximately 15% of patients demonstrate a germline mutation.[3,7]

Patients with a germline mutation are at increased risk of developing a neuroblastic intracranial malignancy, most frequently a pinealoblastoma, and this has been termed “trilateral” retinoblastoma – it occurs in approximately 3% of all cases, and up to 10% of those with bilateral or familial retinoblastoma.[3]

In poorly developed countries, as in the majority of sub-Saharan Africa, most patients with retinoblastoma succumb to advanced, disseminated disease, and familial retinoblastoma is uncommonly seen.[1,2,8] In middle-income, developing countries, improved treatment has decreased mortality rates, resulting in a greater number of survivors with heritable RB1 mutations, and later, a corresponding increase in the proportion of familial retinoblastoma cases seen.[8] In developed countries, up to 12% of retinoblastoma cases inherit a RB1 mutation from an affected parent.[7,8]

The genetics of retinoblastoma do not lend preference to any particular sex, and the majority of studies find an equal incidence of the disease in males and females.[9,11] There are, however, several authors that have reported a higher incidence in males.[1,2,4,10,12]

Unilateral retinoblastoma is more common and accounts for approximately two-thirds of all cases in developed countries.[3,7,9] It accounts for an even greater proportion of cases in poorly developed countries, most likely due to higher mortality rates in these populations.[1,2,4,10]

In developed countries the majority of retinoblastoma cases present before the age of five years. Bilateral retinoblastoma typically occurs at a younger age than unilateral disease.[11,13] The mean age at presentation for both unilateral and bilateral retinoblastoma is higher in poorly developed countries, and is most probably due to delayed presentation.[1,2,3]

Late presentation is invariably the cause for increased mortality rates in poorly developed countries and reports from African countries including the Democratic Republic of Congo, Nigeria, Tanzania, Mali, South Africa and Kenya demonstrate this.[1,2,10,12,15,16,17,18] A South African study by Wainwright et al in 2011 reported that the average time delay between the onset of symptoms and diagnosis of retinoblastoma was 10.1 months.[17] This is similar to other African studies, with delays generally in excess of 6 months, and up to 15 months being reported.[1,2,15] Nyamori et al found that in Kenya, even patients with a family history of retinoblastoma had a delayed presentation.[12] Late presentation in developing countries is thought to be a result of poor awareness of retinoblastoma by both the public and healthcare professionals, difficulties accessing healthcare in remote areas, cultural beliefs, as well as regional differences in attitudes towards disease.[2,3,8,19]

The presenting signs of retinoblastoma in the developed world are most commonly leukocoria (“white pupil”) or strabismus (squint).[1,20] Other presenting signs include proptosis (protrusion of the globe), eyelid swelling, and signs of intraocular inflammation. Reports from sub-Saharan Africa suggest that leukocoria and proptosis, rather than strabismus, are the

commonest presentations of retinoblastoma in this population[1,2,10,15,21] The difference in presentations is probably linked to delayed diagnosis, with patients presenting with advanced disease when globe displacement and extraocular spread has occurred.[11]

Retinoblastoma without treatment is almost invariably fatal. Management of the disease is often complex and highly individualized. It is guided by several factors such as the threat of metastatic disease, risk for second cancers, systemic status, laterality of the disease, size and location of tumour(s), and estimated visual prognosis.[3] Coordinated care is required between the tertiary eye care centre, paediatric oncologists, pathologists and interventional radiologists.[5] Enucleation involves careful removal of the eye with a long section of the optic nerve to minimize any globe trauma and tumour spread into the orbit; it is the favoured approach for extensive retinoblastoma, especially if it is unilateral.[7,20,22,23] Treatment modalities have evolved over recent decades, and available options in developed countries now include intravenous chemoreduction (carboplatin, etoposide, and vincristine), intra-arterial chemotherapy, subconjunctival carboplatin, thermotherapy, cryotherapy, laser photocoagulation, plaque radiotherapy, external beam radiotherapy, and enucleation.[3,20,23] Intravitreal chemotherapy has been trialed recently for recurrent vitreous seeding following failed therapies, with early reports suggesting that extraocular extension of the disease as a result of the injection is rare.[20,24] Over the past decade, there has been a trend towards vision-preserving treatment, and many retinoblastoma patients with bilateral disease who would have undergone enucleation have been

controlled without removing the eye, and without any changes in the mortality rates.[22] In the United States, enucleation rates for patients with unilateral retinoblastoma have also decreased.[5,7,20,22] Authors caution that careful patient selection for eye-conserving treatment is mandatory, and reinforce that retinoblastoma treatment be aimed at child survival, followed by globe salvage and preservation of vision.[5,7,20]

Several classifications of retinoblastoma have been developed as treatment strategies have evolved. The Reese-Ellsworth classification for retinoblastoma was developed in the 1960's, and until recently was the primary classification system used for intraocular retinoblastoma.[5,22] (Appendix B) It was developed to predict treatment success (globe salvage) following radiotherapy, which was a key treatment modality at the time. [5,22] As preferred treatment methods shifted away from radiotherapy in later years, a modified classification system, the International Classification of Retinoblastoma (ICRB), was proposed in 2005. (Appendix C) The ICRB is replacing the Reese-Ellsworth classification in clinical practice as it is more in line with contemporary treatment strategies by better predicting treatment success (globe salvage and avoidance of radiotherapy) with chemoreduction and local treatments.[3,5,22] Less developed countries frequently encounter retinoblastoma when extraocular spread has occurred. In this setting it is more practical to adopt a staging system that addresses extraocular extension of the disease and systemic involvement. Several staging systems for extraocular retinoblastoma have been proposed, however none has been universally and consistently applied.[25,26] Following introduction of the newer ICRB classification for intraocular retinoblastoma, an

international consortium of ophthalmologists and paediatric oncologists reviewed existing staging systems for extraocular retinoblastoma. In 2006 they proposed a new simplified staging system, the International Retinoblastoma Staging System (IRSS), with the aim of better predicting survival.[25] (Appendix D)

In resource-rich countries such as the United States and Canada, survival rates for patients with retinoblastoma approaches 100%.[5,18] This is in stark contrast to poorly developed countries, where the majority of affected children live - survival rates in some of these populations may be less than 20%.[1,2,5,14,18,27,28] Despite more than 90% of affected patients living in poorly developed countries, there is little attention and published literature on disease characteristics in these populations.[27]

1.2 RESEARCH AIM

The aim of this research project was to characterize retinoblastoma in the South African population through a 20-year retrospective analysis of retinoblastoma patient records at two tertiary South African academic hospitals in Johannesburg.

1.3 RESEARCH OBJECTIVES

The study sought to describe retinoblastoma in the research population group in terms of:

A. Total number of retinoblastoma cases over the study period
B. Retinoblastoma cases as a proportion of total paediatric oncology presentations over the study period
    i. Proportion of retinoblastoma to non-retinoblastoma paediatric oncology presentations for each successive five-year period of the study
C. Number of records meeting the inclusion and exclusion criteria
D. Laterality
    i. Proportion of bilateral to unilateral retinoblastoma presentations for each successive five year period of the study
E. Sex distribution
F. Age at presentation
    i. Overall
    ii. By laterality
    iii. By family history
G. Delay to presentation
    i. Overall
    ii. By laterality
    iii. By family history
H. Presenting symptoms
    i. Commonest presenting symptom

ii. Patients with leukocoria as the presenting symptom as a proportion of the total number of patients in whom leukocoria was evident at presentation

iii. Patients with strabismus as the presenting symptom as a proportion of the total number of patients in whom strabismus was evident at presentation

I. Genetic testing

J. Disease stage at presentation

i. By delay to presentation

ii. By family history

iii. By laterality

K. Treatment administered

L. Proportion of patients defaulting care

M. Survival

i. Overall

ii. By stage

iii. By laterality

iv. By family history

v. By delay to presentation

vi. By defaulting care

CHAPTER 2

2.1 STUDY DESIGN

A retrospective clinical case series analysis of patient medical records and histopathological reports of patients with retinoblastoma presenting to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) between 01 January 1992 and 31 December 2011.

2.2 DATA COLLECTION

This study was conducted subsequent to submission of a research protocol to the Human Research Ethics Committee (Medical), University of Witwatersrand. The proposed study received ethics approval from the committee and a clearance certificate was issued, Reference M120726. (Appendix A)

Consent to review patient medical records was obtained from the Chief Executive Officer of CMJAH and from the Superintendent of CHBAH.

Statistical records of the number of paediatric patients presenting with oncological diseases to the paediatric oncology departments at CMJAH and CHBAH were reviewed. The total number of paediatric patients diagnosed with any oncological disease over the duration of the study period for both

hospitals was tallied. This data was recorded for comparison with the total number of retinoblastoma presentations over the study period.

Retinoblastoma patients presenting during the study period were identified through review of a departmental record of all patients presenting to the paediatric oncology departments at CMJAH and CHBAH. The patient name and medical record number were utilised to retrieve the medical records for these patients.

2.2.1 INCLUSION CRITERIA

Cases of retinoblastoma diagnosed on the basis of clinical, imaging or histological findings between 01 January 1992 and 31 December 2011 were included in the study.

2.2.2 EXCLUSION CRITERIA

There were two basic exclusion criteria in the study:

- Cases in which the diagnosis of retinoblastoma was not certain were excluded.
- Patient Medical Records with grossly inadequate record keeping were excluded.

2.2.3 DATA MANAGEMENT

Patient medical records meeting the inclusion criteria were reviewed and relevant data extracted by the primary researcher and recorded in a spreadsheet using Microsoft Excel for Mac 2011. Strict confidentiality was maintained in this study with each patient being assigned a case number to ensure anonymity. Patient names, medical record numbers and any identifiers were available to the primary researcher alone.

The following information was extracted from each patient medical record:

a) Date of presentation

   The initial date of presentation to CMJAH or CHBAH was recorded.

b) Delay to presentation

   The period of time, recorded in months, from the date that symptoms or signs related to the diagnosis of retinoblastoma were initially noticed to the date that medical attention was first sought at any public or private health care facility.

   Some patients were diagnosed with retinoblastoma in the absence of any signs or symptoms, following a screening examination for the disease prompted by a positive diagnosis in a sibling. In these instances the delay to presentation was recorded as zero months. Inadequate record keeping precluded determination of the delay to presentation in some cases. The data entered in these cases reflected that the information was unavailable.

c) Age at presentation

The youngest age, recorded in months, at which the patient initially presented to any private or public health care facility to seek medical attention for symptoms or signs related to the subsequent diagnosis of retinoblastoma.

d) Sex

Recorded as either male or female.

e) Presence of a family history of retinoblastoma

A documented family history of retinoblastoma was recorded as “yes”, along with details of the relationship of the affected family member to the patient. A “no” entry signified the absence of a family history of retinoblastoma.

The data entry “not available” was used in cases where no family history was recorded or in instances where it was not possible to obtain a family history from the patient or persons accompanying the patient.

f) Laterality

Laterality was recorded as being unilateral, bilateral or trilateral as determined at the final date of follow-up available for the patient. The diagnosis of retinoblastoma in a single eye was recorded as unilateral, involvement of both eyes was recorded as bilateral, and cases with both eyes involved in the presence of a neuroblastic intracranial malignancy were recorded as trilateral.

g) Presenting symptom or complaint

The symptom or sign related to the diagnosis of retinoblastoma that prompted the patient or family of the patient to seek medical attention. Other signs or symptoms related to the diagnosis of retinoblastoma that were initially or concurrently noted, but that did not in themselves cause the patient or family of the patient to seek medical attention were excluded.

The presenting symptom or complaint recorded for those patients diagnosed with retinoblastoma in the absence of any signs or symptoms, following a screening examination for a positive family history of the disease, was “screening due to family history”.

The data entry “not available” was used for instances where record keeping was inadequate or the history was not available from the patient, family or guardians of the patient.

h) Other symptoms and signs at time of presentation

These comprised all signs and symptoms related to the diagnosis of retinoblastoma, other than the presenting symptom or complaint, noted by either the patient, family, guardians or health care professionals prior to or at the time of presentation.

The data entry “not available” reflected instances where record keeping was inadequate or the relevant history was unavailable from the patient, family or guardians of the patient.

i) Retinoblastoma staging for each eye

The International Retinoblastoma Staging System (Appendix D) was used to retrospectively stage the disease in each eye after reviewing the results of all histopathological, cytological and radiological investigations performed for the patient.

Patient factors such as defaulting care or refusal of investigations and management precluded staging of the disease both retrospectively and at the time of presentation in some cases. In these instances the stage of the disease was recorded as being unavailable.

The data entry “unavailable” was also used in cases where medical records did not reveal the stage of the disease and inadequate record-keeping did not allow for retrospective staging either.

The ICRB classification (Appendix C) was introduced late in the second half of the study period so that earlier records reflected the Reese-Ellsworth classification, which was the current standard at the time. Insufficient detail of ophthalmological findings at the time of examination in records from the early study period did not allow for retrospective staging of the disease using the newer ICRB classification. Records from the later study period were generally of sufficient detail to allow for intraocular classification by either the Reese-Ellsworth or ICRB classification systems. For consistency and comparison purposes the Reese-Ellsworth classification was therefore used throughout this research report.

j) Treatment administered for each eye

The use of the following treatment options were recorded for each eye:

- Local therapy (laser therapy, cryotherapy or a combination of the two)
- Brachytherapy (either ocular or orbital)
- Intravitreal chemotherapy
- Enucleation
- Exenteration
- Intravenous chemotherapy
- Intra-arterial chemotherapy
- Local radiotherapy (Deep X-ray Therapy, DXT)
- Palliative therapy

In patients with bilateral disease the use of intravenous chemotherapy as a treatment indicated for the stage of disease in one eye was also recorded as a treatment option utilized in the second eye regardless of whether chemotherapy was indicated for the stage of disease in the second eye.

Planned treatment was unable to be administered in some cases due to the patient defaulting or declining care. In these instances only the treatment administered was recorded.

k) Genetic Testing

Medical records were reviewed in each case for evidence of genetic investigations having been conducted on the patient.

In some cases it was not possible to determine whether or not genetic testing had been performed due to inadequate record keeping and an inability to trace early records on current laboratory systems. In these instances a data entry of “not available” was made.

l) Incidences of the patient defaulting or refusing management

Any incident of the patient refusing hospital treatment or defaulting care was positively noted if in the medical record it was also reflected to be a significant event in the management of the patient.

A record was made of the incident regardless of whether it transpired prior to, during, or after treatment.

m) Follow-up period

The follow-up period was determined to consist of all visits subsequent to the completion of any planned treatment for disease, and was recorded in months from the date of last treatment administered to the date of last follow-up.

n) Follow-up status

The follow-up status was recorded as either complete or incomplete. Cases with a recorded follow-up period of any length were considered to be complete. In cases with advanced disease at presentation or with recurrence of disease at an advanced stage where no curative

treatment was planned, the follow-up status was recorded as "complete".

The follow-up status of patients who were treated with curative intent and then transferred to another hospital (other than CMJAH and CHBAH) was considered to be incomplete if there was no follow-up period at the study hospital for the patient subsequent to treatment.

Patients who refused hospital treatment or defaulted treatment permanently were recorded as having an "incomplete" follow-up status regardless of the stage of disease at presentation or at time of default.

Patients who defaulted treatment but returned at a later stage without subsequently defaulting treatment were considered to have a "complete" follow-up status.

o) Patient survival status

The patient's survival status at the last recorded visit was described as either "dead" or "alive".

Where the stage of the disease was so advanced that no curative treatment was planned, the status was recorded as "dead".

Patients who refused hospital treatment or defaulted treatment permanently were recorded as having "undetermined" survival status.

The survival status was recorded as "undetermined" for those patients transferred to another hospital (other than CMJAH or CHBAH).

2.3 DATA ANALYSIS

All data analysis was carried out by the primary researcher using Stata 12 software.[29]

The 5% significance level was used throughout (all tests or parameters with a p-value below 0.05 were significant).

Specific statistical methods and tests utilised are discussed under the relevant sections of the results chapter (chapter 3).

2.4 STAFF AND ADMINISTRATION

This study was conducted by Dr Saadiah Goolam (Ophthalmology registrar) and supervised by Dr Nicky Welsh (Ophthalmology consultant). The primary site of this study was the Paediatric Oncology department at CMJAH and CHBAH.

2.5 ETHICAL CONSIDERATIONS

This study was conducted subsequent to approval of a research proposal submitted to the Human Research Ethics Committee, University of Witwatersrand. An Ethics clearance certificate (Reference M120726) was obtained. (Appendix A) All patient names, medical record numbers and identifiers were kept confidential.

CHAPTER 3

3.1 TOTAL NUMBER OF RETINOBLASTOMA CASES

The total number of retinoblastoma presentations recorded over the 20-year study period was 282. A total of 221 presentations (78%) was recorded at CHBAH, and a total of 61 presentations (22%) was recorded at CMJAH.

3.2 RETINOBLASTOMA AS A PROPORTION OF TOTAL PAEDIATRIC ONCOLOGY PRESENTATIONS

The total number of paediatric oncology presentations over the study period was 4108 (2010 at CMJAH and 2098 at CHBAH), with confirmed retinoblastoma comprising 282 (6.9%) of these.

The number of paediatric oncology and retinoblastoma presentations for each successive five-year period was determined. The proportion of retinoblastoma to non-retinoblastoma paediatric oncology presentations for each of the successive five-year periods is shown in Figure 1.

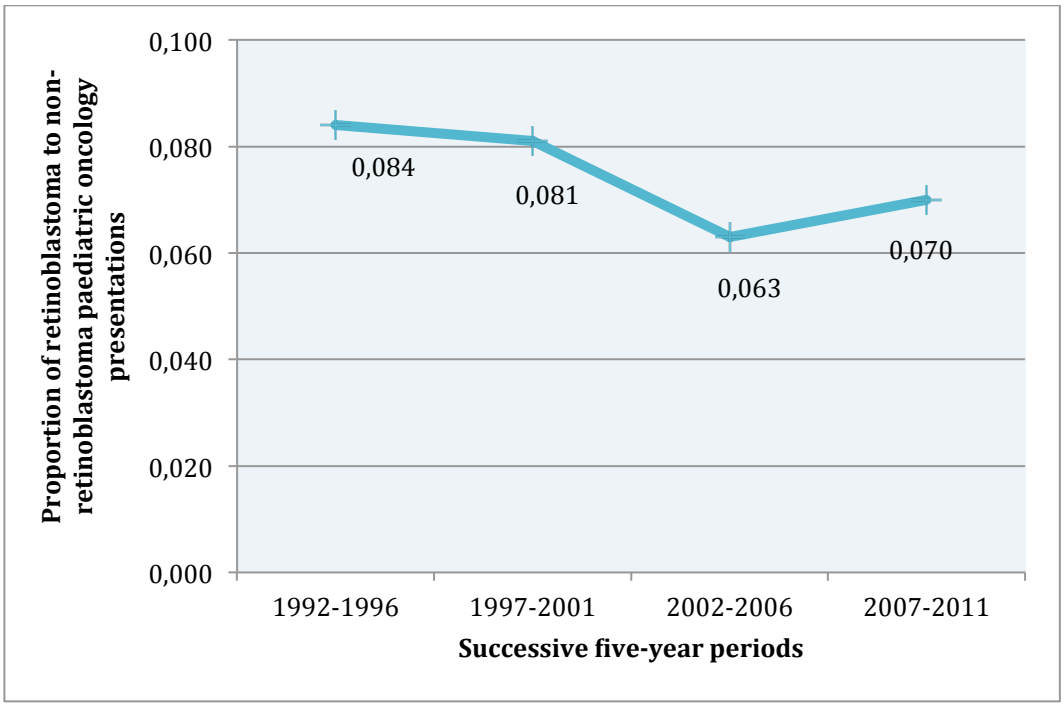

Figure 1. The proportion of retinoblastoma to non-retinoblastoma paediatric oncology presentations per successive five-year period of the study.

There was no statistically significant relationship between the proportions of retinoblastoma to non-retinoblastoma paediatric oncology presentations over the successive five-year periods of the study (X^2 test, p=0.36).

3.3 RETINOBLASTOMA CASES MEETING CRITERIA

A total of 282 cases meeting the inclusion criteria were identified. Of these, 245 cases (86.9%) met the inclusion and exclusion criteria - 37 records were excluded from the study due to inadequate or unavailable medical records. No cases were excluded on the basis of an incorrect or uncertain diagnosis of retinoblastoma. Of the 245 cases, 193 (78.8%) were from CHBAH and 52 (21.2%) were from CMJAH.

3.4 LATERALITY

Table 1. Laterality of disease in the study population

LATERALITY		
	Number of cases	Percentage
Unilateral	160	65.3%
Bilateral	84	34.3%
Trilateral	1	0.4%
Total	**245**	**100%**

The proportion of hereditary (bilateral and trilateral) retinoblastoma to unilateral retinoblastoma for each successive five-year period of the study is shown in Figure 2.

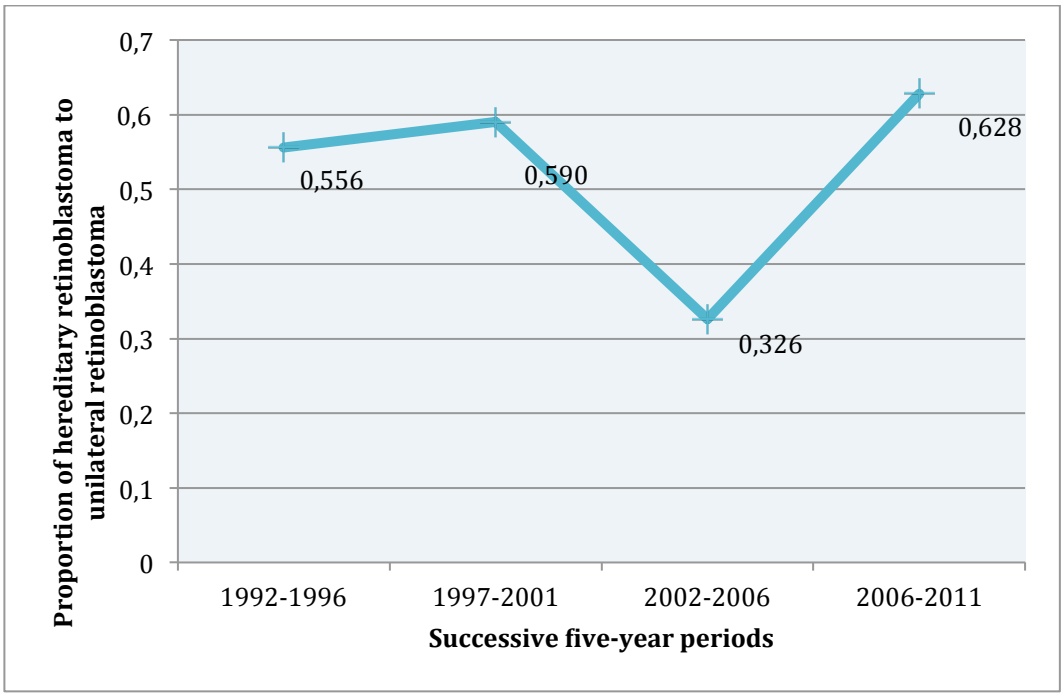

Figure 2. The proportion of hereditary (bilateral and trilateral) retinoblastoma to unilateral retinoblastoma per successive five-year period of the study.

There was no statistically significant relationship between the proportions of hereditary to unilateral retinoblastoma presentations over successive five-year periods of the study (X^2 test, p=0.49).

3.5 SEX DISTRIBUTION

The distribution of male and female patients in the overall study population as well as in the unilateral and bilateral groups is presented in Table 2.

Table 2. Sex distribution in the study population

SEX			
	Overall	Bilateral*	Unilateral
Male	127 (51.8%)	48 (56.5%)	81 (50.6%)
Female	118 (48.2%)	37 (43.5%)	79 (49.4%)
Total	**245**	**85**	**160**

* Includes trilateral retinoblastoma

The overall ratio of male to female in the study was 1.08, and 1.30 in the bilateral group. There was no statistically significant association between sex and laterality (X^2 test, p=0.29).

3.6 AGE AT PRESENTATION

The univariate statistics for the continuous variable “Age at Presentation” (overall and grouped by laterality and family history) are presented in Table 3. Figure 3, Figure 4 and Figure 5 show box and whisker plots for Age at presentation overall, and by laterality and family history respectively.

Table 3. Univariate statistics for age at presentation in the overall study group, and grouped by laterality and family history. (Significant results are marked in red)

AGE AT PRESENTATION*					
	OVERALL	LATERALITY		FAMILY HISTORY	
		UNILATERAL	BILATERAL**	YES	NO
n	245	160	85	17	219
Mean	32.6	39.4	19.7	20.3	33.4
Median	28.0	33.0	17.0	21.0	28.0
Minimum	0.5	1.5	0.5	0.5	1.5
Maximum	238.0	238.0	70.0	47.0	238.0
Lower Quartile	17.0	24.0	8.0	8.0	17.0
Upper Quartile	40.0	47.5	29.0	29.0	40.0
Std. Deviation	26.8	29.3	14.2	14.7	27.5
Skewness	3.01	2.98	0.95	0.39	3.04
Kurtosis	16.27	14.55	1.15	-0.86	15.99
z(skew)	19.25	15.41	3.59	0.65	18.34
z(kurt)	51.99	37.56	2.16	-0.72	48.29
p-value for Shapiro-Wilk test for normality* **	<0.0001	<0.0001	<0.0001	0.35	<0.0001
p-value for Wilcoxon Rank Sum test for differences between groups		<0.0001		0.026	

* Age at presentation in months

** Includes trilateral retinoblastoma

*** Tested at the 1% significance level

3.6.1 Overall

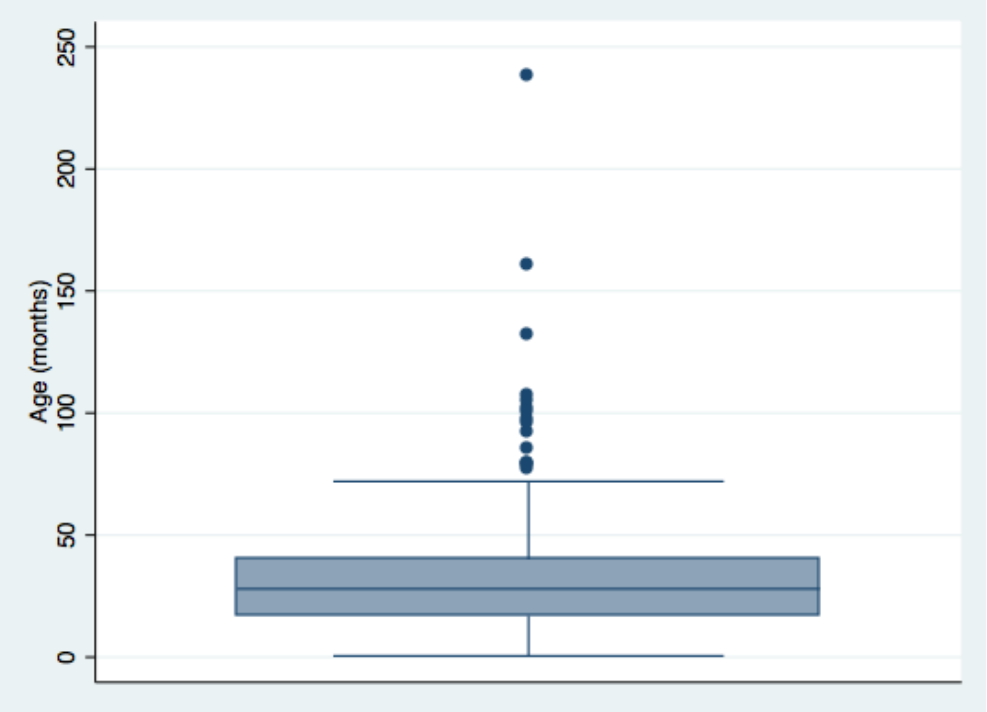

Figure 3. Box and whisker plot of age at presentation in overall population.

Tests for normality and skewness (Table 3) show that the variable is positively skewed and exhibits significant non-normality (p<0001).

3.6.2 Laterality

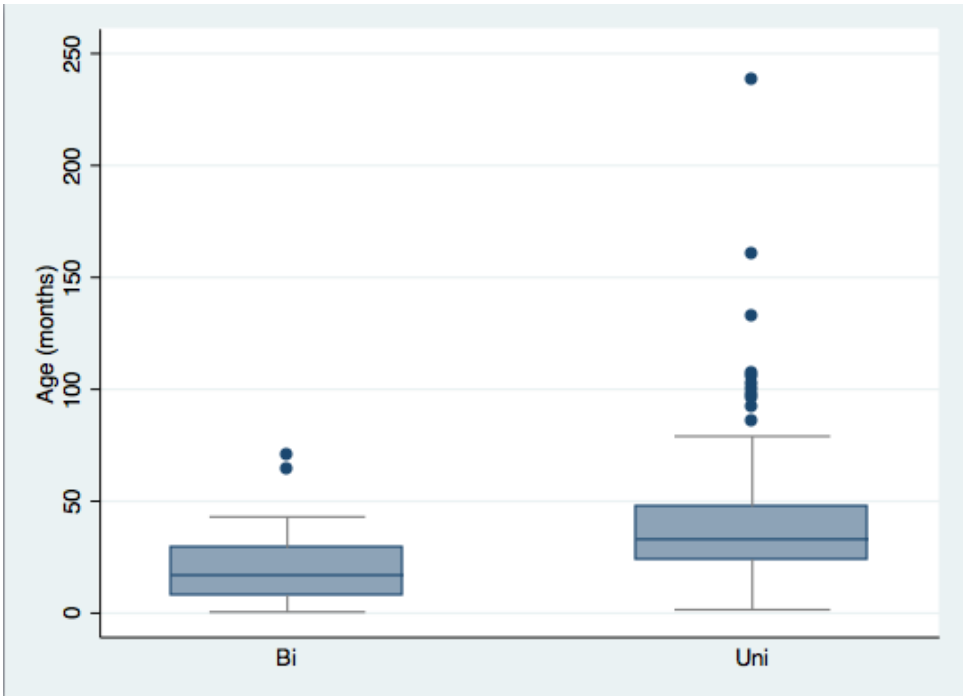

Figure 4. Box and whisker plot of age at presentation by laterality.

Tests for normality and skewness (Table 3) show that the variables are positively skewed and exhibit significant non-normality ($p<0.0001$). Therefore the Wilcoxon Rank Sum test (the non-parametric equivalent of the independent samples t-test) was used for between-group comparisons since the assumptions of the t-test were not met. There was a statistically significant difference between the laterality groups ($p<0.0001$). Patients with hereditary retinoblastoma (bilateral and trilateral) had a lower median age at presentation (17 months) than those with unilateral retinoblastoma (median age at presentation 33 months).

3.6.3 Family History

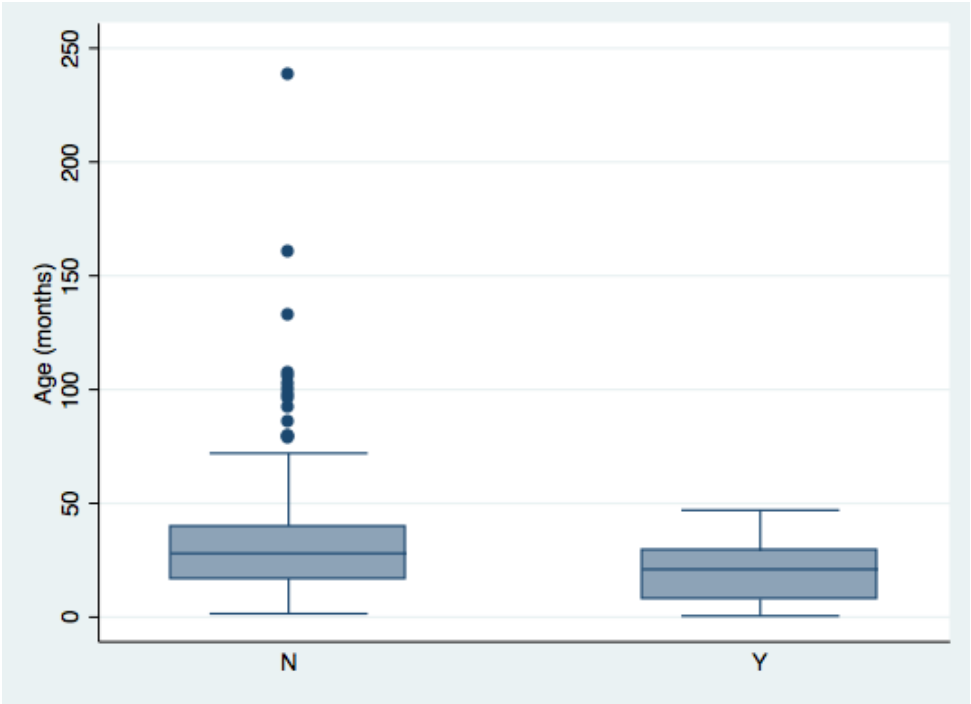

Figure 5. Box and whisker plot of age at presentation by family history. ("Y" indicates a positive family history; "N" indicates no family history of retinoblastoma).

Tests for normality and skewness (Table 3) show that the variable age by presentation is positively skewed and exhibits significant non-normality in the group of patients without any family history of the disease ($p<0.0001$). The Wilcoxon Rank Sum test was thus used for between-group comparison. There was a statistically significant difference between the two groups ($p=0.026$). Patients with a positive family history presented earlier (median age 21 months) than those without a family history of the disease (median age 28 months).

3.7 DELAY TO PRESENTATION

The univariate statistics for the continuous variable “Delay to Presentation” (overall and grouped by laterality and family history) are presented in Table 4. Figure 6, Figure 7 and Figure 8 show box and whisker plots for Delay to presentation overall, and by laterality and family history respectively.

Table 4. Univariate statistics for delay to presentation in the overall study group, and grouped by laterality and family history. (Significant results are marked in red)

DELAY TO PRESENTATION*					
	OVERALL	LATERALITY		FAMILY HISTORY	
		UNILATERAL	BILATERAL**	YES	NO
n	231	148	83	16	213
Mean	7.0	8.5	4.4	4.0	7.2
Median	4.0	5.0	3.0	2.0	4.0
Minimum	0.0	0.0	0.0	0.0	0.0
Maximum	72.0	72.0	24.0	24.0	72.0
Lower Quartile	1.0	2.0	1.0	0.0	2.0
Upper Quartile	10.0	12.0	6.0	4.0	10.0
Std. Deviation	8.7	10.0	5.0	6.3	8.8
Skewness	2.92	2.62	1.96	2.44	2.97
Kurtosis	14.20	11.13	4.33	6.49	14.61
z(skew)	18.11	12.99	7.29	3.99	17.72
z(kurt)	44.06	27.65	8.05	5.30	43.53
p-value for Shapiro-Wilk test for normality* **	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p-value for Wilcoxon Rank Sum test for differences between groups		<0.0001		0.021	

* Delay to presentation in months

** Includes trilateral retinoblastoma

*** Tested at the 1% significance level

3.7.1 Overall

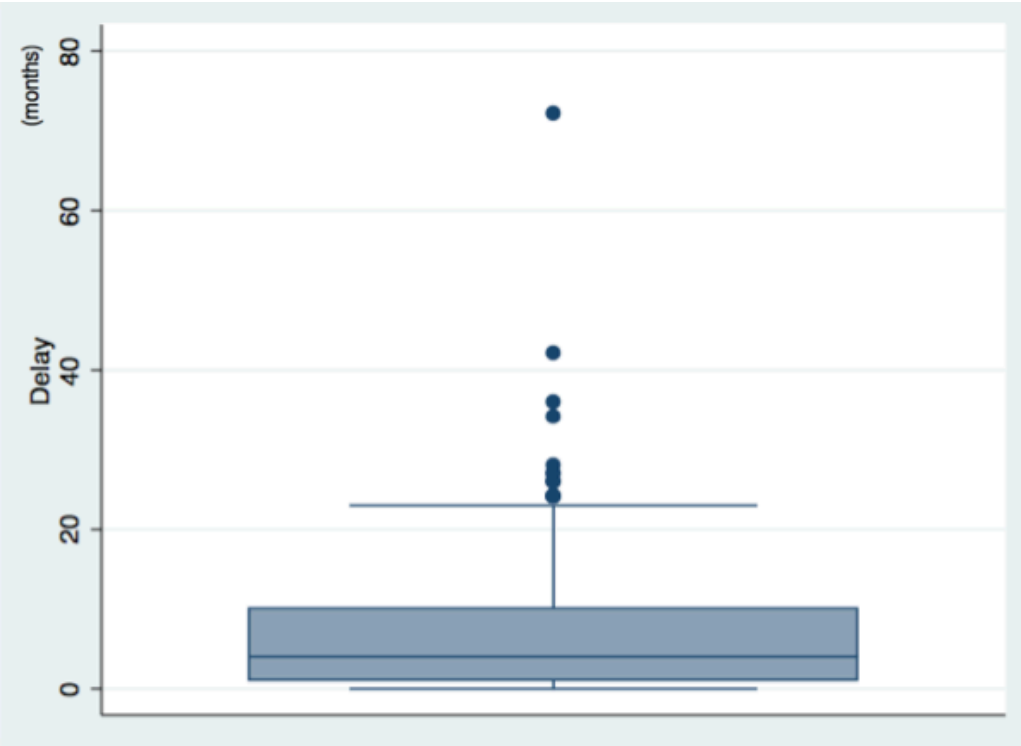

Figure 6. Box and whisker plot of delay to presentation in overall population.

Tests for normality and skewness (Table 4) show that the variable is positively skewed and exhibits significant non-normality (p<0001).

3.7.2 Laterality

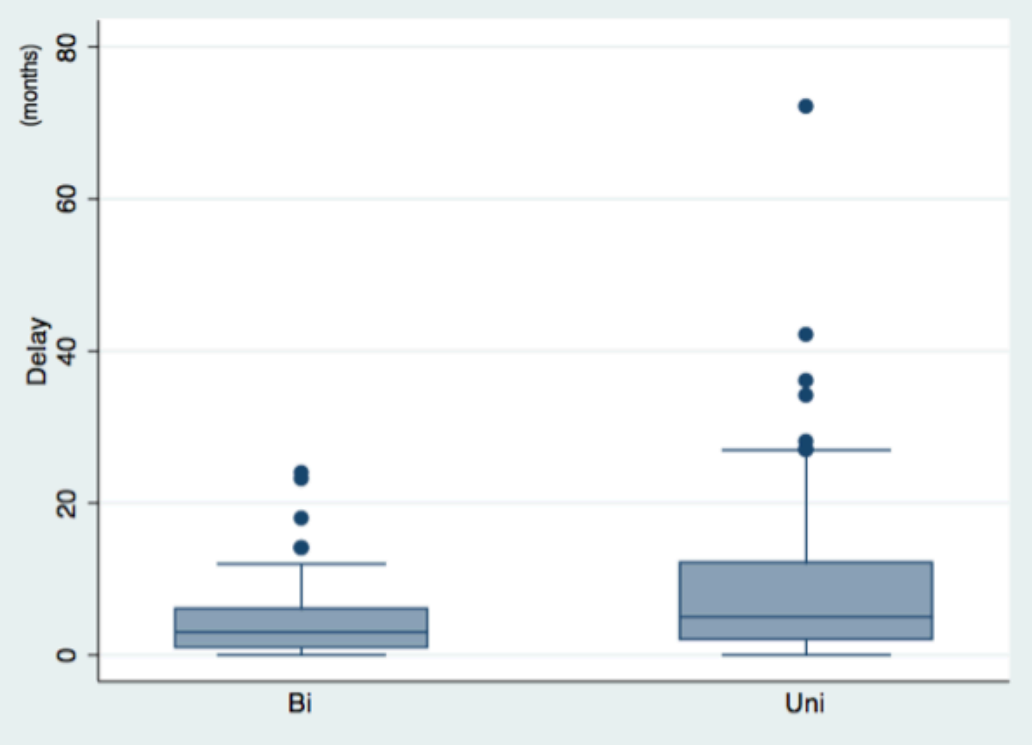

Figure 7. Box and whisker plot of delay to presentation by laterality.

Tests for normality and skewness (Table 4) show that the variables are positively skewed and exhibit significant non-normality ($p<0.0001$). Therefore the Wilcoxon Rank Sum test was therefore used for between-group comparisons. There was a statistically significant difference between the groups ($p<0.0001$). Patients with hereditary retinoblastoma (bilateral and trilateral) had a shorter median delay to presentation (3 months) than those with unilateral retinoblastoma (median delay to presentation 5 months).

3.7.3 Family History

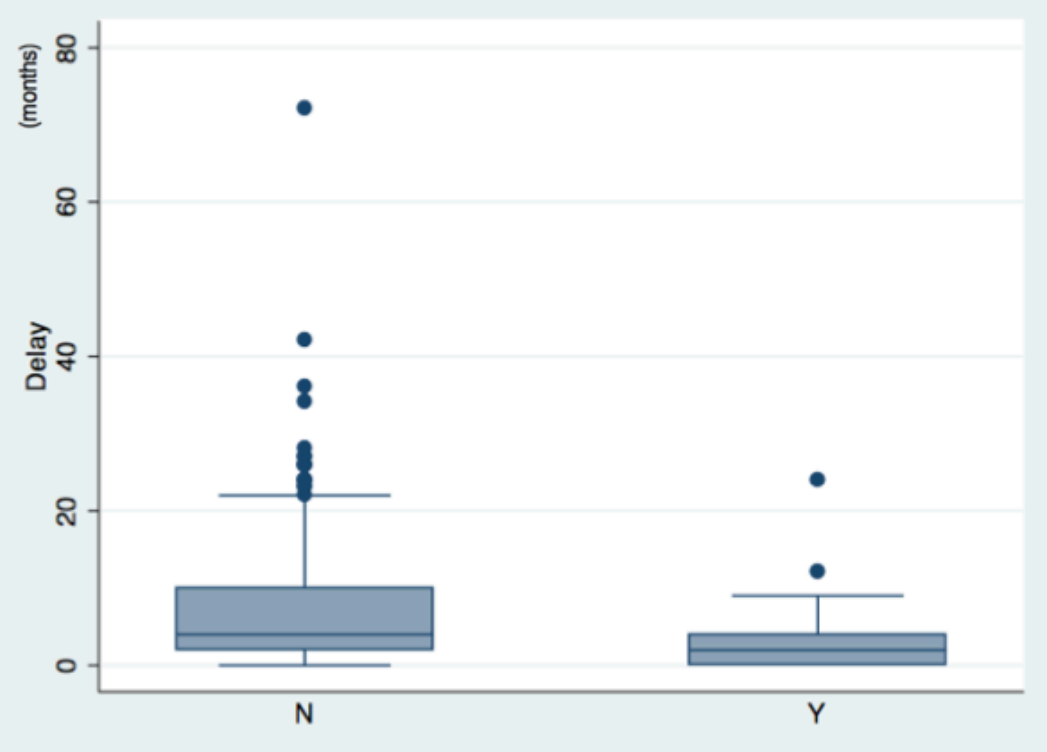

Figure 8. Box and whisker plot of delay to presentation by family history. ("Y" indicates a positive family history; "N" indicates no family history of retinoblastoma).

Tests for normality and skewness (Table 4) show that the variable delay to presentation is positively skewed and exhibits significant non-normality in the group of patients without any family history of the disease ($p<0.0001$). The Wilcoxon Rank Sum test was thus used for between-group comparison. There was a statistically significant difference between the two groups ($p=0.021$). Patients with a positive family history had a shorter delay to presentation (median delay 2.0 months) than those without a family history of the disease (median age 4.0 months).

3.8 PRESENTING SYMPTOMS

3.8.1 Frequency of Presenting Symptoms

Data regarding Presenting Symptoms or complaint was unavailable in four cases. There were no symptoms reported in four cases where the diagnosis of retinoblastoma was made following screening for a positive family history of the disease. Figure 9 illustrates the relative proportion of each presenting symptom as a percentage. The most common presenting symptoms were leukocoria (37.1%) and proptosis (34.7%).

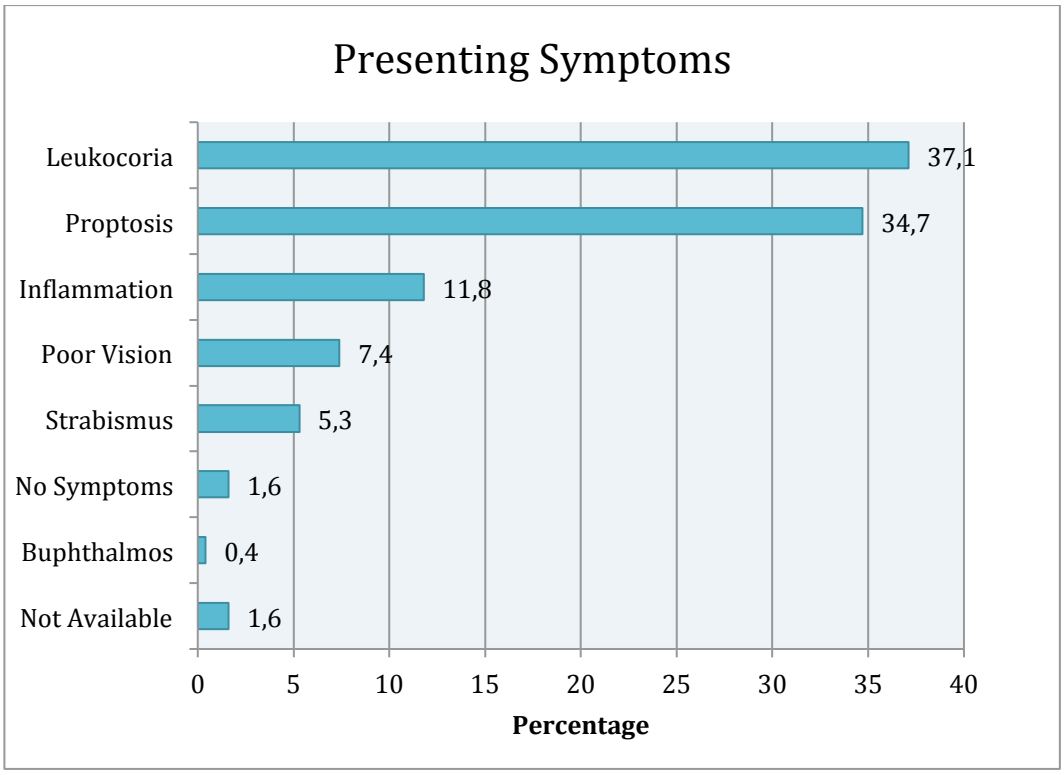

Figure 9. Proportion of each presenting symptom represented as a percentage of total presenting symptoms.

3.8.2 Leukocoria

Leukocoria was present in 186 patients, and was the presenting symptom or complaint in 91 (48.9%) of these patients. Figure 10 illustrates the presenting symptom or complaint in patients with leukocoria evident at presentation.

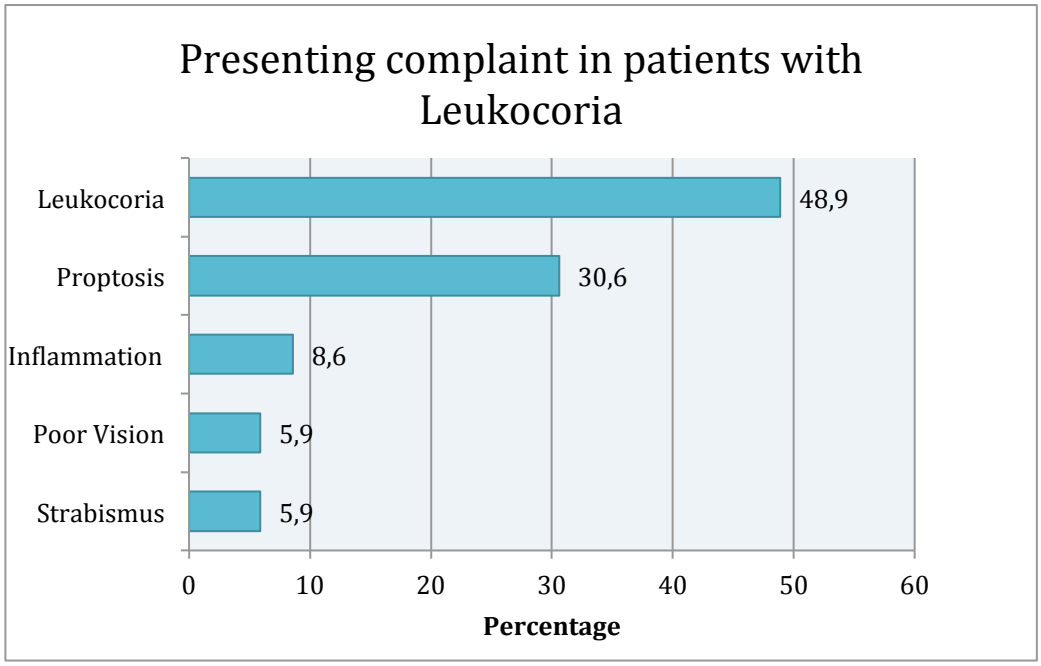

Figure 10. Presenting complaint in patients with leukocoria (186 patients).

3.8.3 Strabismus

Strabismus was present in 25 patients, and was the presenting symptom in 13 (52%) of these patients. Figure 11 illustrates the presenting symptom or complaint in patients with strabismus evident at presentation.

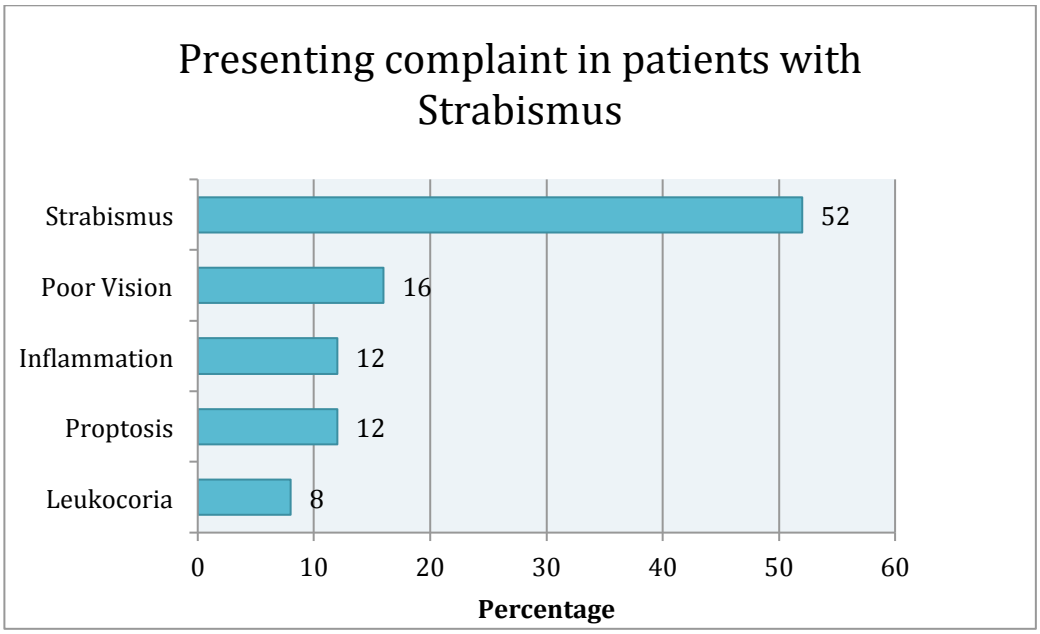

Figure 11. Presenting complaint in patients with strabismus (25 patients).

3.9 GENETIC TESTING

Screening for genetic abnormalities was performed in 162 patients (66.1% of patients). It was not possible to determine if screening investigations had been performed in 3 cases (1.2%).

3.10 DISEASE STAGE

All results are for data pertaining to the stage of disease in the eye with the presenting complaint (i.e. only the first (presenting) eye in patients with bilateral retinoblastoma). Data regarding stage of disease in the eye with the presenting complaint were available in 233 patients, and the results are presented in Table 5.

Table 5. Summary of the frequency of each stage of disease (International Retinoblastoma Staging System) at presentation for eyes with the presenting complaint only.

IRSS *	Number of cases	Percentage
O	4	1.6%
I	59	24.1%
II	68	27.8%
III	40	16.3%
IV	62	25.3%
Not Available	12	4.9%

* International Retinoblastoma Staging System

Further analysis was carried out to determine the relationship, if any, between stage of disease and each of the variables Delay to Presentation, Family History and Laterality.

3.10.1 Stage and Delay to presentation

Delay to presentation was categorised as either A (delay ≤ 6 months) or B (delay > 6 months). Patients with missing data for either delay or stage of disease at presentation were excluded from this analysis.

There was a significant association between Stage and Delay (X^2 test, $p < 0.001$). Patients with Stage 0 disease were then excluded due to the very small number of patients (n = 4), and all of these patients having delay A (≤ 6

months). The chi-square test was repeated and this again demonstrated a significant, moderate association between Stage and Delay ($p < 0.001$, Cramer's V = 0.31).

As shown in Figure 12, a longer delay to presentation (Delay B) was associated with more advanced disease stage (Stage III and IV).

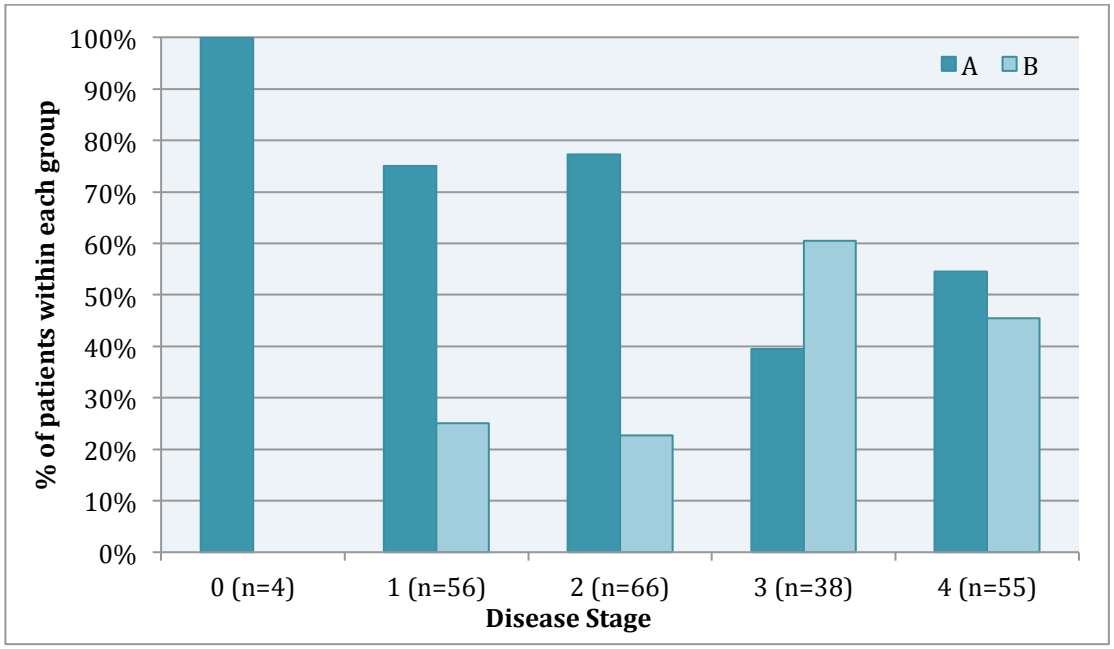

Figure 12. Patients with Delay A (≤ 6 months) and B (> 6 months) as a percentage within each group of Disease Stage.

Multinomial Logistic Regression analysis was performed using Disease Stage as the dependent variable (with Stage I as the reference category) and Delay as the independent variable (with Delay A as the reference category) (Table 6).

Table 6. Summary of Multinomial Regression analysis and Likelihood Type 3 test for Disease Stage with Delay to Presentation as the independent variable. (Significant results are marked in red.)

MULTIINOMIAL REGRESSION ANALYSIS SUMMARY: DELAY								
Effect	Level of Independent variable	Disease Stage	Estimate	Standard Error	Wald Stat.	Lower CL 95,00%	Upper CL 95,00%	p
Intercept 1		2	0.132	0.213	0.382	-0.286	0.549	0.537
Delay	B	2	-0.063	0.213	0.086	-0.480	0.355	0.769
Intercept 2		3	-0.267	0.227	1.384	-0.711	0.178	0.239
Delay	B	3	0.763	0.227	11.339	0.319	1.207	0.001
Intercept 3		4	0.122	0.205	0.351	-0.281	0.524	0.553
Delay	B	4	0.458	0.205	4.981	0.056	0.861	0.026
	Degrees of Freedom		Log-Likelihood		Chi-Square		p	
DELAY	3		-294.1		20.0		0.00017	

Delay was found to be significantly associated with Stage of Disease (p = 0.00017). Patients with Stage III and IV disease were less likely to have Delay A (≤ 6 months) compared to Delay B (> 6 months), compared to patients with Stage I disease.

3.10.2 Stage and Family History

Patients with missing data for either family history or stage of disease at presentation were excluded from this analysis.

Fisher's exact test was used to test for an association between Disease Stage and Family history since the assumptions of the chi-square test were not met in this case. A significant association was found between the two variables (p

< 0.001). The test was then repeated with Stage 0 disease excluded (due to the very small number of patients overall with Stage 0 disease (n = 4), with all four of the patients with Stage 0 disease having a positive family history). There was no significant relationship between Disease Stage (I – IV) and Family history (p = 0.56).

Delay was already shown to be significantly associated with Stage, and therefore Multinomial Regression analysis was performed to determine the relationship between Stage and Family history whilst controlling for Delay. Stage 0 was excluded due to the small number of patients (n = 4), and lack of data for Delay B or negative family history in this group. The reference categories were Disease Stage I, Delay A and negative Family history. With Family history as the only independent variable analysed, there was no significant effect of family history on Disease Stage (p = 0.48). With both Delay and Family history as independent variables, Delay was found to have a significant effect on Stage (p = 0.00049) while Family history did not (p = 0.72) (Table 7).

Table 7. Summary of Multinomial Regression analysis for Disease Stage with Family history as the independent variable; and Likelihood Type 3 test for Delay and Family history as the independent variables. (Significant results are marked in red.)

MULTIINOMIAL REGRESSION ANALYSIS SUMMARY: FAMILY HISTORY								
Effect	Level of Independent variable	Disease Stage	Estimate	Standard Error	Wald Stat.	Lower CL 95,00%	Upper CL 95,00%	p
Intercept 1		2	0.487	0.445	1.195	-0.386	1.359	0.274
Delay	B	2	-0.057	0.213	0.072	-0.476	0.361	0.789
Family History	Y	2	0.394	0.429	0.846	-0.446	1.235	0.358
Intercept 2		3	-0.390	0.637	0.375	-1.638	0.858	0.540
Delay	B	3	0.717	0.229	9.805	0.268	1.166	0.002
Family History	Y	3	-0.083	0.632	0.017	-1.322	1.156	0.895
Intercept 3		4	0.350	0.479	0.535	-0.589	1.289	0.465
Delay	B	4	0.461	0.206	5.034	0.058	0.864	0.025
Family History	Y	4	0.250	0.472	0.281	-0.675	1.175	0.596
	Degrees of Freedom		Log-Likelihood		Chi-Square		p	
DELAY	3		-289.8		17.8		0.00049	
FAMILY HISTORY	3		-299.8		2.5		0.48	

Family history was thus found to have no significant association with Disease Stage (I –IV) overall and when controlling for Delay.

3.10.3 Stage and Laterality

No patients were excluded as there was no missing information regarding laterality of the disease.

There was a significant, weak relationship between Laterality and Disease Stage (X^2 test, p = 0.006, Cramer's V = 0.25). The test was repeated with Stage 0 excluded due to the small number of patients in this group (n = 4), and all of them having bilateral disease. There was a no significant relationship between Disease Stage (I –IV) and Laterality (X^2 test, p = 0.083).

Delay was already shown to be significantly associated with Stage, and therefore Multinomial Regression analysis was performed to determine the relationship between Stage and Laterality whilst controlling for Delay. Stage 0 was excluded due to the small number of patients (n = 4), and lack of data for Delay B or Unilateral disease in this group. The reference categories were Disease Stage I, Delay A and Unilateral disease. With Laterality as the only independent variable analysed, there was no significant effect of laterality on Disease Stage (p = 0.083). Multinomial Regression analysis was repeated with both Delay and Laterality as independent variables. Delay was found to have a significant effect on Stage (p = 0.0006) while Laterality did not (p = 0.52) (Table 8).

Table 8. Summary of Multinomial Regression analysis for Disease Stage with Laterality as the independent variable; and Likelihood Type 3 test for Delay and Laterality as the independent variables. (Significant results are marked in red.)

MULTIINOMIAL REGRESSION ANALYSIS SUMMARY: LATERALITY								
Effect	Level of Independent variable	Disease Stage	Estimate	Standard Error	Wald Stat.	Lower CL 95,00%	Upper CL 95,00%	p
Intercept 1		2	0.200	0.223	0.801	-0.238	0.637	0.371
Delay	B	2	-0.021	0.217	0.009	-0.446	0.404	0.923
Laterality	Bilat	2	0.208	0.191	1.191	-0.166	0.582	0.275
Intercept 2		3	-0.312	0.254	1.509	-0.810	0.186	0.219
Delay	B	3	0.745	0.231	10.450	0.293	1.197	0.001
Laterality	Bilat	3	-0.100	0.247	0.165	-0.585	0.384	0.685
Intercept 3		4	0.129	0.222	0.339	-0.306	0.565	0.560
Delay	B	4	0.462	0.209	4.880	0.052	0.871	0.027
Laterality	Bilat	4	0.019	0.209	0.008	-0.390	0.429	0.927
		Degrees of Freedom	Log-Likelihood		Chi-Square		p	
DELAY		3	-291.7		17.3		0.00061	
LATERALITY		3	-284.1		2.2		0.52	

Laterality was thus found to have no significant association with Disease Stage (I –IV) overall and when controlling for Delay.

3.11 TREATMENT ADMINISTERED

Patients who defaulted care prior to planned treatment were excluded from the analysis of treatment for stage of disease. 311 eyes in total were included for analysis.

3.11.1 Stage 0

38 eyes were treated for Stage 0 disease (IRSS, subject to further staging using intraocular classification system). All Stage 0 disease occurred in patients with bilateral retinoblastoma. The vast majority of these were recorded as having been treated with intravenous chemotherapy which was indicated as a treatment for the stage of disease in the first, presenting eye (stage of disease was more advanced than the second eye with Stage 0 disease).

Small tumours (Group I and Group II, Reese-Ellsworth Classification, n = 34) were treated predominantly with local therapy (laser photocoagulation and/or cryotherapy) (94.1%), and a smaller proportion received brachytherapy (26.5%) in addition to this. One patient in this group was treated with Intravitreal chemotherapy as well as Intra-arterial chemotherapy.

No patients with Group III or IV disease (Reese-Ellsworth Classification) were treated (other than with enucleation).

Four patients with Group V disease were treated with a combination of local therapy (laser photocoagulation and/or cryotherapy) and brachytherapy. One patient received intravitreal chemotherapy in addition to local therapy and brachytherapy.

3.11.2 Stage I

81 eyes were treated for Stage I disease. All 81 eyes underwent enucleation, 4.9% received brachytherapy, 7.4% received DXT and 59.3% received

intravenous chemotherapy. In 37.5% of the patients that received intravenous chemotherapy, the treatment was an indication for the stage of disease in the first eye and was also reflected as a treatment for Stage I disease in the second eye.

3.11.3 Stage II

74 eyes were treated for Stage II disease. All 74 eyes were enucleated, 90.5% were treated with intravenous chemotherapy, 46.0% received DXT and 2.7% were treated with Brachytherapy prior to enucleation.

3.11.4 Stage III

40 eyes were treated for Stage III disease. 85% of eyes were enucleated and 15% were exenterated. All patients received intravenous chemotherapy and 87.5% received DXT.

3.11.5 Stage IV

78 eyes were treated for Stage IV disease. Treatment in this group was largely palliative. 16.7% of eyes were enucleated, 1.3% were exenterated, 19.2% received chemotherapy, 15.3% received DXT and 79.5% received palliative treatment alone.

3.12 PROPORTION OF PATIENTS DEFAULTING CARE

65 patients (26.5%) were identified as having defaulted care. These consisted of patients who refused hospital treatment altogether as well as those who

defaulted during treatment (if this was also noted in the medical record to be a significant event in the patient's management).

3.13 SURVIVAL

Patients that were transferred to another hospital prior to follow-up as well as patients that defaulted care before any treatment was initiated were excluded from this analysis.

Kaplan-Meier survival curves were determined for the overall study population, as well as for Disease Stage, Laterality, Family History, Delay and Defaulting care. The Kaplan-Meier curves are presented under the corresponding sections that follow.

3.13.1 Overall Survival

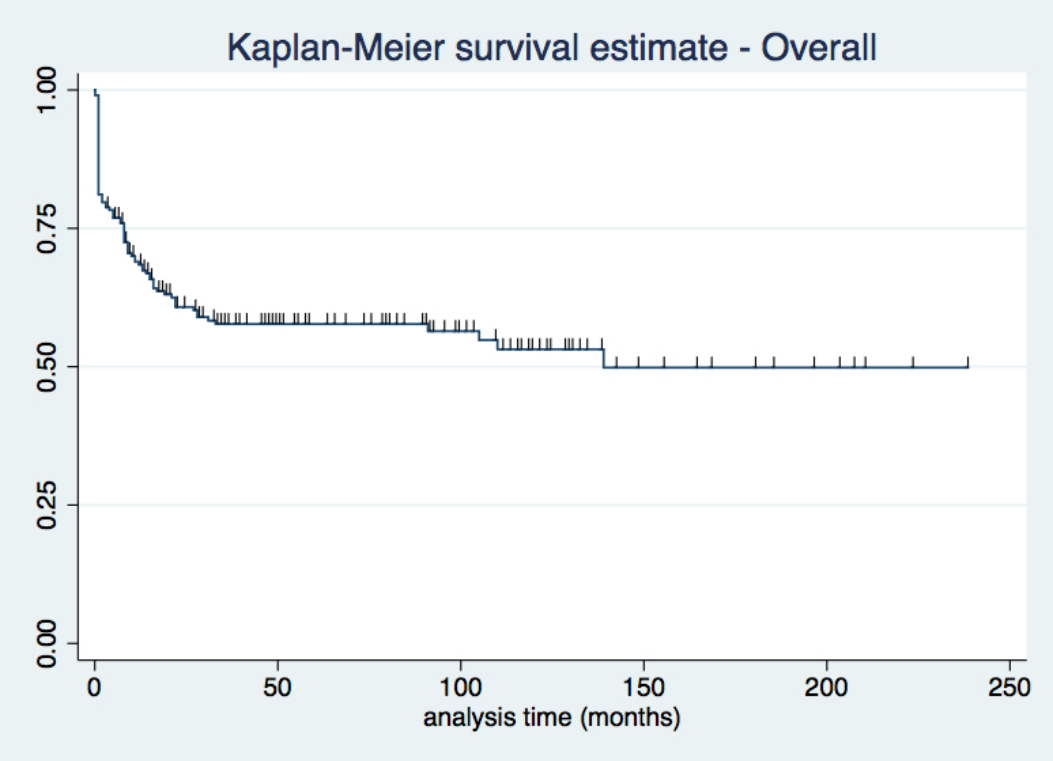

Figure 13. Kaplan-Meier survival curve for the overall study group

There was a 57.7% five-year survival rate in the overall study population.

3.13.2 Stage

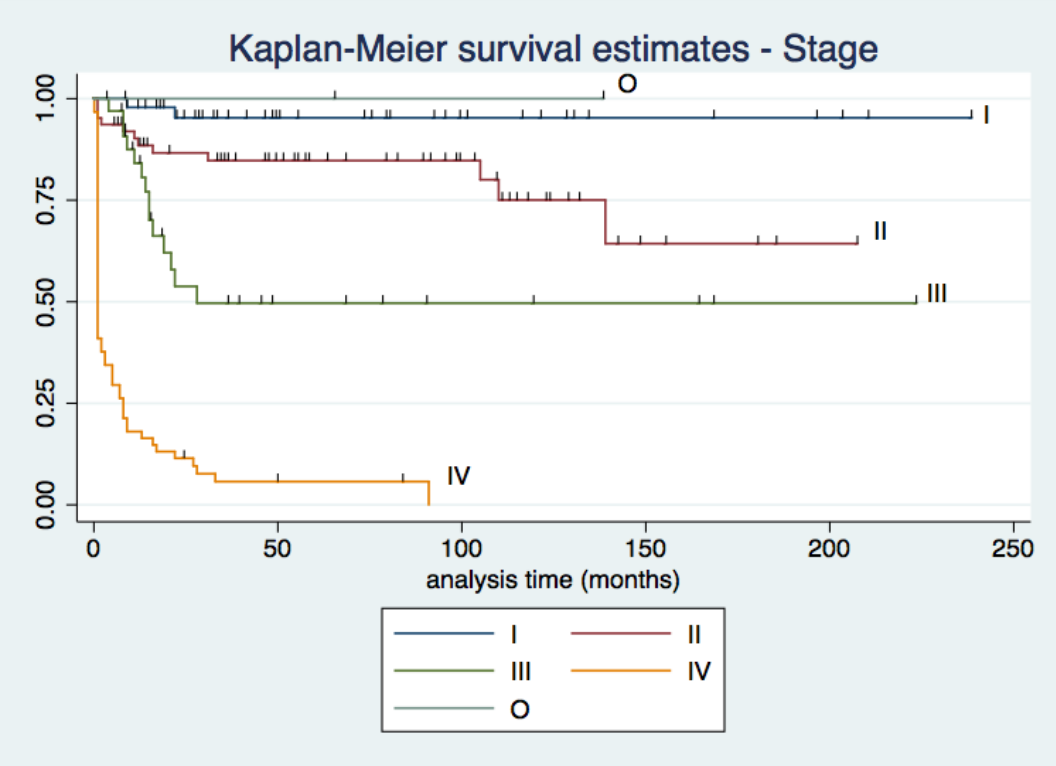

Figure 14. Kaplan-Meier survival curves for stage of disease at presentation

The five-year survival rates for stage of disease are presented in Table 9.

Table 9. Five-year survival estimates for stage of disease at presentation

STAGE OF DISEASE	FIVE-YEAR SURVIVAL
O	100%
I	95.3%
II	84.8%
III	49.7%
IV	5.7%

The logrank test for differences in survival between the stages of disease was significant ($p < 0.0001$) with more advanced disease stage being associated with poorer survival rates.

3.13.3 Laterality

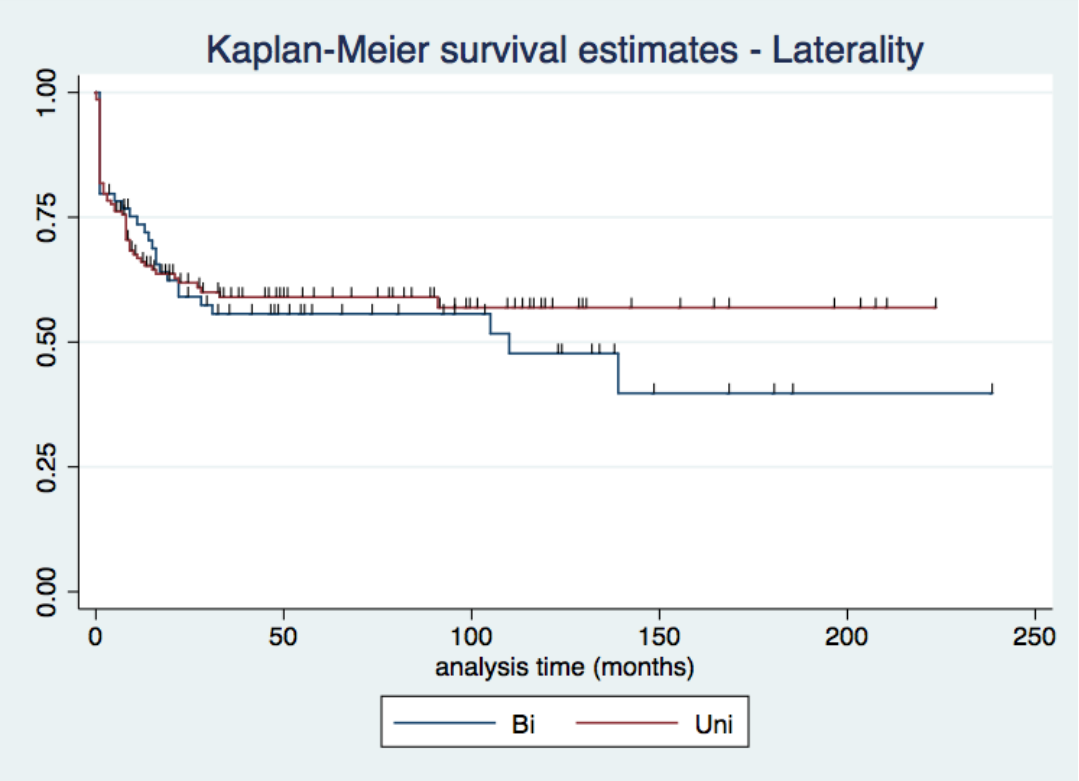

Figure 15. Kaplan-Meier survival curves for laterality of disease (Bi – bilateral (includes trilateral disease), Uni – unilateral)

The five-year survival was 55.7% in the bilateral group and 59.0% in the unilateral group. The logrank test for differences between the two groups was not significant (p = 0.62).

3.13.4 Family history

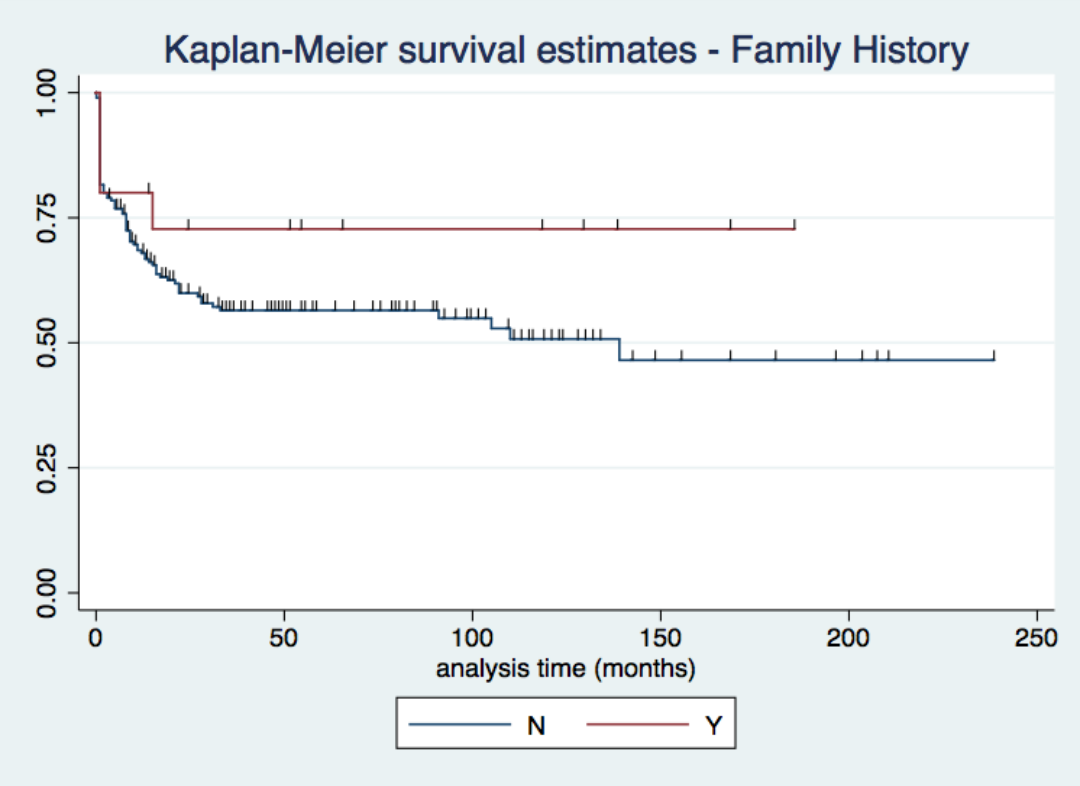

Figure 16. Kaplan-Meier survival curves for Family history of retinoblastoma (N – no family history, Y – positive family history).

The five-year survival was 56.5% in the group without a family history of retinoblastoma and 72.7% in the group with a positive family history for the disease. The logrank test for differences between the two groups was not significant (p = 0.19).

3.13.4 Delay to Presentation

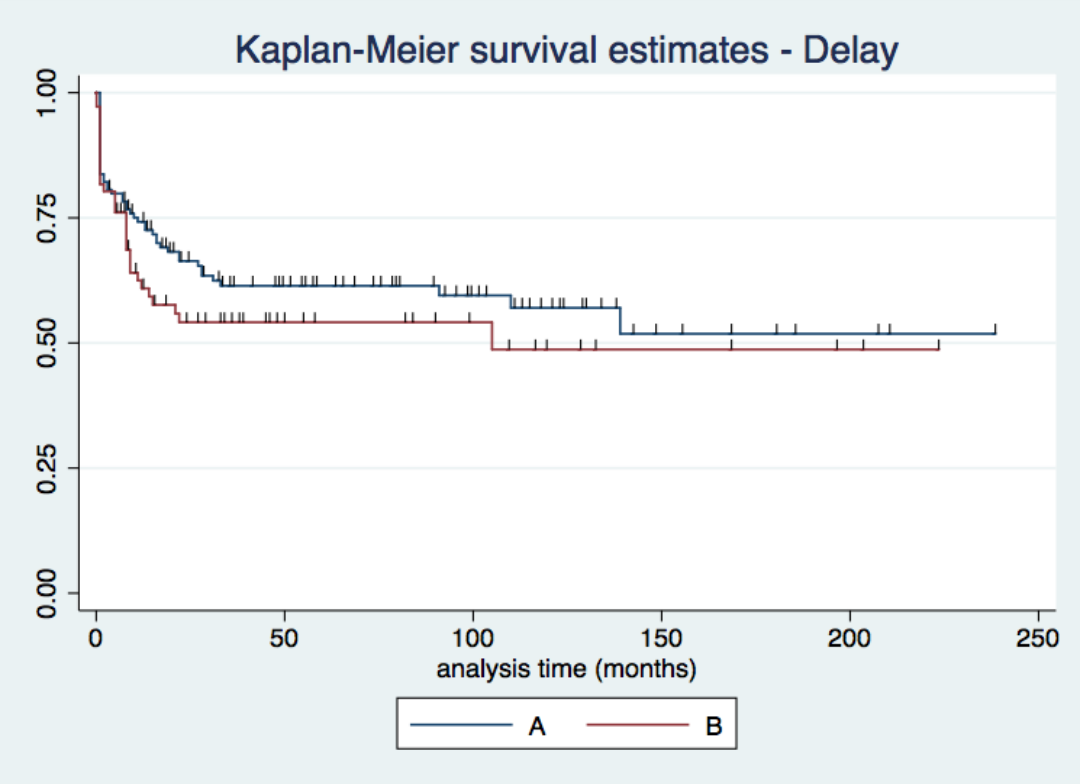

Figure 17. Kaplan-Meier survival curves for Delay to presentation (Delay A: ≤ 6 months, Delay B: > 6 months).

The five-year survival was 61.4% in the group with Delay A, and 54.1% in the group with Delay B. The logrank test for differences between the two groups was not significant (p = 0.23).

3.13.4 Defaulting Care

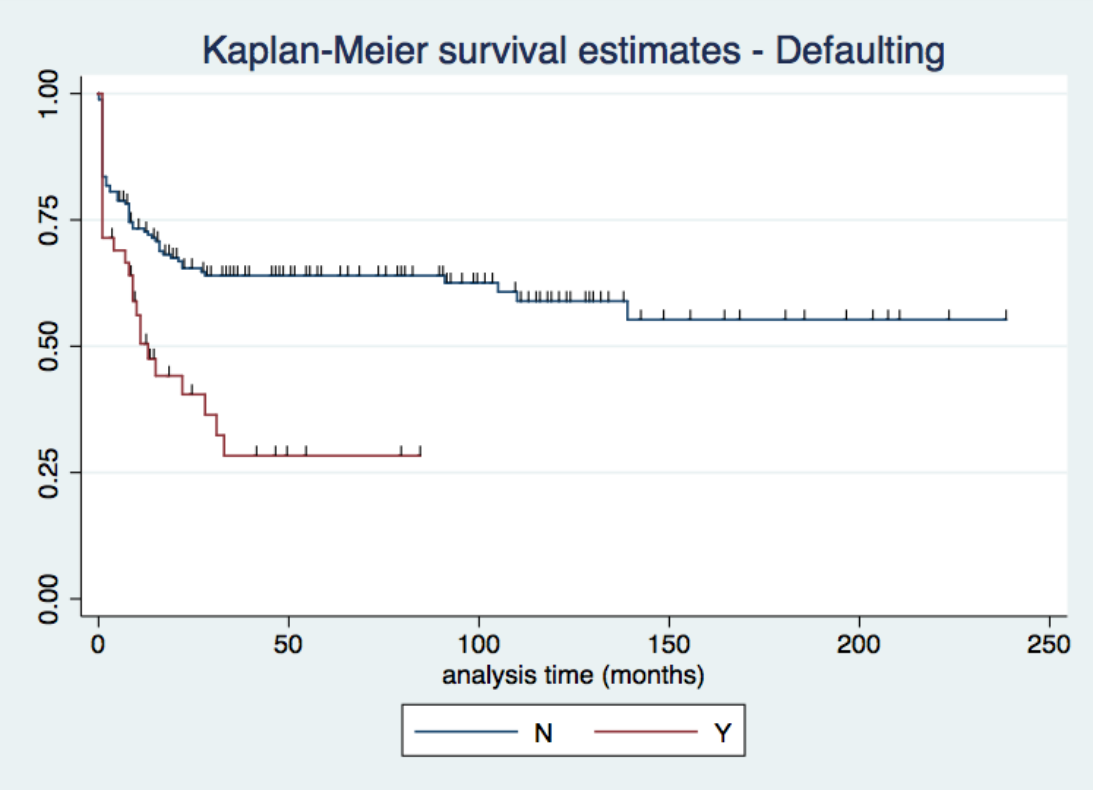

Figure 18. Kaplan-Meier survival curves for Defaulting care (Y – patients defaulting care, N – no significant default).

The five-year survival was 28.3% in the group that defaulted care, and 64.0% in the group without default. The logrank test for differences between the two groups was significant, with patients in the group that defaulted care having a poorer survival outcome (p = 0.0004).

CHAPTER 4

DISCUSSION

Retinoblastoma accounted for 6.9% of overall paediatric oncology presentations over the 20-year study period. This is higher than most developed countries (2% - 4%) but lower than the rates suggested in other developing countries in Africa (10% - 15%).[4,10,28] There was no statistically significant relationship between the proportion of retinoblastoma to non-retinoblastoma paediatric oncology presentations over successive five-year periods of the study (p=0.36), suggesting that there was no underlying trend in the proportion of retinoblastoma to non-retinoblastoma paediatric oncology presentations over the 20 years.

A total of 282 cases of retinoblastoma was seen over the study period with the majority recorded at CHBAH (78%). Of the 282 patients with retinoblastoma, 245 (86.9%) met both the inclusion and exclusion criteria with 37 patients being excluded due to inadequate or unavailable medical records. Lack of availability of complete medical records is a feature not uncommon in developing countries in Africa.[2,14]

Unilateral retinoblastoma comprised approximately two-thirds of patients (65.3%), with hereditary (bilateral and trilateral) disease making up the remaining approximately one-third of patients (34.7%). This is consistent with the two-thirds unilateral and one-third bilateral distribution of disease reported in the developed world.[3,7,30,31] There was no statistically significant relationship between the proportion of bilateral retinoblastoma to unilateral

retinoblastoma over successive five-year periods of the study (p=0.49). This suggests that there was no underlying trend in the proportion of bilateral to unilateral retinoblastoma over the 20-year period. The lack of any significant change in the proportion of bilateral to unilateral retinoblastoma also suggests a stable germline mutation in the study population.

Screening for genetic abnormalities was performed in approximately two-thirds of patients in the study population. This study did not analyse the results of any genetic testing performed due to difficulties in accessing results of investigations in the early study period as well as differences in the type of genetic tests performed over the study period.

The genetics of retinoblastoma would anticipate an equal incidence of the disease in males and females. While several authors have suggested a male preponderance in retinoblastoma[1,2,4,10], the results of this study are in keeping with the majority of reports that indicate no significant difference in the incidence of retinoblastoma in males and females.[3,7,9] In addition, this study found no statistically significant association between sex and laterality (p=0.29).

Unilateral disease is known to occur at an older age than bilateral disease, with the average age at presentation for both varying according to the developmental status of the population concerned. The mean age at presentation in the study population overall (32.6 months, median 28.0 months), and for unilateral disease (39.4 months, median 33 months) and bilateral disease (19.7 months, median 17.0 months) is higher than the corresponding mean ages at presentation reported for each category in the

developed world.[3,13,30] This study reports a statistically significant relationship between mean age at presentation and the variables laterality (p<0001) and family history (p=0.026). As expected, patients with bilateral disease and those with a positive family history of retinoblastoma presented earlier than their counterparts. This is consistent with findings on the mean age at presentation for unilateral and bilateral disease reported widely in the literature.

Other African countries have also reported higher mean ages at presentation compared with the developed world, which, as in our study, is largely due to late presentation.[1,2,12,14,21] The mean delay to presentation in the overall study group was 7.0 months (median 4.0 months). There was a statistically significant relationship between delay to presentation and the variables laterality (p<0.0001) and family history (p=0.021). Patients with bilateral disease and those with a positive family history for the disease had a shorter median delay to presentation than their counterparts.

Late presentation is a feature in developing countries, with patients commonly presenting at a stage when extraocular spread of the disease has occurred. The commonest presenting symptoms in the study population were leukocoria (37.1%) and proptosis (34.7%), compared to the developed world where leukocoria and strabismus are the commonest presenting symptoms. This finding is similar to reports from other developing countries in Africa, and is the result of delayed presentation and diagnosis of the disease. [1,2,10,15,21] Of the total number of patients with leukocoria only 48.9% had leukocoria as their presenting complaint. Similarly, only 52% of patients with strabismus had this symptom as their presenting complaint. This suggests a lack of awareness in

the general population and probably primary health care workers as well (who are likely to see the children regularly for immunisation and developmental checks) as to the significance of leukocoria and strabismus as signs of a possible underlying neoplastic process.

In keeping with the findings of significant delays to presentation and presenting symptoms indicative of advanced disease stage, the vast majority of patients presented at a stage where globe salvage was not possible. Intraocular Classification systems were not helpful in this setting, and the International Retinoblastoma Staging System was used for staging of the disease. Patients frequently presented with extraocular retinoblastoma, with 27.8% presenting at Stage II, 16.3% at Stage III and 25.3% at Stage IV (Table 5). Only four (1.6%) patients were diagnosed at Stage 0 (where treatment did not necessitate enucleation), and all four of these patients were diagnosed with the disease subsequent to a screening examination prompted by the diagnosis of retinoblastoma in a sibling.

Delay to presentation was found to be significantly, and independently associated with Disease Stage at presentation ($p = 0.00017$), with a longer delay to presentation (> 6 months) associated with more advanced disease stage (Stage III and Stage IV). Family History and Laterality were not significantly associated with Disease Stage at presentation.

Late presentation with advanced disease stage in the presenting eye implied that largely only the second eye diagnosed in bilateral retinoblastoma cases was subject to treatment for Stage 0 disease. Newer treatment modalities such as intravitreal and intra-arterial chemotherapy more commonly used in

the developed world have not had much opportunity for use in this study. However at the close of the study period it is evident that these newer treatment modalities are being included in the treatment options available to select patients presenting earlier in the stage of the disease. Patients with Stage I disease were treated almost entirely with enucleation alone. Stage II disease was treated largely with enucleation coupled with intravenous chemotherapy, and this was supplemented by DXT in close to half of the cases. Stage III disease was treated predominantly with either enucleation or exenteration (in a smaller proportion of patients), intravenous chemotherapy and DXT. Stage IV disease received palliative treatment alone in the majority of cases.

Advanced disease stage at presentation is accompanied by poor survival outcomes. This study reports a 57.7% five-year survival rate in the overall study population. Disease stage at presentation, as expected, was shown to be significantly associated with survival rates ($p < 0.0001$), with more advanced disease stages having poorer survival outcomes (Table 9). The five-year survival rate for Stage 0 is based on analysis of the only four patients with Stage 0 disease at presentation, and is therefore not likely to be a true representation of survival rates for this Stage of disease in the general population. The five-year survival rate for Stage I disease was 95.3% which is close to the overall five-year survival rates reported in the developed world.[3,18,27] This suggests that overall survival rates may approach that of the developed world if patients were to present as early with minimal delay in accessing treatment. Stage II disease was associated with an 84.8% five-year survival rate, Stage III with 49.7% and Stage IV with 5.7%. Other than disease

stage at presentation, only defaulting care was found to be significantly associated with survival outcomes (p = 0.0004). Patients who defaulted care had a 28.3% five-year survival rate compared with 64.0% for patients without default. Delay to presentation was not found to be significantly associated with survival outcomes, however it is significantly and independently associated with disease stage at presentation. Laterality and family history were not significantly associated with survival outcomes.

CONCLUSION

This study provides information regarding patient demographics, social challenges in management, and patient outcomes in comparison to developed countries and to reports from other African populations. Like many reports from Africa, this study reflects the particular difficulties with late presentation and high rates of patients defaulting or refusing hospital treatment. The treatment practices employed in this setting probably have little influence on survival outcomes compared with advanced disease stage at presentation and defaulting care. Educational campaigns and screening programs aimed at increasing awareness and allowing for earlier detection of disease as well as decreasing rates of default are imperative in addressing the poor survival outcomes in our population.

This study provides us with the necessary information to accompany and support proposals for primary health care awareness programs, patient education initiatives, state hospital resource allocation planning and finally, this study serves as a platform for comparison with future research in this area.

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APPENDIX A

ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Saadiah Goolam

CLEARANCE CERTIFICATE	**M120726**
PROJECT	A 20-Year Retrospective Study at Two Tertiary Academic Hospitals in Johannesburg
INVESTIGATORS	Dr Saadiah Goolam.
DEPARTMENT	Division of Opthalmology/Div of Neurosciences
DATE CONSIDERED	27/07/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 27/07/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Nicky Welsh

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX B

REESE ELLSWORTH CLASSIFICATION

Group I

a) solitary tumor, < 4 disc diameters in size, at or behind the equator

b) multiple tumor, none > 4 disc diameters in size, at or behind the equator

Group II

a) solitary tumor, 4–10 disc diameters in size, at or behind the equator

b) multiple tumor, 4–10 disc diameters in size, behind the equator

Group III

a) any lesion anterior to the equator

b) solitary tumor >10 disc diameters behind the equator

Group IV

a) multiple tumors, some >10 disk diameters

b) any lesion extending anteriorly to the ora serrata

Group V

a) massive tumors involving more than half the retina

b) vitreous seeding

APPENDIX C

INTERNATIONAL CLASSIFICATION OF RETINOBLASTOMA

Group	Subgroup	Quick Reference	Specific Features
A	A	Small tumors	RB ≤3 mm
B	B	Larger tumor	RB >3 mm
		Macula	Location ≤3 mm to foveola
		Juxtapapillary	Location ≤1.5 mm from optic disc
		Subretinal fluid	Clear subretinal fluid ≤3 mm from RB margin
C		Focal seeds	
	C1		Subretinal seeds ≤3 mm from RB
	C2		Vitreous seeds ≤3 mm from RB
	C3		Both subretinal and vitreous seeds ≤3 mm from RB
D		Diffuse seeds	
	D1		Subretinal seeds >3 mm from RB
	D2		Vitreous seeds >3mm from RB
	D3		Both subretinal and vitreous seeds >3 mm from RB
E		Extensive RB	Occupying >50% of globe or neovascular glaucoma
			Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space
			Invasion of postlaminar optic nerve, >2 mm of choroid, sclera, orbit, or anterior chamber

APPENDIX D

INTERNATIONAL RETINOBLASTOMA STAGING SYSTEM

Stage 0: Patients treated conservatively (subject to presurgical ophthalmologic classifications)
Stage I: Eye enucleated, completely resected histologically
Stage II: Eye enucleated, microscopic residual tumor
Stage III: Regional extensiona a) Overt orbital disease b) Preauricular or cervical lymph node extension
Stage IV: Metastatic disease a) Hematogenous metastasis: 1. single lesion 2. multiple lesions b) CNS extension: 1. Prechiasmatic lesion 2. CNS mass 3. Leptomeningeal disease