A 20-Year Retrospective Review of Retinoblastoma at Two Tertiary Academic Hospitals in Johannesburg, South Africa

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Keywords

Retinoblastoma · Ocular oncology · South Africa · Mortality

Abstract

Aim: This paper presents a 20-year review of retinoblastoma in Johannesburg, South Africa, aiming to better characterize the disease in this sub-Saharan setting. **Methods:** The study represents a retrospective case series of retinoblastoma patients presenting to Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital between January 1, 1992, and December 31, 2011. **Results:** The total number of cases identified was 282, with 245 meeting the study inclusion criteria. Retinoblastoma comprised 6.9% of the total pediatric oncology presentations; 65.3% were unilateral, 34.3% bilateral, and 0.4% trilateral. The overall male-to-female ratio was 1.08. The mean age at presentation overall was 32.6 months (median 28.0), in the unilateral group 39.4 months (median 33.0), and in the bilateral group 19.7 months (median 17.0). The mean delay to presentation overall was 7.0 months (median 4.0). The most

frequent presenting symptoms were leukocoria (37.1%) and proptosis (34.7%). The distribution of disease stages at presentation (International Retinoblastoma Staging System) was 1.6% stage 0, 24.1% stage I, 27.8% stage II, 16.3% stage III, and 25.3% stage IV. 26.5% defaulted care. The 5-year Kaplan-Meier survival estimate was 57.7% overall. **Conclusion:** This study shows that delayed presentation and refusal of therapy remains a significant barrier to effective treatment in this African setting.

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Introduction

Retinoblastoma is the most frequent pediatric intra-ocular malignancy worldwide, and in Africa it is the most common and important life-threatening ocular neoplasm [1, 2]. In Europe, North America, and Australia, retinoblastomas account for 2–4% of total neoplasms in children, with similar relative frequencies in Asia, while in African populations retinoblastoma is reported to ac-

count for 10–15% of childhood cancers [3]. Epidemiological studies suggest a worldwide incidence of approximately 1 in 16,000–18,000 births per annum [4]. In resource-rich countries such as the USA and Canada, survival rates for patients with retinoblastoma approach 100% [4, 5]. This is in stark contrast to resource-poor countries, where late presentation is invariably the cause for increased mortality, and survival rates in some of these populations may be less than 20% [2, 4–9]. Despite more than 90% of affected patients living in resource-poor countries, there are few studies on disease characteristics in these populations [8]. This study involved a 20-year retrospective review of retinoblastoma cases at two tertiary academic hospitals in Johannesburg, South Africa, and aimed to better characterize the disease in this sub-Saharan setting.

Methods

Medical and histopathological records of retinoblastoma patients presenting to the pediatric oncology departments at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) between January 1, 1992, and December 31, 2011, were included for review. CMJAH and CHBAH are tertiary hospitals, primarily serving as the referral centers for the greater Johannesburg area and the North West province but also providing tertiary services to a large region of northeast and central South Africa, and the families of migrant workers from the neighboring states of Lesotho, Mozambique, and Zimbabwe. All retinoblastoma patients seen by ophthalmologists and primary healthcare workers are referred to the pediatric oncology units who are responsible for coordinating their multidisciplinary management.

The patients admitted with a possible diagnosis of retinoblastoma routinely underwent radiological assessment for trilateral retinoblastoma (predominantly by CT imaging, with MRI performed more often in the latter half of the study period). Retinoblastoma was diagnosed on clinical and radiological findings, and where enucleation was performed, the diagnosis was confirmed on histopathology (histopathological specimens are processed at a single center servicing both hospitals). Cases in which the diagnosis of retinoblastoma was uncertain or where record-keeping was grossly inadequate were excluded from this study.

The following information was extracted from each medical record: date of presentation, delay to presentation, age at presentation, sex, family history of retinoblastoma, laterality, presenting symptom or complaint, retinoblastoma stage in each eye, treatment administered for each eye, any incidence of the patient defaulting or refusing hospital treatment, period of follow-up, and survival status at last follow-up visit. The date of presentation was the initial date that the patient was seen at either CMJAH or CHBAH. Delay to presentation was the period of time, recorded in months, from the date that symptoms or signs (related to the diagnosis of retinoblastoma) had initially been noticed to the date that medical attention was first sought at any public or private

healthcare facility. Where patients were diagnosed in the absence of any signs or symptoms, following a screening examination of a patient with a family history of retinoblastoma, the delay to presentation was recorded as 0 months. The presenting symptom or complaint was that which prompted the patient or family of the patient to seek medical attention. The International Retinoblastoma Staging System was used (retrospectively in some cases) to stage the disease in each eye after reviewing the results of all histopathological, cytological, and radiological investigations performed on the patient [10]. The treatment administered for the stage of disease in the presenting eye was recorded. Unless otherwise stated, all bilateral retinoblastoma presented in the Results section include any trilateral cases seen. Specific statistical methods and tests utilized will be included in the results section where relevant. A *p* value <0.05 was considered significant.

Results

A total of 282 retinoblastoma cases were recorded, comprising 6.9% of the total pediatric oncology presentations over the 20-year study period. Of these, 245 cases met the study inclusion criteria, with 37 excluded due to inadequate or unavailable medical records. None of the cases were excluded on the basis of incorrect or uncertain diagnoses. Table 1 presents the data related to the number of cases seen, sex distribution, age at presentation, and delay to presentation.

Retinoblastoma was unilateral in 65.3% of the patients, bilateral in 34.3%, and trilateral in 0.4% (1 patient). The overall male-to-female ratio in the study was 1.08, and 1.30 in the bilateral group. No statistically significant association between sex and laterality was found (χ^2 test, *p* = 0.29). Patients with bilateral retinoblastoma had a significantly lower median age at presentation than those with unilateral disease (17.0 vs. 33.0 months, *p* < 0.0001). There was also a statistically significant difference in delay to presentation between the unilateral and the bilateral group (5.0 vs. 3.0 months), with the bilateral group having a shorter median delay (*p* < 0.0001). The most common presenting symptoms were leukocoria (37.1%) and proptosis (34.7%). Other presenting symptoms included inflammation, poor vision, strabismus, and buphthalmos. There were no symptoms reported in 4 cases (1.6%), where the diagnosis of retinoblastoma was made following screening in a patient with a positive family history for the disease.

Table 2 presents the data related to disease stage at presentation, the predominant treatment administered for each stage of disease, and the Kaplan-Meier 5-year survival estimates for the overall study population as well as for each stage of disease. The International Retinoblas-

Table 1. Number of retinoblastoma cases included in the study, laterality, sex distribution, age at presentation, and delay to presentation

	Overall	Unilateral	Bilateral
Number of cases	245	160	85
Male-to-female ratio	127:118	48:37	81:79
Age at presentation, months			
Mean + SD	32.6+26.8	39.4+29.3	19.7+14.2
Median (IQR)	28.0 (17.0, 40.0)	33.0 (24.0, 47.5)	17.0 (8.0, 29.0)
Delay to presentation, months			
Mean + SD	7.0+8.7	8.5+10.0	4.4+5.0
Median (IQR)	4.0 (1.0, 10.0)	5.0 (2.0, 12.0)	3.0 (1.0, 6.0)

Table 2. Disease stage at presentation (International Retinoblastoma Staging System [IRSS]), predominant treatment administered for each stage of disease, and Kaplan-Meier 5-year survival estimates overall and for each stage of disease

IRSS	Number of cases	Percentage of cases	Treatment administered	5-year survival, %
Stage 0	4	1.6	local therapy	100
Stage I	59	24.1	enucleation	95.3
Stage II	68	27.8	enucleation; intravenous chemotherapy	84.8
Stage III	40	16.3	enucleation or exenteration; intravenous chemotherapy; deep X-ray therapy	49.7
Stage IV	62	25.3	palliative	5.7
Data unavailable	12	4.9		
Overall				57.7

toma Staging System was used to stage disease, and the results presented pertain to the eye with the presenting complaint, i.e., only the first (presenting) eye in the case of bilateral disease.

Multinomial regression analysis revealed that patients with a delay to presentation of less than 6 months were less likely to have stage III or IV disease than those with a delay of more than 6 months ($p < 0.001$). Laterality and family history of retinoblastoma did not have any significant effect on disease stage ($p = 0.083$ and $p = 0.56$, respectively).

Table 2 presents the predominant treatment modalities utilized for each stage of disease in the presenting eye. Local therapy included the use of laser photocoagulation, cryotherapy, or a combination of the two. Intravenous chemotherapy (carboplatin, etoposide, and vincristine) when administered consisted of 6 cycles. Unilateral retinoblastoma with stage I disease was treated almost entirely with enucleation alone. In the latter half of the study period, patients with bilateral disease re-

ceived intravenous chemotherapy prior to enucleation of the presenting eye. Stage II disease was treated largely with enucleation coupled with intravenous chemotherapy, and this was supplemented by deep X-ray therapy 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 deep X-ray therapy. Stage IV disease received palliative treatment alone in the majority of cases.

Sixty-five patients (26.5%) defaulted care. These were patients who refused hospital treatment altogether ($n = 18$), as well as those who defaulted during treatment ($n = 47$). Follow-up was considered complete in 212 cases, and of these, 123 patients were alive at the end of the study period or at the last follow-up; in these surviving patients, the follow-up period ranged from 3.0 to 238.0 months (mean 71.9, median 55). Patients who had attended their last scheduled visit were included amongst those considered to have completed follow-up.

Fig. 1. Kaplan-Meier survival estimates for the overall study population.

Fig. 2. Kaplan-Meier survival estimates for each stage of disease.

Survival rates were determined using Kaplan-Meier survival curves (Table 2; Fig. 1, 2), which were plotted for the overall study population, as well as by disease stage, laterality, family history, delay, and defaulting care. 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 analysis. Table 2 presents the 5-year survival data for the overall population and for each stage of disease. Apart from disease stage at presentation ($p < 0.0001$), only defaulting care ($p = 0.0004$) was significantly associated with poorer survival outcomes.

Discussion

Retinoblastoma accounted for 6.9% of the overall pediatric oncology presentations over the 20-year study period, which is lower than the rates suggested for other African countries [3, 9, 11]. Interestingly, our rate of trilateral retinoblastoma (1 patient, 0.4%) was unexpectedly low compared to the reported rates of 3% overall and as high as 10% among those with bilateral disease [1]. It is possible that some cases that defaulted care prior to radiological assessment at our units may have been missed.

Our mean and median ages at presentation are higher than those reported for each category in the developed world. Kruger et al. [12], in their South African study, also report higher median ages at presentation, which is due to late presentation. Delay is invariably the cause of increased mortality rates in resource-poor countries; re-

ports from African countries including the Democratic Republic of Congo, Nigeria, Tanzania, Mali, South Africa, and Kenya demonstrate this [2, 5, 6, 11–16]. The average delay to presentation in our population was 7.0 months, which is lower than that reported earlier from Johannesburg by Poyiadjis et al. [16] in 2011 (10.1 months) but similar to that in other African populations, where delays generally in excess of 6 months and up to 15 months have been reported [2, 6, 14, 16]. Nyamori et al. [13] found that in Kenya, even patients with a family history of retinoblastoma had a delayed presentation. Late presentation in developing countries is thought to be a result of poor awareness of retinoblastoma by both parents and healthcare professionals, difficulties accessing healthcare in remote areas, cultural beliefs, and regional differences in attitudes towards disease [1, 6, 17, 18]. Patients are frequently diagnosed at a stage when extraocular spread of the disease has occurred, and thus, as in other African studies, proptosis was a common presentation in our population [2, 6, 11, 14, 19]. Intraocular classification systems are not helpful in this setting where the vast majority of patients present at a stage where globe salvage is not possible, and the International Retinoblastoma Staging System was therefore adopted at our study facilities [10]. Intraocular classification systems are used for the few patients presenting early enough; only 4 of our patients were diagnosed at stage 0 (where treatment did not necessitate enucleation), and all of these were diagnosed subsequent to a screening examination prompted by the diagnosis of retinoblastoma in a sibling. Late presentation with an advanced disease stage in the present-

ing eye implied that possibly only the second eye diagnosed in bilateral 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 been used extensively in this study. However, at the close of the study period it was evident that these newer treatment modalities were being included in treatment options available to those presenting earlier.

Our poor survival outcomes (57.7% 5-year survival overall) are the result of delay with advanced disease stage at presentation, further compounded by high incidences of patients defaulting care. The 5-year survival for stage I disease was 95.3%, which suggests that our survival rates may approach those of the developed world were our patients to present at a similar stage to those in resource-rich environments [1, 5, 8]. Treatment practices employed in this setting probably have little influence on survival outcomes.

The primary limitations of this study are the lack of availability of complete medical records (13.1% of the cases were excluded on this basis) and poor follow-up, both of which are features common to retrospective African reports [6, 7].

Nevertheless, it is clear that interventions to increase case detection rates and streamline referrals are indicated and may include outreach programs and education of referring healthcare workers. Health interventions introduced within the time period of this study have included the introduction of free healthcare for children below the age of 6 years in 1994, as well as the introduction of compulsory community service in 1998, incorporating rural areas of the country [12]. Kruger et al. [12] reported on the outcomes of children with retinoblastoma in South Africa prior to (1993–2000) and after (2001–2008) the introduction of such healthcare initiatives and found that, while not statistically significant, there was a trend towards more limited disease and better survival in the latter period of the study [12]. A further initiative by the National Department of Health and the Childhood Cancer Foundation in 2001 involved a 6-month awareness campaign of the warning signs of childhood cancer directed at primary healthcare workers and the public in the North West and Gauteng provinces [12, 16]. This campaign resulted in an increase in the number of new referrals to the Baragwanath oncology unit, but did not impact the advanced disease stages seen at presentation [16].

While pilot projects of this nature have enjoyed limited success, these initiatives might be more fruitful and cost-effective were they designed to fit into an existing

framework for the education of primary healthcare workers and parents alike on issues pertaining to children in our targeted 0- to 2-year age bracket [12, 16]. The Expanded Programme on Immunization (EPI) is a powerful national initiative aimed at reducing child mortality in line with the Millennium Development Goals established by the United Nations in 2000 [20]. A lot of effort and resources have been invested in addressing just the sort of issues that pose challenges to our retinoblastoma survival rates. These include education of parents on the merits of vaccination programs and the importance of adhering to a vaccination schedule. Primary healthcare workers have been involved in education campaigns and engaged in trying to identify challenges to the achievement of EPI goals [20]. It might be useful to perhaps consider incorporating a retinoblastoma awareness program into an existing government initiative, such as the ongoing EPI education drive, which would help reduce costs and enhance the likelihood of success.

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Statement of Ethics

This study received approval from the University of Witwatersrand Human Research Ethics Committee.

Disclosure Statement

None of the authors have any conflicts of interest, sponsorship, or funding arrangements related to this research to disclose.

References

- 1 Shields CL, Shields JA: Basic understanding of current classification and management of retinoblastoma. *Curr Opin Ophthalmol* 2006; 17:228–234.
- 2 Kaimbo WK, Mvitu MM, Missotten L: Presenting signs of retinoblastoma in Congolese patients. *Bull Soc Belge Ophthalmol* 2002;283: 37–41.
- 3 Yeole BB, Advani S: Retinoblastoma: an epidemiological appraisal with reference to a population in Mumbai, India. *Asian Pac J Cancer Prev* 2002;3:17–21.

- 4 Houston SK, Murray TG, Wolfe SQ, Fernandes CE: Current update on retinoblastoma. *Int Ophthalmol Clin* 2011;51:77–91.
- 5 Dimaras H, White A, Gallie B: The Kenyan National Retinoblastoma Strategy: building local capacity in the diagnosis and management of pediatric eye cancer in Kenya. *Ophthalmology Rounds*, July/August 2008, vol 6, issue 4.
- 6 Kazadi Lukusa A, Aloni MN, Kadima-Tshimanga B, Mvitu-Muaka M, Gini Ehungu JL, Ngiyulu R, Ekulu Mfutu P, Budiongo Nzazi A: Retinoblastoma in the Democratic Republic of Congo: 20-year review from a tertiary hospital in Kinshasa. *J Cancer Epidemiol* 2012; 2012:920468.
- 7 Bekibele CO, Ayede AI, Asaolu OO, Brown BJ: Retinoblastoma: the challenges of management in Ibadan, Nigeria. *J Pediatr Hematol Oncol* 2009;31:552–555.
- 8 Canturk S, Qaddoumi I, Khetan V, Ma Z, Furmanchuk A, Antoneli CB, Sultan I, Kebudi R, Sharma T, Rodríguez-Galindo C, Abramson DH, Chantada GL: Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. *Br J Ophthalmol* 2010;94:1432–1436.
- 9 Scheffler AC, Abramson DH: Retinoblastoma: what is new in 2007–2008. *Curr Opin Ophthalmol* 2008;19:526–534.
- 10 Chantada G, Doz F, Antoneli CB, Grundy R, Clare Stannard FF, Dunkel IJ, Grabowski E, Leal-Leal C, Rodríguez-Galindo C, Schwartzman E, Popovic MB, Kremens B, Meadows AT, Zucker JM: A proposal for an international retinoblastoma staging system. *Pediatr Blood Cancer* 2006;47:801–805.
- 11 Boubacar T, Fatou S, Fousseyni T, Mariam S, Fatoumata DT, Toumani S, Abdoul-Aziz D, Marouf KM: A 30-month prospective study on the treatment of retinoblastoma in the Gabriel Touré Teaching Hospital, Bamako, Mali. *Br J Ophthalmol* 2010;94:467–469.
- 12 Kruger M, Reynders D, Omar F, Schoeman J, Wedi O, Harvey J: Retinoblastoma outcome at a single institution in South Africa. *S Afr Med J* 2014;104:859–863.
- 13 Nyamori JM, Kimani K, Njuguna MW, Dimaras H: The incidence and distribution of retinoblastoma in Kenya. *Br J Ophthalmol* 2012;96:141–143.
- 14 Bowman RJ, Mafwiri M, Luthert P, Luande J, Wood M: Outcome of retinoblastoma in east Africa. *Pediatr Blood Cancer* 2008;50:160–162.
- 15 Freedman J, Goldberg L: Incidence of retinoblastoma in the Bantu of South Africa. *Br J Ophthalmol* 1976;60:655–656.
- 16 Poyiadjis S, Wainwright L, Naidu G, Mackinnon D, Poole J: The Saint Siluan warning signs of cancer in children: impact of education in rural South Africa. *Pediatr Blood Cancer* 2011;56:314–316.
- 17 Chantada GL, Dunkel IJ, Qaddoumi I, Antoneli CB, Totah A, Canturk S, Nawaiseh I, Fandiño A, Pífano I, Peksayar G, Ribeiro KB, Abramson DH: Familial retinoblastoma in developing countries. *Pediatr Blood Cancer* 2009;53:338–342.
- 18 Dimaras H, Dimba EA, Gallie BL: Challenging the global retinoblastoma survival disparity through a collaborative research effort. *Br J Ophthalmol* 2010;94:1415–1416.
- 19 Essuman V, Ntim-Amponsah CT, Akafo S, Renner L, Edusei L: Presentation of retinoblastoma at a paediatric eye clinic in Ghana. *Ghana Med J* 2010;44:10–15.
- 20 Wiysonge CS, Ngcobo NJ, Jeena PM, Madhi SA, Schoub BD, Hawkrigge A, Shey MS, Hussey GD: Advances in childhood immunisation in South Africa: where to now? Programme managers' views and evidence from systematic reviews. *BMC Public Health* 2012; 12:578.