

Survival among retinoblastoma patients at the Kenyatta National Hospital, Kenya

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ABSTRACT

Background: Retinoblastoma has a high cure rate if detected and treated early. Though there is paucity of data of the outcome of retinoblastoma management in Africa, literature shows wide disparity in survival between children with retinoblastoma in the developed and the developing countries.

Objective: To estimate the 3 year survival of patients diagnosed with retinoblastoma at Kenyatta National Teaching and Referral Hospital, Kenya.

Methods: This was a retrospective audit of records of patients admitted with retinoblastoma between January 2000 and December 2004. Demographic data, clinical presentation, intra-operative findings and histology report were recorded and parents/guardians were contacted to ascertain the patients' outcome. The data was analyzed using the Statistical Package for Social Scientists version 12 and survival calculated using the Kaplan-Meier survival probability curve.

Results: The cumulative 3-year survival was 26.6%. The mean survival time for the survivors was 68 months (SD 16.6) and the Kaplan-Meier survival probability at 36-months of follow-up was 0.2. The factors that significantly influenced good outcome were; age at presentation of <12 months, early disease at presentation (leucocoria only) OR=4.13(1.48-11.68) p<0.001, intraocular disease on histology OR=8.5(2.23-34.49) p<0.001 and total delay to management of ≤5 months OR=3.5(1.31-9.68) p=0.005. Proptosis and tumor recurrences were associated with 100% mortality.

Conclusions: The survival of patients with retinoblastoma was found to be very low. The main reasons were the late presentation and recurrent disease. The factors associated with poor outcome were presentation with proptosis, metastatic disease, extraocular disease on histology and delay in diagnosis to management of >5months.

Key words: Retinoblastoma, Outcome of ocular cancers, Survival, Cancer, Kenyatta National Hospital (KNH) East Africa, Africa

INTRODUCTION

The incidence of retinoblastoma in Kenya has been estimated to be 1:17,000 live births^{1,2}. Retinoblastoma patients in developed countries have very good prognosis for survival, with overall survival rates of over 90%^{3,4}. The survival of retinoblastoma patients in Africa is scanty and this was the first study on the outcome of retinoblastoma in Kenya. Presence or absence of extraocular disease is the most important prognostic factor⁶⁻⁹ with other aggravating factors being extra retinal involvement with extension within the choroid, the sclera and the optic nerve¹⁰. Duration of symptoms before treatment also influences the outcome^{6,13}.

MATERIALS AND METHODS

This was a retrospective study at the Kenyatta National Hospital, Kenya's largest teaching and referral hospital. It included records of all patients admitted with retinoblastoma at Kenyatta National Hospital between 1st January 2000 and 31st December

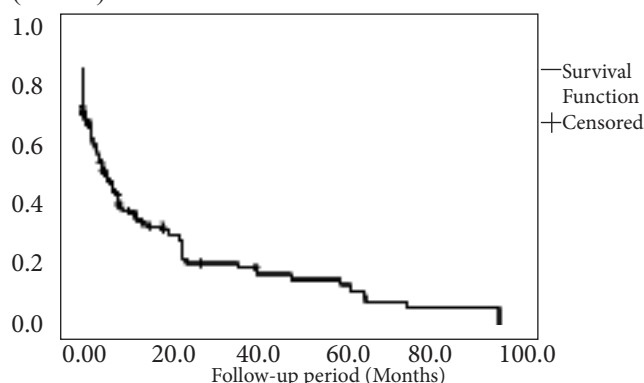
2004. Kenyatta National Hospital serves Kenya's population of over 30 million and parts of western Uganda. The eye clinic receives new patients as well as those referred by ophthalmologists and non-physician eye care workers for investigations and for specialized treatment including chemotherapy. Examination under anesthesia augmented with ocular ultrasound was performed for all patients. Histology of enucleated eyes was done at the University of Nairobi, Department of Human Pathology. Patients with a clinical diagnosis of retinoblastoma with or without histological confirmations were included. All records of patients whose histopathological report ruled out retinoblastoma were excluded. Approval was obtained from the Kenyatta National Hospital's Ethical Board. The International Code of Diseases was applied in computerized and manual retrieval of all files coded for retinoblastoma. Demographic details, clinical/surgical findings, histology report, parents' or guardians' contact and details of the last follow up in clinic were obtained. Parents or guardians were contacted via telephone or letters to determine patients' outcome and in case dead, the cause of death if known. Data obtained was analysed using the Statistical Package for

Social Scientists (SPSS) Version 12. Survival rate was calculated by simple cumulative survival rate method and using Kaplan-Meier survival probability curve.

RESULTS

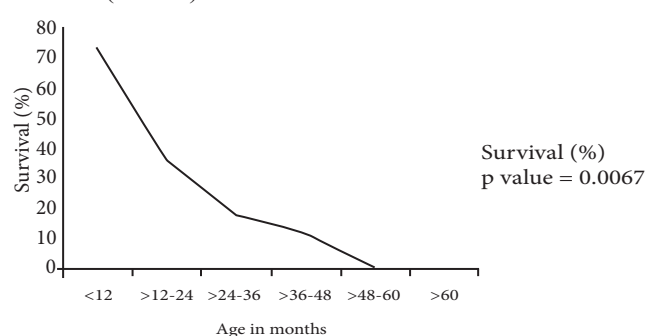
The records of 160 patients were identified but only 105 patients had been followed up for at least three years and hence qualified for the 3-year survival analysis. The cumulative 3-year survival rate was $28/105=26.6\%$. Mean survival time of the children who died during the period of follow up was 5.1 months (SD 6.4) with a range of 1-30 months from presentation. Mean survival time for the survivors was 68 months (SD 16.6) from presentation, with a range of 41-96 months. Probability of survival at 36 months was 0.2 as calculated on the Kaplan-Meier survival probability curve (Figure 1).

Figure 1: Kaplan-Meier Survival probability curve (n=105)



There were 57 males (54%) and 48 females (46%) with a male to female ratio of 1.16:1. The mean age at presentation was 37.5 months (SD 27) with a range of 1-144 months. The age at presentation was found to significantly influence survival (p value = 0.0067) (Figure 2).

Figure 2: Association between age at presentation and survival (n=105)



Seventy six patients (72%) had unilateral disease while 29(28%) had bilateral disease. No patient had trilateral

disease. Laterality was not found to be significantly associated with survival, OR 1.4 (0.5-3.5) $p=0.532$. The mean age at presentation of the bilateral cases was 24.4 months (SD 18.1) while that of unilateral cases was 39.9 months (SD 26.1) and the difference was statistically significant ($p<0.001$), however laterality was not found to influence survival.

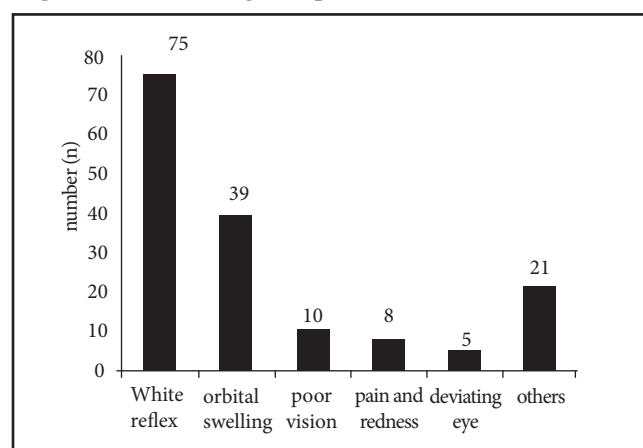
Only nine patients (8.5%) had positive family history of retinoblastoma, 39 patients (34.3%) had negative family history. Though it was not found to significantly affect survival with OR 0.32 (0.01-3.13) $p=0.285$, family history was not recorded in 55.2% of patient records. The mean delay between onset of symptoms and management was 12 months (SD 11.5 months) with a range of 13 days to 61 months. Delay significantly influenced survival with a delay of 5 months or less having better survival ($p=0.005$) (Table 1).

Table 1: Association between delay to treatment and 3-year outcome (n =105)

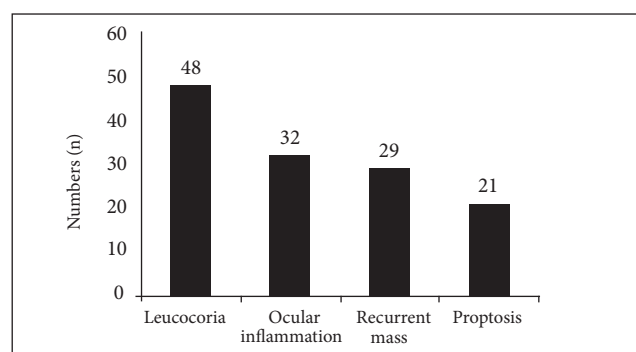
Duration in months	Outcome	OR 95% CI	p-value
	Alive n (%)	Dead n (%)	
≤ 5	18 (64.3)	26 (33.8)	3.53 (1.31-9.68) 0.005
≥ 5	10 (37.5)	51 (66.2)	

The main presenting complaints were white reflex in the eye 71%, swelling of the eye 37%, poor vision 9.5%, pain and redness 7.6% and deviating eye 5% (Figure 3).

Figure 3: Presenting complaints



Three patients were diagnosed during scheduled screening by examination under anesthesia due to positive family history of retinoblastoma and thus had no complaints whatsoever. On clinical examination leucocoria was found in 46% of patients, ocular inflammation 30%, recurrent mass in the socket 27% and proptosis in 20% of cases (Figure 4).

Figure 4: Clinical findings (n=105)

Seventeen (16.2%) patients had tumor cells seen on cerebrospinal fluid microscopy, four patients had CT scan evidence of intracranial metastasis while one had ultrasonographic evidence of abdominal metastasis. Patients who presented with leucocoria only were four times more likely to be alive at 3-year follow up than those who had other ocular findings (Table 2). This is in sharp contrast to 48% of the 105 patients who presented with either proptosis (21, 20%) or tumor regrowth after enucleation (29, 27.6%). This was associated with very poor outcome of 100% mortality rate within 12 months of presentation to the hospital (Table 3). It is important to note that 65% of the patients who died within the 3 year follow up had either proptosis or recurrent masses.

Table 2: Association between early presentation with (leukocoria only) and 3-year outcome (n =105)

Leucocoria only	Outcome		OR 95% CI	p value
	Alive n (%)	Dead n (%)		
Yes	14 (50)	15 (19.5)	4.13(1.48-11.68)	p=0.001
No	14 (50)	62 (80.5)		

Table 3: Association between late presentation with proptosis and tumour regrowth and 3-year outcome

Clinical Presentation	Outcome		OR 95% CI	P-value
	Alive, n (%)	Dead, n (%)		
Proptosis				
Yes	-	21 (27.3)	-	<0.001
No	28 (100.0)	56 (72.7)		
Tumour regrowth				
Yes	-	29 (37.7)	-	<0.001
No	28 (100.0)	48 (62.3)		

Table 4: Association between histology and 3-year outcome (n =105)

Histology findings	Outcome		OR 95% CI	p-value
	Alive n (%)	Dead n (%)		
Intraocular	15(53.6)	12 (15.6)	8.5(2.23-34.49)	p=0.001
Extraocular	5 (17.9)	34 (44.2)		
Inconclusive/ Missing reports	8 (28.5)	31 (40.2)		

Histopathological findings were divided into two categories of intraocular and extraocular diseases based on the available histology report. For bilateral cases in which both eyes were enucleated, for the purpose of correlating the extent of tumour involvement, the eye with the greater extent of tumour involvement was considered. Majority of the patients had extraocular involvement. Only 6 out of 105 patients were reported as having choroidal invasion (without involvement of the sclera and ciliary body). Of these six patients, five were dead at the end of three years and one was alive. Twenty one patients (20%) had missing histology records and the extent of the tumor was not indicated in the histology report of 14 cases (13.3%) thus were considered inconclusive. In addition, the parents/guardians of four patients (3.8%) declined enucleation.

Table 5: Multivariate analysis (n = 105)

Variables	Hazard ratio	95% confidence interval hazard ratio	p-value
Sex (ref=female)			
Male	0.762	[0.459, 1.265]	0.294
Laterality (ref=bilaterality)			
Unilaterality	1.354	[0.743, 2.465]	0.322
Age	1.005	[0.997, 1.014]	0.216
Total delay	1.007	[0.987, 1.028]	0.499
Leucocoria only (ref=yes)			
No	2.057	[1.070, 3.957]	0.031*
Histology –(ref=Inconclusive to the extent of spread)			
No histology	0.898	[0.404, 1.997]	0.792
Tumor confined to eye globe	0.279	[0.121, 0.645]	0.003*
Tumor involving optic nerve up to resection margin	0.745	[0.359, 1.543]	0.428
Extrasccleral spread	0.902	[0.398, 2.042]	0.804

On multivariate analysis, only presentation with pure leucocoria and histology findings of tumour confined to the globe were found to be independently associated with survival (Table 5).

DISCUSSION

The three year survival for retinoblastoma patients at Kenyatta National Hospital was found to be very low (26.6%) compared to developed countries and some developing countries in Asia where data indicate high survival rate of even up to 96% at 5 year follow up^{4,9,11,12}. Data on survival in Africa is scanty; however a study done in the neighbouring country of Tanzania revealed similarly poor outcomes. The study found a DFS probability of 0.23 (standard error=0.07)⁶. There are several factors that could explain the poor survival of retinoblastoma patients in our set-up. Being a referral centre, Kenyatta National Hospital mostly admits patients who have been treated at other centres and are only referred when the case is complicated. This results in both late presentations due to delays in the referral system and presentation with advanced disease both of which are associated with poor outcome. The primary care providers in Kenya are often non-physicians and ophthalmologists are few in rural areas where the majority of the population lives and this further compounds the situation.

The total delay to management was found to influence the 3-year outcome with a total delay of >5 months significantly associate with a negative outcome

quite similar to studies in Asia¹¹. According to a study at KNH in 2000 (unpublished) the main reasons for delay in presentation of retinoblastoma patients were ignorance among medical care personnel at primary health care facilities, ignorance among the general population on the symptoms of retinoblastoma and poverty.

The mean age of presentation of 37.5 months (SD 27) was much higher compared to developing countries. This could be a reflection of the delay in presentation in Kenya survival rate was highest amongst patients who presented at 12 months of age or earlier and reduced dramatically in the older age groups. Increasing age at diagnosis and delay in referral has been shown to increase the risk of extraocular retinoblastoma¹⁰.

Majority of the patients presented with clinical features of advanced retinoblastoma. Studies done in Nigeria and Tanzania similarly reflect this advanced disease presentation¹⁴. The advanced stage of disease was found to be associated with very poor outcome quite similar to results of a study done in Turkey¹³. Majority of the patients had histopathology features of extraocular disease and this was shown to significantly influence the 3-year outcome similar to findings of studies in Asia and Africa^{5,11}.

Challenges in the area of histopathology were evident in the fact that 20% of the patients did not have conclusive reporting on the extent of the disease while 13% had no histology report. This may have introduced bias in the correlation between extent of disease and

survival and should be borne in mind when interpreting these results. It is worthy to know that ophthalmologists in our resource-challenged set-up often rely on clinical diagnosis of retinoblastoma as not all patients get histological confirmation and this challenge has been documented in Tanzania as well⁵.

The main challenge encountered in the study was follow up of the patients to determine the outcome. Where no contact was made, consideration was made in data analysis and interpretation. Incomplete data including missing or incomplete referral notes, inadequate history taking by the ophthalmologists, lack of a standardized format in reporting of histology as well as missing reports could have introduced bias in the results. This should be borne in mind when interpreting the results. They also point to the areas of weakness in the public awareness and health care delivery in Kenya and the region indeed as articulated in the study done in Tanzania⁵. These need the concerted effort by all to improve the outcome of this treatable childhood disease in this region. Indeed following these findings a Kenya National Retinoblastoma Strategy was launched whose main areas of focus are increasing awareness, improving medical management (including quality of histology reporting) and supporting families of retinoblastoma children. All this is aimed at improving the survival of retinoblastoma patients in Kenya¹⁵.

ACKNOWLEDGEMENT

We would like to acknowledge the contribution of the staff in the medical records department at the Kenyatta National Hospital. Special thanks to the Christoffel Blindenmission (CBM) for providing funding to carry out this study as part of the first author's Masters in Medicine thesis fulfillment. The authors do not have monetary grants for disclosure.

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