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ORIGINAL RESEARCH

A 15-Year Review of Retinoblastoma at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria

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Abstract

Background: Retinoblastoma (RB) is a rare and highly aggressive eye cancer in children. Late diagnosis of the disease usually results in a very low disease-free survival rate in the developing world.
Objectives: To review the prevalence, pattern, and treatment outcomes of retinoblastoma in a Nigerian tertiary centre.
Methods: This was a retrospective study of the clinical records of all new patients aged 16 years and below with a clinical diagnosis of retinoblastoma at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria, between January 2008 and December 2022. The sociodemographic and clinical data of children with the disease were obtained from the clinical records, and the data were analysed.
Results: The hospital prevalence of retinoblastoma was 0.15%. The male-to-female ratio was 1.2:1, with a mean age of 3.4 years. Unilateral disease accounted for 74.4% of cases, and extraocular manifestations accounted for 71.8% of the cases studied. The most common and earliest presenting symptom was leukocoria. One-third of the cases did not receive any treatment for retinoblastoma. The majority of the children (69.2%) were lost to follow-up, and only two (5.1%) were alive.
Conclusion: The prevalence of retinoblastoma at this hospital was low, but most cases were unilateral and presented as extraocular disease. Although the disease is potentially curable, the treatment outcome remains poor in this setting due to late presentation at the hospital.

Keywords: Childhood cancer, Embryonal tumour, Leukocoria, Retinoblastoma, Clinical outcome.

Introduction

Retinoblastoma (RB) is a rare but highly aggressive eye cancer primarily affecting children. The disease may present as unilateral (affecting one eye), bilateral (affecting both eyes), or, in rare cases, trilateral when another intracranial tumour coexists with bilateral retinoblastoma. [1,2] It can be hereditary or non-hereditary. [3-5] Globally, 8,000 new cases are diagnosed annually, thus accounting for 3% of all paediatric cancers. [6-10] The highest incidence of retinoblastoma is observed in low-income countries among children under five, particularly within the first two years of life. [9,11-13] retinoblastoma can progress rapidly and metastasise if left untreated, but timely and appropriate treatment often leads to successful outcomes. [14,15]

Over the past forty years, advances in treatment have significantly improved outcomes, achieving a disease-free survival rate of almost 100% in the developed world. [16, 17] However, in developing countries like Nigeria, outcomes are much poorer, with high mortality rates. [18, 19] Late presentation of the disease due to a lack of public awareness, treatment abandonment because of the high cost of care, and the high level of poverty generally lead to an exceedingly low disease-free survival rate in our setting.

In Nigeria, retinoblastoma is reported as one of the five leading childhood malignancies [7-9, 15,20, 21] and the most common intraocular eye tumour in most studies, predominantly spanning all geo-political zones, with very few cases from the southwestern region. [13,14,22] Moreover, some of these studies lack sufficient data specific to that area. Additionally, some of these studies (conducted by pathologists or ophthalmologists) often encompass a wide range of ocular cancers, including retinoblastoma, which limits detailed insights into retinoblastoma alone. This underscores the urgent need for dedicated research efforts in the southwestern region to address these gaps effectively.

This study aims to fill this gap by reviewing retinoblastoma cases over 15 years at a tertiary centre in southwestern Nigeria. The goal is to understand the epidemiological trends and treatment practices in this area. By analysing this extensive dataset, we hope to gain insights that will help improve management strategies and outcomes for retinoblastoma in developing countries. The main objectives of this study were to assess the prevalence of retinoblastoma, describe the clinical presentations, treatment patterns and treatment challenges, and outcomes. This research underscores the urgent need for targeted interventions and a multidisciplinary approach to ensure timely and effective management of retinoblastoma in resource-limited settings.

Methods

This was a retrospective study of the clinical records of all new patients aged less than 16 years with a clinical diagnosis of retinoblastoma at the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, between January 2008 and December 2022. Ethical approval was obtained from the hospital's Ethics and Research Committee. The sociodemographic and clinical data obtained included age at presentation, sex, residential town, earliest presenting complaint, duration of presenting complaint, laterality of the disease, extent of the disease, modality of treatment, treatment challenges and outcome.

Age at presentation was stratified into three groups: zero to five years, six to ten years and 10 to 15 years. The residential town was divided into those within Osun State, where the hospital was located, and those outside it. The earliest presenting complaint for each of the patients was identified and documented. The duration of presenting complaints was grouped into less than six months, between six months and one year and greater than one year.

Laterality of the disease was determined based on the clinical diagnosis at presentation: unilateral if one eye was affected, bilateral if both eyes were affected. The clinical diagnosis at presentation was made based on a clinical history and a detailed clinical examination, including a slit lamp examination, tonometry and dilated fundoscopy (using a binocular indirect ophthalmoscope), where possible, for identification of retinoblastoma lesions. Using the International Intraocular Retinoblastoma Classification (IIRC), the extent of the disease was classified as intraocular or extraocular based on clinical diagnosis and other supporting clinical findings from radiological results, examinations under anaesthesia, and pathology results, where available.

Extraocular disease was defined as an extraocular tumour(s) involving the orbit, including the optic nerve, based on:

1. Radiological evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues, or
2. Clinically evident with proptosis and orbital mass.
3. Intraocular disease was any extent of the primary tumour that was neither 1 nor 2 above.

Modality of treatment was grouped based on available modalities, including chemotherapy, enucleation and exenteration, and radiotherapy (for patients referred to other hospitals for radiotherapy and returned for further treatment). Some patients received more than one modality of treatment, while others did not receive any treatment in the hospital and were classified as receiving "No treatment".

The outcome was determined based on the patients' last follow-up clinical notes. If a patient defaulted from follow-up, the outcome was classified as "Unknown". The challenges documented for all patients were identified and summarised as "Yes" if they experienced financial constraints, irregular follow-up visits, discharge against medical advice, suboptimal hospital services, or default from previous retinoblastoma treatment elsewhere, and "No" if they had not.

“Financial constraint” referred to all patients who experienced delays in treatment due to a lack of funds. "Irregular follow-up" referred to patients who missed their scheduled follow-up date or were lost to follow-up. “Discharged against medical advice” referred to patients who requested discharge for any reason before the completion of their treatment. “Suboptimal hospital services” referred to patients who experienced delays in their treatment due to hospital logistical issues, industrial actions, COVID-19 lockdowns, or the unavailability of the modality of treatment they required, such as focal therapies and radiotherapy. "Default from previous retinoblastoma (RB) treatment elsewhere" included patients diagnosed with retinoblastoma and had chemotherapy, surgery or any other treatment specific to retinoblastoma before presenting to our hospital.

The data on sociodemographic characteristics, clinical characteristics and management challenges were presented as frequencies and proportions and summarised using tables. In contrast, the Mann-Whitney U test was used to compare the means of two non-normally distributed variables. A significant p-value was set as < 0.05 at a 95% confidence interval.

Results

There were 39 new patients aged less than 16 years who had a diagnosis of retinoblastoma. The total number of patients aged less than 16 years seen during the study period was 22099, giving a hospital prevalence of 0.15%.

There were 21 males and 18 females with a male-to-female ratio of 1.2:1. The age range was 28 days to 9 years. The mean age was 3.04±1.97years. The mean age for bilateral disease was 2.94±2.19 years (range 30 days to 7 years), which was younger than the mean age for unilateral disease (3.06±1.95 years; range 28 days to 9 years). The difference in mean age between the two groups was not statistically

significant (t = -0.144, p = 0.886). The mean duration of presenting complaint was 7.7±7.4 months, with a range of 1 day to 24 months, and 1/3 of the patients presented to the hospital 6 months or more after the first symptom. The mean duration of symptoms in patients with intraocular tumours was 0.30±0.33 years, and in patients with extraocular tumours was 0.74±0.65 years. The difference between the mean duration of symptoms between the two groups was not statistically significant (t = -1.712, p = 0.097).

The gender distribution and frequency of age groups, residential town, earliest symptom and duration of presenting complaint are shown in Table I.

Table I: Sociodemographic characteristics of 39 children with retinoblastoma (2008 – 2022)

Characteristic	*Male (%)*	*Female (%)*	*Total (%)*
	n = 21)	**n = 18**	**N = 39**
Age at presentation (years)			
0-5	18	17	89.7
6-10	3	1	10.3
11-15	0	0	0.0
Residential town			
Within Osun State	13	6	48.7
Outside Osun State	9	11	51.3
Earliest presenting complaint			
Leukocoria	16	12	71.8
Right eye swelling	3	5	20.5
Strabismus	3	0	7.7
Duration of presenting complaint			
< 6 months	17	9	66.7
6 months to 12 months	2	3	12.8
>12 months	3	5	20.5

There were more patients with unilateral (29; 74.4%) than bilateral (10; 25.6%) disease. Extraocular presentation was more frequent (28; 71.8%) than intraocular presentation (11; 28.2%). One third (13; 33.3%) of the patients did not receive any treatment for retinoblastoma, and the outcome for most (27; 69.2%) of the patients was unknown because they were lost to follow-up or discharged against medical advice.

Out of the 13 (33.3%) patients who did not receive treatment, 11 had financial constraints, and one was a patient with unilateral intraocular Group B disease that was referred to another tertiary hospital for focal therapy because this was unavailable in our centre. One was not treated because the father preferred spiritual healing. The known mortality rate of all the new retinoblastoma patients was 15.4%. Only two children were documented as alive and still regularly attending follow-up clinics, as shown in Table II.

Financial constraint (31; 79.5%) was the most common challenge encountered in the management of retinoblastoma, followed by irregular follow-up visits (26; 66.7%). For the suboptimal hospital services, three of the 11 cases documented were due to the COVID-19 lockdown, another three to industrial actions, while the rest were due to hospital logistics, such as a lack of theatre space for surgery and the unavailability of anticancer drugs (Table III).

Table II: Clinical characteristics of 39 retinoblastoma cases (2008 – 2022)

Parameters	*Frequency*	*Percentage*
Laterality		
Bilateral	10	25.6
Unilateral	29	74.4
Right	20	51.3
Left	9	23.1
Extent of Disease		
Intraocular tumour	11	28.2
Extraocular tumour	28	71.8
Orbital only	13	33.3
Orbital + Lymph node metastasis only	7	17.9
Distant metastasis	8	20.5
Modality of treatment		
Chemo alone	9	23.1
Chemo & enucleation	8	20.5
Chemo & exenteration	8	20.5
Chemo & Radiotherapy	1	2.6
No treatment	13	33.3
Outcome of treatment		
Unknown (lost to follow-up)	27	69.2
Died	6	15.4
Referred	4	10.3
Alive	2	5.1

Table III: Management challenges in 39 retinoblastoma patients, 2008 - 2022

Variable	*Yes (%)*	*No (%)*
Financial constraint	31 (79.5)	8 (20.5)
Irregular follow-up visits	26 (66.7)	13 (33.3)
Discharge against medical advice	9 (23.1)	30 (76.9)
Suboptimal hospital services	11 (28.2)	28 (71.8)
Default of patients from previous RB treatment elsewhere	6 (15.4)	33 (84.6)

Discussion

Retinoblastoma is a potentially curable disease; however, the prognosis for survival is dependent on early diagnosis and appropriate therapy. The primary concern about retinoblastoma in developing countries is the high mortality rate. The incidence of retinoblastoma from this study was approximately three cases per year and comparable to the findings in Anambra, Eastern Nigeria as reported by Nwosu *et al.*, [13] but much lower than 17 and 18 cases per year reported from the other centres, in Northern Nigeria [14-15] and 22 and 27 cases per year reported from Mali [16] and Côte d'Ivoire [17] in West Africa respectively. This low incidence may be due to differences in accessibility and uptake of retinoblastoma care across centres. Furthermore, a lack of awareness of the

availability of retinoblastoma services could also be a contributing factor. A two-way referral system between primary/secondary health centres and tertiary hospitals could help improve the accessibility of patients' access to retinoblastoma services. In addition, periodic health talks on child eye care at all levels of the health care system may improve awareness about the availability and accessibility of retinoblastoma services.

There was no gender predilection among the children studied. This is consistent with the findings of other researchers in both developed and developing countries. [4,5,18,19] However, a study in India by Chawla and Singh reported a male preponderance, which they suggested could be due to a lack of attention towards the girl child in their country. [23]

The majority of the children in this study were below 5 years of age, of whom two-thirds were three years of age or younger. This is comparable to findings from previous studies on the epidemiology of retinoblastoma. [14,16,18,24,25] Similarly, this finding provides a rationale for targeting children under five years for the provision of free retinoblastoma services in both government and private hospitals to ensure better access to eye care and retinoblastoma interventions.

A delay of more than six months after the first symptom was observed in a third of patients in the present study. This finding is significant because of the impact of early diagnosis on prognosis and survival. Several reports have shown that late presentation is one of the challenges of managing retinoblastoma in low and middle-income countries such as Nigeria. [4,17,26,27] Bekibele *et al*. reported that late presentation was the most common reason for late diagnosis of retinoblastoma in their study population. [28] Furthermore, Fabian *et al.* reported that low income and older age at presentation were independent and significant predictors of advanced retinoblastoma. [4] Eye health education with emphasis on early recognition and referral of patients with common presenting symptoms and signs of retinoblastoma at primary and secondary levels of care can help reduce the prevalence of late presentation and thus improve outcomes of treatment. This may be achieved by including eye health education in the curriculum of Community Health Extension Workers, who are primarily involved in taking care of children at the community level in Nigeria.

The most common earliest symptom of retinoblastoma in this study was leukocoria, consistent with previous reports. [4,5,16] However, three-quarters of the patients already had extraocular disease, and more than a third of the patients had lymph node or distant metastasis at presentation. The proportion of those with lymph node or distant metastasis in this study was higher than in some published reports [4,22,26,27,29] but similar in proportion to reports by Lukamba *et al.* and Ali *et al.* [17,18] Goolam *et al.* found that patients with a presentation of less than six months were less likely to have regional extension or metastatic disease than those with a delay of more than six months. [26] The high proportion of patients who presented more than six months after the onset of symptoms may be responsible for this finding of advanced metastatic disease in this study. This implies that late presentation with advanced disease remains a significant challenge in our settings, underscoring the need for eye health education with emphasis on improving access to retinoblastoma care facilities.

Unilateral retinoblastoma was three times more common than bilateral retinoblastoma in this study, and this compares favourably with most findings globally, where unilateral retinoblastoma was found to be common than bilateral retinoblastoma. [4,5,14] Even though our findings were based on history and clinical examinations and not genetic studies due to their unavailability, the family history of retinoblastoma was positive in only two cases. The two patients were siblings from the same parents, and both had bilateral retinoblastoma.

This suggests that somatic mutations may be more common than germline mutations in the pathogenesis of retinoblastoma cases seen at our centre. Consequently, the cure rate may be higher if patients with retinoblastoma had presented for treatment earlier.

A third of the patients in this study did not receive treatment for retinoblastoma. This was lower than the reports of 42.3% by Bekibele *et al.* [28] and 70.7% by Musa *et al.* [24] but higher than the report of 8% from Sudan. [18] In addition, about two-thirds of all the patients defaulted from follow-up, and their outcomes were largely unknown. The commonest reason identified in these groups of patients was financial constraint. Financial challenges could be alleviated by providing free or insured treatments for patients with retinoblastoma. In this study, the outcome of retinoblastoma was poor, with only two patients known to be alive and well. A myriad of challenges could have contributed to this poor outcome; late presentation, coupled with financial constraints at the time of treatment, was the most common challenge identified in this study. This was similar to reports from other low-income countries.[30] Other challenges included irregular follow-up visits, discharge against medical advice, suboptimal hospital services and default of patients from treatment elsewhere. These findings can be used to advocate for the establishment of a fully equipped regional centre for free or insured retinoblastoma treatment, including genetic studies, to help alleviate some of these challenges and improve the treatment outcomes for children with retinoblastoma.

Conclusion

This study reported a low hospital prevalence of retinoblastoma, with unilateral disease and extraocular presentation as the most common manifestations. Although the disease is potentially curable, the treatment outcome remains poor in our setting due to late presentation. By identifying the challenges in patient management, solutions that improve the outcomes of our patients may be proposed.

Authors' Contributions: AO, ABA and BSA conceived and designed the study. AO, ABA and AOA curated, analysed and interpreted the data. AO, ABA and BSA drafted the manuscript, while AO and ABA revised the draft for sound intellectual content. All the authors approved the final version of the manuscript.
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