Original Research Article

Experience with Retinoblastoma at a Tertiary Centre in Port Harcourt, Nigeria: Trends in Outcome

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ABSTRACT

Background: Retinoblastoma is the most common primary intraocular malignancy in children, and remains the most curable of all childhood cancers in the developed world. However, ocular and patient survival rates have remained very low in resource limited countries, where more than 90% of children with retinoblastoma live.

Objectives: To review the pattern of presentation of children with retinoblastoma at the University of Port Harcourt Teaching Hospital (UPTH), Nigeria, and compare their treatment outcome with what was obtained in the previous decade in same centre.

Methods: All patients with retinoblastoma admitted into the Paediatric Oncology Unit of the UPTH from January 2011 to June 2017 were reviewed. Their demographics, clinical profile and outcome of treatment were analyzed using SPSS version 20.0.

Results: Nineteen children had retinoblastoma which represented 11% of all childhood malignancies. Eight(42%) males and 11(58%) females, all under-fives, were studied with M:F=1:1.4. Mean duration of symptoms was 29.6 weeks, with majority(73.7%) having been ill for more than 3 months. White spot in the eye and eye protrusion were commonest presenting complaints while loss of vision was found in all affected eyes. More children(57.8% versus 30.8% previously) were lost to follow up, 5(26%) died and 3(15.7%) completed treatment, whereas none did a decade earlier.

Conclusion: Retinoblastoma affected only under-five children. Late presentation with proptosis and loss of vision were common presenting features. A marginal improvement in outcome was noted while high default rate and lack of radiotherapy facilities in the State had remained important challenges to completion of therapy.

Key words: Experience, Retinoblastoma, Tertiary centre, Nigeria, Trends, Outcome

1. INTRODUCTION

The burden of childhood cancers as a growing public health challenge is increasingly being recognized worldwide, including in the developing nations.[1] Retinoblastoma (RB), an embryonic tumour that develops from the immature cells of the retina, is the most common primary malignant intraocular tumour of childhood. It occurs approximately in 1:20,000 live births, has hereditary and non-hereditary (sporadic) pattern of transmission, and has no gender or race predilection. The non-hereditary form is usually unilateral (60%) while the hereditary one (40%) manifest either as unilateral or bilateral disease and is characterized by early onset.[2-4] The disease is found almost exclusively in childhood as presentation is unusual after 5 years of age.[5,6] Retinoblastoma is considered to be associated with loss of function of both alleles of the RB tumour suppression gene located on chromosome 13, although recent findings propose that epicentric factors and aneuploidy play central roles in the cause of this disease.[7]

In developed countries, RB is regarded as a rare tumour accounting for approximately 3% of all childhood malignancies and its current management has resulted in an improved survival

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to a rate of astounding 99% with more than 90% retaining normal visual acuity in at least one eye.[8] Whereas in developing nations, including african countries, where the majority of retinoblastoma cases live, it is considered one of the most frequent paediatric solid tumours with a higher incidence and survival rate estimated at 40%.[5,8,9] This has been attributed to several factors, including lack of awareness, late presentation, parental cultural practices and traditional belief system, treatment abandonment/refusal of enucleation, absence of adequate healthcare facilities among others.[3,8,10-12] Sometimes also, early signs of the disease, usually a 'white' reflex or leukocoria and strabismus, are subtle and are often missed, which could lead to delay in diagnosis and oftentimes loss of vision or even loss of life.[3]

Blindness on the other hand, has implications for all aspects of the child's development and is a significant burden to society in that the cost of lost of productivity and of rehabilitation and education of the blind is very high and increasing. The control of blindness in children is a priority within the WHO's Vision 2020 programme, whose aim is controlling the leading causes of blindness with a view to eliminating them.[13]

In Nigeria, despite several reports, the prevalence of RB cannot be fully ascertained as available studies are usually hospital-based and regional, showing marked variation across different regions. It was found to be the two most common childhood malignancies in Kano, Zaria and Shagamu, where RB accounted for 14 to 37% of cancers seen in children,[14-17] while it accounted for a lesser proportion, 5- 8% of childhood malignancies in Anambra, Jos, Ilorin and Port Harcourt.[12,18-20] Outcome of treatment on the other hand was found to be very poor, as many patients were lost to follow up after first or second course of chemotherapy,[19,21] while few patients, none in some series, completed their treatment.[21,22]

This study thus aimed to illustrate the clinical profile of retinoblastoma at a tertiary centre in southern Nigeria, and compare treatment outcome with what was obtained in the previous decade, as such documentation will increase awareness among parents, medical practitioners and relevant authorities about this important cause of blindness and mortality in children.

2. METHODS

The study was conducted at the University of Port Harcourt Teaching Hospital (UPTH) which is located in Rivers State, South-south region of Nigeria. It is a tertiary care hospital which serves as a major referral centre for patients from within the State, with its under-15 population of 2,437,138 (47% of its population) and neighbouring states.[23]

In this retrospective study, all cases of retinoblastoma admitted into the Oncology Unit of the Paediatric Department from January 2011 to June 2017 were reviewed, as well as those who were seen at the Paediatric Ophthalmology Clinic of the hospital during the same period. Cases were identified from clinic records and data on each patient collected from hospital notes. Variables studied included biodata, duration of illness, clinical presentation, site involved, treatment and outcome.

Diagnosis of retinoblastoma was based on the clinical and radiologic evaluation, including ocular ultrasonography, with or without CT/MRI of orbit and brain to evaluate the extend of disease and spread. Histological confirmation of diagnosis was obtained for those who had surgery. None of the patients had a positive family history of ocular cancer and genetic studies were not done.

Children with very huge tumour were given neo-adjuvant chemotherapy for 3 months prior to enucleation, while others had initial enucleation, followed by chemotherapy with intravenous vincristine, etoposide and carboplatin given at 3-weekly interval for 6 cycles.[7] Patients were also offered radiotherapy. The hospital however lacks such facility. Thus, those who could

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afford it had to travel to other states where radiotherapy is available. Cost of investigations and treatment were all out of pocket expenses.

Outcomes of treatment included: completed treatment and still being followed up, loss to follow-up and died. Children who were discharged against medical advice (DAMA) as well as those who absconded from hospital and those who were not seen in the 6 months prior to collection of this data were considered lost to follow-up and abandoned treatment. None was undergoing active therapy at the time of this study.

Approval for the study was obtained from medical ethics committee of the hospital. Data were entered into a Microsoft Excel Spread Sheet and analyzed using SPSS version 20.0. Chi-Square test was used to test for significance. P values < 0.05 were considered significant. Results are presented using tables and charts.

3. RESULTS

A total of 178 children were admitted for childhood cancer during the period under review. Eleven (6%) had incomplete data and were excluded from the study. Out of 167 cases analysed, 20 children had ocular malignancies. Nineteen(95%) of them had RB, representing 11.3% of all childhood cancers seen at the UPTH (Figure 1. Prevalence of retinoblastoma), while rhabdomyosarcoma accounted for 5% (1 case) of childhood ocular malignancies.

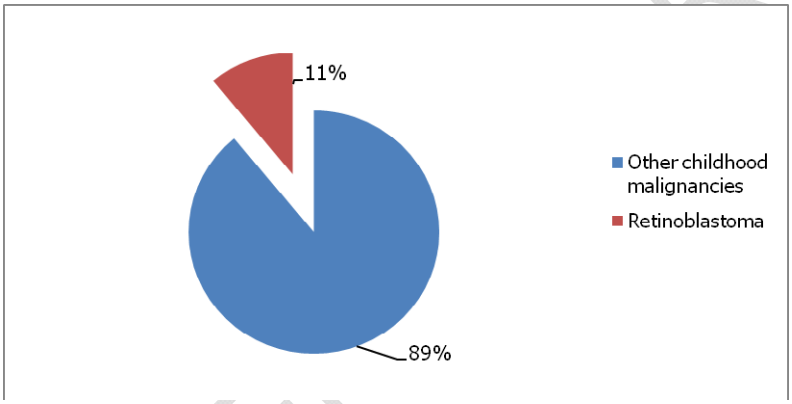

Figure 1. Prevalence of retinoblastoma at the University of Port Harcourt Teaching Hospital

Age range of children diagnosed with retinoblastoma were between 2 and 48 months, with a mean ± standard deviation (SD) age of 28.0 ± 12.5 months and median age of 30 months at presentation. Females were more affected (58%) with M:F = 1:1.4. The 36-48 months age bracket had the highest number of children (7cases- 36.8%), while infants represented 10.5% of the study population (Table 1.).

Table 1. Age and gender distribution of the study population

Age at presentation	Male (%)	Female (%)	Total
1 - 11 months	1 (5.3)	1 (5.3)	2 (10.5)
12 - 23 months	1 (5.3)	3 (15.8)	4 (21.1)
24 - 35 months	3 (15.8)	3 (15.8)	6 (31.6)
36 - 48 months	3 (15.8)	4 (21.1)	7 (36.8)
TOTAL	8 (42)	11 (58)	19 (100)

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The mean duration of symptoms prior to presentation was 29.6 weeks and median of 24 weeks, with a range of 3 to 104 weeks. Fourteen children (73.7%) had symptoms of the disease for more than 3 months, while 2 (10.5%) presented within 1 month of their onset (Table 2). More than half of the children (57.8%) had metastasis involving mainly the central nervous or skeletal system at diagnosis.

Table 2. Duration of illness and presence of metastasis at diagnosis

Duration of illness	**Metastasis at diagnosis**		
	Yes (%)	No (%)	**Total (%)**
1- 4 wks	1 (5.3)	1 (5.3)	2 (10.5)
5- 8 wks	1 (5.3)	1 (5.3)	2 (10.5)
9-12 wks	1 (5.3)	0	1 (5.3)
≥ 13 wks	8 (42.1)	6 (31.5)	14 (73.7)
Total (%)	11 (58)	8 (42)	19 (100)

Table 3 showed the clinical features of children who were diagnosed with RB. The commonest symptoms were white spot in the eye (73.6%), protrusion of the eye (63%) and inability to see with the affected eye (57.8%). All were however found to have loss of vision in the affected eye (100%), in addition proptosis (63%), leukocoria (47.3%) and fungating mass (36.8%) were common signs at presentation. There was a total of 24 eyes affected, with the right eye being the most involved (42%) while bilateral disease was found in 5(26%) children with average age at presentation of 17.5 months, and 31.8 months for those with unilateral disease.

Table 3. Frequency distribution of clinical features and site involvement

Presenting symptoms	**Frequency**	**Percentage**
White spot in the eye	14	73.6
Protrusion of the eye	12	63
Inability to see with affected eye	11	57.8
Redness of the eye	7	36.7
Deviation of the eye	2	10.6
Pain in the eye	1	5.3
Signs at presentation		
Loss of vision in affected eye	19	100
Proptosis	12	63
Leukocoria	9	47.3
Fungating mass	7	36.8
Inflammation	4	21
Eye discharge	3	15.7
Squint	1	5.3
Raised intra cranial pressure	1	5.3
Site involved		
Right eye	8	42
Left eye	6	32
Both eyes	5	26

Figure 2 showed the frequency distribution of outcome for treatment received. Three children (16%) completed their anti-cancer therapy with or without radiotherapy, and have remained disease free for at least 48 months while more than half of the study population (58%) were lost to follow up. Out of the 6 children who received chemotherapy only, 3 had surgery done in other centres several months earlier, but did not received chemotherapy for financial reasons, and presented to our facility with recurrence of the disease; while others

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commenced chemoreduction and were awaiting surgery. Parents of 3 (16%) children absconded before treatment could be commenced.

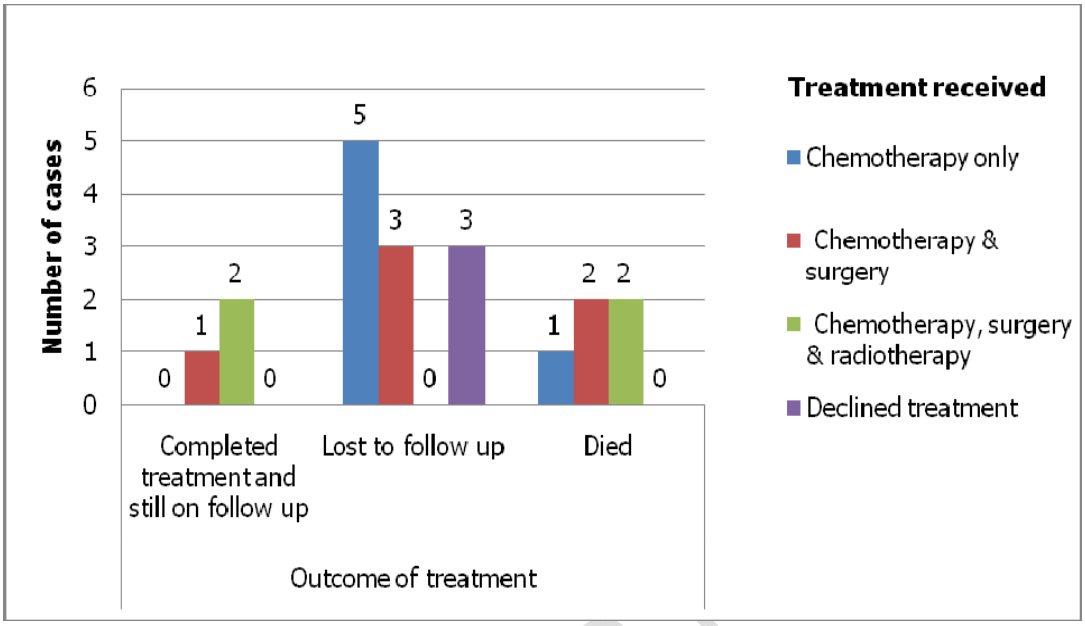

Figure 2. Frequency distribution of outcome for treatment received

Figure 3 showed a comparison of outcome with report of a previous study in same centre. There was an increase in the number of children who completed therapy as well as those who had radiotherapy, but more also were lost to follow up.

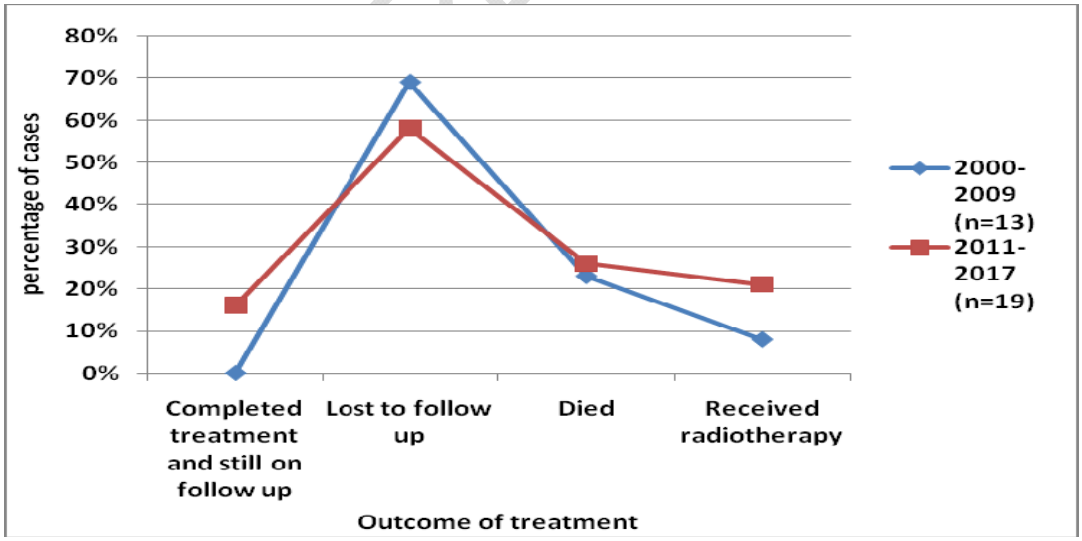

Figure 3. Trends in outcome of treatment from 2 studies in same centre

4. DISCUSSION

Retinoblastoma is one of the major causes of irreversible blindness in children and its impact on the quality of life of children is doubtless enormous. In the present series, it accounted for 11.3% of all childhood malignancies, corroborating with the 10.5% found by Owoeye *et al* in Ilorin.[4] This figure is higher than the 8% reported by Fubara *et al* in our centre a decade earlier when they studied solid tumours in children and adolescents.[20] It is however lower than reports from series in northern parts of the country where RB was reported to be the most common paediatric cancer accounting for 30% of all childhood malignancies in Kano, and second most common in both Zaria(17%), and Sagamu in south-western Nigeria(21%). [15,17,24] Whereas, highest rates in Africa were recorded in Mali(42%) and Uganda(24%).[25] Authors partly attributed the relatively high proportions of RB in Kano and Zaria (both in northern Nigeria) to the fact that the pathology laboratories in those centres also served major eye specialist referral centres in those states. Also, the recognition of a linkage of non-familial RB with poverty may account for its high prevalence in developing nations.[15]

The median age at presentation in this study was 30 months, with 10% of the subjects presenting before their first birthday. Similar findings were reported in the Ilorin study, while it was at disparity with reports in India where median age at presentation was 24 months, with 42% of the study population presenting on or before 12 months of age, and in Southern Brazil with 35.7% presenting in that same age bracket.[4,5,9] It was not surprising that more subjects in these 2 series had bilateral disease, 52% in India, 32.9% in Brazil, compare to 26% in our series, as this type is known to usually present earlier in life.[5,9] But a decade earlier in our centre, no case of bilateral RB was found aver the 10 year review period.[21]

Also, the disparity may be associated with higher incidence of unilateral (sporadic) RB over bilateral cases in Africa.[4] Besides, it has been stipulated that the poor survival rate of the disease in developing nations may possibly be related to the low rate of bilateral disease in Africa as affected children do not survive to reproductive age to transmit the mutant genes to their offsprings, while poorly understood environmental factors may also be implicated.[4,26]

However, the early presentation in the India and Brazil series may also be due to better awareness about early signs of the disease, better access to health care, as well as larger sample size.

On the other hand, the age at diagnosis in the present series was lower than 41 months as was obtained in Yaoundé where none of their subjects were below 1 year of age, 27% were older than 5 years of age and only 1(9%) had bilateral disease. This is in line with previous documentation that unilateral cases of RB increase significantly with increasing age at diagnosis, while the bilateral cases decrease significantly.[27,28]
The median duration of symptoms prior to presentation was 24 weeks, which is rather late but of common occurrence in developing nations, and unfortunately this pattern has persisted in our environment after a decade.[3-5,21] This may be a reflection of the negative health seeking behaviors and cultural practices in our environment as patients often seek alternative means of healing before coming to hospital, lack of awareness of both the populace and health care personnel, among others.[27,28] The fact that initial symptoms are painless, may also explain the delay in presentation. A lower duration was reported in Kenya where a progressive reduction of the delay between onset of symptoms to presentation at the referral centre was achieved, and was attributed to the awareness campaigns focusing on retinoblastoma in the country.[29]

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More than half of patients in this study had metastasis at diagnosis, which is much higher than that expected in developed countries, but also higher than reports in the India(26%) and Brazil(10%) studies, which are also developing nations.[5,9] The delay in presentation may account for this disparity, but specific reasons for the delay were not explored in this study.
The clinical presentation of retinoblastoma, usually with leukocoria in more than half of the patients, which is best seen in low artificial lighting or in a flash photo, agrees with previous reports.[4,5,10,21] Others include strabismus, deteriorating vision, changes in pupil size and, proptosis as the disease progresses, while pain is unusual.[3,30,31] Unfortunately, all patients in this study were found to have loss of vision in the affected eye, which was higher than 90% reported in DR Congo, and is likely to be related to the duration of symptoms.[32] Much lower values have also been reported, 30.8% in Western Nigeria and 2.4% in Ethiopia where, proptosis was more prevalent than leukocoria.[4] The reason for the disparity in the rate of blindness is not clear and may be subject for future research.[4,33]

For cases with bilateral disease, the denial of a family history of RB we obtained is similar with other african studies.[4,21] A possible reason for this may be the usual reticence for disclosure of health issues exhibited by people in our environment. Furthermore, the lack and/or affordability of facilities for genetic studies remain a huge challenge for confirmation of this type of RB.

Cancer treatment is generally expensive and often times requires prolonged hospital stay, especially if the child has advanced disease. Parents/caregivers have to bear the costs of treatment including drugs, diagnostic investigations, meals, transportation and hospitalization. Thus, many families of affected children in resource poor countries experience financial difficulties, as health insurance and resources to support them are virtually nonexistent, and minimum wage often unrealistic, further compromising survival.

The high default rate despite pre-treatment counselling and high mortality observed in this study have been reported in previous series in Low- and Middle-Income Countries and constitute important barriers for good outcome.[4,8,21,26,31] Sixteen percent of patients in this series completed their treatment with or without radiotherapy, against none in the earlier study, showing a marginal improvement in outcome (p= .13), and these patients are still being followed up at least 48 months later, while none had more than 36 months of follow up post enucleation in the previous study.[21] Thus, measures to significantly improve this trend are needed and should be explored urgently. These include among others, establishment of a National Retinoblastoma Programme and/or twinning initiatives as done in some African nations that resulted in favourable outcomes such as early detection, prompt referral, increased treatment and follow-up compliance.[26,29,34]

Study Limitations:
The unavailability of radiotherapy in our State increases the challenges to optimal treatment of RB, the lack of access for genetic studies which may have enhanced the quality of the study constitute limitations to this study. Furthermore, reasons for delay in presentation were not explored, which might have explained some of the reasons for their poor health seeking behaviour.

5. CONCLUSION

All children with RB present before their 5th birthday in our environment. Late presentation with loss of vision and proptosis were prevalent. A marginal improvement in outcome was noted while high default rate and lack of radiotherapy in the State had remained important challenges to completion of therapy. There is an urgent need to increase awareness of both the populace and health care providers with prompt referrals to facilitate early detection and

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implementation of curative therapy. Free health care for all childhood cancers with social support to ensure completion of therapy are also recommended to improve outcome

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