INTRODUCTION

Retinoblastoma is the most common primary intraocular malignant tumor of childhood. Worldwide incidence is one case per 15,000–20,000 live births, which corresponds to about 9000 new cases every year. It accounts for about 3% of all childhood cancers. In Africa, it is one of the most common pediatric tumors. In Nigeria, studies have found retinoblastoma to be the second most common childhood tumor. Retinoblastoma arises as a malignant proliferation of immature retinal neural cells, called retinoblasts, which have lost both RB1 tumor suppressor genes. However, in the presence of nonmutated RB1 genes, amplification of the MYCN oncogene might initiate retinoblastoma.

The care of patients with retinoblastoma is best provided by a multidisciplinary team of specialists including ophthalmologist, pediatric oncologists, pathologists, and other specialists.
Musa, et al.: Challenges of retinoblastoma management

The treatment of retinoblastoma has changed significantly over the last four decades enabling the neoplasm to evolve from an invariably fatal tumor to a largely curable cancer. Treatment modalities currently available for retinoblastoma include focal therapy (cryotherapy, conventional laser photocoagulation, transpupillary thermotherapy, photodynamic therapy, and plaque radiotherapy), external beam radiotherapy, systemic chemotherapy, and enucleation. As a result of the advances in treatment and early presentation, survival of retinoblastoma is > 90% in developed countries. Globe-preserving treatment modalities have become the trend in recent years. This is related to earlier detection of the disease, recognition of more effective chemotherapeutic agents and more focused local treatment modalities. Chemotherapy is currently the most important treatment modality for globe salvage in retinoblastoma patients. Combination chemotherapy with vincristine, carboplatin, and etoposide is usually administered in 6 cycles, but up to 13 cycles are sometimes required to control the disease. When combined with focal therapy (multimodality approach), it is generally quite successful for less advanced tumors. Other globe-sparing therapies include periocular carboplatin, selective ophthalmic artery chemoreduction, and intravitreal melphalan. The advanced stages of retinoblastoma continue to provide the greatest difficulty for management, and external beam radiotherapy, enucleation, and exenteration are often employed in addition to chemoreduction to promote the child’s quality of life.

Therefore, this study sets out to present the clinical profile and treatment outcome of patients with retinoblastoma managed in a Nigerian tertiary eye care facility highlighting the challenges with a view to improving the management of the disease.

MATERIALS AND METHODS

A retrospective chart review of patients diagnosed with retinoblastoma at the ophthalmology outpatient clinic of Lagos University Teaching Hospital, Lagos, Nigeria, between January 2012 and December 2015 was done. Data obtained from the case files of patients include demographic characteristics of patients and their parents, presenting complaint, laterality of disease, tumor stage using the International Classification of Retinoblastoma, investigations, histopathology findings, treatment given, and outcome. The caregivers were also contacted using the documented phone numbers to ascertain the status of the patients as well as to find out the reason for their default. Data analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp: Armonk, NY, USA). The associations between continuous and categorical variables were analyzed using Student's t-test and Chi-square test, respectively. P < 0.05 was considered statistically significant. Ethical approval for this study was obtained from the Health Research and Ethical Committee of our institution.

RESULTS

This review included 54 eyes of 41 patients between the ages of 2 months and 5 years. Thirteen (31.7%) patients had bilateral retinoblastoma [Figure 1] while 28 (68.3%) had unilateral disease. The overall mean age at presentation was 24.4 ± 11.4 months. The mean age at presentation of bilateral cases was lower (21.7 ± 11.4 months) compared to unilateral cases (25.7 ± 11.4 months) as shown in Table 1. This was however not statistically significant (P = 0.30). The majority (56.1%) of the patients presented between 19 and 30 months of age. There were 18 males and 23 females giving a male-to-female ratio of 1:1.3. Although the proportion of female patients was more for bilateral retinoblastoma (69.2%) compared to unilateral cases (50%), this was not statistically significant (P = 0.21). Twenty-seven (65.9%) patients were Yoruba while 10 (24.4%) were of the Igbo ethnic group. Twenty-four (58.5%) patients were Christians while the remaining (17, 41.5%) were Muslims. The tumor was bilateral in 13 (31.7%) cases and unilateral in 28 (68.3%) cases. Of the total number of unilateral cases, 18 (64.3%) were found in the right eye while 10 (35.7%) cases involved the left eye. The time between the onset of symptoms

| Age at presentation (months) | Total | Bilateral, n (%) | Unilateral, n (%) | All cases, n (%) |
|-----------------------------|-------|------------------|------------------|-----------------|
| ≤1-12                       | 35    | 2 (5.3)          | 1 (3.6)          | 3 (7.3)         |
| 13-24                       | 16    | 5 (38.5)         | 6 (37.5)         | 21 (51.3)       |
| 25-36                       | 15    | 5 (33.3)         | 6 (21.4)         | 11 (26.8)       |
| 37-48                       | 13    | 1 (7.7)          | 4 (14.3)         | 5 (12.2)        |
| 49-60                       | 0     | 0                | 1 (3.6)          | 1 (2.4)         |
| Total                       | 77    | 22.7±11.4        | 25.7±11.4        | 24.4±11.4       |

| Sex                          | Total | Female, n (%) | Male, n (%) | All cases, n (%) |
|------------------------------|-------|---------------|-------------|-----------------|
| Female                       | 41    | 9 (21.9)      | 32 (78.1)   | 41 (100)        |
| Male                         | 13    | 4 (30.8)      | 9 (69.2)    | 13 (100)        |
| Total                        | 54    | 23 (46.3)     | 31 (53.7)   | 54 (100)        |

5D = Standard deviation
and clinical presentation ranged from 2 weeks to 2 years with a mean of 5.7 ± 5.3 months [Table 2]. This lag time in presentation was at least 1 month in 87.8% of the patients.

The mean values of the documented ages of the patient’s fathers and mothers were 37 ± 7.4 years and 30 ± 4.3 years, respectively (the ages of 13 fathers and 11 mothers were not documented). There was no known family history of retinoblastoma in any of the patients studied.

Leukocoria was the most common presenting complaint documented in 32 (59.2%) eyes followed by proptosis (12, 22.2%), ocular deviation (3, 5.6%), redness (3, 5.6%), eye enlargement (2, 3.7%), and poor vision (2, 3.9%). Groups D and E were the most common intraocular tumor stages documented in 16 (29.7%) and 15 (27.8%) eyes, respectively [Table 3]. Thirteen (24.1%) eyes had orbital involvement while one patient (2.4%) had metastatic disease. Ocular ultrasound scan was the imaging modality performed in 22 (53.7%) patients. All ultrasound scans showed intraocular calcification and tumor masses. Two patients presented with brain computed tomography (CT) scan results and only one patient had magnetic resonance imaging (MRI) done. MRI was the preferred imaging modality in the study center. There was no evidence of trilateral retinoblastoma on CT or MRI in the three patients. Abdominal ultrasound scan in the patients with metastatic disease showed liver metastasis. Twenty-nine patients (70.7%) defaulted from clinic after the first or second presentation and did not receive treatment while 10 (24.4%) commenced treatment. The remaining two (4.9%) patients requested for referral letters (one referral was to the United States of America while the other was to another teaching hospital within Nigeria due to proximity). There were no statistically significant associations between treatment uptake and gender, ethnicity, and religion with Fisher’s exact P values of 0.46, 0.44, and 0.71, respectively [Table 4]. Out of the 10 patients who commenced for the treatment, 4 (40%) had incomplete treatment while the remaining 6 (60%) completed their treatment as summarized in Table 5. Only 6 (21.4%) of 28 patients offered enucleation at presentation (Group E) or modified enucleation after chemoreduction (orbital disease) consented. There were no statistically significant associations between treatment uptake and gender, ethnicity, and religion with Fisher’s exact P values of 1, 0.14, and 0.65, respectively [Table 6]. Chemotherapy (vincristine, etoposide, and carboplatin for six courses every 21 days) was commenced in eight patients, but the recommended six courses were completed in six patients. Only 2 (20%) of the 10 patients who commenced for the treatment had globe salvage treatment. One had bilateral retinoblastoma (Group D and B) and underwent chemoreduction of tumor after which she was referred for transscleral thermotherapy in another teaching hospital. The second patient had unilateral (Group D) retinoblastoma and underwent nine courses of chemotherapy as well as radiotherapy leading to tumor regression. However, he had a relapse of the tumor 6 months after the completion of treatment and was offered enucleation but defaulted thereafter. Five of the six patients whose eyes were surgically removed had histological confirmation of retinoblastoma. The histological report of one patient who had modified enucleation was not available in the case file. Of the five available histological reports, four were moderately differentiated while one was poorly differentiated. Furthermore, the cut end of the optic nerve showed tumor cells in two histological reports while the remaining three had no involvement of the cut end of the optic nerve.

As at the time of this study, only two patients adhered to regular follow-up appointments. One of them was a 2-year-old child while the other was a 6-year-old on

### Table 2: Distribution of duration before presentation and laterality

| Duration before presentation (months) | Affected eye | All cases, n (%) |
|--------------------------------------|--------------|-----------------|
|                                     | Bilateral, n (%) | Unilateral, n (%) |
|                                      |              |                 |
| <1                                   | 1 (7.7)      | 4 (14.3)        | 5 (12.2) |
| 1-6                                  | 7 (53.8)     | 15 (53.5)       | 22 (53.6) |
| 7-12                                 | 2 (15.4)     | 8 (28.6)        | 10 (24.4) |
| >12                                  | 3 (23.1)     | 1 (3.6)         | 4 (9.8)  |
| Total                                | 23 (100)     | 28 (100)        | 41 (100) |
| Mean±SD                              | 6.5±7.6      | 5.3±4           | 5.7±5.3  |

SD=Standard deviation

### Table 3: Retinoblastoma grading of 54 eyes at presentation

| Retinoblastoma staging | Frequency (%) |
|------------------------|---------------|
| Group A                | 1 (1.8)       |
| Group B                | 2 (3.7)       |
| Group C                | 6 (11.1)      |
| Group D                | 16 (29.7)     |
| Group E                | 15 (27.8)     |
| Orbital disease        | 13 (24.1)     |
| Metastatic disease     | 1 (1.8)       |
| Total                  | 54 (100)      |

### Table 4: Associations between demographics and treatment uptake

| Demographics | Treatment uptake | P     |
|--------------|------------------|-------|
| Gender       |                  |       |
| Male         | Yes, n (%)       | 37.6  |
| Female       | No (defaulted), n (%) | 14 (82.4) | 17 (100) | 0.46* |
| Ethnicity    |                  |       |
| Yoruba       | Yes, n (%)       | 5 (20) |
| Non-Yoruba   | No (defaulted), n (%) | 5 (80) | 25 (100) | 0.44 |
| Religion     |                  |       |
| Christianity | Yes, n (%)       | 7 (29.2) |
| Islam        | No (defaulted), n (%) | 3 (70.8) | 24 (100) | 0.71* |

*Two patients who asked for referral were excluded, †Fisher’s exact
3 monthly and yearly examination under anesthesia, respectively. In March 2017, the caregivers were contacted using the documented phone numbers to ascertain the status of the patients as well as to find out the reason for their default. Sixteen (39%) phone lines were inactive, 11 (26.9%) patients were still alive, and unfortunately, 14 (34.1%) patients were dead. The reasons for default are shown in Table 7. The results of the Kaplan–Meier estimates of survival of treatment default are shown in Table 8. About two-thirds (65.9%) of patients defaulted from treatment within 1 week while about a quarter (24.2%) were retained in care at 10 weeks.

**DISCUSSION**

Approximately 80% of children with retinoblastoma are diagnosed before 3 years of age and the diagnosis of retinoblastoma in children 6 years or older is extremely rare. This compares favorably with the finding in this study where 85% of the patients presented before the age of three and the oldest age at presentation was 5 years. Furthermore, 32% of the patients in this study had bilateral retinoblastoma. This is similar to the observations of Ajaiyeoba et al., Lim et al., and Subramaniam et al. However, lower proportions of bilateral disease were recorded in other studies in Nigeria. The mean age at presentation of 24.4 months in this study is lower than the findings from previous Nigerian studies. This could be due to the higher prevalence of bilateral disease in our study population. Patients with bilateral disease usually present at a younger age than patients with unilateral disease. However, similar age at presentation (25.7 months) was observed in Singapore where bilateral disease was recorded in 31.4%. In developed countries, the mean age of diagnosis is <24 months. In approximately 20% of children diagnosed with bilateral retinoblastoma, there is a family history of the disease. There was no family history of retinoblastoma in our study. This disparity may be due to the possibility that these patients with retinoblastoma almost invariably succumb to the disease without an opportunity to transmit the gene as opined by Kaimbo et al. who documented similar findings in Congo.

There were 18 males and 23 females giving a male-to-female ratio of 1:1.3. Although the proportion of female patients was more for bilateral retinoblastoma (69.2%) compared to unilateral cases (50%), this was not statistically significant (P = 0.21). Owoeye et al. and Abdu and Malami also reported female predilection while Adio and

### Table 5: Treatment extent and outcome among 10 retinoblastoma patients

| Treatment extent                                      | Remark          | Alive/Dead | Frequency (%) |
|-------------------------------------------------------|-----------------|------------|---------------|
| Chemotherapy only (3-4 courses then defaulted)        | Incomplete      | Dead       | 2 (20)        |
| Chemotherapy + transpupillary thermotherapy (another hospital) | Complete        | Alive      | 1 (10)        |
| Enucleation + chemotherapy                            | Complete        | Alive      | 3 (30)        |
| Enucleation + chemotherapy + radiotherapy             | Complete        | Alive      | 1 (10)        |
| Enucleation then defaulted                            | Incomplete      | Dead       | 1 (10)        |
| Modified exenteration then defaulted                  | Incomplete      | Inactive phone lines | 2 (10)        |
| Chemotherapy + radiotherapy                           | Complete        | Alive      | 1 (10)        |
| Total                                                 |                 |            | 10 (100)      |

### Table 6: Associations between demographics and enucleation/modified exenteration uptake

| Demographics | Enucleation/modified exenteration uptake | P*  |
|--------------|-----------------------------------------|-----|
| Gender       | Yes, n (%)                              |     |
| Male         | 2 (20)                                  | 1   |
| Female       | 4 (22.2)                                |     |
| Ethnicity    | Yes, n (%)                              |     |
| Yoruba       | 3 (14.3)                                | 0.14|
| Non-Yoruba   | 3 (42.9)                                |     |
| Religion     | Yes, n (%)                              |     |
| Christianity | 4 (26.7)                                | 0.65|
| Islam        | 2 (15.4)                                |     |

Table 6: Associations between demographics and enucleation/modified exenteration uptake

### Table 7: Information obtained from phone calls to the caregivers

| Outcome                              | Frequency (%) |
|--------------------------------------|---------------|
| Inactive phone lines                 | 16 (39)       |
| Sought second opinion but patient is dead | 3 (7.3)   |
| Patient is dead and did not need further conversation | 11 (26.8)
| Attending follow-up clinic           | 2 (4.9)       |
| Patient is fine and no need for follow-up | 4 (9.8)  |
| Patient is fine but caregivers have relocated | 2 (4.9)  |
| Patient is fine but being followed up in another hospital | 2 (4.9)  |
| Patient is alive but caregivers have no money for surgery | 1 (2.4)  |
| Total                                | 41 (100)      |

### Table 8: Kaplan-Meier estimates of survival (from default to treatment)

| Interval start time (weeks) | Number remaining | Cumulative event (defaulted) | Cumulative survival (S) | SE | Cumulative F[=1-S] |
|---------------------------|------------------|-----------------------------|-------------------------|----|-------------------|
| 0                         | 41               | -                           | -                       | -  | -                 |
| 1                         | 27               | 14                          | 0.659                   | 0.074 | 0.341           |
| 2                         | 19               | 20                          | 0.500                   | 0.080 | 0.500           |
| 3                         | 15               | 24                          | 0.395                   | 0.078 | 0.605           |
| 4                         | 11               | 27                          | 0.310                   | 0.075 | 0.690           |
| 6                         | 10               | 28                          | 0.282                   | 0.074 | 0.728           |
| 10                        | 6                | 29                          | 0.242                   | 0.073 | 0.758           |

SE=Standard error
and Ibadan. However, in developing countries, the 5‑year survival rate is still very low.\(^\text{[23]}\) In this study, only 24.2% of patients were retained in care at 10 weeks. A limitation of this study is the inability to analyze the reasons for late presentation as these were not clearly documented in most of the case folders.

**CONCLUSION**

Late presentation of retinoblastoma with advanced disease was frequent in this study making globe salvage difficult. Furthermore, high default rates coupled with noncompletion of treatment were the major challenges facing retinoblastoma management in this center. In the light of the foregoing, there is a need for a robust awareness campaign on the signs and symptoms of retinoblastoma, stressing the need for early presentation as well as treatment adherence in a bid to stem the tide of avoidable mortality from retinoblastoma. In addition, there is a need for a prospective, multicenter study on retinoblastoma to generate data that can be used as a strong advocacy tool to attract the attention of government and nongovernmental organizations to the need to confront this most common intraocular childhood malignancy.

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**Conflicts of interest**

There are no conflicts of interest.

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Over 70% of the patients defaulted from the clinic after one or two presentations. High rates of default were also reported in Kano\(^\text{[21]}\) and Ibadan.\(^\text{[21]}\) This highlights yet another challenge in the management of retinoblastoma in Nigeria. Surgical eye removal (enucleation/modified exenteration) with adjuvant chemotherapy/radiotherapy was the main treatment modality in this study due to late presentation. In fact, the two patients who had incomplete chemotherapy were being worked up for enucleation after chemoreduction but they defaulted. High rates of enucleation have also been reported in studies done in other parts of Nigeria\(^\text{[26,29‑30]}\) and Asia.\(^\text{[18,19,25]}\) Furthermore, there was a low uptake of surgical eye removal in this study as only 21.4% consented. Similar experiences were documented in Port Harcourt\(^\text{[22]}\) and Ibadan.\(^\text{[23]}\)

A survival rate of 97% had been reported in the United Kingdom\(^\text{[31]}\) and more than 93% in the United States.\(^\text{[32]}\) However, in developing countries, the 5‑year survival rate is still very low.\(^\text{[23]}\) In this study, only 24.2% of patients were retained in care at 10 weeks. A limitation of this study is the inability to analyze the reasons for late presentation as these were not clearly documented in most of the case folders.

Another 9-month-old male patient with bilateral retinoblastoma. Figure 1: A 9-month-old male patient with bilateral retinoblastoma.
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