Original Article

Modes of Presentation, Management and outcome of Retinoblastoma Treatment at University Teaching Hospital

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ABSTRACT

***Objectives**:* To establish the presentation, management and short-term outcomes of retinoblastoma treatment at UTH from January 2006- December 2012.

***Method**:* This was a retrospective case series study of the modes of presentation, management of retinoblastoma and treatment outcomes 6 months after initiation of treatment at UTH from January 2006- December 2012. The data was collected from registers for the eye unit inpatient and outpatient, histopathology laboratory, pediatric oncology department as well as patients' files. The data collected included demographics, clinical presentation, histopathology reports, treatment modalities, and treatment outcome at 6 months after initiation of treatment. The statistical analyses were performed using the statistical package SPSS version 20.

Results: There were 57 African participants in the study of which 26 (45.6%) were males and 31 (54.4%) were females. The youngest was 0.75 months old while the oldest was 132 month old. The average age of the participants was 31.1 months old (with a standard deviation of 21.96). The average time lag from the onset of symptoms to treatment at UTH was 9.27 months with a minimum of one month and a maximum of 36 months. 71.2% had unilateral retinoblastoma, 28.8% had bilateral retinoblastoma however no trilateral retinoblastoma was observed. The most common presentations were proptosis (47.3%), leukocoria (36.8%), phthisis bulbi (4%), hyphema (2%), orbital cellulitis (1%) and uveitis (1%). The common treatment regimens were enucleation and chemotherapy (28.8%), exenteration and chemotherapy (15%), enucleation, chemotherapy and radiotherapy (3.4%). Moreover, 8.5% had enucleation only whilst 3.4% had exenteration, chemotherapy and radiotherapy treatment regimen. In the study, the treatment outcomes 6 months post initiation of treatment were abandoned treatment 17.5%, while 49.2% died and 33.3% were alive.

Conclusion: The common presentation was proptosis (47.3%) and leukocoria (36.8%). The most common treatment outcome was death, alive followed by abandonment treatment. Treatment was completed in 22% of the participants. Delay in diagnosis of retinoblastoma remains a challenge as seen in the study by the high mean lag time and late presentation. The diagnosis of retinoblastoma from the referral centers was accurate in 50 % of the patients. Awareness of retinoblastoma to primary health care givers and parents will help to improve early referrals. Further, we recommend the integration of knowledge of retinoblastoma into the curriculum of primary health care giver to facilitate quick referral of patient.

INTRODUCTION

Retinoblastoma is the most common primary ocular malignancy of childhood. The incidence of retinoblastoma is reported to ranges from 1:10 000 in South Africa to 1:34 000 in the Netherlands.[1] In Zambia, a study done by Chintu *et al* showed that the most common cancer in children was Lymphoma (36.95%) followed by

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retinoblastoma (12.46%) and Kaposi sarcoma (12.17%). There has been a statistically significant increase in the incidence of retinoblastoma during the HIV period. Apart from this no other difference in the epidemiological features has been noted. The age ranged from 3 months to 10 years, with an average of 3.35 years. The male to female ratio was 1.3:1. Most of the patients were diagnosed after their first birthday.[2] Various studies reveal no significance difference in male and female ratio.[3]

Over 95% of children with retinoblastoma in developed countries survive the malignancy whereas in developing countries survival is as low as 6.8%.[4] The reason for this difference in survival rate in developed countries has been attributed to early detection and prompt treatment of retinoblastoma while the tumour is still intraocular. In developing countries, 90% of patients with retinoblastoma present with extra-ocular disease due to late recognition and presentation. Several other factors play a role in late presentation resulting in poor prognosis due to high mean age at diagnosis, the interval between the onset of symptoms and treatment (lag-time). This delay in diagnosis is also attributed to lack of knowledge by parents and primary health care professionals resulting in late referral to tertiary hospital.[5]

The management of retinoblastoma requires a multi-disciplinary team of an ophthalmologist, paediatric oncologist, paediatric radiation oncologist, pathologist, nurse and social worker. The most important objective in the management of a child with retinoblastoma is survival of the patient, and the second most important goal is preservation of the globe. Treatment modalities include surgery, chemotherapy and radiotherapy. The major challenge faced in treating children with retinoblastoma includes refusal and abandonment of treatment. In some cases patient refuse treatment and seek traditional and spiritual remedies while the tumor remains unchecked.[5] Thus temporal refusal has resulted in delay in treatment. The rate of 69.2% intra-ocular tumors at first admission versus only 15.4% at readmission and 30.8% extra-ocular tumors at first admission versus 73.1% at readmission shows significant inverse correlation between the delay caused by therapy refusal and progression to the extra-ocular stage of the tumors.[6]

Approximately 25% of cases of retinoblastoma are found in Africa however the outcome and survival of patients is poor.[7] Retinoblastoma is curable tumor if it is diagnosed early. The treatment of retinoblastoma is highly dependent on modes of presentation, timely diagnosis and advancement of the disease.

This study looked at the modes presentation, management of retinoblastoma and treatment outcome 6 months after initiation of treatment at university teaching hospital in Lusaka.

METHODOLOGY

This was a retrospective case series study of the patients who were diagnosed with retinoblastoma at UTH in pediatric oncology and eye unit in departments of pediatrics and surgery respectively from January 2006-December 2012. The Data was collected from the patients' files, histopathology reports, pediatric oncology and eye unit registrars. The data collected included demographics, clinical presentation, pathology reports, treatment modalities and treatment outcome at 6 months after initiation of treatment. The patients included in the study had a clinical diagnosis of retinoblastoma, below the age of 15 years and /or histological diagnosis of retinoblastoma. The exclusion criteria were missing records and unclear diagnosis of retinoblastoma. Ethic approval was obtained from UNZABREC. A waiver of ethics of review was obtained, as there was no interaction with the patients during this study. The statistical analyses was performed using statistical package STATA version 12 (StataCorp, college station, TX, USA).

RESULTS

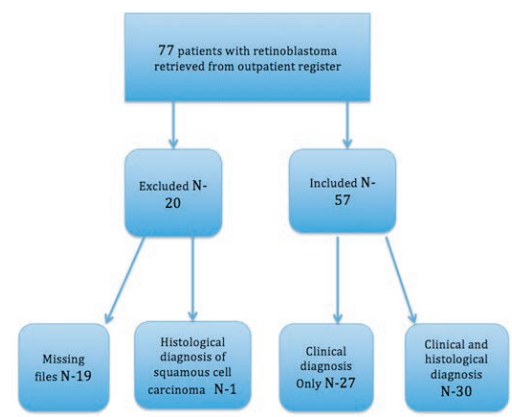

Figure 1 - PATIENT FLOW DIAGRAM

Distribution of cases by province

Thirty (51.1%) came from provincial hospitals, 17 (29.3%) came from district hospitals, 6 (10.3%) came from health centers, 3 (5.2%) were self-referrals, and 2 (3.4%) were from private hospitals. The majority of the patient from the district hospitals came from Southern province followed by Central and Northern province. Seventeen (29.3%) came from Southern Province, 8 (13.8%) each came from Western, Central, and Lusaka Provinces, 6 (10.3%) came from Eastern Province, 5 (8.6%) each came from Northern and Luapula Provinces, and 1 (1.7%) came from Copperbelt Province.

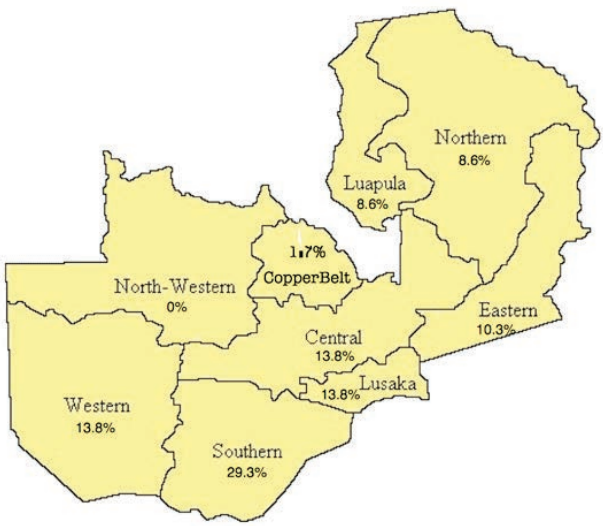

Figure 2: the map of Zambia showing frequency of retinoblastoma by province

Demographic characteristics

All the cases were African. Twenty-six (45.6%) were males while 31 (54.4%) were females. The youngest was 0.75months old while the oldest was 132 months old. The average age of the participants was 31.1 months old (with a standard deviation of 21.96). The mean age was 9.27 months

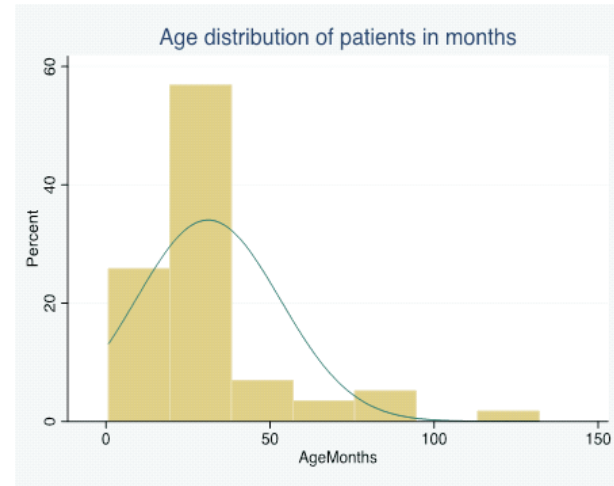

Figure 3: AGE DISTRIBUTION OF PARTICIPANTS

Age in months
Minimum: 0.75 months
Maximum: 132 months
Mean: 9.27 months
Median: 25.5 months
25-75% percentile - 19-36

MODES OF PRESENTATION

71.2% had unilateral retinoblastoma, 28.8% had bilateral retinoblastoma however no trilateral retinoblastoma was observed. The most common presentations were proptosis (47.4%), leukocoria (36.8%), phthisis bulbi (4%), hyphema (2%), orbital cellulitis (1%) and uveitis (1%).

Table 1: MODES OF PRESENTATION

Presentation	Number of eyes	Percent (%)
Proptosis	45	47.37
Leukocoria	35	36.84
Phthiscal eye	4	4.21
Anterior staphyloma	3	3.16
Hyphema	2	2.11
Fungating mass	2	2.11
Bone prominence in skull	1	1.06
Hypopion	1	1.06
Orbital cellulitis	1	1.06
Uveitis	1	1.06
TOTAL	96	100

LAG-TIME

The average time lag from the referral institution to UTH was 9.27 months with a minimum of one month and a maximum of 36 months.

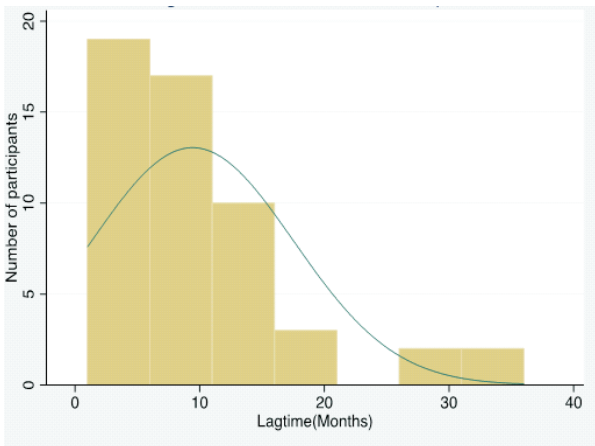

Figure 4: LAGTIME DISTRIBUTION OF THE CASES

Lag time in months

Minimum	:	1
Maximum	:	36
Mean	:	9.3
Median	:	7

INVESTIGATION

57.6% of the patients had Examination Under Anesthesia (EUA) of the fundus that confirmed retinoblastoma, however no staging and details of high risk were provided in the patients records.

The following types of investigations were conducted at UTH and confirmed the likelihood of retinoblastoma. Thirty-four (57.6%) were CT-Scan, 23 (39.0%) were ultrasound, and 4 (7.5%) were skull X-Rays. The imaging studies showed intraocular mass with calcification thus confirming the likelihood of the diagnosis of retinoblastoma. No MRI was conducted.

Histological diagnosis

In the study, 30 cases had histological results, 10 cases had missing results and 17 were clinically diagnosed because of disease advancement. The cases that had histological diagnosis included the following; 26.7% were reported to have optic nerve involvement, 40 % had a diagnosis of retinoblastoma, 26.7% had a diagnosis of retinoblastoma with optic nerve clear of tumor whilst 6.7% were well-differentiated retinoblastoma.

TREATMENT ADMINSTERED AND TREATMENT OUTCOME

The majority of the patients received surgical based treatment regimen that included: enucleation and chemotherapy regimen (28.8%), exenteration and chemotherapy (15.3%) and enucleation only (8.5%). Patient that received chemotherapy regimen only (22.1%)were receiving neo-adjuvant chemotherapy and died before any surgical management could be initiated. One patient did not receive any treatment as guardians refused the treatment option offered (enucleation) and later abandoned treatment. Radiotherapy was administered in 10.2 % of the patients; moreover, this was in combination with enucleation and chemotherapy (3.4 %) or exenteration and chemotherapy (3.4%). Treatment was completed in 22.8% of the cases and was in complete in 75.4 % of the cases. In the study, the treatment outcomes 6 months post initiation of treatment were abandoned treatment 17.5%, while 49.2% died and 33.3% were alive.

Table 2: TREATMENT REGIMEN AND OUTCOME

Treatment regime	Treatment out come			Total
	Died	Alive	Abandoment	
Enucleation,chemotherapy	10	5	2	17
Chemoreduction	6	1	0	7
Exenteration, chemotherapy	6	0	3	9
Exenteration,chemotherapy, radiotherapy	1	2	1	4
Chemotherapy	2	3	0	5
Enucleation only	1	2	2	5
Enucleation,exenteration,chemotherapy	1	0	0	1
Exenteration only	1	0	1	2
Enucleation,chemoreduction	0	1	0	1
Chemoreduction, enucleation,chemotherapy	0	1	0	1
Enucleation,chemotherapy, radiotherapy	0	2	0	2
Exenteration,radiotherapy	0	1	0	1
Chemotherapy, radiotherapy	0	1	0	1
None	0	0	1	1
Total	28	19	10	57

Most death occurred in patients who had following treatment regime administered: enucleation, chemotherapy regimen (10) and exenteration, chemotherapy regimen (6)

Table 3: TREATMENT OUTCOME

	Number of children	Percentage
Died	28	49.2
Alive	19	33.3
Abandoned	10	17.5
Total	57	100

Table 4: TIME TAKEN IN DAYS BEFORE THE ABANDONMENT OF TREATMENT

	N	Minimum	Maximum	Mean	Std. Deviation
Time taken before outcome (in days)	10	8	186	107.6	68.14

Table 5: ABANDONMENT OF TREATMENT AND DISTRIBUTION PER PROVINCE

	Number of patients	Percent
Northern	1	10.0
Western	2	20.0
Central	3	30.0
Southern	2	20.0
Eastern	2	20.0
Total	10	100.0

There was no patient from Lusaka province, Luapula province who abandonment treatment. The majority of the patients come from Central (30%), Southern (20%), Western (20%) and Eastern provinces (20%).

DISCUSSION

DEMOGRAPHIC CHARACTERISTICS OF CASES

Fifty-seven African patients were included in the study with a male to female ratio of 1:1.2. The youngest was 0.75 months and the oldest was 132 months with a mean age 31.1 months and standard deviation of 21.96. In Brazil, the oldest child was 144 months, which was slightly lower than what was noted in the study.[8] However, our findings were similar to Gunalp *et al* in Turkey where the youngest patient was 0.66 months and oldest was 192 months.[9] In contrast to this study, in Nigeria, the minimum age at presentation was 4 months and the maximum age was 60 months (mean 30.69±14.2 months).[10]

CLINICAL PRESENTATION OF RETINOBLASTOMA

In the study, the common presentation was proptosis with 47.3%. Proptosis is a feature of late presentation. Proptosis as presenting sign was also a common finding, in other developing countries including: Nigeria (84.6%), Zimbabwe (65%), Pakistan (52.2%), and India (25.5%).[11, 12, 13] These study findings are likely to be due to delayed presentation of patients. In contrast to the developed countries where proptosis as presenting sign was a rare occurrence: USA (0.5%) and South Korea (1.4%).[13]

Leukocoria as presenting sign in the study was 36.8%, which was of low frequency as compared to other countries: Ghana (87%) and China (77.1 %).[14,15] With the majority (70.2%) presenting with unilateral eye involvement, the study findings were similar to those of Congo (79%).[16]

LAG-TIME

The average lag-time (from onset of symptoms to initiation of treatment) was 9.27 months with a maximum of 36 months. The lag time in the study was much higher than that reported in several studies.[17,18] However, in a study done in Tanzania, the mean lag time was 10 months which was slightly higher than that attained in the study.[19] It was noted in Honduras, that awareness campaigns increased the number of patients being referred to the paediatric oncology unit and a decrease in lag time (from 7.2 months to 5.5 months).[20] In order to achieve early detection of retinoblastoma, it is important that the first contact physicians and healthcare workers are able to recognize the common signs and symptoms of retinoblastoma early resulting in prompt referral. In the study, it was noted that the diagnosis of retinoblastoma from the referral centers accurate in 50.8% of the participants while 43.9% were inaccurate. Leal *et al* found that in developing countries an important factor that contributed to delay in diagnosis was lack of knowledge of the disease.[21] The Zambian health delivery comprises of a three level health care systems, which

includes District, Provincial and Central hospitals. Patient with retinoblastoma pass through the established referral system prior to procuring definitive treatment at UTH. Going by the study findings, the referral system in its current form is fraught with impediments that delay the speed of access to definitive treatment for retinoblastoma.

INVESTIGATIONS

EUA of the fundus confirmed the likelihood of the diagnosis of retinoblastoma, however, the medical records lacked the staging of retinoblastoma and there was no mention on high-risk features. This was similar to a study done in Sudan where EUA findings were not comprehensive and lacking high-risk features.[22] There was no record of ICRB but it is important in predicting of chemoreduction and focal therapies. Thus, in our setting a comprehensive EUA with ICRB staging will help in offering the best treatment options for retinoblastoma patients.

The imaging studies done at UTH included CT scan (57.6%), ocular ultrasound (39.0%) and skull X-ray (4%) demonstrated features consistent with the diagnosis of retinoblastoma. However, MRI was not available at UTH during the period of this study. Brisse *et al.* demonstrated that CT Scan sensitivity was very low even in patients with marked optic nerve invasion. Whilst, MRI was 60% sensitive to detect post laminar invasion in the normal sized optic nerve and had 95% Negative predictive value (NPV). Further, MRI reduces the risk of second tumors by avoiding ionizing radiation and has high resolution for soft tissue contrast.[23] MRI is now available at UTH, thus MRI should used in investigation of retinoblastoma patients as will give us important details of post laminar invasion of optic nerve.

HISTOLOGICAL DIAGNOSIS

The histological diagnosis is important informing retinoblastoma therapy decision. In 52.5% of sample population had a histological diagnosis of retinoblastoma. Of those who had histological diagnosis 40% had diagnosis of retinoblastoma that was incomplete without comment of optic nerve status and no mention of differentiation of the tumor. A general comment of retinoblastoma with optic nerve involvement was made on 26.7% of the specimens, this was much lower in our study than reported by Biswas *et al* from India (32.3%) and Badhu *et al* (37%) from Nepal.[24,25] Eye pathology examination done by experienced ocular pathologists is critical for identifying high-risk patients. High risk for extra-ocular recurrence on histopathological examination of enucleated eyes, include invasion of the post-laminar optic nerve, choroid, sclera and in some studies, involvement of the anterior chamber has also been considered high risk.[26,27,28] In developing countries, it is estimated that the extra-retinal extension to the outer layers of the affected eye occurs in 50% of the cases.[29]

TREATMENT OUTCOME

At to 6 months follow up 49.4% of participants died, 23.7% were alive and 17% had abandoned treatment. Abandonment of treatment was a challenge and was similar to several studies.[30,10] In this study, Abandonment of treatment occurred at an average time of 107.6 days, the earliest to have abandoned treatment was at 8 days and the latest was 186 days. The majority of the patients that abandoned treatment were from Central province. Abandonment of treatment can be attributed to lack of knowledge on retinoblastoma by the parents, long hospital stay and financial constrains. In a study conducted at UTH under the paediatric oncology unit from 2008 to 2010, Slone *et al* demonstrated that about 45% of the patient abandoned treatment and this was alluded to the distant from the treatment center. Close proximity to the treatment center was associated with a decreased risk of abandonment of treatment. Further, distance played a role in delaying the initial presentation of children who eventually abandon treatment.[31] In Nigeria, abandonment of treatment was attributed to social and economic constrains[32]. In Malawi, absence of the guardian from home and the extra cost of hospital stay were the reasons for abandoning treatment.[33]

Death from retinoblastoma was the most common outcome in this study. Almost half of the entire study population patients died. This poor outcome can be attributed to several challenges that have been noted in this study. Firstly, the lack of knowledge on retinoblastoma by the primary health care workers who are first contact in the referral chain in Zambia could have resulted in late presentation, high lag-time and delay in diagnosis. Secondly, lack of comprehensive staging work

up, incomplete pathological reports, and absence of a team approach to management of retinoblastoma were noted in this study. These challenges can be overcome by early detection campaigns to parents and primary health care workers. Reduction in lag time was achieved through awareness programs has resulting in as seen in several studies.[23,34] Twinning with developed countries to facilitate mentorship and supervision as seen in Jordan where twinning had a positive impact on survival and ocular salvage was noted.[35] Further, a multidisciplinary team approach is paramount to the successful treatment of retinoblastoma at UTH.

CONCLUSION

The common presentation was proptosis with 47.3%, leukocoria with 36.8% and phthisis bulbi with 4%. The most common treatment outcome was death, alive followed by abandonment treatment. Treatment was completed in 22% of the participants. Delay in diagnosis is a challenge as seen in the study by the high mean lag time and late presentation. Further, the diagnosis of retinoblastoma from the referral centers was accurate in 50 % of the patients. Awareness of retinoblastoma to the primary health care givers and parents will help to improve early referrals.

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