

PRESENTATION OF RETINOBLASTOMA AT A PAEDIATRIC EYE CLINIC IN GHANA

V. ESSUMAN¹, C. T. NTIM-AMPONSAH¹, S. AKAFO¹, L. RENNER² and L. EDUSEI³
¹Ophthalmology Unit, Department of Surgery, ²Department of Child Health, and ³Department of Pathology
 University of Ghana Medical School, PO Box 4236, Accra, Ghana

Corresponding Author: Dr. Vera Essuman

E-mail: vadessuman@yahoo.com

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SUMMARY

Background: Retinoblastoma, the commonest childhood malignant intraocular tumour, is usually diagnosed early with over 90% survival rate in developed countries. In developing countries, the diagnosis is late resulting in less than 50% survival.

Objective: To determine retinoblastoma stages at presentation and patients' outcomes.

Design: Retrospective case series.

Methods: The clinical and histopathological records of children with retinoblastoma seen from May 2004 to December 2005 were studied. Data was analysed for mode of presentation, laterality, clinical staging using Reese-Ellsworth (R-E) classification, histopathological high risk features (HHRF) for metastasis, and patient outcome.

Setting: Ophthalmology Unit, Korle-Bu Teaching Hospital, Ghana.

Results: Twenty-three patients presented with retinoblastoma over the period. Males were 12(52.2%). The age range from 1 to 84 months, mean 36.3(±22.15) and median (36 months). Nineteen (82.6%) had unilateral and 4(17.4%) bilateral disease. The common clinical presentations were leukocoria in 20(87.0%), proptosis 8(34.8%), strabismus 5(21.7%) and red eye 5(21.7%). The clinical features were commensurate with R-E stage V in 20(87.0%) patients, 2(8.7%) with orbital recurrence and 1(4.3%) with post-enucleation anophthalmos. HHRFs were present in 9(75%) enucleated eyes with invasion of optic nerve as the commonest site (7/9). The patients were followed up for 1 day to 19 months. Eight abandoned treatment, 2 were discharged for palliative treatment, 2 out of 5 with metastasis died and 6 had no metastases at their last visit. Common sites for metastasis were the bone marrow, brain and orbit.

Conclusion: Majority of the patients presented with advanced disease manifesting as leukocoria, proptosis, RE stages V disease and poor outcome.

Keywords: leukocoria, metastasis, Reese-Ellsworth, retinoblastoma, tumour.

INTRODUCTION

Retinoblastoma is the commonest intraocular tumour in childhood affecting about 1 child in 20,000.¹ It accounts for about 3% of cancers in children younger than 15 years of age.¹ Untreated, retinoblastoma is almost uniformly fatal,² but with availability of resources for early detection and treatment, the survival rate has improved from approximately 30% in the 1930s to over 90% in the 1990s in developed countries.^{3,4,5,6} However, in developing countries, the majority of patients with retinoblastoma present with advanced disease with the resultant 5 year survival of less than 50%.^{7,8,9}

The factors for this poor prognosis may include late presentation with a high mean age at diagnosis,^{10,11} interval between onset and treatment of more than 5 months, a lag time before treatment exceeding 2.5 months, extraocular disease,¹² higher occurrence of poorly differentiated tumours,¹³ presence of other histopathological high risk features (HHRF) for metastasis, and other factors such as lack of knowledge about the disease and its outcome, high costs of hospital care (diagnosis and treatment), and lack of resources for care. Improvement in survival in developing countries will require measures that enhance early reporting through health education,¹⁴ early and cheaper means of screening those at risk and early diagnosis of affected patients, as well as early, affordable and effective forms of treatment including means of funding such as national health insurance or government-funded schemes.^{15,16,17}

At the Paediatric Department of Ghana's premier teaching hospital, Korle Bu Teaching Hospital, Accra, retinoblastoma was found to be the second commonest childhood tumour after Burkitt's lymphoma.¹⁸ Retinoblastoma was the commonest malignant intraocular childhood cancer seen at the Eye Clinic of the same hospital, and as elsewhere, and formed about 50% of ocular tumours seen at the clinic.¹⁹ Only about 38% of the retinoblastomas were diagnosed before the age of 3 years.¹⁹

Unfortunately over a decade after this study, anecdotal observations showed that children with retinoblastoma attending the same clinic were increasingly presenting late with advanced disease and fatal outcomes and there had been no active intervention to address this trend.

As survival in patients with retinoblastoma is inversely related to the stage of the disease at presentation,²⁰⁻²⁴ we carried out this study to determine the stages of retinoblastoma in our patients at presentation and their relation to outcome. This will serve as baseline data for further studies and help plan interventions for improvement in survival.

MATERIALS AND METHOD

A retrospective case series of all children seen at the Korle-Bu Teaching Hospital Eye unit with a diagnosis of retinoblastoma, from May 2004 to December 2005, was determined from clinical and histopathological records of the hospital. Data was compiled on demographic characteristics, clinical examinations, investigations, histopathology findings, treatment given and their outcomes. The information was recorded on pre-designed forms.

The initial evaluation of the children included complete ophthalmological and systemic examination in collaboration with the Paediatric Oncology Unit. The ophthalmological evaluation included visual acuity, slit lamp examination and dilated-fundus examination with scleral indentation under general anaesthesia. The systemic evaluation included full blood count, lumbar puncture for cerebrospinal fluid (CSF) cytological analysis, bone marrow aspirations for tumour cells, chest x-rays and examination for other evidence of metastases.

The basis of diagnosis of retinoblastoma was: a leukocoria associated with a retinal mass, with chalky areas, blood vessels coursing over it, with or without subretinal fluid, and or a proptosis preceded by a history of a 'cat's eye' or a shiny white spot in the eye. This was with or without confirmation by imaging studies i.e. C.T. scan or ultrasonography, looking for presence of calcifications in an intraocular mass arising from the retina. The clinical diagnosis could not be confirmed by imaging studies in some patients as they were not affordable to their carers. Treatment given included enucleation alone, chemotherapy and enucleation, or combined chemotherapy, enucleation and external beam radiation. Chemotherapy included vincristine, etoposide, carboplatin or cyclophosphamide and intrathecal methotrexate when indicated according to a local protocol.

Data was analysed for mode of presentation, laterality, clinical staging of disease using Reese-Ellsworth (R-E) classification (Box 1), presence of HHRF for metastasis in enucleated eyes and patient outcome.

Box1 Reese-Ellsworth Classification for Retinoblastoma²⁵

Group I	a. Solitary tumor, less than 4 disc diameters in size, at or behind the equator b. Multiple tumors, none over 4 disc diameters in size, all at or behind the equator.
Group II	a. Solitary tumour, 4 to 10 disc diameters in size, at or behind the equator. b. Multiple tumors, 4 to 10 disc diameters in size, all at or behind the equator.
Group III	a. Any lesion anterior to the equator. b. Solitary tumor larger than 10 disc diameters in size behind the equator.
Group IV	a. Multiple tumors, some larger than 10 disc diameters. b. Any lesion extending anterior to the ora serrata.
Group V	a. Massive tumors involving over half the retina. b. Vitreous seeding.

HHRF were uveal infiltration involving the iris, ciliary body or choroid, anterior chamber seeding, scleral or extra scleral infiltration and optic nerve invasion i.e. lamina cribrosa, retrolaminar or transection margin of optic nerve.

Patient outcome was defined as alive with metastases, without metastases or with second malignant neoplasm; or dead with metastases, with second malignant neoplasm or from other causes.

RESULTS

Twenty-three patients were seen with retinoblastoma within this 20 month period. The male:female ratio was 1.1:1. The age ranged from 1 to 84 months, with a mean of 36.3 (± 22.15) months and median of 36 months. Nineteen (82.6%) patients had unilateral and 4(17.4%), including a neonate, had bilateral disease. There was no trilateral retinoblastoma seen). With regards to the bilateral cases, the parents of only one patient could be examined in an attempt to determine the inheritance pattern. They had normal ocular findings. The parents of the other 3 children abandoned treatment of their children as soon as the diagnoses were confirmed and counseling on the disease and its management offered. Hence the inheritance pattern could not be ascertained.

The common presentations were leukocoria 20 (87.0%), proptosis 8 (34.8%), strabismus 5 (21.7%) and red eye 5 (21.7%). Other presentations included fungating and necrotic orbital mass 2 (8.7%), buphthalmos with enlarged and cloudy cornea 2 (8.7%) flat anterior chamber 3 (13.1%), rubeosis 1 (4.4%), and hyphaema 1 (4.4%).

Table 1 Baseline Characteristics of Patients with Retinoblastoma

Total number	23
Interval between enucleation & metastasis (mths)	
Range, Mean, SD	0.2-7, 5.72, 2.71
Investigations	
CT Scan confirmation of diagnosis (n=13)	
- intraocular	9 (69.2%)
- extraocular (Optic Nerve.& Brain)	4 (30.8%)
Ultrasonography (B mode)	
- intraocular (n=1)	1
Bone Marrow infiltration (n=7)	4 (57.1%)
CSF (normal) (n= 4)	4 (100%)
Initial Treatment given 12 patients	
Primary enucleation	7 (58.3%)
Chemoreduction +Enucleation	4 (17.4%)
Chemoreduction + Eucleation + EBRT	1 (4.3%)
Histopathological High Risk Features (in 12 enucleated eyes)	
Presence of risk factors	9 (75%)
Unknown	1 (8.3%)
No Risk Factors	2 (16.7%)

Twenty patients (87.0%) presented with R-E stages V: 3 with Va, 11 with Vb and 6 with Vb with orbital inflammation or extension; 2 (8.7%) others presented with orbital recurrence and 1 (4.3%) with post-enucleation anophthalmos after treatment elsewhere with histology proven diagnosis.

Results of investigations for confirmation of diagnosis and for metastases are as illustrated in Table 1.

One or more HHRF for metastasis were present in 9 (75%) of the 12 enucleated eyes: invasion of optic nerve 4 including 1 transection margin, uveal infiltration 1, combined optic nerve and uveal infiltration 2, extra-scleral and orbital fat extension 1, and combined extra-scleral, uveal and optic nerve invasion 1.

Seven of the enucleations were primary, for clinical diagnoses and treatment of intraocular retinoblastoma. Four of these showed HHRFs: invasion of optic nerve 2, uvea 1, combined uvea and optic nerve 1. One patient whose histopathology report and specimen could not be traced, and also defaulted from follow up shortly after surgery, presented 9 months post surgery with orbital recurrence.

The patients were followed up for 1 day to 19 months, mean 5.7 (SD±5.67) and mode of 8 months. At the last follow up, which was variable, 6 alive were patients with no metastasis while 5 had metastasis. At follow-up periods of 3 and 6 months, 3 patients were alive including 1 with metastasis; at 12 months only 1 was alive without metastasis and at 18 months only one was alive with metastasis. Parents/carers of eight (34.8%) patients defaulted treatment, 2 (8.7%) were discharged home on account of advanced disease with financial difficulty for palliative care at peripheral hospitals near their residential areas and 2 (8.7%) died with metastasis at 4 and 13months respectively. No second malignant tumour was seen (Table2).

The commonest site for metastasis was the bone marrow - 4 out of the total number of 7 patients who had metastasis (5 who were alive with metastasis and 2 who died with metastasis). Other sites were the brain/CNS 2, orbit 2, and combined brain and orbit 1. One child with brain metastasis also showed metastases to the skull.

DISCUSSION

This study showed that majority of the patients (82.6%) presented with unilateral retinoblastoma. This conforms with studies from both developed and developing countries although this proportion seems higher in our small series.^{9,10,16} The mean age of diagnosis was high at 36.3 months. This finding confirms observations from other developing countries in Africa and the Asia.^{9,10,20} A higher mean age at diagnosis has been found to be associated with advanced or metastatic retinoblastoma.²¹ This is in sharp contrast with the findings from developed countries, where the mean age of diagnosis is less than 24 months.⁵

Table 2 Outcome in 23 patients with retinoblastoma

Duration of follow up (months)	Total number of patients No. (%)	Alive Without metastases No. (%)	Alive with metastases No. (%)	Defaulted/ Discharged No. (%)	Dead With metastases No. (%)
<3	8 (34.8)	1(4.3)	2 (8.7)	5(21.7)	
3	6 (26.1)	2 (8.7)	1 (4.3)	2 (8.7)	1 (4.3)
6	5 (21.7)	2 (8.7)	1 (4.3)	2 (8.7)	
12	2 (8.7)	1 (4.3)			1 (4.3)
18	2 (8.7)		1(4.3)	1 (4.3)	
	23 (100)	6(26.1)	5 (21.7)	10 (43.5)	2 (8.7)

The common clinical presentations of leukocoria, proptosis squint and red eye from this study are also comparable to those in other developing countries.^{10,11,22-24} These features together with other signs such as, secondary glaucoma, fungating mass, hyphaema and flattened anterior chamber are known signs of advanced disease or high risk for metastasis.^{2,23} A study of 29 patients in Congo revealed the common presenting signs to be leukocoria, 49%, followed by proptosis (28%). Other signs were strabismus, red eye, anterior scleral staphyloma, hyphema and buphthalmia.¹¹ In Kenya, an analysis of 470 oculo-orbital tumours demonstrated proptosis to be the hallmark, and the commonest manifestation at first attendance of orbital disease, with retinoblastoma being an important cause and that its presence depicted late or advanced disease.²² These studies show that proptosis, a late sign, is a common presentation of retinoblastoma in developing countries compared with the developed world^{11,22,24}, a fact that validates the late or advanced presentation of most of our patients.

A study in New Delhi, India, which reviewed 392 patients with retinoblastoma, found all of them at presentation to have R-E grade V retinoblastoma, which represents advanced disease.²⁴ Sahu et al in their retrospective study of 296 affected patients with retinoblastoma, over an 8 years period, in Mumbai, India, also found a predominance of advanced-stage disease with 74.5% presenting with Reese-Ellsworth group IV and V disease.²⁰ These findings are supported by our study.

In Saudi Arabia, a study which assessed the value of various tests including bone marrow aspiration, lumbar puncture, and radionuclide scans, as part of the initial

workup for metastases, found only 9.9% of the 101 patients who had bone marrow studies with tumour infiltration, and 4.3% of the 94 patients with lumbar punctures yielding positive results.²⁷ The rate of bone marrow metastasis is relatively high in our study, but this may be due to the small numbers in our study therefore we cannot make any meaningful comparison with this larger series from Saudi Arabia. Similarly, the percentage of our patients who had CSF analysis, or CT imaging is too small to allow any meaningful comparison. The lack of confirmation of diagnoses with imaging studies and the inability to have full metastatic work-up for some of the patients, due to financial difficulties was also a significant limitation on final diagnoses and extent of tumour metastases. Consistent systematic investigations will be required in the future to allow such comparisons.

Optic nerve, choroid, extra scleral and anterior chamber infiltration are all recognized HHRFs for metastasis.²⁶⁻³² Seventy-five percent of enucleated eyes in our series had one or more HHRF for metastasis. Optic nerve invasion was the commonest site of extraocular invasion in our series and correlates with that in other studies.¹⁰

Our study has added to the importance of subjecting all enucleated eyes for histopathological analysis in order to identify those with HHRFs, the presence of which have adverse predictive value on prognosis.²⁶⁻³¹

Progressively small numbers of patients continued with follow up thus for 12 and 18 months durations there were only 1 without metastasis and 1 with metastasis respectively.

This was also reflected in more than a third of the patients either abandoning treatment, 34.8%, or discharged with advanced disease and financial difficulty (8.7%), the latter group for palliative care at peripheral hospitals near their homes. In Honduras, a study assessing the impact of public education on the late diagnosis of retinoblastoma was carried out from July 1995 to January 2005. The study showed that the proportion of patients diagnosed with advanced retinoblastoma i.e. with extra-ocular disease, declined from 73% of the 59 diagnosed cases during the eight previous years (July 1995-June 2003) before the campaign, to only 35% of the 23 diagnosed cases during the post-campaign period (June 2003-January 2005), ($P = 0.002$). However, more than one-third of patients in both time periods either refused therapy or abandoned treatment.³³ This high default rate identifies with our study.

We do acknowledge the limitations of this study. The small numbers analysed makes it difficult comparing our results with those from centres with larger series; similarly, it is impossible to make inferences for the whole population from this series. However the importance of the disease, being both sight and life threatening, renders the findings significant. Secondly, our centre is the only tertiary hospital in Ghana with a paediatric eye unit and thus the final referral point. This could explain the reason for all the patients encountered being those with advanced disease. Other general ophthalmologists in smaller or peripheral hospitals manage the less complicated cases by enucleation. This is because caretakers of the affected children sometimes refuse referrals to the bigger hospitals on account of long distance and cost. (Essuman V. *Conversation with General Ophthalmologists: Regional Eyecare Planning Workshop, Accra, 12th May 2005*).

Ghana has a population of about 22 million, with 41% (i.e. 9 million) being children less than 15 years. Using a similar retinoblastoma age-standardized rate (ASR) from Nigeria (7.4/million: IARC, 1998) which shares similar geographic and demographic features in the West African Sub-region, implies that about 67 new cases of retinoblastoma should be seen in Ghana each year, of whom only 14 get to the Eye Unit of Korle-Bu each year (23 in 20 months). This suggests that about 53 children per annum with retinoblastoma do not get to the tertiary centre at Korle-Bu. These patients may seek treatment from general ophthalmologists in the periphery or from alternate medical practitioners such as traditional healers and spiritualists.

It is of great interest to know how many of them get treatment in peripheral eye hospitals and the magnitude of retinoblastoma in the country. This requires further studies. A national register of childhood tumours, including retinoblastoma will be helpful.

In conclusion, majority of the patients presented with advanced disease manifesting as leukocoria, proptosis, R-E stages V disease and poor outcome. These findings have highlighted the late stage of presentation of patients with retinoblastoma in our hospital, problems with default and funding of treatment. Further studies are needed into: why they present late, the high default rate, ways of improving early reporting, cheaper ways of funding treatment, the magnitude of retinoblastoma in the country and how many of them seek treatment at peripheral hospitals from general ophthalmologists, in order to improve on survival.

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