OUTCOME OF GLOBE PRESERVATION THERAPY IN PATIENTS WITH BILATERAL RETINOBLASTOMA AT THE KENYATTA NATIONAL HOSPITAL, KENYA

DR. REBECAH NAMWEYI NANDASABA

H58/81151/12, MBChB.

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DECLARATION

I declare that this is my original work and it has never been published or presented for a degree in any other university.

PRIMARY INVESTIGATOR

DR. REBECAH NAMWEYI NANDASABA

H58/81151/12 , MBChB.

SIGNATURE..... DATE.....

APPROVAL:

This dissertation has been submitted for examination with our approval as supervisors at the University of Nairobi.

DR LUCY NJAMBI

MBChB, MMED (OPHTHALMOLOGY), FEACO

LECTURER, DEPARTMENT OF OPHTHALMOLOGY

UNIVERSITY OF NAIROBI

SIGNATURE..... DATE.....

DR. KAHAKI KIMANI

MBChB. M.MED (OPHTHALMOLOGY), FEACO, MSC (CEH)

CONSULTANT OPHTHALMOLOGIST

SENIOR LECTURER, DEPARTMENT OF OPHTHALMOLOGY

UNIVERSITY OF NAIROBI

SIGNATURE..... DATE.....

DEDICATION

This book is dedicated to my parents B Nabisino and J Nandasaba for the unwavering support, encouragement and love. Indeed, I see far by standing on your shoulders.

To Family and Rose Nakhungu for your support.

To all the brave young soldiers that battle retinoblastoma. In each battle, you triumph.

"*In order to succeed we must first believe that we can…*"

Nikos Kazantzakis

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Above all I give gratitude to God for making all things possible.

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

CNS – Central Nervous System

EBRT – External beam radiation therapy

EUA – Examination under anaesthesia

IAC – Intra-arterial chemotherapy

IIRC – International Intra-ocular Retinoblastoma Classification

KNH – Kenyatta National Hospital

MRI – Magnetic resonance imaging

RE – Reese Ellsworth

UON – University of Nairobi

VA - Visual acuity

CONTENTS

ABSTRACT

Aim

The past 60 years have seen an evolution in treatment of retinoblastoma from primary enucleation to attempts to salvage the globe and preserve vision in addition to saving life. The developed countries have reported good success rates. Globe preservation was introduced in KNH as early as the 1980s but started being practiced routinely in 2008. This study set out to determine the outcome of globe preservation in Kenya, KNH, from January 2008 to December 2014.

Design

A descriptive retrospective case series.

Methods

Using the ICD 69.2 records of a total of 35 patients diagnosed with bilateral retinoblastoma who underwent globe salvage at KNH between January 2008 to December 2014 were retrieved for the study. Data on demographics, presenting complaints, relevant examination findings, globe preservation modalities employed and globe salvage outcomes was collected. Analysis was done using STATA version 13.

Results

The mean age at presentation was 16.8 months (SD = 12.2, range 2 - 36 months), median 13 months (IQR 6-24). Mean duration between onset of symptoms to presentation at KNH was 7.2 months (SD = 7.3), median duration of 6 months (IQR 3-10). Out of the 35 salvage eyes 12 (34.3%) were Group A eyes, 11 (31.4%) Group B, 5 (14.3%) Group C and 7 (20.0%) Group D.

Twenty patients (57.1%) patients received systemic chemotherapy for intraocular chemoreduction of the tumours in the salvage eye. Only 2(5.7%) patients received sub-tenon carboplatin. The main modes of focal consolidative therapy was laser photocoagulation and thermotherapy and cryotherapy. No patient had EBRT of plaque radiotherapy as it was not available.

Seven (20.0%) patients had relapse with a median survival time for tumour to relapse of 6.8 months. Nine patines (25.7%) developed new tumours with a median time to development of new tumours of 6.5 months.

Fourteen (40.0%) eyes were salvaged with preservation of vision. Of these 12 (85.7%) were Group A and B eyes. Mean duration to salvage was 7.27 months (SD = 4.62). Six eyes (18.18%) were enucleated with a mean duration to enucleation of 15.7 months (SD = 15.51).Nine (25.7%) got lost to follow up and 3 patients (8.6%) developed metastatic disease and globe salvage was abandoned.

Conclusion

The main treatment modalities employed at the KNH were laser photocoagulation and cryotherapy complemented with systemic chemotherapy where intraocular chemoreduction was required. Forty percent of eyes were salvaged using the resources available. However our rate was low compared to the developed countries.

Tumour relapse occurred in 20% of patients with subretinal seeding being a risk factor. Twenty five percent of patients developed new tumours which was similar to other international studies.

Recommendation

Efforts should be made towards seeking treatment early, improve patient adherence to follow up and introduction of EBRT, plaque radiotherapy and more advanced treatment for patients with Group C and D eyes.

A prospective study is also recommended.

INTRODUCTION AND LITERATURE REVIEW

1 INTRODUCTION

1.1BACKGROUND

Retinoblastoma is the most common primary intraocular malignancy of childhood. [1]

It accounts for about 3 % of all childhood cancers. Internationally retinoblastoma occurs in about 1:17000 live births with ranges from 1:14,000 to 1:20,000 live births. No sex predilection has been demonstrated. The tumour occurs bilaterally in about 30%- 40 % of cases.[1]

In Kenya the incidence of retinoblastoma stands at 1:17,030 live births which is in keeping with the international incidence rate. This figure, however, could be an underestimation bearing in mind that there may be a number of cases that never report to hospital.[2]

Approximately 90 % of cases are diagnosed in patients younger than three years with the mean age at diagnosis depending on family history and laterality of the disease. Patients with a family history of retinoblastoma present at a mean age of 4 months in developed countries. Patients with bilateral disease present at a mean age of 12 months while patients with unilateral disease present at a mean age of 24 months.[1] Studies done in Kenya by Nyawira et al, 2013, and Nyamori et al, 2009, found the mean age at presentation for unilateral disease ranged from 35.9 to 39.89 months and bilateral disease from 24.34 to 26 months. [2, 3] The mean age at the presentation for children with familial disease was 32.8 months and non-familial was 33.1 months [2]

Over time the management of retinoblastoma has changed from purely enucleation of the diseased eye, to use of chemotherapy agents and currently to a combination of chemotherapy and local/focal control of intraocular tumours in eyes that are amenable to salvage (globe

preservation) with the aim of preserving the eye and saving vision in addition to preserving the patient's life. This is especially important in children with bilateral retinoblastoma. Numerous studies have been done to evaluate the outcomes of globe preservation and in developed countries good results have been recorded. In Kenya globe preservation therapy for children with bilateral retinoblastoma has been in practice since 2008 at the Kenyatta National Hospital. No study has been done to evaluate the outcomes so far in terms of preservation of the eyes/globe and vision in patients with bilateral retinoblastoma who qualified to undergo this treatment. This study sets out to establish this.

1.2 AETIOLOGY/ GENETICS

Retinoblastoma arises from malignant transformation of primitive retinal cells before final differentiation. [4] These cells usually disappear within the first few years of life making it rare for tumour to occur after the age of 8 years.[1]

The gene responsible for the development of retinoblastoma is RB1 (a tumour suppressor gene) which maps out a locus within the q14 band of chromosome 13. RB1 gene codes for the protein pRB which binds to DNA and controls the cell cycle at the transition from G1-phase to S1-phase thereby inhibiting cell proliferation.[5]

Genetic studies by Cavenee et al, 2006, proved that retinoblastoma was related to a mutant allele in the RB1 gene. [6] This mutation inactivates the RB1 gene leading to loss of its tumour suppression function and therefore uncontrolled cellular proliferation that leads to retinoblastoma.

Geneticist Dr. Alfred Knudson postulated a 'two hit theory' in the development of retinoblastoma where he deduced that two genetic alterations or 'hits' of the 13q14 band were

necessary for retinoblastoma development. In patients with heritable disease the first hit is acquired via the germline and thus present in every cell. The second hit required for disease development in these predisposed patients occurs in a somatic mutation in a single cell that would then expand into a tumour. In patients with non-heritable disease both hits were acquired via somatic mutation by a precursor cell. The difference in point of acquisition of first hit explains the earlier onset of retinoblastoma in heritable versus non-heritable disease.[7]

Although the two hits are necessary for the development of retinoblastoma further studies have demonstrated that further genomic changes are required for tumour progression. These changes have been termed M3 to Mn.[8]

In more recent studies it has been demonstrated that amplification of MYCN oncogene might initiate development of retinoblastoma in the presence of non-mutated RB1 genes. About 18% of children diagnosed with non-familial unilateral retinoblastoma before the age of six months will have MYCN amplification and no RB1 mutation. The tumour presents at an early age of 4-5 months, is unilateral and quite aggressive with rapid growth.[9, 10, 11]

About 6-10 % of patients have been found to actually have positive family history of retinoblastoma.

1.3 HISTOLOGY

Three types of growth patterns have been described in retinoblastoma.

In endophytic pattern the tumour grows from the retinal surface into the vitreous cavity with seeding occurring throughout the eye .[1, 4]

Exophytic pattern involves the tumour growing beneath the retina (sub-retinal space) and may be associated with serous retinal detachment.[1]

In diffuse infiltrative pattern of growth the tumour invades the retina without endophytic or exophytic growth.[4] It is usually unilateral and presents in children older than five years of age. It is often mistaken for intermediate uveitis of unknown aetiology.

A clinicopathological correlation study done by Matthew W et al on 67 eyes primarily enucleated for advanced retinoblastoma showed that growth patterns were equally distributed. [12]

1.4 METASTATIC SPREAD

Retinoblastoma metastasis, when it occurs, is usually within one year of diagnosis of intraocular tumour and carries a high mortality risk.[5] Common sites of retinoblastoma metastasis include regional lymph nodes, skull bones, scalp, distal bones, spinal cord, abdominal viscera and lungs. [1, 4] The commonest site of metastasis of retinoblastoma is the central nervous system (CNS) which, in a study by Leal-Leal, 2006, was found to be 83.9 %.[13.] This occurs via optic nerve invasion and carries a high mortality risk. Long term survival of patients is achievable if the CNS is not involved, otherwise, once involved, prognosis becomes poor.[5]

1.5 CLINICAL PRESENTATION

Clinical presentation is usually within the first one year in patients with bilateral disease and at about two years in patients with unilateral disease [4].

Presentation varies slightly in different age groups. Among patients less than five years the presenting signs include leukocoria (60 %), strabismus (20%), ocular inflammation (5 %), hypopyon, hyphaema, iris heterochromia, spontaneous globe perforation, proptosis, cataract,

secondary glaucoma, nystagmus, tearing and anisocoria.[1] A study by Dongsheng et al, 2013, found that the commonest presentation of retinoblastoma at initial diagnosis was leukocoria at 70.47 % of patients studied.[14]

In the age bracket of five years and above presenting complaints include leukocoria (35%), decreased vision (35%), strabismus (15%), floaters (5%) and pain (5%).[1]

At first presentation indirect ophthalmoscopy with scleral indentation is usually performed (mandatory) in both eyes after full mydriasis. [4]

1.6 CLASSIFICATION

Classification or staging of tumour is a description of how far the malignant cells have spread. Prognosis is then extrapolated from the stage of the tumour. The Reese Ellsworth classification was used for a long time in the management of retinoblastoma but is slowly being abandoned as it was based on outcome following EBRT[15]. The shift of retinoblastoma management from EBRT to use of chemotherapy and other local consolidative treatment necessitated a review of classification that is in keeping with the change.

The international intraocular classification of retinoblastoma has now been adopted as it gives better prediction of outcome based on chemotherapy and local consolidative therapy. [15]

International intraocular retinoblastoma classification[15]

Group A -Very low risk. Eyes with small discrete tumours away from critical structures.	Tumours 3mm or less. Confined to the retina. >3mm from the foveola >1.5mm from optic disc. No vitreous or sub-retinal seeding.
Group B – Low risk. Eyes with no vitreous or sub-retinal seeding and discrete retinal tumour of any size or location.	Tumour not in group A. No vitreous or sub-retinal seeding. Sub-retinal fluid <5mm from the base of the tumour.
Group C – moderate risk. Eyes with only focal vitreous or sub-retinal seeding and discrete retinal tumours of any size and location.	Seeding local, fine and limited. Treatable with a radioactive plaque. Tumours discrete and of any size or location. Up to one quadrant of sub-retinal fluid.
Group D – High risk eyes. Eyes with diffuse vitreous or sub-retinal seeding and/or massive non-discrete endophytic or exophytic disease. Eyes with more extensive seeding than group C.	Massive and/or diffuse intraocular disseminated disease. More than one quadrant of retinal detachment. Fine greasy vitreous seeding or avascular masses. Sub-retinal seeding, plaque-like.

Group E- Very high risk eyes. Eyes that have been destroyed anatomically or functionally by the tumour.	Massive intraocular haemorrhage. Irreversible neovascular glaucoma. Aseptic orbital cellulitis. Tumour anterior to anterior vitreous face.Tumour touching the lens. Diffuse infiltrating retinoblastoma. Pthisis or prephthisis

1.7 TREATMENT

Retinoblastoma management has evolved greatly over the past 60 years with care becoming more and more sophisticated. Management has transformed beyond purely achieving patient cure to trying to salvage the globe and preserve vision especially in patients with bilateral disease. This has seen the rates of enucleation drop over time with clinicians attempting to salvage the globe instead.[16]

One study carried out in Australia showed a drastic drop in bilateral enucleation rates from 36% between 1956 - 1976 to 7% between 1990 - 2000. In the time period, 1990 to 2000, globe preservation was attempted and 62%, of preserved eyes in bilateral retinoblastoma had visual acuity better than 20/40. [16]

This evolution in management of bilateral disease has been influenced by the fact that although enucleation still remains the definitive treatment of retinoblastoma, eye prosthesis can have

variable cosmetic outcomes and enucleation at a young age can result in orbital hypoplasia to a similar extend as that observed with radiation therapy. Enucleation also still attracts significant social stigma in some cultures and in children with bilateral disease, bilateral enucleation is indeed visually devastating. [16] This is further strengthened by the fact that with early disease detection and current modes of treatment cure of retinoblastoma is possible.

The current management of retinoblastoma consists of several modalities of treatment guided by the principles of first preserving life, then the eye and finally vision. These modalities include enucleation, chemotherapy, photocoagulation, cryotherapy, external beam radiation therapy (EBRT) and plaque radiotherapy. For metastatic disease, management includes chemotherapy, radiation and bone marrow transplant.[1] Bone marrow transplant is currently not done in Kenya.

With this evolution in approach to retinoblastoma management the involved team is usually multidisciplinary being inclusive of an ocular oncologist, paediatric oncologist, radiation oncologist, counselor and a social worker.

1.7.1 GLOBE PRESERVATION

Globe preservation employs the use of systemic chemotherapy for reduction of the tumour size in combination with focal consolidative therapy to achieve tumour destruction. Focal therapies deprive the tumours of their blood supply and act synergistically with chemotherapy by disrupting the retinal-blood barrier thus enhancing penetration of the chemotherapy agents into tumour.[16]

A literature review of several peer reviewed papers on globe preservation therapies by Bhavana C et al, 2013, showed that the globe preservation therapies currently employed include systemic chemoreduction, focal consolidation with laser photocoagulation, cryotherapy, thermotherapy,

plaque radiotherapy and local chemotherapy via sub-conjunctival, subtenon or intra-arterial routes. [17]

Promising results in survival rates, avoidance of enucleation and vision preservation have been so far achieved with globe conservation therapy.[18] This has been attributed to early detection of disease, prompt referral to specialized treatment centers and advancement in treatment modalities.[18]

National Cancer Institute's (United States of America) cancer information summary about retinoblastoma treatment noted that systemic chemotherapy in combination with local control resulted in tumour control and ocular salvage rates of more than 90% in group A and B eyes, 70-90% in group C eyes and 40-50 % in group D eyes as of December 2013.[19]

A retrospective observational study done in Australia by V Lee et al, 2003, on 107 patients to quantify the rates of eye preservation and patient survival, local tumour relapses, recurrences and development of new tumours in the remaining eye of children with bilateral retinoblastoma with one eye enucleated established that aggressive conservative treatment achieved a good rate of globe salvage without impairing survival. The three year survival rate of the patients studied was 93 %.[20]

1.7.1.1 CHEMOTHERAPY

Chemotherapy use in treatment of intraocular retinoblastoma was introduced in the 1990s. It was adopted in combination with focal therapies to achieve control of the disease and avoid the use of EBRT. Chemotherapy in children with bilateral disease is indicated for chemoreduction of large tumours that cannot be treated with focal therapies alone. Focal therapies are then employed to eradicate remaining disease.[21]

This combination of chemotherapy with focal consolidative therapy has been shown in studies to achieve good control of retinoblastoma. A study by Beck MN et al, 2001, on 24 patients to evaluate the efficacy of first line chemotherapy in preventing EBRT and/or enucleation in patients with retinoblastoma found that chemotherapy together with intensive laser therapy was effective in patients with RE groups I-III permitting the avoidance of EBRT in the majority of patients thus reducing the risk of long term sequelae. The results were however disappointing for patients with groups IV and V retinoblastoma who eventually needed EBRT or enucleation.[22]

1.7.1.2 SYSTEMIC CHEMOTHERAPY

Systemic chemotherapy involves a multidrug combination consisting of Carboplatin, Etoposide and Vincristine. [1] This is used in combination with focal therapies as chemotherapy alone does not cure retinoblastoma. Systemic chemotherapy with focal therapies is indicated for bilateral disease for IIRC group B, C or D eyes. [23]

Systemic chemotherapy causes a reduction in tumour volume and allows consolidative focal therapy with laser, cryotherapy or radiotherapy.[1] These are administered intravenously every 3-4 weeks for 4-9 cycles. Serial examinations under anesthesia (EUA) are carried out after specific periods of time to monitor tumour response and administer consolidative focal therapies.[1]

Vincristine, carboplatin and epipodophylotoxin have been used with an 80.9% - 100% globe salvage rate in Reese Ellsworth (RE) group I-IV eyes and 36.1% in RE V eyes.[16]

The combination of carboplatin and vincristine has shown a 74% - 94% globe salvage rate in RE group I- IV eyes and 62% in RE group V eyes. The success rates have been improved with the addition of cyclosporine.[16] Cyclosporine is used in combination with VEC to overcome drug

resistance seen in retinoblastoma that is conferred by P- glycoprotein which causes efflux of vincristine and tenoposide in-vitro. [21]

Systemic chemotherapy has been found to be protective from systemic metastasis and pinealoblastoma, minimizes on long term secondary cancers and has few systemic and no ocular toxicities. [2 4] Side effects when present include myelosurpression with increased susceptibility to bacterial infections. Ototoxicity and renal toxicities are rare.[21] Etoposide has been shown to increase risk of leukemia with repeated use. [25]

1.7.1.3 LOCAL CHEMOTHERAPY

Work on subconjunctival or perioccular carboplatoin started at an experimental level more than 10 years ago. [26] So far sub-conjunctival carboplatin with or without systemic chemotherapy has been used in treatment of retinoblastoma as adjuvant treatment for tumours with persistent vitreous seeding aimed at increasing vitreous concentrations. [1, 16] Indications include bilateral disease with one eye enucleated, contraindication to systemic chemotherapy and an eye with persistent vitreous seeding. Limited peritomy is made in the quadrant closest to the main tumour or site of vitreous seeding. A gauge 19 cannula is attached to a 3 ml syringe with 2 ml of carboplatin at a concentration of 10mg per ml. It is then advanced into the intraconal space and injected slowly to avoid reflux.[16] Complications of this treatment modality include orbital myositis, periocular fibrosis, optic neuropahthy, optic nerve atrophy and necrosis, pseudopreseptal cellulitis and severe aseptic ocular cellulitis.[1, 16, 27] A study by Reza Karkhaneh et al, 2006, showed that subtenon carboplatin did not increase efficacy of systemic chemotherapy in treatment of intraocular retinoblastoma. [28]

Interventional radiology selective canalization of the ophthalmic artery with local delivery of chemotherapeutic agents is yet another modality in local chemotherapy delivery in management of retinoblastoma.[1] Intra-arterial chemotherapy (IAC) provides excellent tumour control for eyes with slightly more advanced disease and can be used to treat eyes that fail other methods. [24] The three principal chemotherapeutic agents used are melphalan, topotecan and carboplatin.

In a study done by Peterson et al, 2011, melphalan was injected via ophthalmic artery of 17 eyes classified as International Intraocular Retinoblastoma Classification (IIRC) D or Reese Ellsworth group Vb pending enucleation. Using this protocol there was a decrease in the enucleation rate to 23.5 %. Its role in eyes with less advanced disease though is yet to be elucidated.[29]

In yet another study by Rajanaporn P et al, 2012, intra-arterial chemotherapy in combination with intravenous chemoreduction achieved a globe salvage rate of 88% of eyes studied. [30]

Local toxicities of IAC, however, can be vision threatening and long term systemic toxicities are yet to be fully understood. [24] Carol LS et al found that treatment with IAC for retinoblastoma can lead to mild and severe short term ocular complications including eyelid edema, blepharoptosis, cilia loss, and orbital congestion with orbital dysmotility. These resolved within 6 months. IAC should therefore be used with caution.[31]

1.7.1.4 PHOTOCOAGULATION AND HYPERTHERMIA

Laser is one of the mainstay focal therapies employed in retinoblastoma management and it works by coagulating all the blood supply to the tumour leading to subsequent necrosis and by physically destroying tumour and viable tissue with direct heat. [21, 23]

Argon laser (532nm – green light) is used to treat tumours <3mm in thickness and basal dimensions <10mm.[1] In the case of larger tumours laser is used in combination with chemotherapy to achieve disease control.[19] Its application has transitioned from applying 2-3 rows of encircling retinal photocoagulation to the current thermotherapy where infrared light is applied directly on the tumour.[1, 19] This is achieved using an indirect ophthalmoscope and diode laser 810 nm to provide hyperthermia by direct application to the tumour raising the temperature to 45 to 60 degrees centigrade with direct cytotoxic effect.[1, 21]

Effective disease control is achieved with 2-3 session spaced at 3-4 weekly intervals.[21]

With successful control laser results in a flat pigmented scleral scar or a flat white gliotic appearance devoid of tumour blood vessels.[23]

Brenda Gallie et al, 1996, did a study that demonstrated that, when used in combination with chemotherapy, retinoblastoma cure can be achieved depending on stage of tumour.[32] In a study by Steven SK et al, 2012, chemotherapy achieved 51-65% tumour control when used alone in RE group I-IV and this rose to 62-100% when focal laser was added to management. For RE group V this rose from 25-37% to 47-83% tumour control rate.[33]

The side effects of laser photocoagulation include retinal detachment, vitreoretinal traction, retinal vascular occlusion, preretinal fibrosis, and peripheral ischaemia with repeated treatment

leading to neovascularization. Excessive laser can lead to vitreous haemorrhage or vitreous seeding. With an inadequately dilated pupil burns to the iris, pupil deformities and cataracts can occur. [23, 21] In a study done by AO Schuler, 2003, on ocular and orbital complications observed in children following retinoblastoma treatment in 73 children, thermotherapy complications occurred in 9 % of the eyes studied. Among the complications transient corneal opacification was 6%, focal iris atrophy 8.5%, peripheral lens opacity 6%, circumscribed transient retinal detachment 3% and diffuse choroidal atrophy occurred in 3% of eyes.[34]

In another study by Shields et al on thermotherapy for retinoblastoma iris atrophy occurred in 36% of cases, peripheral focal lens opacity in 24%, retinal detachment in 5%, retinal vascular obstruction in 2%, and transient localized serous detachment in 2% of cases. No patients developed corneal scarring, cataract lens opacity, iris or retinal neovascularisation or rheumatogenous retinal detachment.[35]

1.7.1.5 CRYOTHERAPY

Cryotherapy is focal consolidative therapy indicated for anteriorly located tumours of <3mm thickness and with a basal diameter of <10mm.[1] It induces rapid freezing of tissues resulting in destruction of cell membranes and vascular endothelial damage with resultant thrombosis and subsequent tumour infarction. [21, 23] It is applied under direct visualization using indirect ophthalmoscope or fundus camera (RetCam[TM]) [1, 23] A cryoprobe is used to indent the sclera then nitrous oxide is used to cool the probe. [23] A triple freeze-thaw technique is then used to destroy the tumour and underlying choroid. [23] Good cure rates have been achieved via this method with 97% of tumours <3mm diameter being cured permanently. [23, 36]

Cryotherapy is also used to increase access of chemotherapeutic agents into the vitreous by breaking the blood retinal barrier. In this case the tissues are frozen and thawed once. The chemotherapeutic agents should thereafter be administered within 72 hours of cryotherapy. This is indicated for group D eyes with vitreous seeding and recurrences. [23]

Complications associated with cryotherapy include transient conjunctival oedema, transient localized serous retinal detachments and vitreous haemorrhage in large or previously irradiated tumours. [21] Freezing of calcified lesions should not be done to avoid retinal tears. [23]

1.7.1.6 PLAQUE RADIOTHERAPY

Also known as internal radiation therapy, plaque radiotherapy involves putting radioactive material in a small carrier (plaque) made of gold or lead to shield nearby normal tissues from radiation. It is then sewn onto the eyeball and left for a number of days (36-72 hours). The radiation emitted travels very short distances with most of the radiation remaining focused on the tumour. Side effects include damage to retina and optic nerve.[37] Plaque radiotherapy is applicable to tumours <8mm in thickness and <16mm basal diameter. Isotopes used include iodine 125 and ruthenium 106.[1]

When employed following chemoreduction, good tumour control rates of 94.4 - 95% have been achieved with 5 year eye preservation rate of 86.5 %. [38, 39]

1.7.1.7 EXTERNAL BEAM RADIATION THERAPY

EBRT is indicated in eyes with extensive vitreous seeding and for patients with disease progression while undergoing chemotherapy.[4, 40] EBRT focuses radiation beams from a source outside the body onto the cancer. Long term remission is achievable with doses ranging from

35Gy – 46Gy.[41] Other studies have also shown good local tumour control with doses of 4000cGy – 4500 cGy administered at 200cGy fractions with minimal retinal late effects. [40]

In a study by Chan MPY et al 36 eyes were treated with EBRT and globe salvage was achieved in 83.3% of eyes. Visual acuity was taken in 19 eyes of which 52.6 had VA of 6/9 to 6/5, 15.8 had VA of 6/18 to 6/36 and 31.6 had VA 6/60 or worse.[42]

Complications of EBRT include cataracts, midface hypoplasia and optic nerve neuropathy.[1] A study by FL Wong et al showed that radiation treatment increased the risk of development of secondary cancers in retinoblastoma patients with genetic predisposition. A radiation- dose response relationship was demonstrated for all sarcomas.[43]

In a study by Anteby I et al, 1998, on ocular and orbital complications following retinoblastoma treatment 20% of irradiated eyes developed cataracts in a mean period of 18 months, 12% developed radiation retinopathy in a mean duration of 37 months and all eyes has mild transient keratitis. [44]

1.7.2 ENUCLEATION

Enucleation remains the definitive management of retinoblastoma. Primary indications for enucleation include, tumour involving > 50% of the globe, optic nerve involvement, anterior segment involvement, neovascular glaucoma, choroidal invasion, limited visual potential in the affected eye.[1] Secondary indications include failure of all treatment modalities, obstructed direct visualization of an active tumour by a vitreous haemorrhage, corneal opacity or cataract. [21] In bilateral retinoblastoma the eye with the more advanced tumour, ie group E eye, is enucleated. [45]

Careful handling of tissues is imperative during the procedure with care being taken to avoid puncturing the globe. Care is also taken to obtain an optic nerve length of at least 10 mm or more.[1] A long optic nerve minimizes the chances of cutting through the tumour and leaving residual disease at the surgical margin. [21]

Good cosmesis is achieved by use of an orbital implant which is integrated with the extraocular muscles and fitting of a prosthesis. [21, 45]

Acute complications following enucleation include haemorrhage, post-operative ecchymosis and lid oedema, conjunctival chemosis and socket infection. Long-term complications of enucleation include orbital fat atrophy, ptosis, superior sulcus atrophy and shrinking of the bony orbit if no implant is placed at the time of surgery.[45]

In a study by Anteby et al, 1998, on ocular and orbital complications following treatment of retinoblastoma in 73 children, 11% developed marked discharge post enucleation, 9.6 had implant extrusion and 3% developed a contracted socket [45]

1.8 REGRESSION PATTERNS FOLLOWING LOCAL THERAPY

Following treatment retinoblastoma tumours regress in different patterns which include type 1 or cottage cheese pattern which is a calcified mass, type 2 or fish-flesh pattern which appears as a non-calcified translucent mass that can be difficult to differentiate from active tumour, type 3 pattern which has mixed features of type 1 and 2 patterns and lastly type 4 pattern which appears as a flat atrophic scar. Occasionally it may disappear leaving no scar, type 0.[5]

Factors determining the regression pattern are dependent on the size and location of tumour. Most small tumours result in a flat scar. Intermediate tumours exhibit patterns ranging from a flat to partially calcified tumour and large tumours result in calcified remnants.[46]

The appearance of regressed tumour also changes over time. Three months following treatment the predominant pattern is type 3 while after 6 to 8 months post treatment the predominant pattern is type 4. [47]

Overall with access to modern care prognosis stands at a survival rate of over 95 % in developed countries.[1] This good survival rates justify the efforts of salvaging the globe and preserving vision. Although the survival rates in East Africa are lower compared to developed countries globe salvage still remains relevant with treatment becoming better with improving survival rates.[3, 48]

2. JUSTIFICATION.

The management of retinoblastoma has transformed over the years from purely achieving patient cure to trying to salvage the globe and preserve vision especially in patients with bilateral disease. With these, rates of enucleation have dropped over time as clinicians attempt to salvage the globe instead. [14] Promising results in survival rates, avoidance of enucleation and vision preservation have been achieved with globe conservation therapy.[16] Globe salvage allows for preservation of useful vision and good cosmesis. The social stigma associated with bilateral enucleation is also avoided.

Globe preservation is being done at the Kenyatta National Hospital in children with bilateral retinoblastoma who have had one eye with severer (advanced) disease enucleated and the remaining eye with less advanced disease preserved. This has been in practice since 2008. No study had been done to determine the outcome of globe preservation therapy in our setting since this aspect of retinoblastoma management started being practiced.

This study set out to identify the specific modes of globe preservation employed in the management of children with bilateral retinoblastoma treated at KNH who qualify to undergo globe preservation, establish the outcomes of our management in terms of globe and vision preservation and complications, and identify gaps that may influence management and outcomes.

3. OBJECTIVES

3.1 BROAD OBJECTIVE

To determine the outcome of globe preservation therapy in patients with bilateral retinoblastoma treated at the KNH.

3.2 SPECIFIC OBJECTIVES

- To determine the globe preservation therapy modalities used for treatment of children with bilateral retinoblastoma treated at the KNH.
- To determine the outcome of eye/globe preservation in patients with bilateral retinoblastoma who underwent globe preservation therapy at KNH.
- To determine the proportion of relapse and development of new tumours in patients with bilateral retinoblastoma undergoing globe preservation therapy at the KNH.

4. METHODOLOGY

4.1 STUDY DESIGN

The study was a descriptive retrospective case series.

4.2 STUDY POPULATION

All patients with bilateral retinoblastoma confirmed on histology who had one eye enucleated and the other eye undergone globe preservation therapy between 1st January 2008 – 31st December 2014.

4.3 STUDY AREA

The study was carried out at the Kenyatta National Hospital, currently the largest national referral, teaching and research hospital (in association with The University of Nairobi) located in Nairobi County, Kenya. It was established in the year 1900 as the Native Civil Hospital. In 1952 it was renamed King George VI and later in 1964 the name was changed to Kenyatta National hospital.

It is currently the biggest hospital in East and Central Africa and serves as a referral center for the region. It has a capacity of 2000 beds, outpatient attendance of 89,000 patients annually and 600,000 in patients annually. It provides specialized services with various specialists' clinics and wards. Patients on management for retinoblastoma are admitted in the eye ward 9D on level 9 of the main hospital building.

Majority of the patients with retinoblastoma from different parts of the country are referred to KNH for management of the cancer. Children affected by retinoblastoma from the neighboring countries, especially Somalia, are also referred for specialized treatment at the KNH. It receives

54 retinoblastoma patients on average per year. It is one of the two centers in the country offering specialized treatment and care of patients with retinoblastoma. The team involved with managing retinoblastoma patients is inclusive of ophthalmologists, haematoncologists and radiation oncologists and nursing team.

4.4 STUDY DURATION

The study duration was from 1st September 2013 to 31st January 2015 following ethics committee approval.

4.5 INCLUSION CRITERIA

All patients with bilateral retinoblastoma with one eye enucleated who underwent globe preservation therapy at the Kenyatta National Hospital between January 1st 2008 – December 31st 2014 were included in the study.

4.6 SAMPLE SIZE

Bilateral retinoblastoma is a relatively rare condition and the patient numbers are comparatively low therefore all patients who met the inclusion criteria were included in the study.

4.7 DATA COLLECTION, MANAGEMENT AND ANALYSIS

After obtaining ethical approval all medical records of patients who had been treated for retinoblastoma at KNH from January1st 2008 – December 31st 2014 were retrieved from the records department using the international code for diseases for retinoblastoma ICD-9. This was done with the assistance of a medical records officer at the KNH records department. The records were further verified using a list of patients treated for retinoblastoma complied from the admissions records from the ward and theatre records during the same period. The patient

records were then grouped into those with bilateral and unilateral disease. The files of patients who had been treated for bilateral retinoblastoma were further grouped into those that met the inclusion criteria and those that failed. Patient records of patients treated for unilateral disease and those with bilateral retinoblastoma who failed to meet the inclusion criteria were returned to the records office.

Data was then be collected by the primary researcher from patient records treated for bilateral retinoblastoma that met the inclusion criteria using a data collection form (Appendix I). The data collection form captured the demographic data of patients, their presenting complaints, examination findings, globe preservation therapy that each patient underwent and the outcome of treatment by the time of this study.

The data was then entered into Microsoft access for storage. Thereafter it was validated, cleaned and any missing information filled in. The information gathered was backed up in an external hard disc.

All information gathered was kept under lock and key and all soft copy information secured by a password under the custody of the primary investigator. All hard copies of data collected will be destroyed after 5 years by burning.

Data analysis was done using STATA version 13 (stata corp, college station, Texas).

4.8 MATERIALS USED

- Data collection forms
- Stationary (ball pens, pencils)
- Flash disk for storing data
- Folders

4.9 ETHICAL CONSIDERATION

Approval was sought from the Kenyatta National Hospital – University of Nairobi Ethics Committee prior to research carried being out. Permission to collect data was also sought from the KNH.

The patient identification numbers were coded on a separate form and only patient code numbers appeared in the data collection form.

The names of the clinicians or surgeons were not recorded.
Information gathered in the data collection form was accessed by the primary investigator, supervisors and statistician only. Data was stored in a computer's Microsoft access database.

Thereafter the data collection forms will be destroyed after 5 years by burning.

4.10 STUDY LIMITATIONS

The anticipated study limitations included:

- Missing patient records.
- Incomplete and missing information / data in patient records.
- Patients who were lost to follow up during the planned study period could bias the eventual results.

4.11 STUDY DEFINITIONS

The definitions that were used in the study to assess and determine outcome of globe preservation therapy were as follows:

Primary failure: failure of primary treatment to control tumour. Unresponsive tumour or persistence of tumour despite treatment.

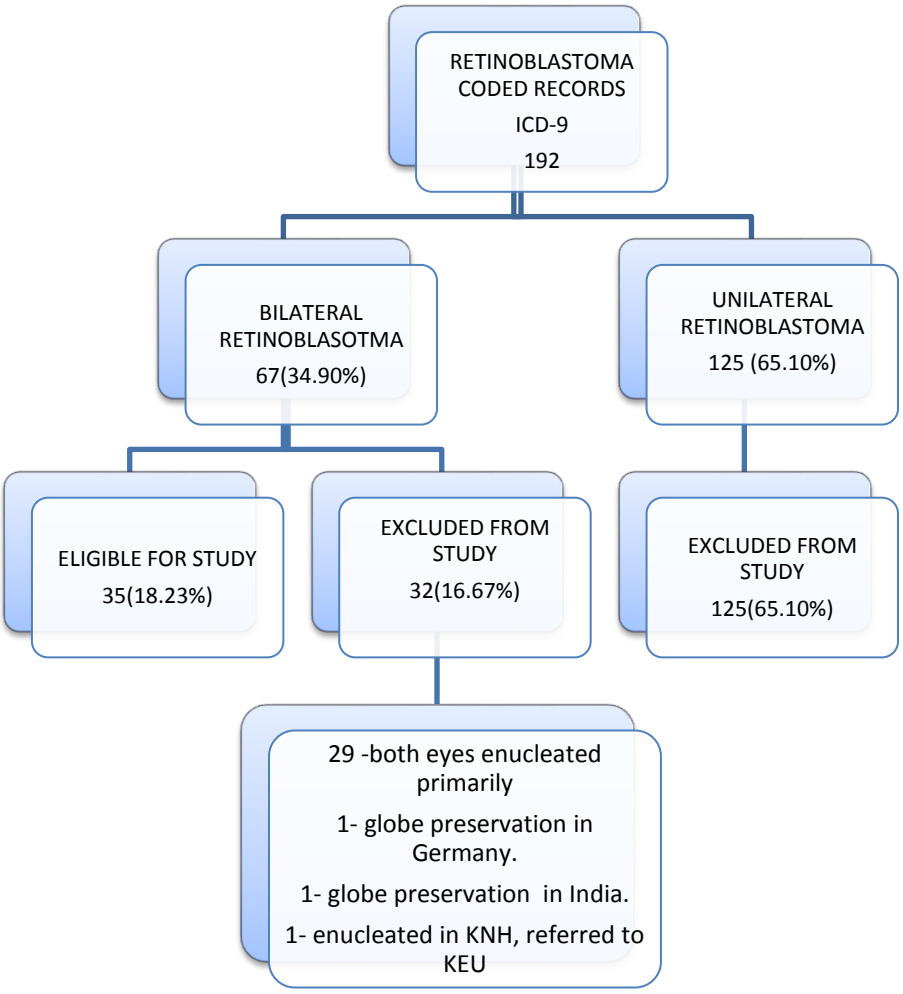
Regression: complete resolving of the tumour upon treatment.

Relapse /Recurrence: re-growth of intraretinal tumours, vitreous seeding or sub-retinal seeds after initial favorable response.

5 RESULTS

A total of 192 files were retrieved. Of these, 125 patients had unilateral retinoblastoma and were excluded from the study. The remaining 67 (34.90%) had bilateral retinoblastoma but 32 (16.67%) patients were excluded as 29 had both eyes enucleated primarily and two patients had had their tumours successfully controlled and eyes salvaged in other treatment centers; one in Germany and the other in India respectively. One patient underwent treatment at Kikuyu Eye Hospital. 35(18.23%) were eligible for the study.

PATIENT RECORDS RETRIEVAL FLOW CHART



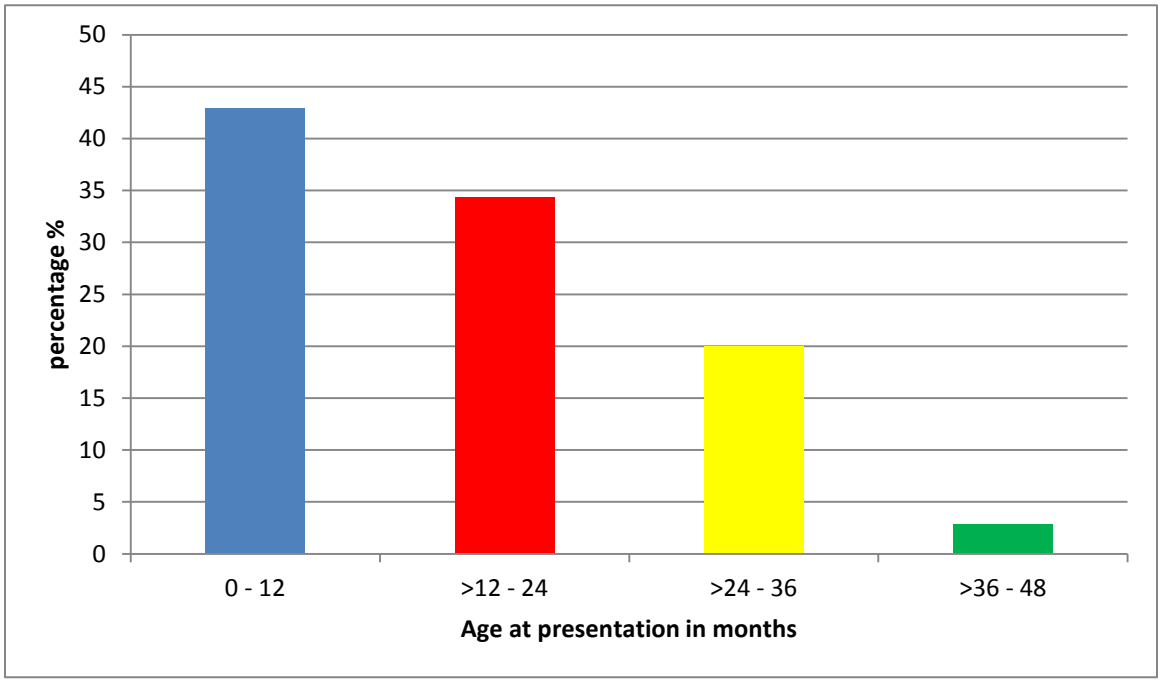
5.1 DEMOGRAPHICS

Table 1: Distribution of patients by country of residence

COUNTRY	FREQUENCY n=35	PERCENTAGE (%)
KENYA	32	91.4
SOMALIA	2	5.7
ETHIOPIA	1	2.9
TOTAL	35	100

The patients in Kenya were from Nyanza, Central Rift Valley, Central, Eastern and Coastal regions.

Figure 1: Age at presentation in months



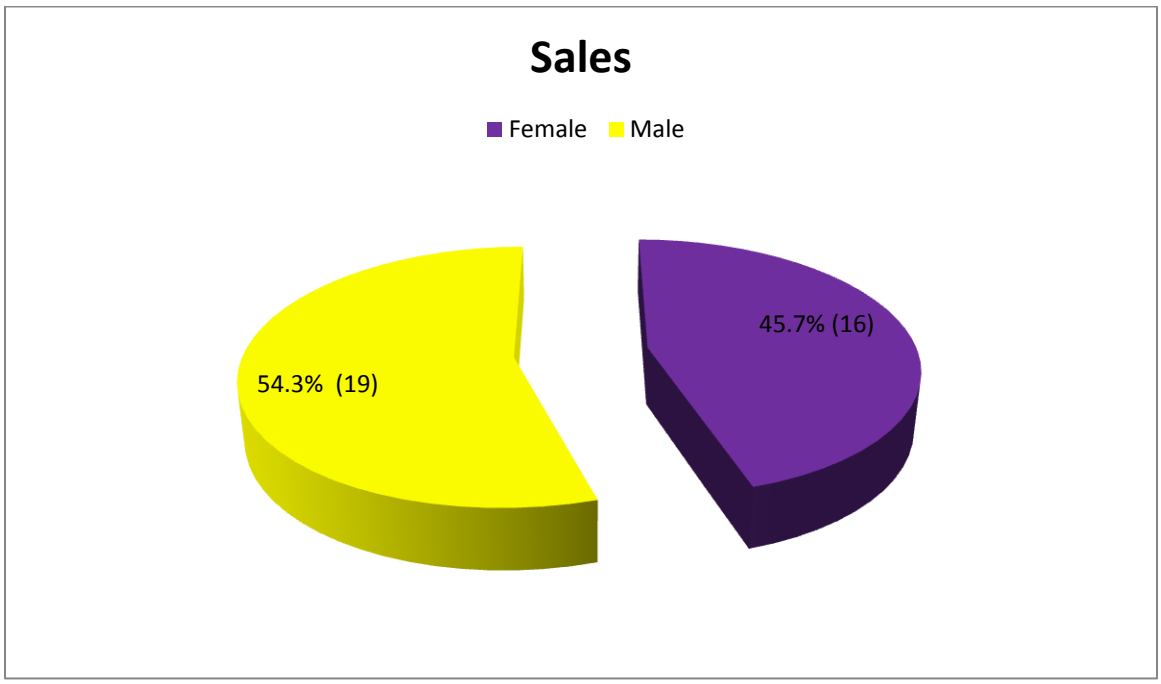
Most of the patients were less than one year old at presentation: 15 (42.9%). Of these, majority (9 patients) were between 1.5 to 6 months.

There was one patient who was 4 years old at the time presentation (2.9%).

The mean age at presentation was 16.8 months (SD=12.2). Median age at presentation was 13 months (IQR: 6-24).

Range: 1.5 months to 48 months.

Figure 2: Distribution of patients by sex



There were slightly more males than females with a 1:1.2 male to female ratio

There was no statistical difference between male and female respondents (p-value=0.6)

5.2 PRESENTATION

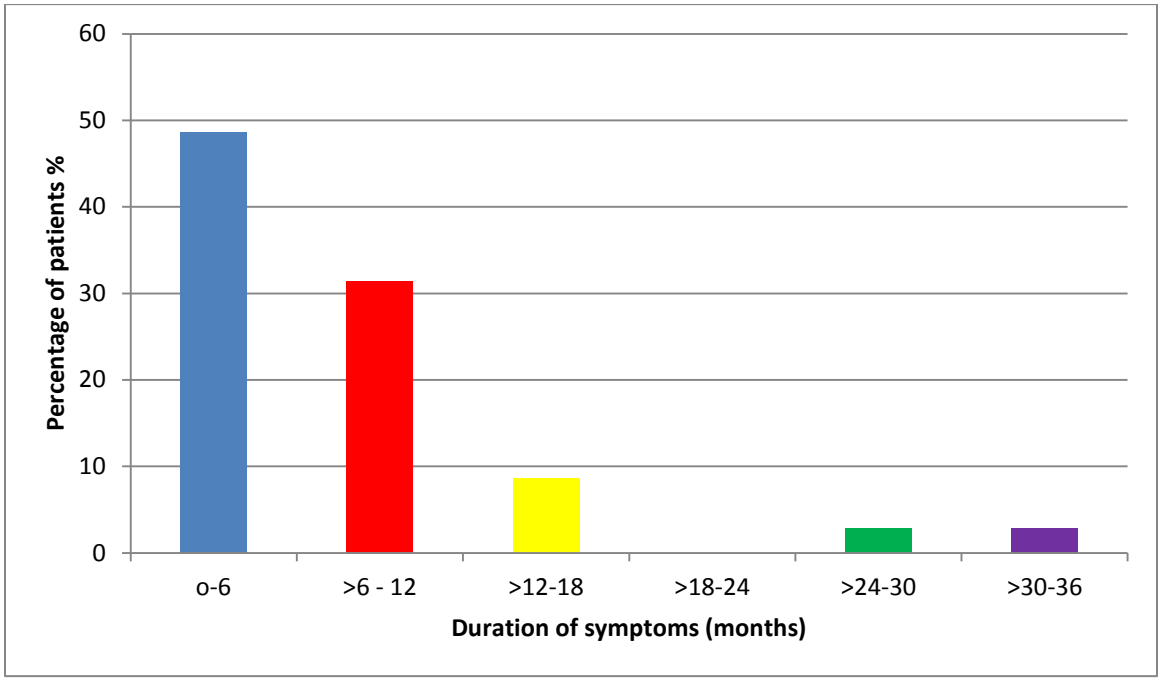
Patients' presenting complaints at admission

At presentation complaints concerning the non-salvage eyes included white reflex (34 patients; 97.7%), proptosis (6; 17.1%), redness (6; 17.1%), tearing (2: 5.7%) and hyphema (1: 2.9%). Some patients presented with more than one complaint.

. In the salvage eyes 4 patients reported history of white reflex too and 31 patients did not have any complaints.

Figure 3: Duration of symptoms

Duration of symptoms n=33

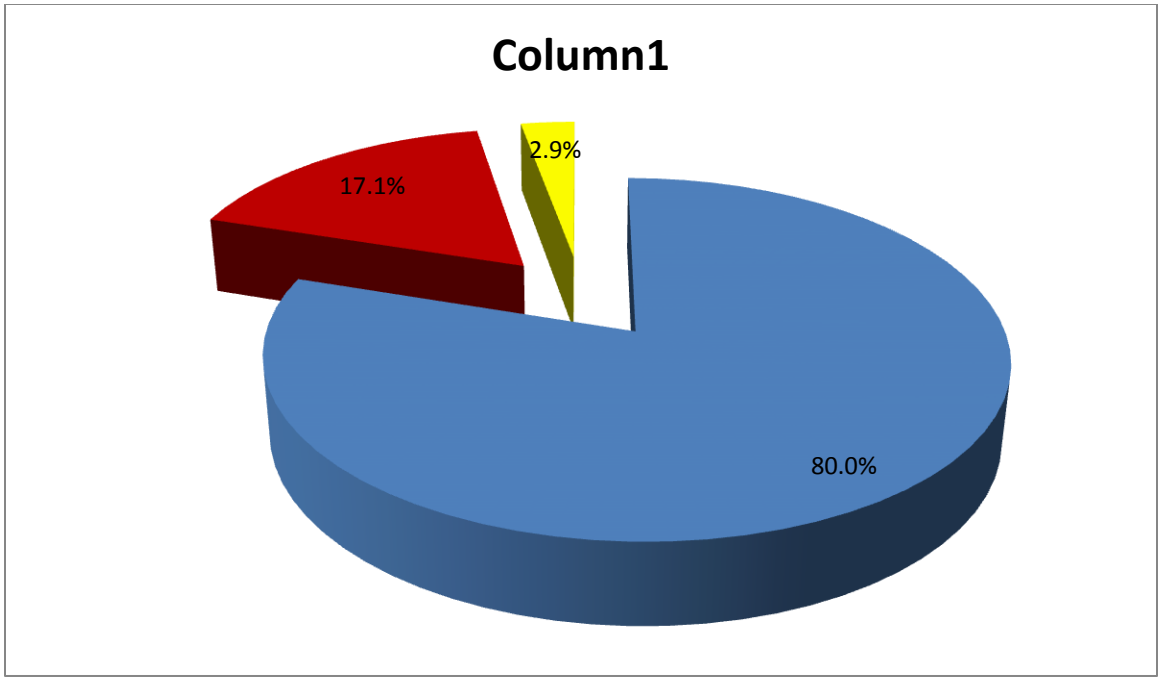


*2 patients had incomplete records

The mean duration of symptoms prior to presentation to KNH was 7.2 (SD=7.3) months

The range was 0.8 months (3 weeks) to 36 months.

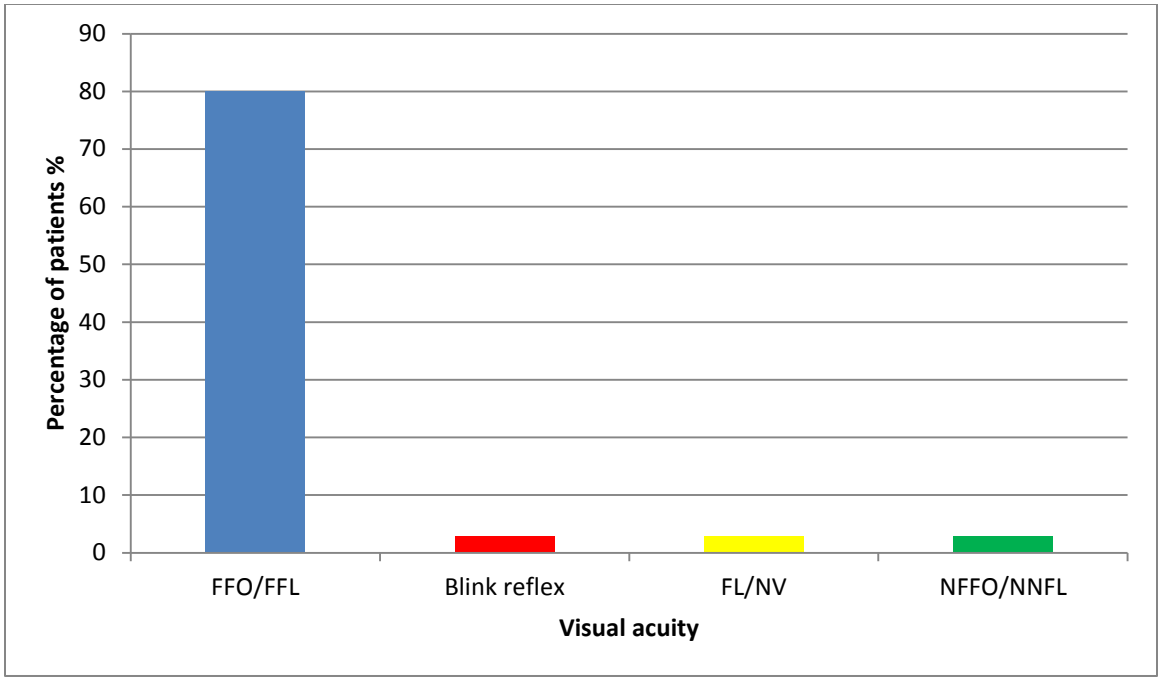
Figure 4: Family history of retinoblastoma



17.1 % of patients had a positive family history of retinoblastoma.

One patient's family history was unavailable.

Figure 5: Presenting visual acuity at first admission; salvage eye. n=31



4 patients (11.4%) had some missing data*

- FFL/FFO - Fixating and following light/objects
- FL+NV - Following Light + Navigational vision
- NFFO/NFFL - Not fixating nor following objects or light

Majority of the patients could fixate and follow light. One was 7 weeks old at admission and vision was recorded as blink reflex. Later during follow up he was able to fixate and follow light.

One patient could not fixate or follow objects or light because the eye had a large tumour covering the macular and disc.

Table 2: IIRC classification of the salvage eyes

1st EUA IIRC staging	Frequency n=35	Percentage (%)
A	12	34.3
B	11	31.4
C	5	14.3
D	7	20.0
TOTAL	35	100.0

Majority, 65.7 % (23), were Group A and B eyes.

Table 3: Number of tumours per eye

No. of tumours	Number of eyes	Percentage (%)
1-2	25	71.4
3-4	4	11.4
5-6	5	14.3
>6	1	2.9
Total	35	100
Location of tumours (n=88)	**Tumours per eye**	**Percentage (%)**
Posterior pole	58	65.9
Periphery	30	34.1
Total	88	100

Mean number of tumours per eye was 2.5.

Range of number of tumours per eye was 1 to 12.

5.3 TREATMENT

Table 4: Salvage eye treatment modalities.

TYPE	NUMBER OF SALVAGE EYES	PERCENTAGE (%)
CHEMOREDUCTION + LASER	8	22.9
CHEMOREDUCTION ONLY	8	22.9
CRYOTHERAPY ONLY	6	17.1
LASER ONLY	5	14.3
LASER + CRYOTHERAPY	4	11.4
CHEMOREDUCTION + LASER + CRYOTHERAPY	3	8.6
CHEMOREDUCTION + CRYOTHERAPY	1	2.9
TOTAL	**35**	**100**

Eight (22.9%) patients had chemoreduction only and did not proceed to focal consolidative therapy as one developed metastatic disease and care was changed to palliation, one died from metastatic disease during follow up. In three other patients the eyes were enucleated due to poor response to chemoreduction prior to commencement of focal consolidative therapy. Three patients were lost to follow up prematurely.

5.3.1 Chemotherapy for intraocular chemoreduction.

Systemic chemotherapy

A total of 20 (57.1%) patients received systemic chemotherapy for intraocular chemoreduction of tumours in the salvage eye. Of these 12 (34.3%) also had high risk pathology in the non – salvage eye.

Periocular chemotherapy

Only 2 (2.5%) patients, both with Group D eyes, received periocular chemotherapy. The agent administered was carboplatin which was injected in the sub-tenon space. Both patients received 2 courses each.

Table 5: Type of systemic chemotherapy for intraocular chemoreduction

Type of chemotherapy	Intraocular chemoreduction: n=20
High dose VEC	13
Normal dose VEC	7
Mean number of courses	**6**
Range of number of courses administered per patient	**2 - 13**

Of the 20 patients who received systemic chemotherapy for intraocular chemoreduction, 9 also had high risk disease on histology in the enucleated non-salvage eye and 3 had extraocular disease at presentation.

Table 6: Mean number of chemotherapy courses received for intraocular chemoreduction as per IIRC group: n=20

IIRC	No. of patients	Mean No. of courses	Range
A	1	6	0
B	8	7	3-13
C	4	5	5-8
D	7	5	3-9

n=20: number of patients who received systemic chemotherapy for intraocular chemoreduction of tumour in the salvage eye.

One patient with group B disease had 11 courses of chemotherapy with poor response to treatment and the eye was eventually enucleated. Another patient with group B disease also had poor response to chemotherapy and the tumour eventually involved the disc.

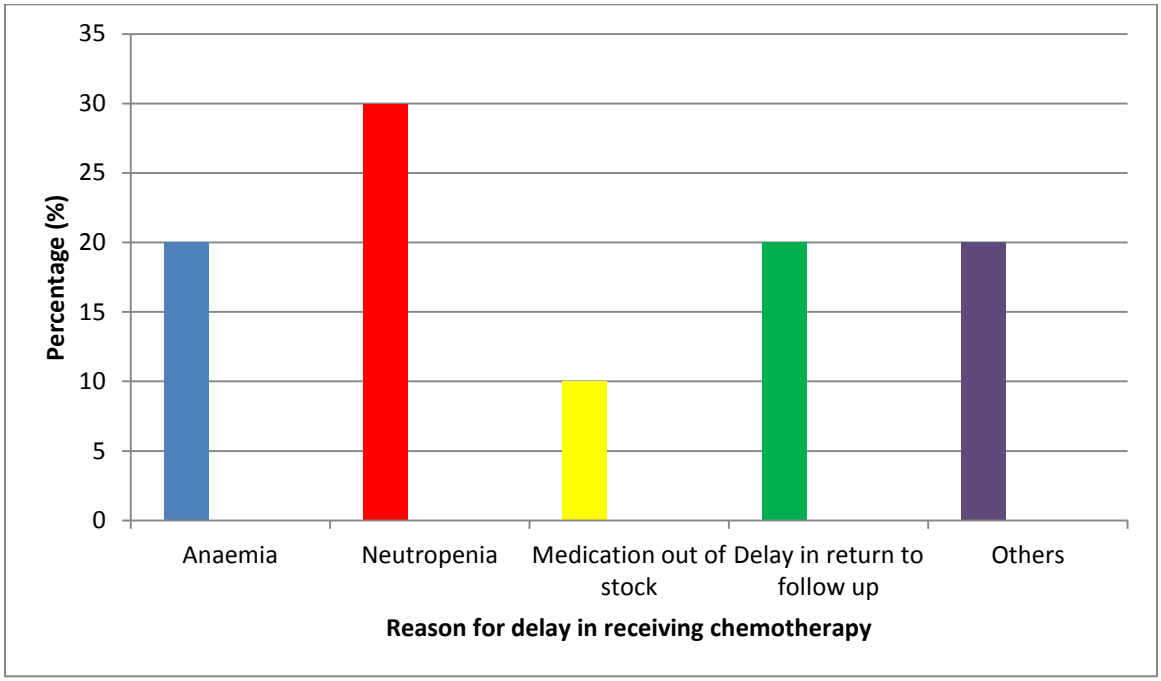
Table 7: Delay between courses during administration of systemic chemotherapy for intraocular chemoreduction in salvage eye; n=20

Delay	Frequency n=20	Percentage (%)
Yes	10	50.0
No	9	45.0
Incomplete records	1	5.0
Total	20	100

n= 20: number of patients who received systemic chemotherapy for intraocular chemoreduction of tumour in the salvage eye.

(Delay was defined as duration of one week or more between the day a patient was scheduled to receive systemic chemotherapy to the actual day the systemic chemotherapy was administered.)

Figure 6: Reason for delay in administration of systemic chemotherapy for intraocular chemoreduction in salvage eye: n=10



Delay = > one week from date scheduled for chemotherapy.

*Others: one patient: cellulitis of one hand following leakage of chemotherapy agents from IV line. Second patient: return date pushed forward to coincide with date scheduled for EUA.

Mean 3 weeks

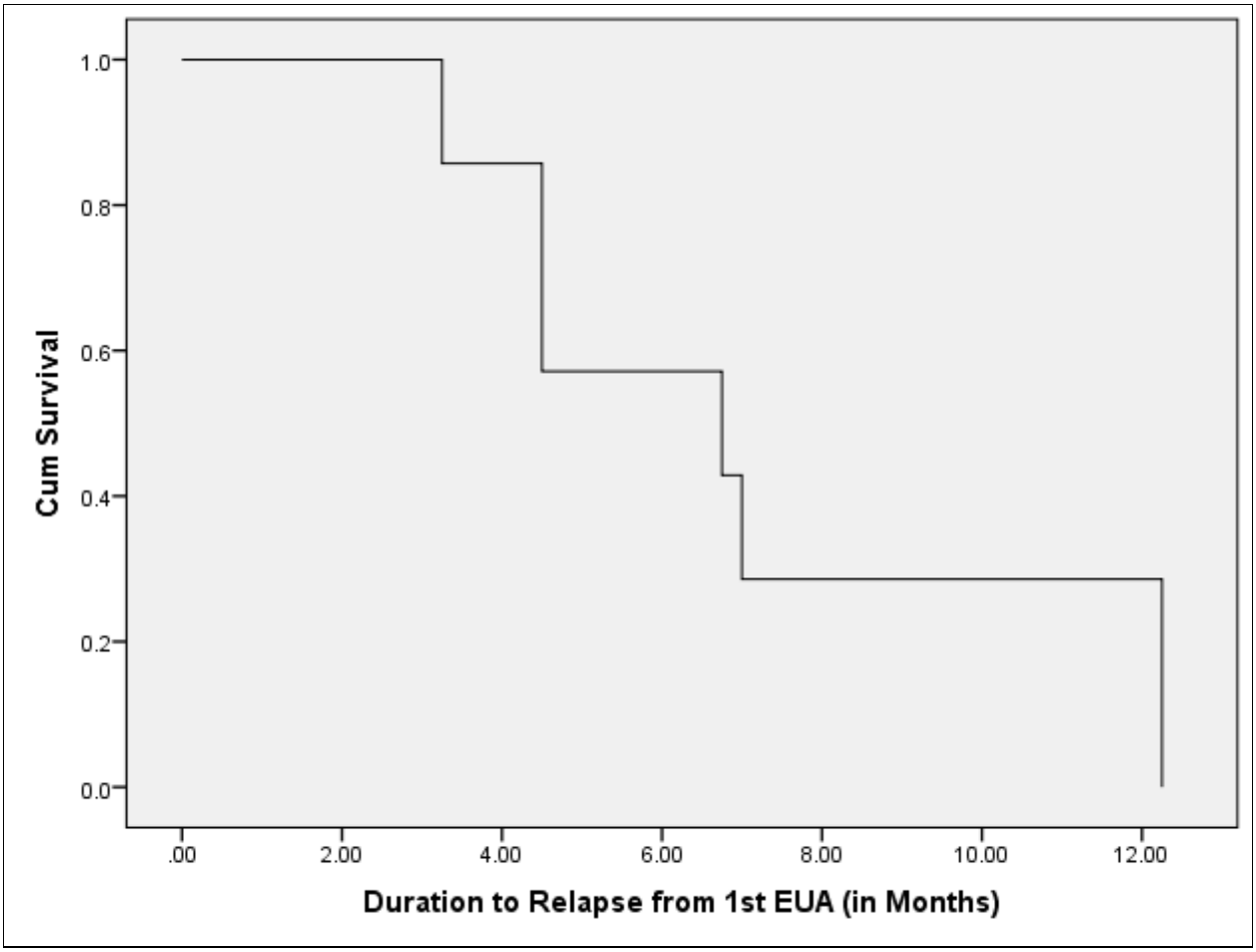
Duration of delay ranged between 1 to 12 weeks.

5.4 FOLLOW UP

5.4.1 Tumour relapse during follow up.

Seven (20.0%) patients experienced relapse with tumours re- growing after demonstrating a favourable response.

Figure 7: Relapse of tumours during the follow up period



The median survival time for tumor relapse from 1st EUA was 6.8 months (27 weeks). Mean duration to relapse was 7.2 months (28.9 weeks). Range 3.3 – 12.3 months (13 to 49 weeks).

Table 8: Characteristics of eyes that had tumour relapse

Characteristic	Frequency n=7
IIRC staging	
A	2
B	2
C	1
D	2
Delay in-between chemotherapy administration	
No	3
Yes	2
Missing / incomplete data	2
Outcome at last follow up	
Control not achieved	3
Lost to follow up	3
Tumours controlled	1

n=7: number of eyes that had tumours relapse

5.4.2 Occurrence of new tumours during the follow up period.

A total of 9 (25.7%) patients developed new tumours during the follow up period.

Table 9: Time from 1st EUA to development of new tumours during follow up (per eye): n=9

Time to development of new tumours in months	Frequency n=9	Percentage (%)
0 – 6	5	55.6
>6 – 12	3	33.3
>12 – 18	0	0.0
>18 - 24	1	11.1

n=9: number of eyes that developed new tumours during follow up

Mean time to development of new tumours was 6.5 months

Range 1 to 20.5 months.

Table 10: Number of new tumours per eye: n=9

Number of new tumours	Number of eyes	Percentage
1 - 2	5	55.6
3 - 4	3	33.3
>4	1	11.1

n=9: number of eyes that developed new tumours

One patient developed a total of 6 new tumours during the course of follow up

Mean number of new tumours per eye was 2.4 tumours

Range 1 – 6 new tumours.

Table 11: Ages at which patients developed new tumours: n=9

Age in months	Frequency n=9	P value
0 - 6	2	0.112
>6 - 12	2	0.660
>12 - 18	1	0.753
>18 - 24	2	0.660
>24 - 30	1	0.882
>30 - 36	1	0.255

n=9 Number of patients who developed new tumours during follow up

Majority of new tumours developed in children younger than 24 months of age.

Development of new tumours reduced with age at presentation.

There was no significant statistical differences between the age categories and developing new tumor.

Table 12: Mean duration to development of new tumours per IIRC group: n=9

IIRC	Frequency	Mean time to developing a new tumour (weeks)
A	4	40.8
B	1	4
C	2	17
D	2	15

n=9 Number of patients who developed new tumours during follow up

5.4.3 Enucleation of salvage eye during follow up.

A total of 6 (17.1%) salvage eyes were enucleated during follow up.

Table 13: Duration from 1st EUA to enucleation of salvage eye n=6

DURATION FROM 1ST EUA TO ENUCLEATION (MONTHS)	FREQUENCY
0 – 12	3
>12 – 24	1
>24 – 36	1
>36 – 48	1

n=6: number of eyes enucleated that were undergoing globe salvage

Majority of the eyes were enucleated within the first 12 months of treatment.

The mean duration from time of diagnosis was 15.7 months (SD=15.5).

The median duration from time of diagnosis was 9.5 (IQR3-33) months.

Range was 2 months to 37 months.

Table 14: IIRC staging of enucleated eyes

Of the 6 eyes that were enucleated 3 were Group B eyes and 3 were Group D eyes at first EUA. One B eye eventually progressed to a D eye prior to enucleation.

	IIRC STAGING AT 1ST EUA	IIRC STAGING AT LAST EUA	REASON FOR ENUCLEATION
1	B	B	Disc involvement with poor response to treatment (chemoreduction)
2	B	D	Progression to group D with poor response to treatment (chemoreduction)
3	B	B	New tumour at the disc with poor response to treatment (chemoreduction)
4	D	D	Poor response to treatment (chemoreduction)
5	D	D	Poor response to treatment (chemoreduction)
6	D	D	Disc involvement , poor response to treatment (chemoreduction)

All patients underwent tumour chemoreduction but the tumours did not respond well enough to reach a size amenable to focal consolidative therapy.

Almost all patients received normal dose VEC for chemoreduction.

Range of number of courses of systemic chemotherapy received: 2 to16

5.4.4 Overall outcome

Table 15: Summary of events and outcomes during treatment and follow up

Outcome	Number of patients	Percentage (%)
Well controlled (globe salvaged)	14	40.0
Lost to follow up	9	25.7
New tumour occurrence during follow up	9	25.7
Recurrence during follow up	7	20.0
Enucleated	6	17.1
Still undergoing treatment	4	11.4
Intracranial Metastasis or death.	3	8.6

Of the salvage eyes in which tumour control was achieved 7 were Group A, 5 were Group B, 1 was group C and one was group D.

Mean duration taken to control all tumors was 7.27 (SD=4.62) months. Median duration taken to control all tumors was 7 (IQR: 3-11) months with a range of 1.5-14 months.

Patients with active tumours at last EUA had Group C or D eyes. Of these one had been on follow up for 4 months, one for 24 months and one for 36 months.

Table 16: Visual acuity at last follow up visit. n=29

VISUAL ACUITY	FREQUENCY	PERCENETAGE (%)
FFO/FFL	28	96.6
PL	1	3.4
TOTAL	29	

*6 (17.1%) of patients were enucleated.

All patients whose tumours were controlled had good vision at the time of their last follow up visit. None of the patients in this study whose preservation eye was not enucleated lost vision at the time of their last follow up visit during the study period.

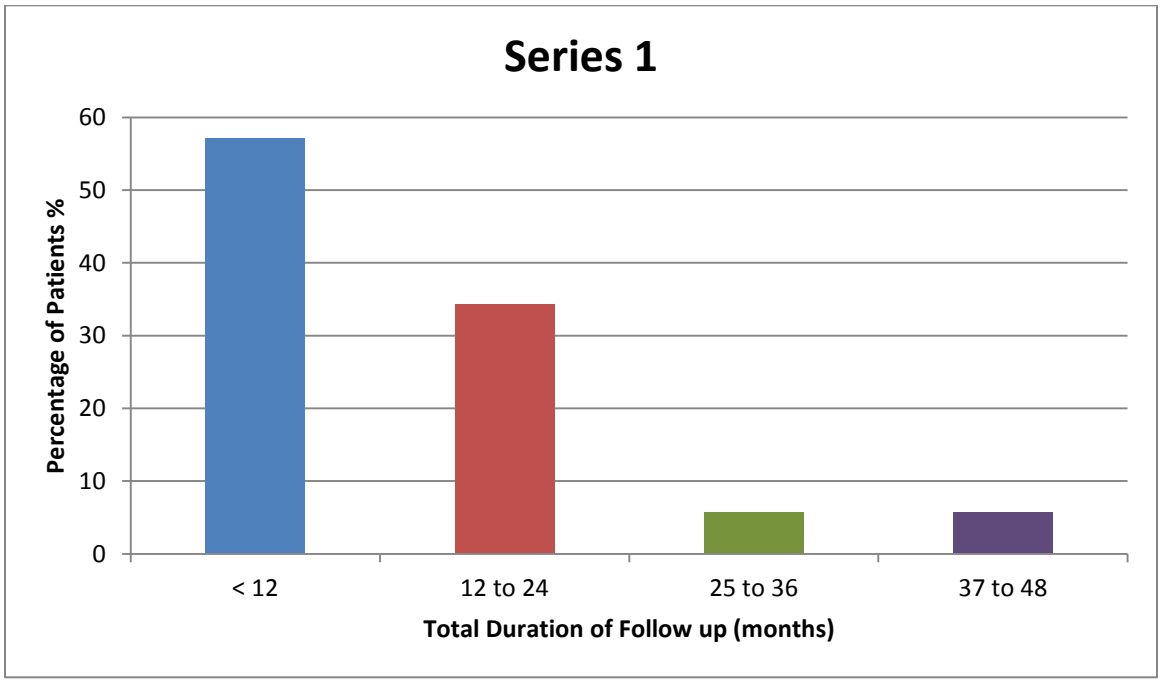
Table 17: Intraocular complications at last EUA

Characteristic	Frequency n=3	Type of focal therapy
Epiretinal haemorrhage	1	Cryotherapy
Hyaloid haemorrhage	1	Laser + cryotherapy
Intraretinal and vitreous cysts	1	Laser

Only 3 (8.6%) patients developed anatomical complications following focal consolidative therapy by the time of their last EUA.

5.4.5 Duration of follow up

Figure 8: Total duration of follow up of patients who underwent globe preservation (in months)

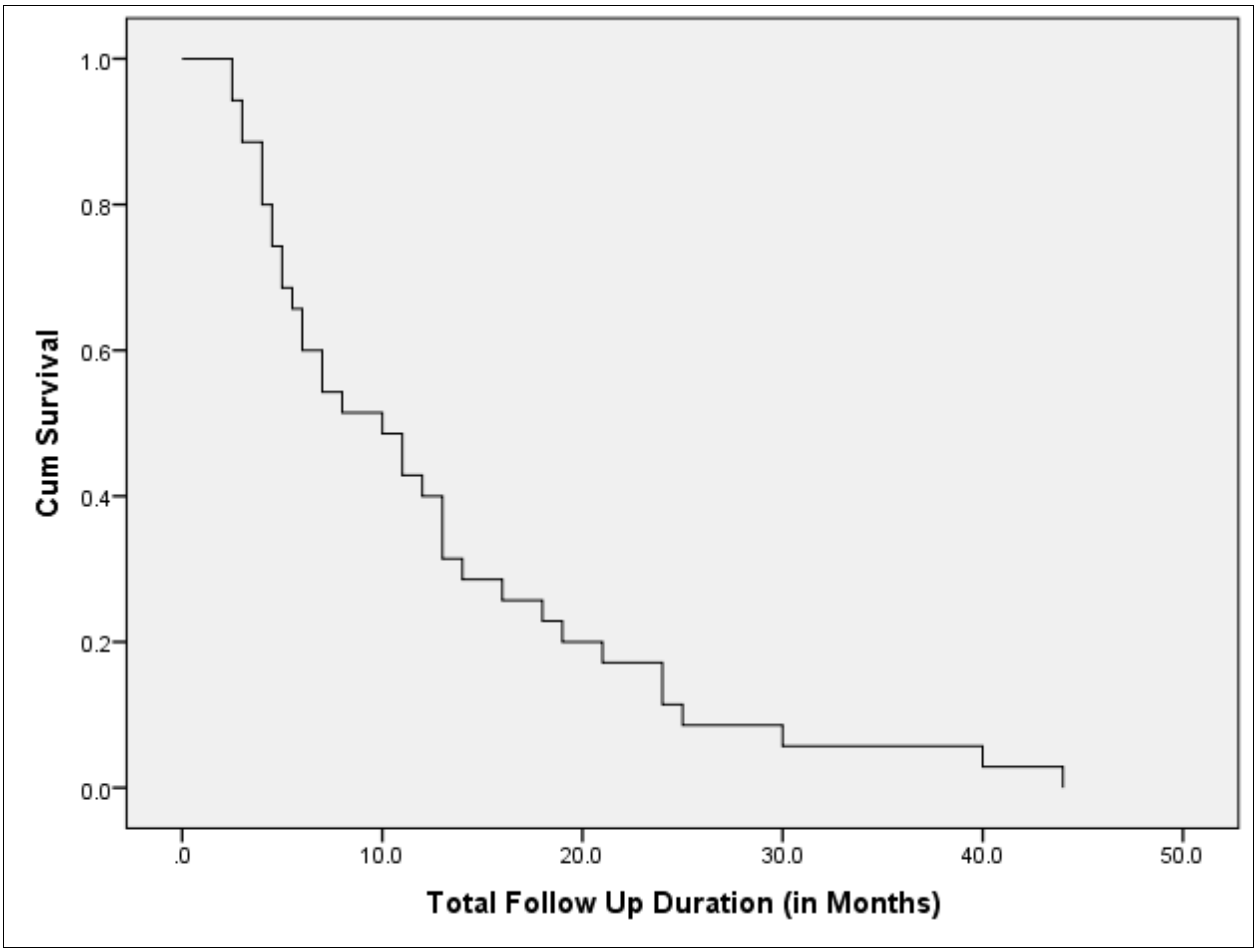


The mean duration of total follow up was 13.2 months (SD=10.5)

Median duration of follow up was 11 (IQR: 5-18)

Range 2.5 months to 44 months.

Figure 9: Kaplan Meier curve on follow up of patients undergoing globe preservation.



Majority of patients were followed for less than 20 months.

20 (57.1%) were followed up for less than 12 months. Of these, 1 patient from Ethiopia was enucleated 3 months after presentation and was discharged for follow up at Menelik Hospital in Ethiopia. 1 died after 5.5 months of follow up as a result of metastatic disease. 2 were enucleated between 4 to 6 months after presentation and did not return for follow up thereafter. 5 presented towards the later part of the study period and were still continuing with follow up with one having achieved control of the tumours already. 1 patient relocated to Kampala, Uganda after tumours were controlled and study eye salvaged. They did not return to follow up thereafter. 8 other patients were lost to follow up altogether. 2 developed metastatic disease and globe salvage was abandoned for palliative care.

9 (25.7%) of the patients were followed up for between 12 to 24 months.

4 (11.4%) had been of follow up for between 25 and 36 months and 2 (5.7%) had been on follow up for > 36 months at the time of their last visit.

DISCUSSION

Over a study period of 7 years a total of 35 patients diagnosed with bilateral retinoblastoma, each with one eye enucleated and the other undergoing globe preservation therapy qualified for inclusion in the study. Of the 35 patients 32 (91.4%) were from Kenya, 2 (5.7%) were from Somalia and 1 (2.9%) was from Ethiopia. The patients from the neighboring countries came as referrals from their health facilities. KNH serves as a referral hospital for neighboring countries for management of patients for modes of treatment that are not available in their institutions.

The respondents from Kenya came from 15 out of the 47 counties in the country. These were mostly counties from the Western, Rift Valley, Central and Coastal regions of the country.

Presentation

Majority of the patients, 15(42.9%), were below the age of 1 year at the time of presentation. Twelve (34.3%) were aged between 1-2 years. Seven (20.0%) were aged between 2-3 years. One (2.9%) was four years old at the time of presentation. This was in keeping with the international pattern where majority of patients with bilateral disease present below the age of one year.[1, 4, 20] The mean age at presentation however was 16.8 months (SD=12.2). Median age at presentation was 13 months (IQR: 6-24).This was due to extreme age of one patient who presented at the age of 4 years.

The patients in this study presented at a younger age compared to earlier studies done in Kenya by Nyawira et al in 2008 and Nyamori et al in 2009 where patients presented aged between 24.3 to 26 months respectively.[2, 3] This could be attributed to more awareness of the disease following an initiative by the ministry of health to include retinoblastoma in the maternal and child health follow up records that alerts both the clinicians and parents to watch out for the symptoms of the disease.

The mean age at presentation however was similar to a study done in Egypt by Azza et al where the mean age at presentation in patients with bilateral retinoblastoma undergoing globe salvage treatment was 16.25 months (range of1.5 -84 months).[49] It was also in agreement to a similar study done in India by Roysakar et al where the mean age of presentation was 16.87 months. [50]

Slightly over a half of the patients, 19 (54.3%), were male. 16 (45.7%) were female. There was no statistical difference between the male and female patients (P value = 0.60). The male to female ratio was 1:1.2. This was comparable to international data where no sex predilection was found.[1, 20]

The most common presenting complaint at admission was a white reflex (97.1%) followed by proptosis and red eye (17.1% each) and squint (11.4%). Other complaints included poor or total loss of vision tearing and hyphema. Majority of the patients, 31(88.6%) did not have complaints concerning the salvage eye at presentation; only four patients (11.4%) reported a white reflex. These finding were in keeping with a study by Nyawira et al who found the commonest presentation in Kenya to be white reflex followed by orbital swelling then pain and redness.[3] The fact that some patients presented with proptosis points towards delayed presentation in seeking definitive medical attention. The presenting complaints in this study were in contrast to a study done by Owoeye et al in Nigeria which demonstrated a much more delayed presentation where 84.6% of patients presented with proptosis and chemosis, leukocoria in 61.5% and hypopyon in 46.1%.[51] Aziz et al in Egypt found leukocoria as the most common presentation at 80.4% and buphthalmos in 3 % of patients. This pointed towards a slightly earlier presentation of patients.[49]

In this study 17 (48.6 %) of patients had had symptoms of retinoblastoma for a duration of between 0-6 months before presentation at KNH. Eleven (31.4%) had had symptoms for a duration of more than 6 months up to 12 months, 3 (8.6%) for a duration of between 12 to 18 months and 2 (5.8%) for more than 24 months. Only one patient presented in less than a month (3 weeks) after symptoms of retinoblastoma were noted. For 2(5.8%) patients some of their medical records were missing and information concerning duration of symptoms prior to presentation at KNH wasn't found. The mean duration of symptoms from time of onset to time of presentation was 7.2 months (SD= 7.3). Median duration of symptom was 6 (IQR=3-10) months.

The mean delay of about 7 months prior to seeking definitive treatment was almost similar to a study by Makite et al in Kenya in 2014 which found a mean overall delay of 8.1 months [52.] The findings in this study were in contrast to one done in Tanzania, also in the East African region, by Bowman et al which found a longer mean lag time to presentation to hospital for definitive

management to be 10 months (SD=17). [48] The shorter delay period in Kenya could be attributed to sensitization programs carried out in the country.[3] This, though, was still in contrast to the more developed countries where patients took a much shorter time. Butros et al in the United States showed a delay of less than 2 months. [53] In Taiwan Ling-Yuh et al found that patients took a mean of 2.5 months between noticing symptoms and seeking definitive treatment where a diagnosis of retinoblastoma was made.[54]

Family history of retinoblastoma was positive in 6 (17.1%) of the patients. Twenty eight (80.0%) did not have a positive family history. One (2.9%) patient did not have information of family history of retinoblastoma as he was an orphan being raised in a children's home. This was higher than reported international rates (5%) and could be due to the fact that the patients studied had bilateral disease and could have had a higher possibility of having familial disease. The findings in this study were almost similar to study findings by C Shields where 25 % of patients with bilateral retinoblastoma had a positive family history but much higher than a study done in India by Roysarkar where 5% of patients reported a positive family history.[5, 55, 50]

At the time first admission majority, 28 (80.0%), of the patients could fixate and follow objects or light with the salvage eye. One patient (2.9%) presented at 7 weeks of age and had not yet developed the ability to fixate and follow objects at the time of admission and vision was recorded as presence of blink reflex. Later as the patient continued with follow up he developed the ability to fixate and follow objects. One other patient, (2.9%), had navigational vision in the salvage eye at first admission but improved to fixating and following objects during treatment and follow up. Having vision in the salvage eye was an important factor that had to be considered as one of the main aims of salvaging a globe is to save vision. This ensures that the patient has a better quality of life. One patient though (2.86%), could not fixate or follow light with the salvage eye at the time of first admission. It was a group D eye with tumour covering the disc and macula. Chemoreduction was attempted for 3 months but due to poor response and failed restoration of vision the eye was eventually enucleated. At this point in time saving the life of the patient took precedence. Four (11.4%) of patients had incomplete records and vision as recorded at admission could not be accessed. In the subsequent follow up visit notes vision was recorded as FFO.

The international intraocular retinoblastoma classification was used to classify the salvage eyes. Majority, 64.7%, were Group A and B eyes. Five (14.3%) were Group C eyes and 7 (20.0%) were Group D eyes. From these findings it was expected that the proportion eyes that would be salvaged would be high as majority of the salvage/study eyes had a good chance of being salvaged having been found with early stages of the disease.[15] This is also supported by a study by Shields et al where it was found that response rate to treatment was greater in Group A and B eyes. The study showed chemoreduction was 100% in Group A eyes, 93% in Group B, 90% in group C and 47% in group D eyes. [56] Our salvage rates however were lower than expected due to loss of patients to follow up, delays in returning for follow up visits allowing the tumours to advance and lack of advanced forms of treatment i.e EBRT and plaque radiotherapy.

Concerning the intraocular tumours documented, there were 88 tumours in all the salvage eyes collectively. Of these, majority, 65.9%, were located posterior to the equator and 34.1% were located anterior to the equator. Majority of the salvage eyes, 71.4 % had between 1 to 2 tumours, 24% had between 3 to 6 tumours per eye and one patient, 2.9%, developed a total of 12 tumours from presentation to time of last EUA. The mean number of tumours per eye was 2.5. Range was 1-12. This was higher than the number of tumours found per eye in the study by V Lee et al where the range of number of tumours recorded per eye was from 1 to 6. It was also higher than a study by Azza in Egypt which found an average of 1.6 tumours per eye (range 1-6). This could be attributed to earlier presentation of patients with concomitant fewer numbers of intraocular lesions in the developed countries.[20, 49]

Treatment

Twenty seven patients (77.2%) had focal treatment of the tumours. Of these group of patients, 8 had both chemoreduction and laser, 6 had cryotherapy only, 5 had laser treatment only, 4 had both laser and cryotherapy treatment, 3 had a combination of chemotherapy followed by laser and cryotherapy and one patient had the tumours treated with both chemoreduction followed by cryotherapy.

Eight (22.9%) patients had chemoreduction only and did not proceed to focal consolidative therapy as one developed metastatic disease and care was changed to palliation, one died from metastatic disease during follow up. For three other patients the eyes were enucleated due to poor

response to chemoreduction prior to commencement of focal consolidative therapy and three were lost to follow up prematurely.

Overall, more than half of the patients in this study, 20 (57.3%), needed chemoreduction with systemic chemotherapy before focal consolidative therapy could be attempted either at admission or during the course of follow up. This was high compared to a study done by Lee at al in Australia where only 13% of patients needed chemotherapy to reduce the intraocular tumour size. [20] The patients in our study delayed in seeking treatment and this could have allowed time for tumours to grow.

Of the 20 (57.1%) patients who received systemic chemotherapy for intraocular chemoreduction of tumours in the salvage eye majority (16) received the chemotherapy after the first EUA while for 5 the decision was made during the course of follow up due to tumour relapse or development of new tumours. 9 of these patients also had high risk pathology in the non – salvage eye and 3 had extraocular disease in the non-salvage eye at presentation. The presence of high risk pathology on histology and extraocular disease in the non-salvage eye was another indicator of patients presenting late. This raised the risk of patients having advanced intraocular disease in the salvage eye which is harder to control. It also exposed the patients to the risk of developing metastatic disease that could change the management plan from treatment to palliative care.

On the type of systemic chemotherapy administered, more than half of the patients (13) received high dose VEC and 7 received normal dose VEC. Those who received high dose VEC were patients who presented from 2012 onwards when the chemotherapy regimen was changed from the normal dose of VEC to high dose VEC. This was informed by an ongoing study in Toronto, Canada where a high dose of VEC is administered in one day and repeated every 21 to 28 days. In Toronto however there is additional use of cyclosporine with granulocyte stimulating factors being given afterwards. The cycle is repeated every 21 to 28 days. The use of cyclosporine is not yet practiced at the KNH and granulocyte stimulating factors are only administered to children with leukopenia due to cost constraints. [57, 58]

Mean number of chemotherapy courses received was 6 with a range of 2-13. This was comparable to a study by Azza et al in Egypt where patients received a mean of 6 courses of

systemic chemotherapy for chemoreduction (range 1to 6).[49] Systemic chemotherapy has been found to play a great role in increasing globe salvage rates with a reduction of need for EBRT or enucleation. On average 2 to 6 courses of systemic chemotherapy have been documented to be effective in achieving adequate chemoreduction. [59, 60]

Of the twenty patients who received systemic chemotherapy 1 had a Group A eye, 8 had Group B eyes, 4 had group C eyes and 7 had group D eyes. On average the patients who had group B eyes had the highest mean number of chemotherapy courses. This was due to one patient receiving 13 courses of chemotherapy in an effort to reduce the tumour prior to focal consolidative therapy. Due to poor response the eye was eventually enucleated. It is possible that the tumour become chemo-resistant at one point. The patients with group D eyes received fewer courses on average due to early enucleation following poor control of tumour and early loss to follow up. Some enrolled towards the end of the study and had been on follow up over a short period by the end of the study duration. Of these group D patients 3 were enucleated at 2, 3, and 6 months respectively. One got lost to follow up after 4 months. Three were still on follow up and had been on treatment for 4, 13 and 30 months respectively.

Among the patients who got systemic chemotherapy half experienced delay of at least one week between the day scheduled for administration of chemotherapy and the actual day when chemotherapy was administered. The mean duration of delay was 3 weeks with a range of 1 to 12 weeks. The most common reason for delay was neutropenia in 3 patients following a previous course of systemic chemotherapy. This was followed by anaemia in two patients and failure of patients to return on time for two other patients. For one patient delay was occasioned by a stock out of chemotherapeutic drugs. One patient developed cellulitis after chemotherapy extravasated into soft tissues from a faulty intravenous cannulation line and systemic chemotherapy was delayed to allow healing. One patient was rescheduled to come at a later date in order to synchronize EUA dates and administration of systemic chemotherapy.

Only 2 (5.7%) patients, both with Group D eyes, received periocular chemotherapy. The agent administered was carboplatin which was injected in the sub-tenon space. Both received 2 courses each. One patient eventually had the eye enucleated and one had not achieved control of the tumours at the last EUA. The fact that control of tumours in these 2 eyes was still hard to achieve despite the boost of administering sub-tenon carboplatin was in keeping with the study by Reza

et al which found that sub-tenon carboplatin did not increase efficacy of systemic chemotherapy in the treatment of intraocular retinoblastoma and does not significantly raise chances of globe salvage in eyes with advanced disease.[26, 28] Sub-tenon carboplatin is also not popular due to its side effects which include severe periocular inflammation with oedema which was observed in the two patients.[26, 27]

The use of intravitreal melphalan is an option that could be pursued in our set up in an attempt to control tumours in eyes with vitreous seeding. The use if intravitreal melphalan in controlling vitreous seeds has posted encouraging results with tumours in most eyes with advanced disease being controlled. The rate of complications is low and dose dependent with some of the documented complications being vitreous haemorrhage, cataracts, salt and pepper retinopathy, posterior synichae, hypotony and phthysis. In reported studies no extraocular extension as a result of the injection has been reported. [61, 62, 63]

Tumour relapse

During the course of treatment and follow up, seven (20.0%) of the thirty five patients in the study experienced relapse of tumours after demonstrating an initial favourable response following commencement of treatment. This was similar to a study done by Azza et al in Egypt where 23.9% (11/46) patients experienced tumour relapse. [49]

In our study the median survival time for tumor relapse from 1st EUA was 6.8 months (SD 3.5). Mean duration to relapse was 7.2 months. Range was 3.3 – 12.3 months. Of the seven patients who relapsed two had IIRC Group A eyes, two had Group B eyes, one had Group C eye and two had group D eyes. Three had associated vitreous seeding or subretinal seeding. In a study done by Shields et al in USA, and Azza et al in Egypt, the strongest risk factor that was associated with relapse of tumour was vitreous and subretinal seeding. [64, 49] Delay in return to follow up also contributed to tumour recurrence in this study. One patient delayed in retuning for a follow up visit for 7 weeks due to financial constraints and the intraocular tumour relapsed after showing an initial favourable response.

Of these seven patients 2 had had delays in between courses during chemotherapy administration and three did not have any delays. Data for two patients was incomplete. It was hard to establish if there was any relationship between delays in chemotherapy administration and rates of relapse

of tumours due to the small numbers of patients and missing data for some patients. Out of the seven patients whose tumours relapsed control was eventually achieved in one patient, three were still undergoing globe salvage therapy at the time of their last EUA and three got lost to follow up.

Development of new tumours

In this study 9 (25.7%) patients developed new tumours. This was comparable to reported frequencies in similar studies. A study done in Australia by V Lee et al found that 23% of patients developed new tumours during follow up.[20] A similar study done by Abramson et al in USA reported 24.8 % of eyes undergoing globe salvage developed new tumours. [65] In India Roysakar et al found a slightly lower proportion of 22.5%.[50] Azza et al in Egypt reported a much lower occurrence of 6.5%.[49] In this study more than half of the new tumours (55.6%) developed within the first six months of follow up. Mean time to development of new tumours was 6.5 months with a range of 1 to 20.5 months. This was longer than a study by Roysarkar et al where the mean interval between initiation of therapy and development of new tumours was found to be 4.4 months with a range of 1.5 to 9 months. [50]

The incidence of developing new tumours in this study reduced with increasing age at presentation. A study by shields et al also found that the biggest risk factor in developing new tumours was young age at presentation; the younger the age at presentation the higher the risk of developing new tumours. [66] In a study done in India 47% of patients who were less than one year old developed new tumours compared to 4.4% of patients older than one year of age. [50] This could be attributed to the still developing retina in younger children. The other risk factor for developing new tumours during or after treatment is hereditary disease. This was not established in this study as it was beyond its scope. [67] In this study it was noted that development of new tumours occurred earlier, 4.0-8.5 months, in patients with advanced disease (Group C and D) compared to those with less advanced disease (Group A and B) at 5.5 – 14.38 months.

On number of new tumours recorded, majority, 5 out of 9, of the salvage eyes developed between one and two new tumours each, 3 salvage eyes developed between three to four tumours each and one salvage eye developed 6 new tumours during the course of follow up. The average number of new tumours that developed per salvage eye was approximately 2 tumours with a

range of 1 to 6. This was almost similar to a study by Roysarkar where eyes undergoing globe salvage developed an average of 1.8 tumours new tumours per eye during follow up.[50]

Overall these findings emphasized further the need for close follow up of patients undergoing globe preservation with regular fundus examination with fully dilated pupils in order to detect new tumours early and initiate treatment. It should be kept in mind that the younger the age of the child at presentation the higher the risk of developing new tumours and high index suspicion should be maintained during EUAs. Over time, the incidence of new tumour development decreases with very few incidences being reported after the age of 5 years.[68] It should be kept in mind however that fundus exams should be continued until at least the age of 10 years.

Enucleation of salvage eye

By the end of the study period 6 (17.1%) of the salvage eyes had been enucleated. The mean duration from time of diagnosis to enucleation was 15.7 months (SD=15.5). The median duration from time of diagnosis was 9.5 (IQR3-33) months. Range 2-37 months. 3 of the enucleated salvage eyes were in group B and the other 3 were Group D eyes. Two of the group B salvage eyes had tumours extending to the optic disc with poor response to treatment. Enucleation was done to avoid increasing the risk of metastasis. One group B eye had a tumour that initially regressed following therapy but later relapsed with associated vitreous seeding. This was preceded by a period of time where the patient got lost to follow up. On subsequent EUAs it was found not to be amenable to globe preservation therapy and the eye was enucleated. One respondent with a group D eye had tumour extending to the optic disc with poor response to treatment and a decision to enucleate the eye to reduce risk of intracranial metastasis was made. The second patient with a group D eye had the eye enucleated after the tumour failed to respond to treatment. The third patient with a group D had the eye enucleated following relapse that was not amenable to focal therapy.

Our proportion of enucleation, 17.1%, was high in comparison to a study done by V Lee et al in Australia in which 4.6% of patients had to have the salvage eyes enucleated.[20] Azza et al in Egypt also recorded a lower enucleation proportion where only 8.3% of patients had been enucleated at the end of their study. [49] This could be explained by the earlier presentation of patients in seeking definitive treatment in the developed countries compounded with availability

of additional modes of focal consolidative therapy ie external beam radiotherapy and plaque radiotherapy which are known to improve globe salvage especially in eyes with vitreous seeding ie Group C and D eyes or eyes responding poorly to cryotherapy and laser therapy which was the main indication for enucleation in the eyes in this study. [50, 52] The enucleation rate was however comparable to a study done in France by Livia et al where 20% of the study eyes were enucleated. [69]

Outcome

At the end of the study period 14 (40.0%) salvage eyes had all their tumours controlled and globe salvaged. Our modes of treatment included systemic chemotherapy, laser therapy, and cryotherapy.

Our salvage proportion was relatively low compared to the salvage proportion in the developed countries. In a study done in France by Livia Lumbrose et al, the globe preservation / salvage proportion in management of 147 eyes was 84 %. Methods used in conservative management were chemotherapy, thermotherapy, cryotherapy and radioactive plaque (iodine 125) brachytherapy. [69] V Lee et el had a globe salvage rate of 95.40%. The modes of treatment used were cryotherapy, chemotherapy, chemothermotherapy, radioactive plaque radiotherapy, lens sparing radiotherapy and whole eye radiotherapy. [20] In India Roysarkar et el found cure rate was 60% (24/40 patients) over a mean follow up period of three years.[50] In Egypt globe salvage was successful in 69.5% (32/46) patients.[49] Although this was lower than the success rates of the west it was still higher than our success rate. Patients had access to EBRT in addition to laser, cryotherapy and chemotherapy.

Of the 14 eyes that were salvaged majority were Group A and B eyes making up 85.7% of all salvaged eyes. 7 (50.0%) Group A eyes and 5(35.7%) Group B eyes. 1(7.1%) was a Group C eye and 1 (7.1%) Group D eye. Mean duration taken to control all tumors was 7.3 months (SD=4.6, range 2-14). Median duration taken to control all tumors was 7 (IQR: 3-11) months with a range of 1.5-14 months. This is keeping with data from the National Cancer Institutes (United States of America) and by the study by V Lee et al done in Australia which demonstrated higher salvage rates in eyes with less advanced disease, Group A and B eyes, or RE group I to III as compared to IIRC Group C and D eyes and RE group IV and V eyes.[19,20] This was further supported by a

study done by Shields et which showed that the international classification of retinoblastoma could be used to predict success in treatment. [70] It is important to note that in this study 9(25.7%) patients were lost to follow up prematurely and of these 5 had Group A eyes and 2 had Group B eyes. Considering the fact that majority of eyes salvaged were Group A and B eyes these eyes had a good chance of being salvaged and would have further improved our globe salvage rates. Of the remaining two patients one had a Group C eye and the other a Group D eye.

At the end of the study period 3 patients (8.6%) still had active tumours in the salvage eye and were still undergoing globe preservation at the time of their last EUA. One had a Group C eye, and two had Group D eyes. Of these one had been on follow up for 4 months, one for 24 months and one for 36 months. It is possible that control of tumours could have been achieved much earlier had EBRT or plaque radiotherapy been available further increasing the numbers of eyes salvaged considering most had been on follow up for a considerable period of time. This is supported by a study done by Chan et al that showed EBRT was highly effective in controlling tumours and salvaging the globe with preservation of useful vision in eyes that had had failed primary chemotherapy and focal treatment in patients with bilateral retinoblastoma. [44] In similar studies carried out in other centers where EBRT was used to treat recurrent tumours and eyes with advanced disease good outcomes were reported with control being achieved in majority of the eyes. [49, 50]

Globe preservation had to be abandoned for 3 (8.6%) patients after they developed signs of intracranial metastasis which was confirmed by CT scan. It was noted that the source of the metastatic tumours was from the non-salvage eyes. Care was changed to palliative management. One of the patients died at the KNH during follow up due to intracranial metastasis.

All the study eyes that were salvaged had vision and patients could fixate and follow objects at the time of their last follow up visit. All the patients who were lost to follow up still had vision and could fixate and follow objects at the time of their last hospital visit. This was an important objective to achieve as one of the main objectives of globe preservation in patients with bilateral retinoblastoma is to preserve vision of the patient and ensure a good quality of life.

The rate of developing complications as a result of focal consolidative therapy was low seeing as only 3 (8.57%) patients developed complications. 1 patient had hyaloid haemorrhage, 1

developed epiretinal haemorrhage and one developed intraretinal and vitreous cysts. Majority of patients did not develop any complications as a result of focal consolidative therapy. The 6 eyes that were enucleated (18.2%) did not have any recorded complications as a result of consolidative therapy by the time they were being enucleated. In a study done by V Lee et al, anatomical complication rate was approximately 28% which was higher than what was observed in our study. This was occasioned by use of whole eye radiotherapy for treatment in Australia which resulted in cataract formation in 22% of patients. [20] In a study by Anteby et al the main cause of complications was related with EBRT treatment where 20%of 73 patients developed cataracts, 12% radiation retinopathy, mild transient keratopathy and keratomalacia. In the Anteby study no complications were observed with laser photocoagulation and cryotherapy of tumours.[41] The lower rate of complications in our study could be attributed to the fact that no patient was exposed to EBRT as it is not yet available in the country.

Follow up duration

Overall the mean duration of patient follow up was13.2 months (SD = 10.5) and median duration of follow up was 11 months (IQR 5-18). Range was 2.5 – 44 months.

Majority of the patients, 20 (57.1%) were followed up for less than 12 months. Of these patients whose follow up was less than 12 months, one patient from Ethiopia was enucleated 3 months after presentation and was discharged for follow up at Menelik Hospital in Ethiopia. One died after 5.5 months of follow up as a result of metastatic disease. Two were enucleated between 4 to 6 months after presentation and did not return for follow up thereafter. Five presented towards the later part of the study period and were still continuing with follow up with one having achieved control of the tumours already. One patient relocated to Kampala, Uganda after tumours were controlled and study eye salvaged after an 11 month follow up period. The patient did not return to follow up thereafter. Two developed metastatic disease and globe salvage was abandoned for palliative care after a 4.5 and 7 months follow up period respectively. Eight other patients were lost to follow up altogether after a follow up duration of between 2.5 to 10 months. From this it is noted that a significant number of patients whose follow up duration was seemingly short was mainly because patients presented with advanced disease that responded poorly to treatment and necessitated early enucleation of the study eye and thereafter the parents did not return for follow up visits or disease metastasized to the brain necessitating change of

management from globe preservation to palliative care at their nearest health facility. Return to home country or relocation to neighbouring countries was another cause of short follow up period. However it is noted though that a significant number of patients were lost to follow altogether. This abandonment of treatment could be attributed to incomplete understanding of the disease and treatment, the pressure of frequent hospital visits on family, need to travel long distances to access KNH and financial constraints. However the numbers of patients lost to follow up in the later part of the study was fewer compared to the earlier half of the study period. This could be due to more awareness of the disease following campaigns focused on retinoblastoma in the country. [52]

Nine (25.7%) of the patients were followed up between 12 to 24 months. 4 (11.4%) had been on follow up for between 25 and 36 months and 2 (5.7%) had been on follow up for > 36 months at the time of their last visit.

The relatively short follow up duration was similar to a study done in Tanzania by Bowmann et al on outcome of Retinoblastoma in East Africa who found mean duration of follow up to be 8 months.[48] A study by V Lee et al in Australia recorded a longer follow up duration of a mean of 44. 3 months (8.1-114, SD = 10.1 months). This could be explained by the longer study period of 13.5 years compared to 7 years in this study and better informed parents in the developed countries with stronger patient tracing systems thus improving adherence to follow up.[20] In a similar study carried out in India the mean follow up was 36 months. [50] In Egypt the mean duration of follow up was also longer than the follow up duration in this study; patients were followed up for an average of 73.2 months.[49]

7 STUDY LIMITATIONS

The main study limitations were incomplete records. Some patients had multiple volumes of files of which in some patients not all were traced. This limited completeness of the data that could be accessed for some parts of the study.

8 CONCLUSION

1. The main modes of treatment modalities employed at KNH were focal consolidative therapy: laser photocoagulation and cryotherapy either alone or in combination. This was supported with use of systemic chemotherapy in cases where tumours required chemoreduction prior to focal consolidative therapy.
2. Tumour relapse occurred in 20% of patients with most recurrences occurring within the first 6 months of follow up. Sub-retinal seeding was an associated risk factor in some of the patients.
3. Twenty five point seven percent of the patients developed new tumours. This was similar to other international studies. The most significant associated risk factor was young age at presentation.
4. Forty percent of patients had their eyes salvaged with useful vision being retained using the resources available at the study hospital. This was however low compared to the salvage rates in the developed countries. Main contributing factors were loss to follow up and unavailability of advanced treatment ie EBRT, plaque brachytherapy.

9 RECOMMENDATIONS

1. Introduce external beam radiotherapy therapy (lens sparing) and plaque radiotherapy to the county as this would improve control of retinoblastoma in eyes with advanced disease with poor response to initial therapy of systemic chemotherapy and focal consolidative therapy.
2. Intravitreal melphalan could be introduced. It may play a significant role in controlling resistant tumours.
3. Improve on measures towards seeking early definitive treatment and adherence to follow up during active treatment and thereafter. These may include a step up the campaigns to educate the public on retinoblastoma and its management and formation of support groups for parent, guardians and children undergoing treatment for retinoblastoma.
4. A prospective study on globe salvage at the hospital.

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SELECTED PATIENT SUMMARIES

PATIENT A

AGE: 2 Years

SEX: Female

DATE OF FIRST PRESENTATION: 13 September 2012

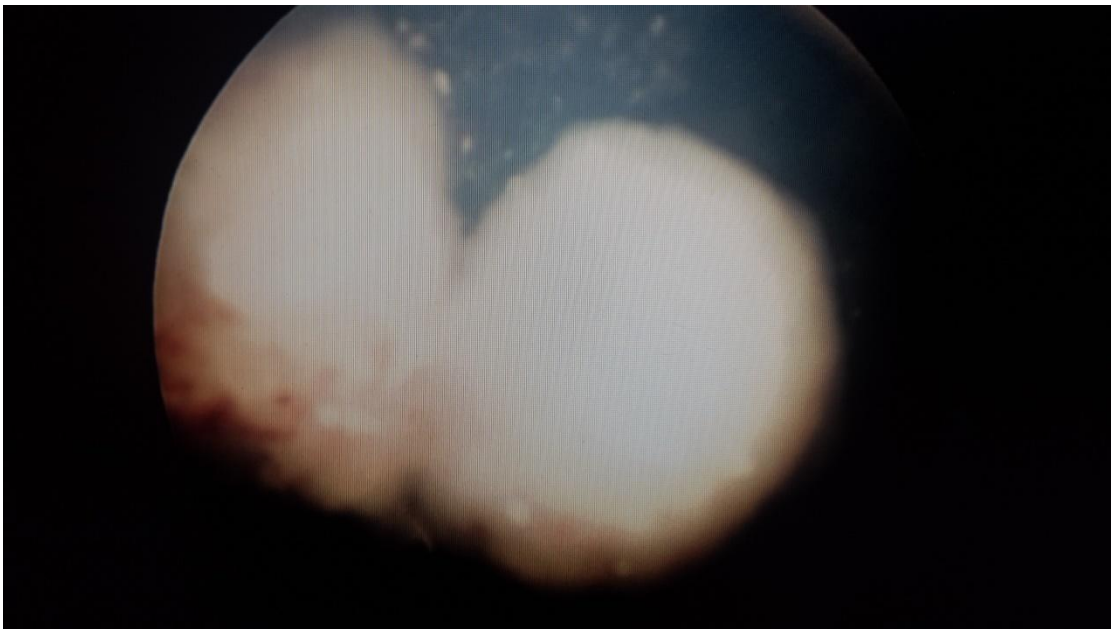
HISTORY

- Patient presented with a history of white reflex in the left eye for a duration of 6 months.
- There was no history of proptosis, redness or squint.
- There were no complaints concerning the salvage eye.
- The left eye was enucleated in August at the Moi Teaching and Referral hospital in Eldoret Kenya .EUA done at the same sitting revealed a tumour in the second eye. Histology unavailable.
- The patient was then referred to KNH for globe salvage treatment.

EXAMINATION FINDINGS

- VA: Right eye could fixate and follow eye. Left eye socket.
- RE: normal anterior segment.
- Systemic exam: unremarkable.

1st EUA RE:



IIRC GROUP D

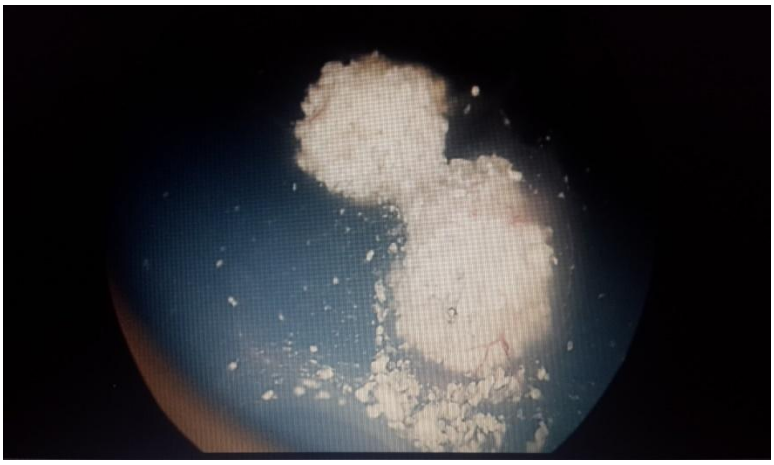
MANAGEMENT PLAN AT ADMISSION

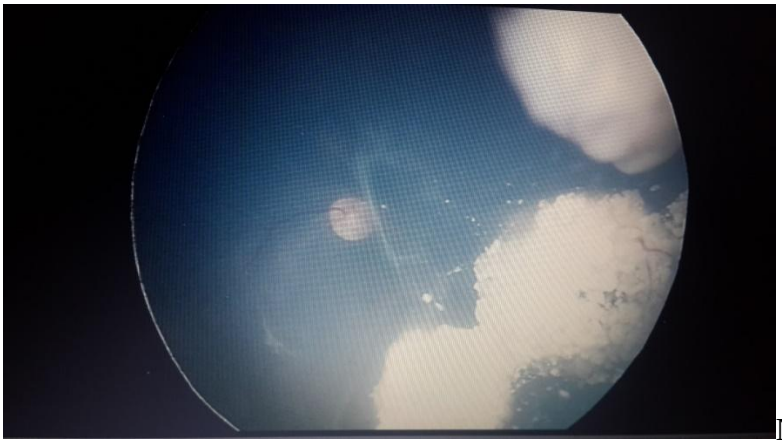
- Chemoreduction.
- Followed by focal consolidative therapy.

SUMMARY OF TREATMENT

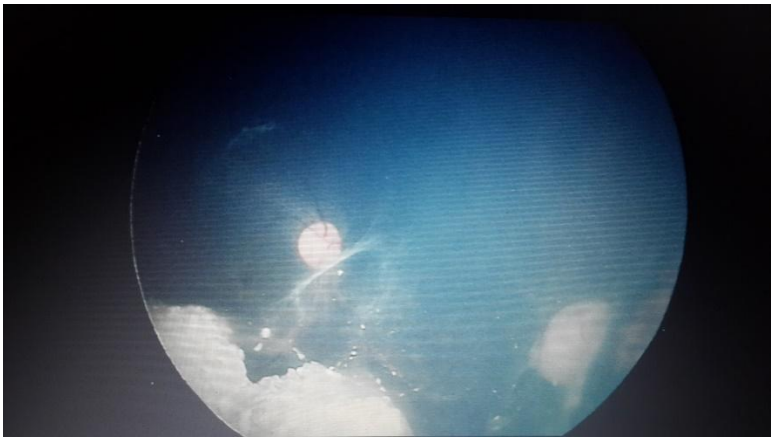
- 12 Courses of systemic chemotherapy: high dose VEC.
- 2 courses of sub-tenon carboplatin.
- Laser thermotherapy.
- Triple freeze cryotherapy.

SUMMARY OF RESPONSE

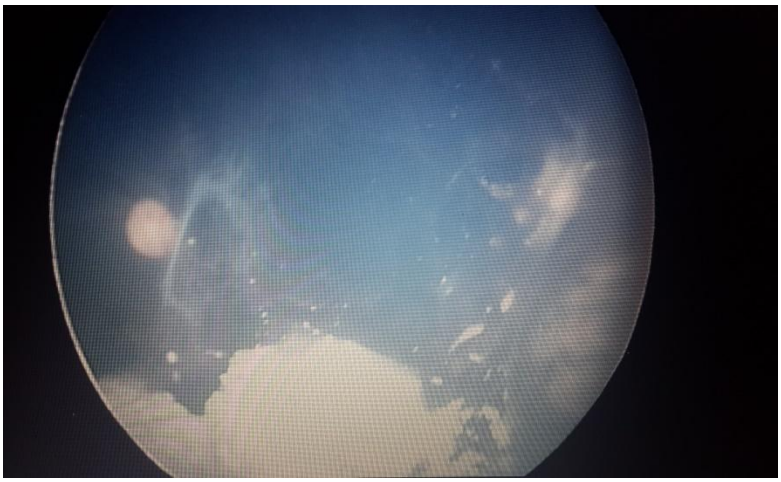

Regression


New tumour 15 weeks from 1st EUA

Vitreous seeds



New tumour 19 weeks from 1st EUA



Regression of new tumour


Remnant active tumour at 4 oclock. Vitreous seeds. December 2014.

VA at last EUA: FFO

Patient is still on follow up and tumours still active.

PATIENT B

AGE: 3 MONTHS

SEX: MALE

DATE OF FIRST ADMISSION: JULY 2010

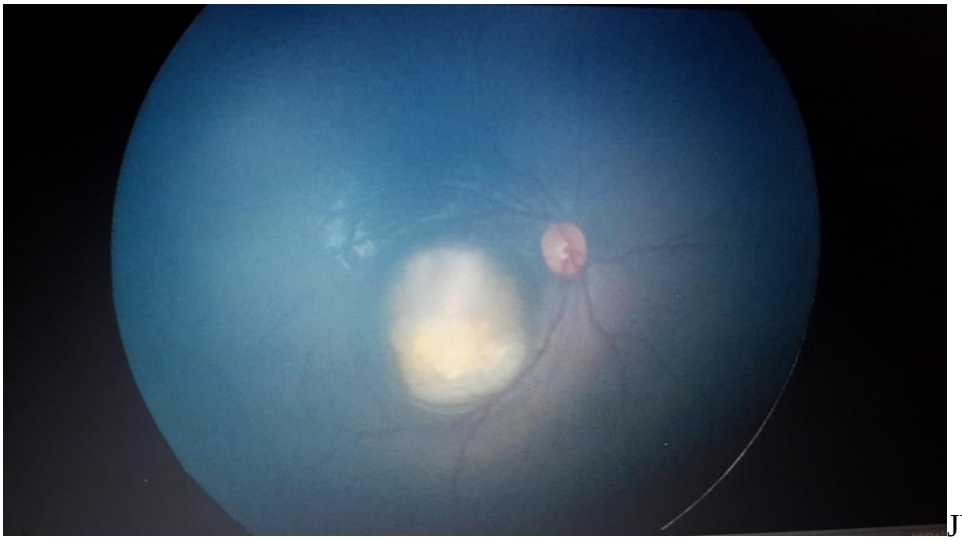
PRESENTING COMPLAINT

- White reflex in the left eye for one month.
- No associated squint, redness or proptosis.
- Positive family history: father had one eye enucleated as a child. 2 siblings dies of retinoblastoma related complications. One uncle died from ocular malignancy.

EXAMINATION FINDINGS

- Right eye able to fixate and follow objects.
- Right eye normal anterior segment findings.
- Left eye socket. (enucleated at kikuyu eye hospital)
- Histology : Pt2b – optic nerve involvement past the lamina cribrosabut not at the resection margin. No choroidal or scleral involvement.

1st EUA

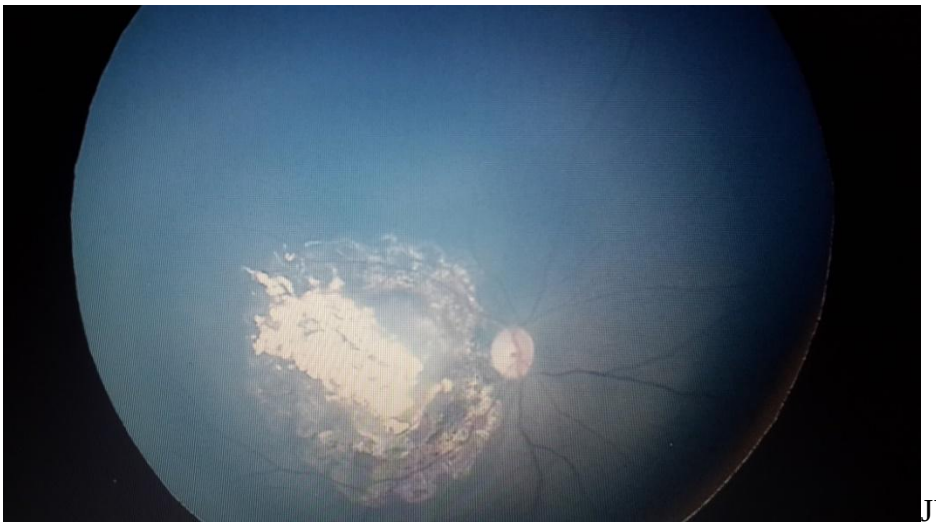
 JULY 2010

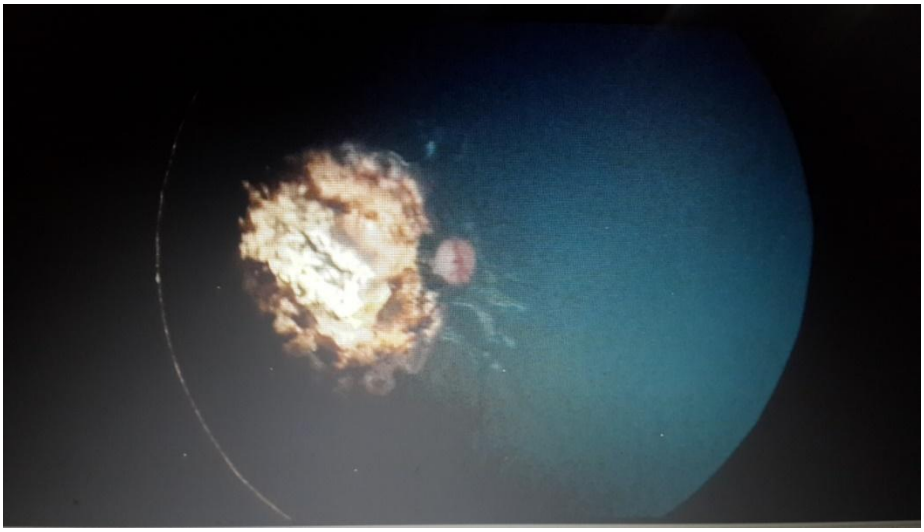
IIRC GROUP B

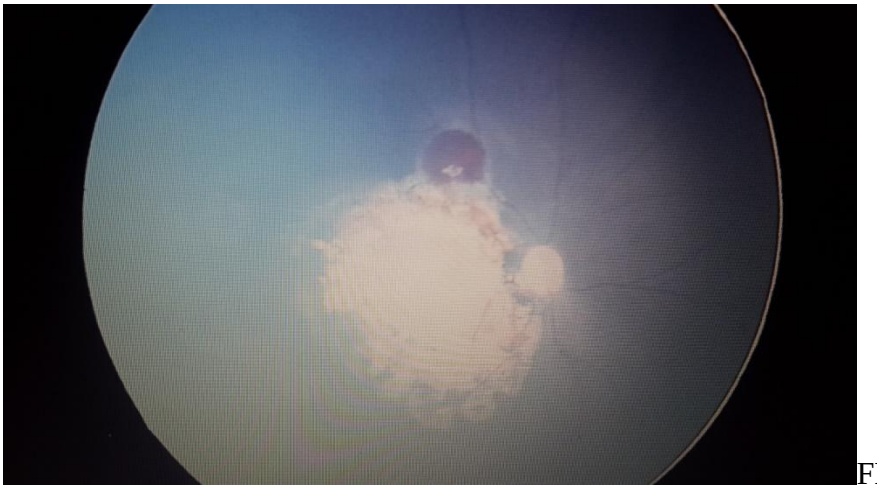
TREATMENT SUMMARY

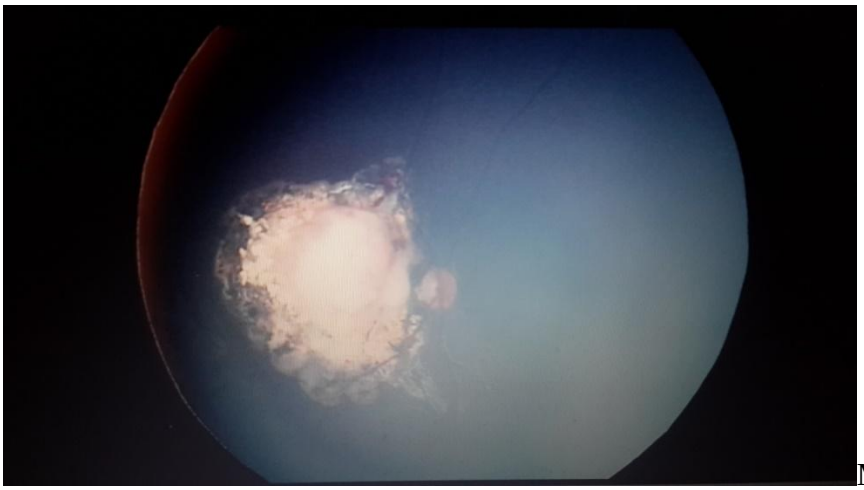
- The tumour was treated with laser thermotherapy.
- Responded well to treatment until October 2011 when the tumour relapsed and started increasing in size. By this time the patient had had 10 laser sessions.
- The patient continued with laser but with continued regrowth of the tumour.
- The tumour was noted to be covering the disc in January 2013.
- Chemoreduction was started. Patient received 10 courses of high dose VEC but with poor response.
- The right eye was enucleated on 12/08/2013, 37 months from the date of first admission.
- Last date of follow up 4/11/2013.
- Total duration of follow up was 40 months.

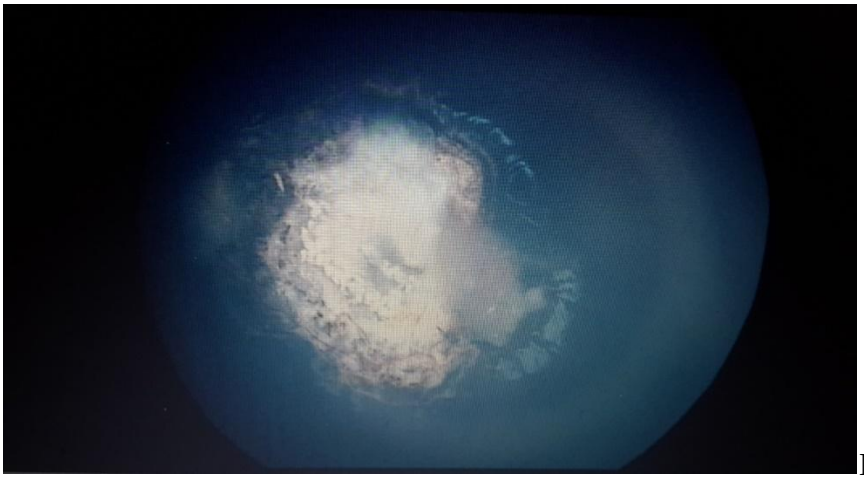
SUMMARY OF RESPONSE

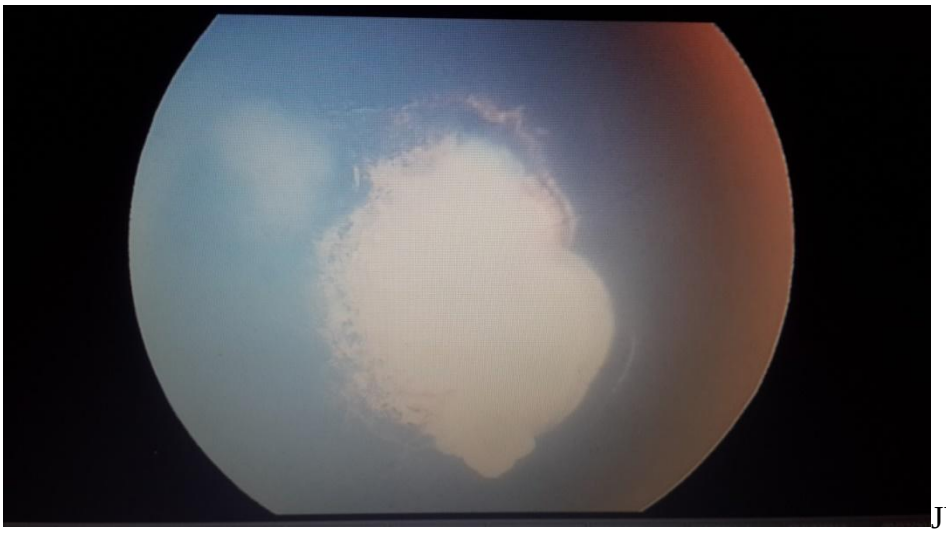

JUNE 2011


OCTOBER 2011

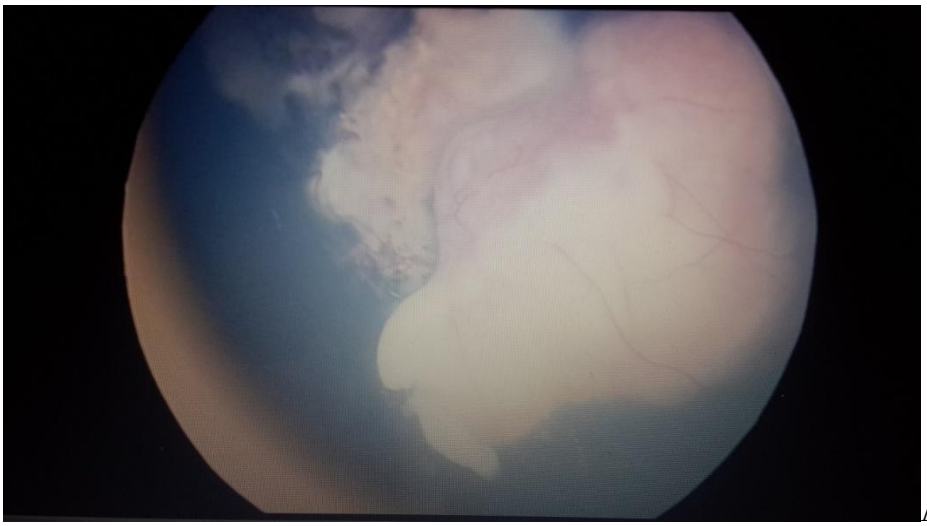

FEBRUARY 2012


MAY 2012


MAY 2013



JUNE 2013



AUGUST 2013

Last EUA finding. IIRC Group D. Eye enucleated.

PATIENT C

AGE: 9 MONTHS

SEX: MALE

DATE OF FIRST ADMISSION: January 2014

PRESENTING COMPLAINT

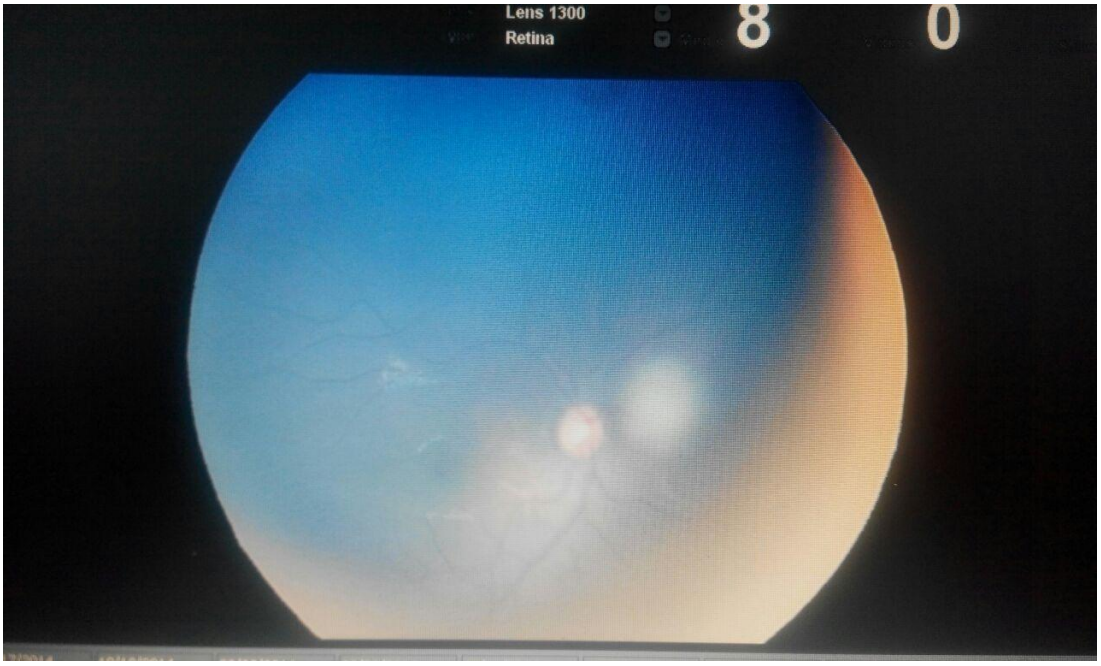
White reflex left eye.

- No associated redness, squint or proptosis.
- Left eye was enucleated.
- Histology: optic nerve prelaminar involvement. Resection margin free. Vitreous, retina and choroidal involvement noted.
- No complaints concerning the salvage eye: right eye.

EXAMINATION FINDINGS

- Right eye able to fixate and follow objects.
- Normal anterior segment.

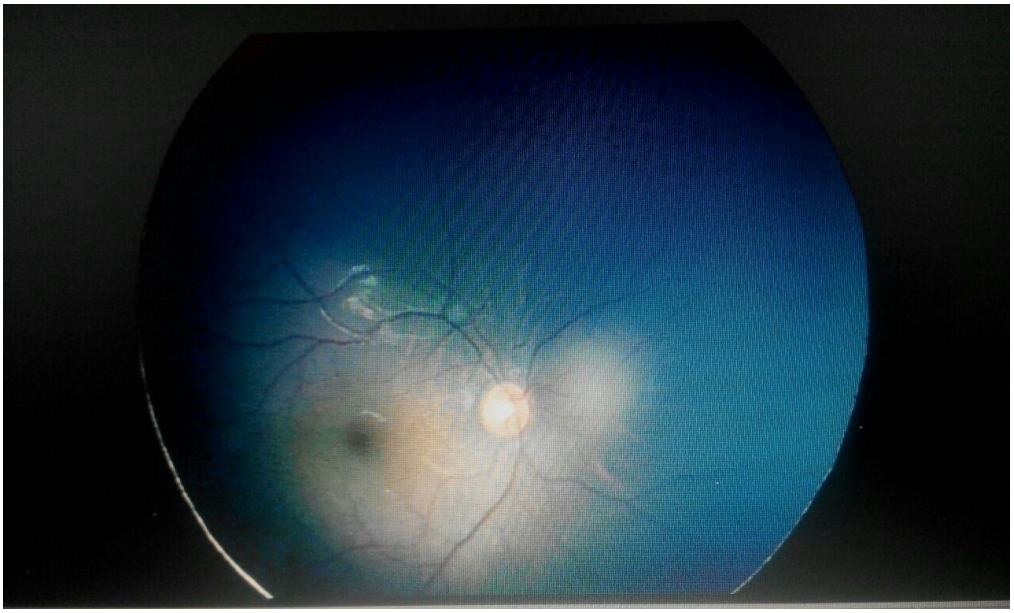
1st EUA



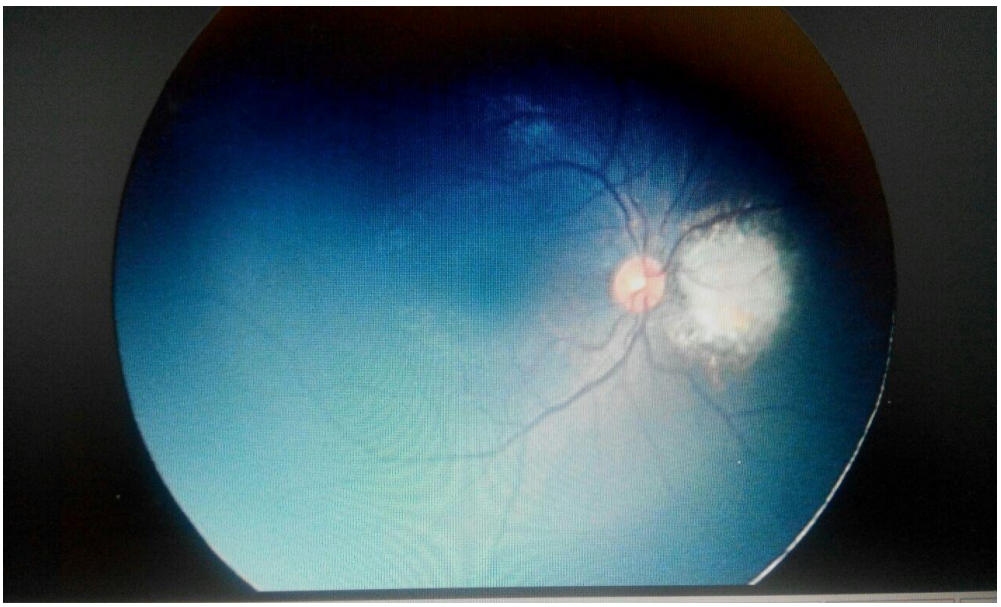
IIRC GROUP A

MANAGEMENT PLAN:

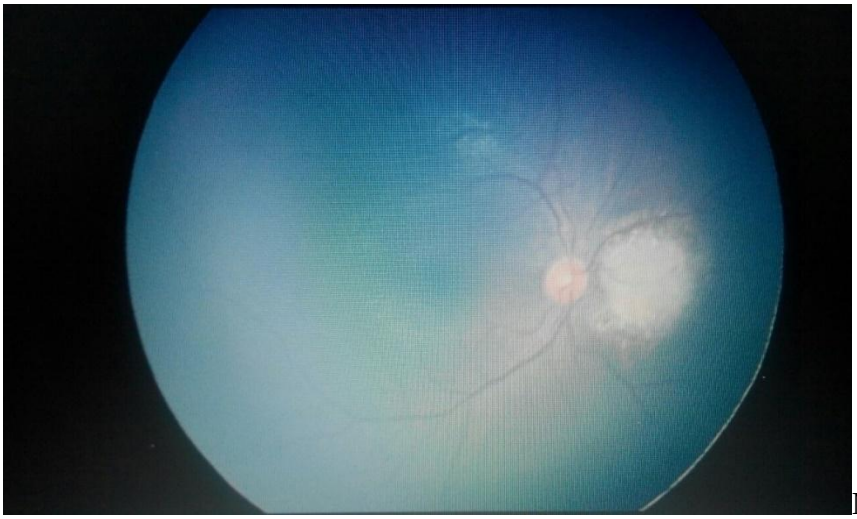
- Laser therapy: 10 sessions.
- Tumour was controlled October 2014: Type 2 regression pattern: fish flesh.

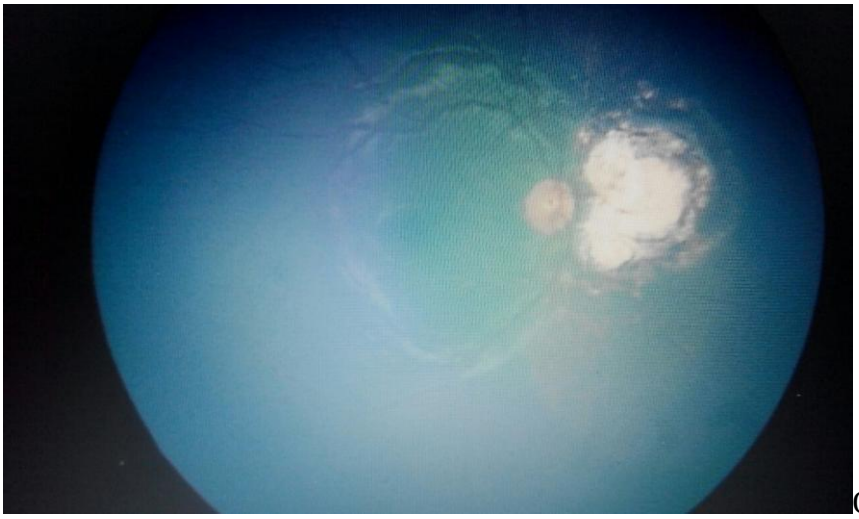


FEBRUARY 2014



APRIL 2014

 MAY 2014

 OCTOBER 2014.

TYPE 2 REGRESSION SCAR.

 DECEMBER 2014.

TYPE 2 REGRESSION SCAR.|

APPENDIX I

DATA COLLECTION FORM

A. BIODATA

PATIENT STUDY NUMBER:

DATE OF BIRTH:

AGE AT PRESENTATION:

SEX:

COUNTY OF RESIDENCE:

B. HISTORY

1. Presenting complaint at admission:

PRESENTING COMPLAINT	RIGHT EYE	LEFT EYE
1.White reflex		
2. Squint		
3. Red eye		
4. Proptosis		

Others (specify)……

2. Positive family history of retinoblastoma ☐

I. Yes
II. No

3. Patient's visual acuity at presentation:

C. CLINICAL FINDINGS

1. Presenting signs at admission

FINDINGS	RE	LE
Proptosis		
White reflex		
Conjunctival injection		
Pseudohypopyon		
Iris rubeosis		
Cataract		
Others (specify)		

2. Eye enucleated after patient presented to hospital ☐

I. RE
II. LE

3. Histological staging of the enucleated eye ☐

4. Systemic chemotherapy administered prior to patient's 1st EUA (tick and fill applicable option).

Yes ☐ No ☐

(If yes fill in the options below)

Indication ……

Type of chemotherapy……..

Number of cycles…….

D. STUDY EYE FINDINGS

1. POSTERIOR SEGMENT FINDINGS IN STUDY EYE (At 1st EUA)

Number of tumour	Size and location of each tumour		Associated findings (vitreous seeding, SRF,RD etc)	IIRC staging	Outline of treatment for eye.
	Size	Location			
1					

E. TREATMENT AND OUTCOMES

1. CHEMOTHERAPY

1a.Systemic chemotherapy administered for intraocular tumour reduction (tick and fill applicable option)

Yes ☐ No ☐

(If yes fill in the options below)

Type of chemotherapy agents……..

Number of courses……..

Duration between each course……..

Any delay in between courses……..

Reason for delay (refer to table below)……

1	Anaemia
2	Neutropenia
3	Systemic infection (specify)
4	Awaiting pre-chemo cryotherapy
5	Unavailability of chemotherapy drugs (out of stock)
6	Delay in return for follow up visit.
7	Lost to follow up
8	Others (specify)

1b. Local chemotherapy administered to study eye for tumour control (tick and fill applicable option)

Yes ☐ No ☐

(If yes fill in the options below)

Type of chemotherapy agent …….

Number of courses…….

2. FOCAL THERAPY / OUTCOME

Tumour No.	Subsequent EUA findings (ref. table 1)							Focal treatment (Ref table 2)	No. of sessions	Outcome of focal treatment (Ref table 1)	Regreaaion pattern (At last EUA, Ref table 3)
	1	2	3	4	5	6	7				
1											

TABLE 1: Subsequent EUA findings after baseline/ 1st EUA examination

1	Primary failure (Failure of primary treatment to control tumour; unresponsive / persistence of tumour)
2	Regression (Tumour reduction in size.)
3	Relapse /Recurrence (Re-growth of intraretinal tumours, vitreous seeding or sub-retinal seeds after initial favourable response
4	Scar

TABLE 2 : Focal consolidative therapy employed to destroy intraocular tumour in the study eye

1	Cryotherapy (therapeutic)
2	Pre-chemotherapy cryotherapy
3	Laser
4	Others (specify)

TABLE 3: Regression pattern of the tumour following successful control

Type 0	No scar
Type 1	Cottage cheese.
Type 2	Fish flesh.
Type 3	Mixed.
Type 4	Atrophic scar.
Not recorded	Not recorded.

3. TIMELIMES FOR EXAMINATIONS UNDER ANAEASTHESIA THAT THE PATIENT UNDERWENT

No. of EUA	Date of EUA

4. INTRAOCULAR COMPLICATIONS FOLLOWING TREATMENT (Fill applicable):

	COMPLICATION
1	Cataract
2	Vitreous haemorrhage
3	Retinal tears
4	Retinal detachment
5	Others (specify)

5. ENUCLEATION OF STUDY EYE

Yes ☐ No ☐

(If yes fill in the option below)

Duration from time of diagnosis (months)……..

F. VISUAL OUTCOMES AT THE LAST VISIT (fill in last applicable VA recorded)

LEA'S CHART:

SNELLENS CHART:

E CHART:

FFO:

FFL:

NPL:

G. DEATH OF PATIENT (tick and fill applicable option)

Yes ☐ No ☐

1. From tumour metastasis
2. Other causes
   (specify)……

Duration from time of first presentation (months) ☐

Date of last Follow up visit……..

TOTAL FOLLOW UP DURATION ☐

APPENDIX II

TIMELINE

ACTIVITIES	SEPT-OCT 2013	NOV-DEC 2013	JAN-FEB 2014	MAR - APR 2014	MAY-JUN 2014	JUL - AUG 2014	SEP-OCT 2014	NOV - DEC 2014	JAN-FEB 2015	MAR - APR 2015	MAY 2015
Proposal development											
Research and ethical committee Approval											
Data collection											
Data analysis											
Report writing and dissemination Of findings											

APPENDIX III

BUDGET

Proposed budget for study on outcome of globe preservation therapy in patients with bilateral retinoblastoma with one eye enucleated at the Kenyatta national hospital, Kenya.

ITEM	**QUANTITY**	**UNIT COST (KSh)**	**TOTAL (KSh)**
PROPOSAL			
Print proposal	2 prints , each 48 pages	10/page	960
Photocopy	3	3/page	432
Bind proposal	5	150	750
Ethics fee	1	2000	2000
Internet services		4000	4000
DATA COLLECTION			
KNH File access fee	1	2500	2500
Stationary		865	865
Flash disc	1	2500	2500
CONTRACTED SERVICES			
Statistician		50000	50000
RESULTS			
Print book	90 pages, 2 prints 22 coloured pages, 8 prints	10/page 20/page	1800 3520
Photocopy	6 copies (90 pages)	4/page	2160
Bind books	8	300	2400
GRAND TOTAL			**73,887**

APPENDIX IV: KENYATTA NATIONAL HOSPITAL, KENYA.

STUDY PATIENT SUMMARY

PATIENT NUMBER	AGE AT PRESENTATION (MONTHS)	SALVAGE EYE IIRC GROUP	TREATMENT	OUTCOME AT LAST EUA/ FOLLOW UP STATUS	DURATION OF FOLLOW UP (MONTHS)
1	36	C	CHEMOREDUCTION ONLY	CONTROL NOT ACHIVED. DISCHARGED HOME FOR PALIIATIVE CARE	4.5
2	4	D	CHEMOREDUCTION ONLY	ENUCLEATED. FOR FOLLOW UP IN ETHIOPIA	3
3	24	C	CHEMOREDUCTION ONLY	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	4
4	3	B	LASER	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	40
5	7	D	CHEMOREDUCTION, LASER	CONTROL NOT YET ACHIVED. ON GOING FOLLOW UP	4
6	36	B	CHEMOREDUCTION ONLY	CONTROL NOT YET ACHIVED. LOST TO FOLLOW UP	2.5
7	19	D	CHEMOREDUCTION ONLY	CONTROL NOT YET ACHIVED. LOST TO FOLLOW UP	6
8	5	B	CHEMOREDUCTION, LASER, CRYOTHERAPY	GLOBE SALVAGED. ONGOING FOLLOWUP	24
9	24	A	CRYOTHERAPY	GLOBE SALVAGED. ONGOING FOLLOWUP	8
10	27	B	CHEMOREDUCTION, LASER	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	44
11	14	A	CRYOTHERAPY	GLOBE SALVAGED. ONGOING FOLLOWUP	7
12	5	A	LASER	GLOBE SALVAGED. ONGOING FOLLOWUP	18
13	48	A	CRYOTHERAPY	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	10
14	29	B	CHEMOREDUCTION, LASER, CRYOTHERAPY	CONTROL NOT ACHIVED. DISCHARGED HOME FOR PALLIATIVE CARE	7

15	9	A	LASER	GLOBE SALVAGED. ONGOING FOLLOWUP	14
16	9	D	CHEMOREDUCTION, CRYOTHERAPY	GLOBE SALVAGED. ONGOING FOLLOW UP	13
17	12	C	LASER, CRYOTHERAPY	CONTROL NOT YET ACHIVED. ON GOING FOLLOW UP	24
18	30	A	CRYOTHERAPY	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	19
19	24	D	CHEMOREDUCTION, LASER, CRYOTHERAPY	CONTROL NOT YET ACHIVED. ON GOING FOLLOW UP	30
20	1.75	B	LASER	GLOBE SALVAGED. ONGOING FOLLOWUP	25
21	6	D	CHEMOREDUCTION ONLY	CONTROL NOT YET ACHIVED. LOST TO FOLLOW UP	4.5
22	10	A	CRYOTHERAPY	GLOBE SALVAGED. ONGOING FOLLOWUP	21
23	13	B	CHEMOREDUCTION, LASER	GLOBE SALVAGED. ONGOING FOLLOWUP	6
24	17	A	CRYOTHERAPY, LASER	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	5
25	15	A	CRYOTHERAPY, LASER	CNOTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	5
26	36	B	CHEMOREDUCTION, LASER	GLOBE SALVAGED. ONGOING FOLLOWUP	12
27	6	A	LASER, CRYOTHERAPY	GLOBE SALVAGED. LOST TO FOLLOWUP	11
28	3	B	CHEMOREDUCTION, LASER	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	13
29	13	B	CHEMOREDUCTION, LASER	GLOBE SALVAGED. ONGOING FOLLOWUP	16
30	4	A	CHEMOREDUCTION, LASER	GLOBE SALVAGED. ONGOING FOLLOW UP	11

PATIENT NUMBER	AGE AT PRESENTATION (MONTHS)	SALVAGE EYE IIRC GROUP	TREATMENT	OUTCOME AT LAST EUA/ FOLLOW UP STATUS	DURATION OF FOLLOW UP (MONTHS)
31	15	C	CHEMOREDCUTION, LASER	GLOBE SALVGED. ON GOING FOLLOW UP	13
32	28	C	CHEMOREDUCTION ONLY	CONTROL NOT ACHIEVED. DIED	5.5
33	22	D	CHEMOREDUCTION ONLY	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	4
34	6	A	CRYOTHERAPY	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	3
35	7	B	LASER	CONTROL NOT YET ACHIEVED. LOST TO FOLLOW UP	3.5

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/48

9th February, 2015

Dr. Rebecca Namweyi Nandasaba
Dept. of Ophthalmology
School of Medicine
University of Nairobi

Dear Dr. Nandasaba

Research Proposal: Outcome of Globe preservation Therapy in patients with Bilateral Retinoblastoma at Kenyatta National Hospital (P610/10/2014)

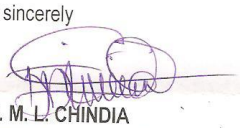
This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 9th February 2015 to 8th February 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.erc.uonbi.ac.ke**

Yours sincerely



PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Assistant Director, Health Information, KNH
The Chairperson, KNH/UON-ERC
The Dean, School of Medicine, UoN
The Chairman, Dept. of Ophthalmology, UoN
Supervisor: Dr. Lucy NJambi, Dr. Kahaki Kimani