DISSERTATION

A 2-Year Retrospective Study On The Pattern Of Retinoblastoma In Kenya

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A dissertation submitted as part fulfilment for the degree of Masters of Medicine in Ophthalmology at the University of Nairobi

by

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DECLARATION

This dissertation is my original work and has not been presented for a degree at any other University

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DEDICATION

This book is dedicated to,

My parents, Katsale and Nyaranga, for the endless love and endurance.

Without you I am none, not one

The affected young heroes for the fight bravely borne,

With God, everything is possible.

"Do not go where the path may lead...

go instead where there is no path

and leave a trail..."

-Ralph Waldo Emerson *(1803 - 1882)*

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ABBREVIATIONS

- AICS — Automated Childhood Cancer Information System
- CNS — Central Nervous System
- CSF — Cerebral Spinal Fluid
- CT scan — Computerized Tomographic Scan
- DOS — Division of Ophthalmic Services in the Kenya Ministry of Health
- EBRT — External Beam Radiation Therapy
- EUA — Examination Under Anaesthesia
- FNA — Fine Needle Aspirate
- ICCC — International Classification of Childhood Cancers
- ICD-O — International classification of Diseases-Oncology
- KEMRI — Kenya Medical Research Institute
- KNBS — Kenya National Bureau of Statistics
- KNH — Kenyatta National Hospital
- KNOW — Kenya National Ophthalmic Workers (annual conference)
- MOH — Ministry of health, Kenya (Ministry of Medical services from April 2008)
- MRI — Magnetic Resonance Imaging
- MTRH — Moi Teaching and Referral Hospital in Eldoret, Kenya
- PHPV — Persistent Hyperplastic Primary Vitreous
- RB — Retinoblastoma
- RB1 — Retinoblastoma gene on 13q14 (long arm chromosome 13, band 14)
- ROP — Retinopathy of Prematurity
- SEER — Surveillance, Epidemiology and End Results database (USA)
- UK — United Kingdom
- USA — United States of America
- UV-B — Ultra-violet B radiation
- WHO — World Health Organization

ABSTRACT

Background: The national epidemiological characteristics of retinoblastoma in Kenya have not been determined. The diagnosis of this cancer is mainly clinical; histology determines tumour extent. Late diagnosis of this otherwise curable malignancy is associated with high mortality.

Aim: To determine the incidence and pattern of presentation of retinoblastoma in Kenya.

Design: A retrospective case series

Setting: All 75 eye care centres in the 8 provinces of Kenya as registered in the Ministry of health eye information system.

Methods: With permission, clinical registers at eye care centers were reviewed to identify cases of retinoblastoma that presented from 1st January 2006 to 31st December 2007. Only centers that reported cases were visited to record patient's clinical and demographic data in a questionnaire. Cross-referred cases were analysed once to avoid double-counting.

Results: A total of 206 suspected cases presented to 46 eye care facilities but 58 cases (28.2%) were lost after referral. Of 148 traced cases, 28.4% were self referrals and of the referred cases, most (21.6%) were from central province. Only 63.5% of cases were finally treated at 2 teaching and referral hospitals.After excluding 3 missing files and 13 cases that were ruled out on histology, 132 confirmed cases(166 eyes) were subsequently analysed. The mean delay in first presentation was 6.75 months and delay after referral was 1.69 months. Leukocoria was the most common presenting complaint (91.7% cases) and sign (71.1% eyes). There were 25.8% bilateral cases and 78.2% unilateral cases with mean ages of 26 and 35.9 months respectively. The male to female ratio was 1.49:1. Only 4.5% had a positive family history. Most (32.6%) cases resided in the Rift valley province. There was no association between ethnicity and bilaterality. The annual incidence of retinoblastoma in 2007 was 1:17,030 live births.

Conclusions: A significant proportion of cases were lost after referral. The late presentation was associated with advanced disease. Leukocoria was the most common finding. Most cases resided in the Rift valley province. The incidence of retinoblastoma was similar to most countries but may be an underestimate.

Recommendations: Public education and screening with the red reflex test by primary health care workers would ensure early detection. Quality control measures in record keeping would ensure accuracy. A retinoblastoma registry would provide accurate estimates through register-based studies. Further research is necessary to investigate the lost cases after referral, delays in presentation and barriers to uptake of services.

1.BACKGROUND

Retinoblastoma is the commonest primary intraocular malignant tumor of the developing retina that occurs in children worldwide, usually before age of 5 years. The tumor occurs in cells that have cancer-predisposing mutations in both copies of the *RB1* gene on chromosome 13q14 which can be unifocal or multifocal and affects all races and sexes equally. In Asia, Africa, and South America where uveal melanoma is relatively rare, retinoblastoma is the most common primary intraocular tumor. In Europe and the USA it is second in overall prevalence reflecting the propensity of lightly pigmented adult Europeans to develop uveal melanoma.

Kenya is a developing country straddling the equator in East Africa with a population of 35 million. There are 42 ethnic groups and 8 administrative provinces. Cancer is a third cause of death after infectious and cardiovascular disease; retinoblastoma ranks tenth among all cancers in Kenya.[1] In the Ministry of health, the Division of Ophthalmic Services (DOS) coordinates eye care services provided by 75 private and public facilities. From 2002 to 2007, an average of 347 cases of retinoblastoma was reported annually in the eye health information system. In 2007 alone, 43 of these facilities reported 378 cases including revisits and cross-referrals. (Appendix VII) The Kenyatta National Hospital (KNH) is the largest teaching and referral center in association with the University of Nairobi. The specialized eye cancer-related services include radiotherapy, medical and surgical oncology, hematology, pathology, palliative care, laser and cryotherapy.

Since 2001, the cancer registry at the Kenya Medical Research Institute (KEMRI) has strived to establish a registration and surveillance system to provide data on the incidence of cancer in Kenya. Presently, only data for Nairobi is captured. Most facilities use the ICD-9 and ICD-10 coding system for all diseases and ICD-O for cancer (retinoblastoma site c69.2: M9510-9512). At KEMRI, all paediatric cancers are encoded into the International classification of childhood cancer (ICCC) recommended by the World Health Organization.[2] The ICCC (retinoblastoma: group V) classifies cancers by histological type unlike ICD which is based on site. This study will ultimately update the national retinoblastoma registry and act as a database for future studies.

2.LITERATURE REVIEW

2.1 Epidemiology

The prevalence of retinoblastoma refers to the estimated population of children who have the disease at any given time. The incidence of retinoblastoma is the number of children under 5 years diagnosed with retinoblastoma divided by the number of children in the same age group or by the number of live born children for each year, respectively (*standard annual analysis*).Variation in annual analysis depends on the number of children in who develop retinoblastoma and the age at diagnosis. This variation is eliminated in *birth cohort analysis* whereby all cases diagnosed in children born in a particular year are cumulated over time and divided by the number of live births during that year.

The population at risk is not necessarily the children alive at any given moment and it is difficult to define it based on the age of the child at diagnosis. The incidence commonly calculated is for children younger than 5 years because only 4% to 10% of the cases are found in children older than 5 years, in whom the incidence is very low (<0.3 to 0.5:1,000,000).[3] Calculations may also be based on children younger than 10 or 15 years by which time all diagnoses have been made.

Retinoblastoma is a developmental cancer. Unnecessary variation introduced by different growth rates of tumours that initiated soon after birth or even pre-partum is minimized if the analysis is based on birth cohorts rather than the year of diagnosis. In the Northern Europe study, Seregard et al found incidence rates based on birth cohorts were slightly lower than those based on annual analysis.[4] Therefore birth cohort analysis has been recommended in epidemiological studies on the incidence of retinoblastoma.

Globally, the incidence of retinoblastoma in various well-studied population groups varies from 1:3,300 to 1:20,000 live births with a higher incidence in some populations. Albert et al reported the highest incidence of 1:3,300 live births in Haiti.[5] (Appendix IX)

In Europe, McCarthy et al found the age standardized (world standard) incidence of 4:1,000,000 children less than 15 years of age in a study of 2283 cases in the Automated Childhood Cancer Information System (AICS). The highest incidence was seen in the first year of life. Over the 20-year period, the overall

incidence increased at a rate of 1% per year but this may have been due to differences in the quality of data registration.[6] In Netherlands, Moll et al reported incidence of 1:17,000 live births in a register-based study.[7] In New South Wales, Azar et al found annual incidence of 8:1,000,000 children less than 6 years old in a 6-year retrospective hospital based study on retinoblastoma.[8]

In a study of 658 cases in the USA Surveillance Epidemiology and End Results (SEER) database, Broaddus et al found that the mean age-adjusted incidence of 11.8:1,000,000 children younger than 5 years was stable over a 30-year period up to 2004.[9] Previously, Tamboli et al had reported incidence of 5.8 and 10.9 per 1,000,000 children younger than 10 and 5 years respectively.[10]

In Asia, Sao-bing et al found an incidence of 4.8 per 1,000,000 children less than 5 years old in a register-based study in Singapore.[11] In Uzbekistan, Mouratova reported cumulative incidence of 5.8:100,000 children less than 5 years which significantly increased over a 21-year period (972 cases). A high incidence of 15.9:100,000 children less than 5 years among Tartars who practice consanguineous marriage emphasized importance of ethnic dimensions in cancer research.[12]

In Japan, Takano et al found an annual incidence of 1:16,000 live births in a retrospective study and 1:49,600 live births for bilateral cases only. A higher incidence of 1:10,331 live births was found in Shimabara district that was largely composed of an immigrant population.[13]

Retinoblastoma affects both sexes and all races equally. Pendergrass et al found no sex difference and no racial predilection between African Americans and Caucasians in the USA.[14] In India, Balkrishna et al found a male to female ratio of 1.4:1 and incidence of 8.2:1,000,000 children less than 5 years in the Mumbai cancer register.[15]

Hooper et al had previously suggested that sunlight UV-B exposure may play a causative role in unilateral (sporadic) retinoblastoma in a study in the USA. However, this was disputed by Jemal et al after adjusting for race and tropical climate in a population-based study on the SEER registry.[16]

In Africa, epidemiological data is limited in many countries. In native South Africans, Freedman et al found incidence of 1:10,000 live births in a 20-year retrospective study.[17] In Namibia Wessels et al found incidence of 5.8:1,000,000 children less than 15 years in a 6-year retrospective study.[18]

In Malawi, BenEzra et al found annual incidence of 2:100,000 children less than 5 years old (1:10,000 live births) with a higher frequency of 1:4,340-3580 live births in two districts. The sex distribution was similar between male and female.[19] In a 6-year retrospective study of 104 cases in Nigeria, Abiose et al found difficulty in determining the true incidence due to lack of accurate demographic and population data at the time. With the relatively low life expectancy and a predominantly young population in the country, the author anticipated an overestimation of the incidence of retinoblastoma.[20]

In Kenya, previous studies on retinoblastoma conducted at the Kenyatta National Hospital (KNH) were non-epidemiological. In a review of cases in 1985, Khan et al found incidence of 1:19,000 live births at KNH and a high prevalence in one populous ethnic group that predominated in both the catchment area of the hospital as well as in the general population.[21]

The incidence of retinoblastoma decreases with advancing age. Most occur before the age of 2 years and are diagnosed before 5 years. In a study of retinoblastoma in older children, Shields et al found only 8.5% of children were over 5 years old at the time of initial diagnosis in the USA.[22]

The median age at diagnosis without a family history is approximately 24 months for unilateral cases but is significantly younger with a family history (bilateral). Leal et al found 73% unilateral and 27% bilateral cases with a mean age at diagnosis of 30 and 18 months respectively in Mexico.[23]

Trilateral retinoblastoma is rare and often diagnosed later than intraocular disease. In a report of 5 cases of trilateral retinoblastoma, Amoaku et al found an average age at diagnosis of 32 months compared to 6 months for intraocular disease.[24]

At the KNH, Khan et al found 63% of cases were unilateral and 37% were bilateral with a mean age at diagnosis of 38 and 21 months respectively.[21] Gakuruh et al reported 58% of cases were unilateral and 42% were bilateral.[25] This was similar to 56% unilateral cases and 44% bilateral cases found by Kimani et al.[26]

Retinoblastoma has been encountered at birth, although this is rare. In a retrospective study of 46 neonatal cases in the USA, Abramson et al found the mean age at presentation of 18 days and a positive family history in 67% of neonates as the most common presenting manifestation followed by leukocoria. Of these neonates, 56% had unilateral disease.[27]

Familial cases present at an earlier stage of the disease than non-familial cases. In a 12-year retrospective study of 17 patients screened for familial retinoblastoma two weeks after birth in the Netherlands, Imhof et al found 56% cases presented in Reese-Ellsworth group I and 72% cases presented in group A of International classification.[28]Familial cases present at an earlier age than non-familial cases. In a retrospective review of cases in the USA with familial retinoblastoma that had a previous normal eye examination, Abramson et al found 62% first eyes were diagnosed by 6 months, 90% by 12 months and 100% by 28 months.[29]

2.2 Genetics and Histopathology

Although retinoblastoma represents only 4% of childhood cancers and less than 1% of all human cancers, it is of widespread interest because it was the first cancer gene to be identified and cloned.[30]In genetic studies in USA Cavenee et al proved the tumour was related to a mutant allele in RB1 gene(chromosome 13q14).[31]The sequence of the 180-kilobase locus has been completed.

Knudson's "two-hit" hypothesis postulates that the development of retinoblastoma requires at least two separate genetic events.[32] In hereditary cases, germinal cells have one normal "anticancer" allele and one defective allele (first hit). The second, normal gene can still restrict the uncontrolled growth of tumors. Later, a mutagenic alteration hits the normal allele, suppressing its function and (second-hit) results in tumor formation. However, in recent comparative genomic hybridization studies, Corson and Gallie found that the

two hits are necessary for initiation but other hits are crucial for progression to retinoblastoma.[33] Individuals heterozygous for a mutation in one *RB1* allele (germline) are predisposed to develop non-ocular tumors like osteosarcoma, parathyroid carcinoma and soft tissue sarcomas.[34]

Retinoblastoma arises from the neuronal cell and cones predominate. New foci are common at the infero-temporal retina which differentiates last. Microscopy shows small, uniform, round or polygonal cells with scant cytoplasm and large, chromatin rich nuclei that stain with hematoxylin and grow around blood vessels. Bilateral cases have similar histology in both eyes. Extraocular tumour has larger cells, few rosettes and little necrosis or calcification. Shuangotsi et al found that *fleurettes* are more differentiated towards photoreceptors, *Homer-Wright* rosettes are also seen in cerebellar medulloblastoma, and *Flexner-Wintersteiner rosettes* are classic for retinoblastoma.[35]

The endophytic tumors originate in the internal nuclear layers of the retina and extend into the vitreous cavity. Exophytic tumors arise in the external nuclear layer and grow into the subretinal space causing retinal detachment, glaucoma and choroid invasion; they are common at the ora serrata. Pallazi et al found endophytic type is more common and correlates with familial cases.[36]

The collagen and vascular stroma is poorly developed with loss of cell cohesion that produces seeding -an unfavorable prognostic sign. Small tumors with limited seeding have better prognosis. The tumor seeds are affected by EBR but escape chemotherapeutic agents due to poor vitreous penetration. Orbital extension follows massive involvement of the posterior choroid and the scleral emissaria which may be worsened by photocoagulation.Shields et al found that massive choroidal invasion increased the risk of metastasis and therefore requires systemic chemotherapy.[37]

Metastasis includes remote and contiguous spread. Hematogenous spread is the most common. Next is the optic nerve directly via lamina cribrosa or choroid border tissue. Growth into the optic nerve 12 mm posteriorly where the central retinal vessels exit the subarachnoid space almost always suggests spread into the cerebrospinal fluid (CSF) and the prognosis for life is poor due to seeding into the ventricles and base of the brain. Lymphatic spread follows orbital extension.

2.3 Clinical Presentation

In the absence of a known family history of retinoblastoma, early tumour in the eye is usually undetected by both the family and primary care physician. Direct ophthalmoscopy or a red reflex test in the first year of life may miss the tumor unless it is large or located in the retina where it reflects transpupillary light. The tumor enlargement is painless and rarely causes a red, inflamed eye early in the disease. Strabismus suggests fovea involvement, but unilateral visual loss may be missed if the other eye has normal vision.

The presenting signs and symptoms depend on the size, location, growth pattern, tumour stage at diagnosis and sophistication of care. Congenital cases may present with massive hyphema and an ectatic megalocornea that spontaneously perforates. Retinoblastoma is occasionally observed in premature infants. Maat et al described retinoblastoma in a foetus at 21 weeks gestation.[38] Leukocoria or "cat-eye" is a classic manifestation of retinoblastoma in the vitreous or with a retinal detachment. Abramson et al found *leukocoria* in 56% and *strabismus* in 23% of cases in USA.[39] Song et al found leukocoria in 80% of 70 cases in Korea.[40] At KNH, Khan et al found leukocoria in 48% of cases[21] and Gakuruh et al also found it was the commonest sign followed by proptosis.[25]

Even in the USA, vague *stigmata of metastasis* such as failure to thrive, somnolence or irritability, may be the initial clue.[9] In many countries, *proptosis* is the commonest presentation but one must exclude *rhabdomyosarcoma* and other causes of rapid progressive proptosis. Kimani et al found leukocoria was the first symptom in 77% and proptosis as the commonest presenting complaint.[26] Iris heterochromia may result from a pre-existing hyphema, *rubeosis irides* or tumour implantation growths. Hyphema or *pseudohypopyon* may leave gray remnants on the iris that mimic juvenile *xanthogranuloma* in infancy as described by Kilby et al.[41] *Mydriasis* may reflect extensive tumor with total retinal detachment. *Poor vision* may result from a slow growing mass that ultimately involves the macula in an older child but infants with massive bilateral tumors also suffer behavioral changes. A *red painful eye*, often with *glaucoma,* may mimic *uveitis. Endophthalmitis*, *panophthalmitis*, and *orbital cellulitis* that begin rapidly over days due to spontaneous tumour necrosis can be mistaken for infection in an eye with opaque media. Corey et al found orbital cellulitis in 5% of cases in the USA.[42]

Trilateral retinoblastoma is the association of a midline intracranial primitive neuroectodermal tumour with heritable retinoblastoma classically in the pineal but also in the intrasellar, suprasellar, parasellar and chiasmatic cistern.The prognosis is poor. Kivela et al recommend routine brain CT or MRI scan be done at the initial diagnosis to demonstrate a calcified mass in the pineal region with or without hydrocephalus.[43]

The differential diagnosis of intraocular retinoblastoma includes other causes of leukocoria such as paediatric *cataract, retinopathy of prematurity, Persistent hyperplastic primary vitreous*, and *Coats'* disease. *Retinal detachment* may be associated with rare syndromes. Infectious causes that mimic may cause leukocoria include toxoplasmic *uveitis* (masquerade syndrome), *Toxocara* granuloma and metastatic *endophthalmitis*. *Cytomegalovirus* retinitis in immunosuppressed children is less common than in adults. *Retinal hemorrhage* is common in neonates after normal delivery but *vitreous hemorrhage* is rare.

Congenital lesions that may cause leucokoria are myelinated nerves, optic nerve coloboma and morning glory disc. A congenital *retinal fold* is a unilateral anomaly in normal eyes, trisomy, ROP or after granulomatous inflammation. *Astrocytic hamartoma* (tuberous sclerosis) has calcification, while *angiomatosis retinae* may cause retinal detachment. *Dictyomas* arise in the anterior segment. Rare lesions are *Norrie* disease, autosomal recessive retinal *dysplasia,* dominant *exudative vitreoretinopathy* and juvenile X-linked *retinoschisis*.

In a retrospective study in France, Vahedi et al found 16% of 486 cases of clinically suspected retinoblastoma had a different pathology; Coats disease (25%), congenital lesions (30%), other tumours (13%), hamartoma (8%), inflammatory (8%), and other diseases (16%). There was no case of ROP and the frequency of PHPV was low due to good screening in France.[44]

2.4 Diagnostic workup

The diagnosis of retinoblastoma is mainly clinical. Fundoscopy may reveal a creamy vitreous mass with telangiectatic vessels, neovascularization and microaneurysms. However, a clear view precluded by inflammatory reaction, retinal detachment or vitreous hemorrhage will require further assessment. with, ultrasonography, radiography, CT-scan, MRI, CSF cytology, histology and bone marrow aspirate.

Calcification and *vitreous seeding* are pathognomonic features of retinoblastoma. Calcification occurs in advanced hemorrhagic or inflammatory retinal disease but the unique fluffy pattern in retinoblastoma is easily seen by ophthalmoscopy or radiography. CT scan confirms calcification, tumour extent or pineal lesions (trilateral). Of 52 cases that underwent CT-scan, Wou et al reported a sensitivity of 96% and 90% of cases showed calcification.[45] MRI will distinguish differences in tissue density by a non-invasive, non-radiating technique. Schueler et al describe the use of a surface coil that further delineates spatial relations in the eye resulting in a high resolution.[46]CT, MRI and X-ray assess distant spread, implying poor prognosis. Ultrasonography is cheap, rapid and safe for diagnosis and monitoring of tumour size after local therapy. Calcification differentiates retinoblastoma from other intraocular pathology. Roth et al found 100% accuracy and calcification in 91% of cases.[47] Zilelioglu et al found the *mixed* pattern was more common than *solid*, *cystic*, and *diffuse infiltrating* patterns.[48]

Histology ultimately confirms the diagnosis and extent of spread. Optic nerve invasion correlates with the 5-year mortality. The *Grabowski-Abramson pathological staging* classifies retinoblastoma into intraocular, orbital, intracranial and hematogenous metastatic disease. In a histopathological study, De Souza et al found neovascularization, necrosis and calcification were the most common findings and invasion of the optic nerve and choroid in 28% and 64% of cases respectively being the most important predictors of patient outcome.[49] Genetic testing is under intensive research in the developed countries but is not available in Kenya and many developing countries.

2.5 Management

At the first visit, a complete history and examination with mydriasis is conducted under anaesthesia to determine the size and site of all tumors. Parents and relatives of affected children are routinely examined for a *retinoma* which is a benign manifestation of a germline RB1 mutation in adults that needs careful follow-up. Spontaneous regression leaves a chorioretinal scar, residual calcium and atypical vessels. In genetic studies in Canada, Dimaras et al found that *RB1* inactivation in the retina induces genomic instability but senescence blocks transformation at the stage of retinoma[50]

Two clinical staging systems are commonly used. The *Reese-Ellsworth* classification determines ocular prognosis and treatment results for intraocular retinoblastoma by size and location of the original tumor. The *New International* classification correlates clinical findings and prognosis for vision and the eye with proposed treatment guidelines. Each eye is assessed separately.

Therapy of retinoblastoma is complex, costly and restricted to specialized facilities. The primary goal of therapy is to save life and secondly to save the eye and vision if possible. The mode of therapy is determined by the threat of metastasis, risk of second cancers, laterality, site, size, visual prognosis and the systemic status. Therapy may be focal, local or systemic.

Laser photocoagulation with Argon laser or Xenon arc is reserved for small posterior tumours with base less than 4.5mm and 2.5mm thick without vitreous seeding in which Shields et al found 70% control and 30% recurrence.[51] **Laser hyperthermia and Chemothermotherapy** utilises ultrasonic, microwave or diode-infrared synergistically to chemotherapy or radiotherapy. Shields et al recommended **Cryotherapy** for small equatorial or peripheral tumours less than 3.5mm in diameter and 2mm thick without seeding.[52] **Radioactive plaque brachytherapy** with Iodine^{125} for local disease preserves the eye. The total dose is 4000cGY fractionated over 1 to 4 days for tumours less than 16mm base and 8mm thick. Shields et al found a 95% 5-year tumour control when Iodine^{125} was used as salvage treatment after chemoreduction.[53] **External Beam Radiotherapy (EBR)** is whole eye irradiation for advanced disease with vitreous seeding. The adverse effects are cataract, vitreous hemorrhage, retinopathy, orbit deformity and secondary cancers which make it unsuitable for infants. Munier et al found that **lens-sparing EBR** was much safer.[54] **Systemic chemotherapy** is indicated for optic nerve invasion, choroidal, orbital and distant metastasis. Intrathecal methotrexate is prophylactic and therapeutic for CNS metastasis. **Chemoreduction** decreases tumour size to facilitate a focused safer therapy. Common agents are Vincristine, Etoposide and Carboplatin. **Combined** radical Surgery, EBR and Chemotherapy may improve survival. **Enucleation** is performed for optic nerve invasion, extrascleral extension, tumour involving more than half the globe, glaucoma and unilateral tumour-related retinal detachment.

Untreated retinoblastoma is invariably fatal. The prognostic indicators that determine the survival of patients include tumour site, size, cellular differentiation, optic nerve involvement, extrascleral spread, and choroid or vortex vein extension. In a retrospective audit of survival among retinoblastoma patients at the KNH, Nyawira et al found a 3-year survival of 26.6% and 100% mortality among patients with proptosis.[55]

Genetic counselling should be offered to every parent having a child with retinoblastoma and to all patients with a positive familial history. Treated first or second eye tumours must be thoroughly reviewed by an ophthalmologist 3-monthly in the first 2 years, 6-monthly for children 3 to 5 years, and thereafter annually into early adulthood. A unilateral case has a 7% probability of developing tumour in the other eye during childhood. Moll et al recommended screening for familial cases of retinoblastoma until the child attains the age of 4 years.[56]Therefore, although retinoblastoma is a life-threatening malignant tumour, the patients can be successfully treated in if an early, accurate diagnosis and prompt referral are made.

3.RATIONALE & OBJECTIVES

3.1Rationale and Justification

The epidemiological characteristics of retinoblastoma in Kenya are not known. The previous studies on this tumour were conducted at the KNH and were non-epidemiological and it is not known how many cases are lost after referral from the other centers.

The cancer registry at KEMRI mainly captures data for Nairobi province only, hence the rest of the country's data remains unknown. There is need for country wide coverage and an updated database.

Ideally, early diagnosis and treatment is desirable even before the stage of leukocoria.[57] In Kenya, late presentation, poor outcome and the associated high cost of treatment is of concern. In 2007, a full course of treatment at the KNH was estimated to cost over Kshs 300,000($4300) and this financial burden and outcome can be optimized by an early detection and treatment protocol.

At the Ministry of Health, periodic morbidity data in the eye health information system captured at health care facilities is often inconsistent and lacks validation. There is need to establish accurate reliable national baseline data for health planning and future reference.

3.2Objectives

Major Objective

- To determine the incidence of retinoblastoma in Kenya in 2007.

Minor Objectives

- To determine the referral pattern of retinoblastoma patients in Kenya.
- To determine the clinical presentations of retinoblastoma in Kenya.
- To determine the distribution of retinoblastoma by age, sex, bilaterality, family history, region and ethnicity.

4.METHODOLOGY

Study design:

A retrospective study of retinoblastoma patients in Kenya.

Study Coverage:

All 75 eye care facilities countrywide as registered in the Ministry of health information system (as at 2008)

Study Population and Period:

The population of children who presented to eye care centers from 1st January 2006 to 31st December 2007.

Sample size and Sampling frame:

All ophthalmologic medical records at eye care facilities between 1st January 2006 and 31st December 2007 obtained from the eye health information system report for 2007 (Appendix VII).

Case Definition of retinoblastoma:

- A recorded clinical diagnosis of retinoblastoma, or
- A recorded histological diagnosis of retinoblastoma.

Inclusion criteria:

- Records of cases with a presumptive diagnosis of retinoblastoma either clinically (leukocoria with a fundal mass) or confirmed by histology that presented in the period under review.

Exclusion criteria:

- Lost, defaced or mis-registered records.

Assumptions:

- All patients with retinoblastoma presented to health facilities and were appropriately referred.
- All eye care health workers diagnosed and referred suspected cases of retinoblastoma.
- All cases of retinoblastoma were recorded accurately in the registers at health facilities.
- A stable general population and accurate national demographic estimates for 2007.

Research Equipment:

- National distribution of the eye care facilities, staff and telephone contacts
- Monthly returns from the division of Ophthalmic services for the year 2007
- Questionnaire

Demographic Data

The population estimates in 2007 from the Kenya National Bureau of Statistics (KNBS) were based on projections from the Kenya National census in 1999. The number of live births and children less than 5 years by province was extracted. (Appendix VI)

Retinoblastoma coding system and the cancer registry

In Kenya, the ICD-9 and ICD-O is used for coding retinoblastoma in health facilities. In the Nairobi cancer registry at the Kenya Medical Research Institute (KEMRI) paediatric cancers are encoded into the International classification of childhood cancer (ICCC) recommended by the World Health Organization.[2] This information was essential during data retrieval at facilities.

Health Care System for Patients with retinoblastoma in Kenya

The national distribution of health facilities, staffing and the estimates of retinoblastoma cases were obtained from the Division of ophthalmic services in the Ministry of health. There were 75 public, private, church-based and non-governmental institutions concerned with eye care. In 2007, the eye health information system reported a total of 378 cases from 43 centers.

Ideally, patients presented to the nearest health facility. If an eye problem was detected and the center did not offer eye care, the patient was referred to an eye care facility. At the eye unit, the patient was examined by an ophthalmic clinical officer who recorded the date, name, age, sex, address, patient number and diagnosis in the outpatient register. If retinoblastoma was suspected, the case was referred to the nearest center with an ophthalmologist. Based on clinical suspicion, the affected eye was enucleated and sent for histology. If the tumour was reported to be unilateral and intraocular, the patient was given a return date to monitor the socket and fellow eye. However, if the tumour was extraocular or the fellow eye was affected, the patient was referred to the nearest center that offered chemotherapy, radiotherapy, cryotherapy or laser. Some patients presented directly to such centers and were treated without further referral. The system of record keeping varied at the different centers. Patient records were either in the form of cards retained by the patient, cards stored at the registry, or file folders. A few centers used computerized filing systems.

Data Collection at the eye care facilities

First, a pilot study was conducted at KNH to pretest the questionnaire and data retrieval system. After revision, amendments and a computer test run, the study was introduced to eye health care staff from 75 centers countrywide at the annual Kenya National Ophthalmic Workers (KNOW) conference facilitated by the DOS in September 2008. Staff at centers that were not represented at the conference were contacted on phone. All staffs were requested to enter eligible outpatient and inpatient records from the *clinic, theatre,* and *oncology* registers into feedback forms that were distributed at the workshop. (Appendix V) The staff were contacted after 2 weeks. Only centers that reported cases were eligible for the data collection visit.

Data was collected between October 2008 and March 2009.The eye centers were classified as mission (church-based), non-governmental, sub-district or district, provincial, teaching and referral hospitals. All centers consented to participation but 46 centers that confirmed availability of records of retinoblastoma were visited by the principal investigator who was assisted at each facility by ophthalmic staff and records clerk. The search words at the registry included *retinoblastoma, leukocoria, white reflex* and *c69.2* (for computerized ICD9 systems). On site, the researcher confirmed the records in the register(s) and entered all relevant details from the patient's card or file into a structured *questionnaire.* (Appendix I) The details were crosschecked and summarized in a *data control register* (MS Excel 2007) to track referrals. (Appendix V)

Control of data quality

In 2006 and 2007, Kenya was free of major events that would influence the source population. There were no adverse migrations or major changes in health policies that affect record-keeping. The period selected was recent enough to ensure archived records were in a retrievable state.All entries were double checked to ensure accuracy and the referred cases were traced to their destination. The completed questionnaires were sorted to identify cross referrals, re-grouped and analyzed once to avoid double counting. Missing and ambiguous data was clarified by phone from informants where possible.

Cases that were lost after referral were analyzed separately using available details obtained from the register at the initial center. Archived records were revisited to ascertain inconsistent entries that became apparent at analysis. All questionnaires were submitted for data entry and analysis.

5.DATA ANALYSIS

The data collected in the structured questionnaire was stored safely waiting data entry.To ensure confidentiality, only the researcher and statistician were allowed to access the filled questionnaires and coded database.

After cross checking for missing entries, a database was designed in MS-Access to allow the researcher to set controls and validation of the variables. Data was entered by the researcher and audited by the statistician. On completion, the data was exported to the Statistical Package for Social Scientists (SPSS – Version 13) for analysis.

The cases were classified into categories of interest and the analyzed results were presented in tables and figures. Odds ratio (OR) with 95% confidence interval (CI) was used to establish the factors that were more likely to explain the patterns of retinoblastoma. A Yates corrected P value of less than 5% was considered statistically significant. The Independent samples t-test was used to compare the equality of Means.

6.ETHICAL CONSIDERATIONS

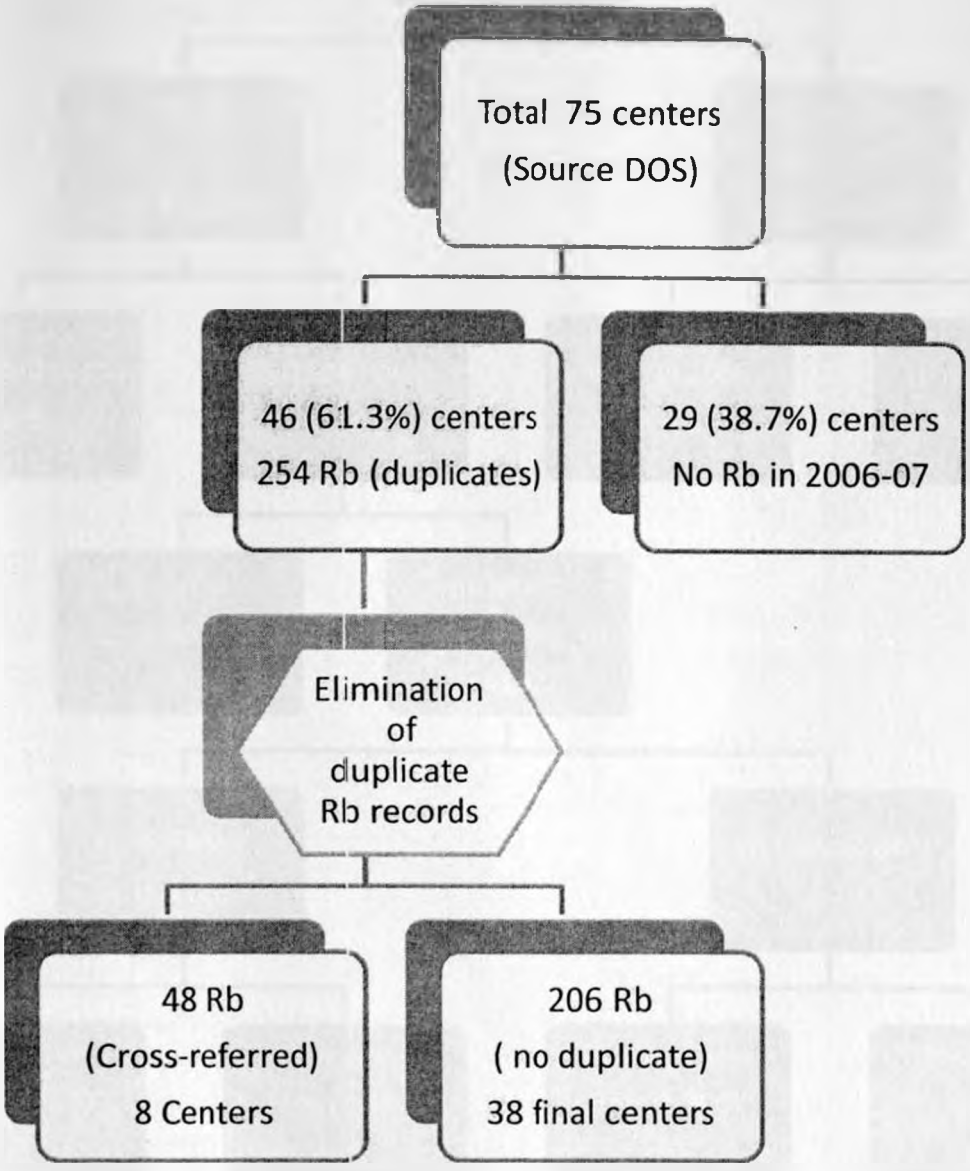
Ethical approval was obtained from the Kenyatta National Hospital ethics board. (Appendix III) A written authorization was also obtained from the Ministry of health regulations committee to grant access to the registry at the eligible health facilities in Kenya. (Appendix IV)

For non-governmental centers, details of the study highlighted in the abstract were discussed with the administration. After addressing protocols specific to each institution, consent was obtained from the participating facility to access relevant medical records. (Appendix II)

All patient information was treated with confidentiality. Names and identification were used for follow up and validation purposes but did not appear on reports. Electronic data was stored in safe custody in a stand-alone computer system with security measures to avert unauthorized access.

7.RESULTS

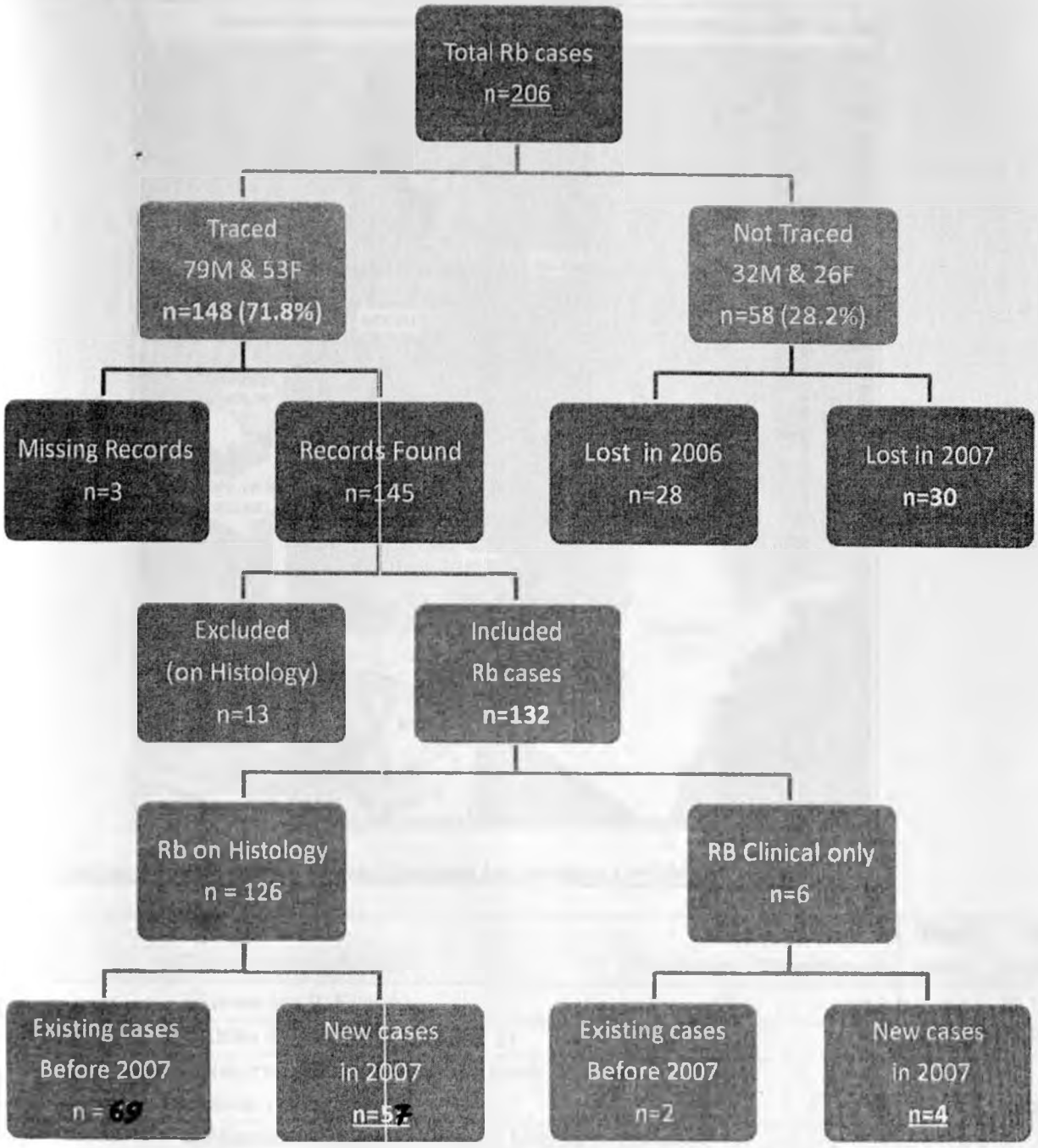
Figure 1: Overview of the participating eye care centers



Key: Rb= Retinoblasoma, DOS=Division of Ophthalmic Services in the ministry of health, Kenya.

Of 75 centers, 29 centers did not attend to any patient with retinoblastoma in the period under review. A total of 254 eligible cases were identified from 46 centers in the eight provinces of Kenya. After consolidating cross-referrals, 206 eligible cases were finally identified at 38 centers.

Figure 2: Overview of cases (n=206)



Key: Rb= Retinoblastoma, M= males, F= females

Although 58 cases were lost after referral, 148 cases were successfully traced to the final centers where they were treated. A total of 16 cases that were excluded consisted of 3 missing files and 13 cases that were ruled out on histology. Of 132 confirmed cases, 74.2% were unilateral and 25.8% were bilateral. There were 57 new cases in 2007, 51 new cases in 2006 and 24 cases were diagnosed before 2006.

7.1 Referral Pattern of retinoblastoma

Figure 3: Lost cases after referral (n=58). Inset: Homa Bay and Kisii

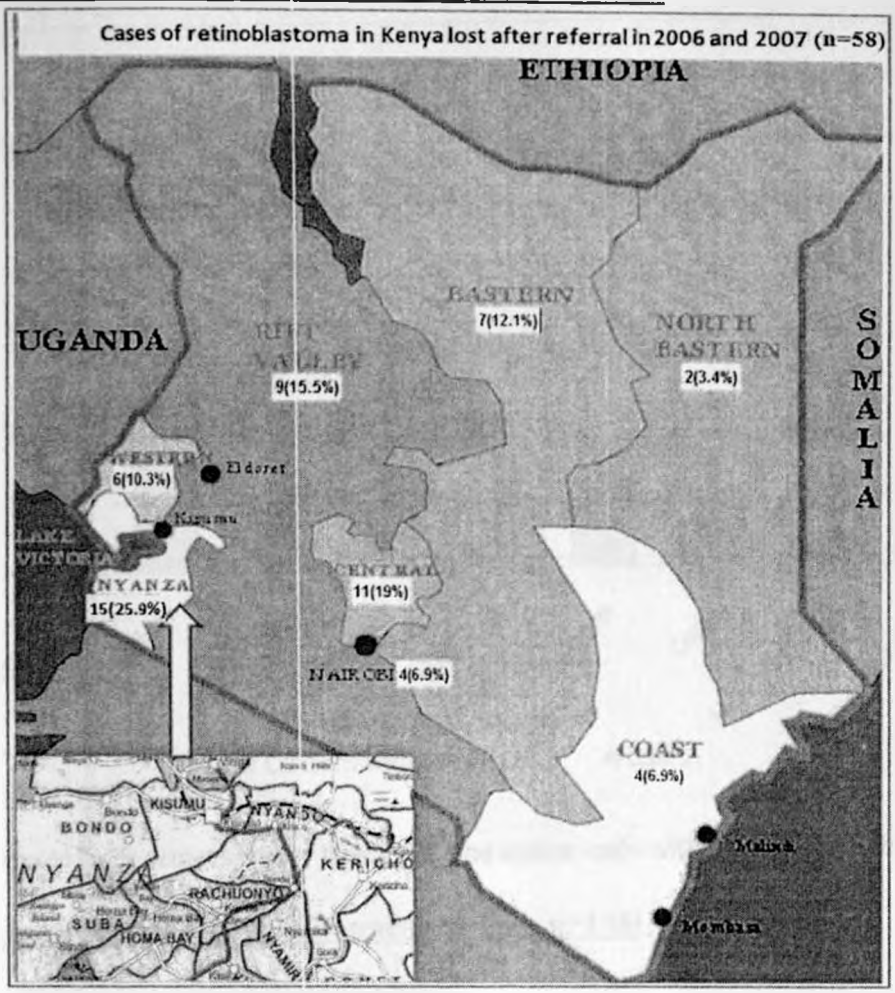
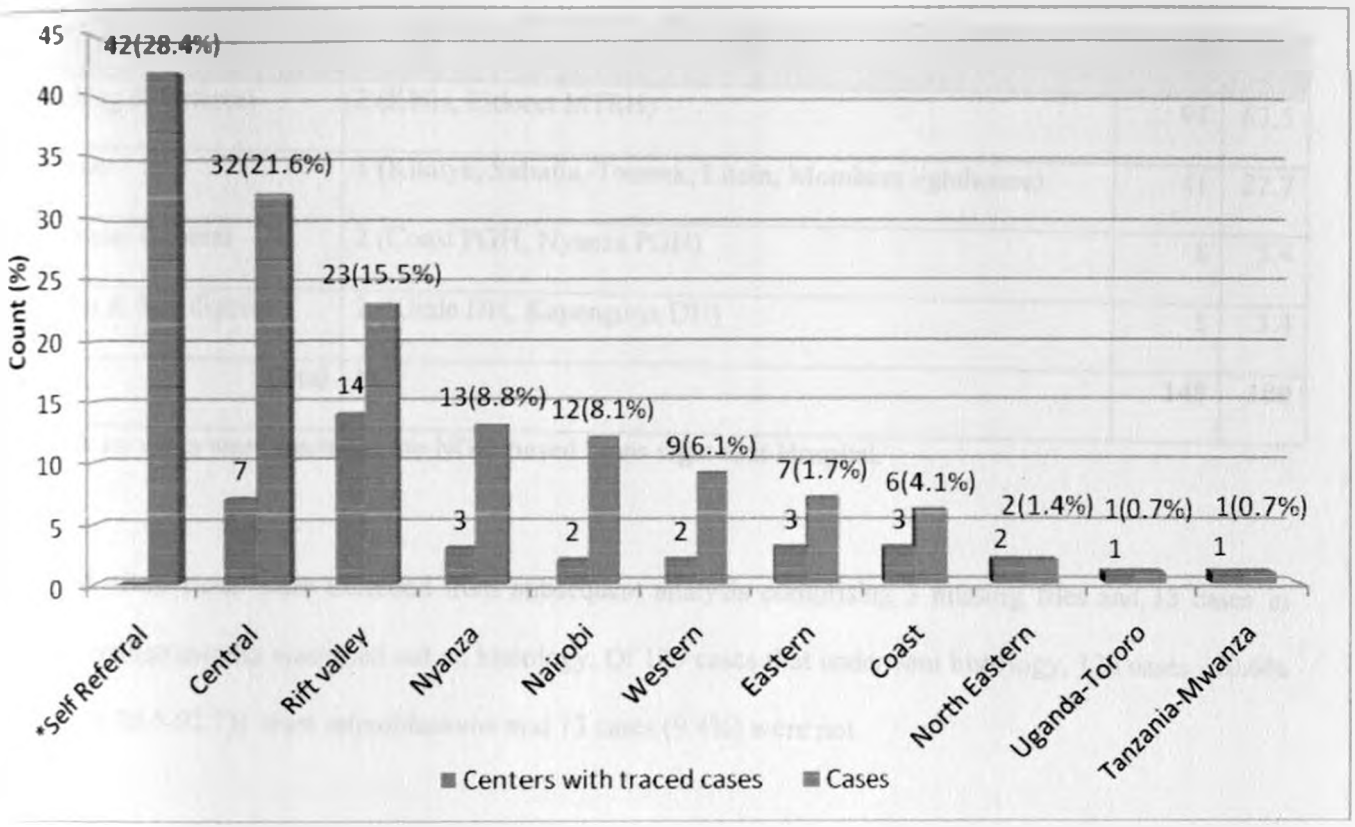


Table 1: Lost and traced cases of retinoblastoma by province (n=206)

Province	Centers with lost cases	Lost cases	Traced cases	Total cases	% Lost
Nyanza	2(Homa bay 9, Kisii 6)	15	17	32	46.9
Central	3(Thika 5, Kiambu 4, Ol Kalau 2)	11	37	48	22.9
Rift Valley	6(Nakuru 3, Iten 2, Kericho 1, Kitale 1, Lodwar 1, Maralal 1)	9	39	48	18.8
Eastern	4(Nyambene 4, Isiolo 1, Meru 1, Moyale 1)	7	7	14	50.0
Western	2(Busia 4, Bungoma 4)	6	19	25	24.0
Coast	3(Malindi 2, Kilifi 1, Kwale 1)	4	7	11	36.4
Nairobi	1(Mbagathi 4)	4	18	22	18.2
North Eastern	1(Garissa 2)	2	2	4	50.0
*Uganda, Tanzania	-	-	2	2	0.0
Total	**22**	**58**	**148**	**206**	**28.2**

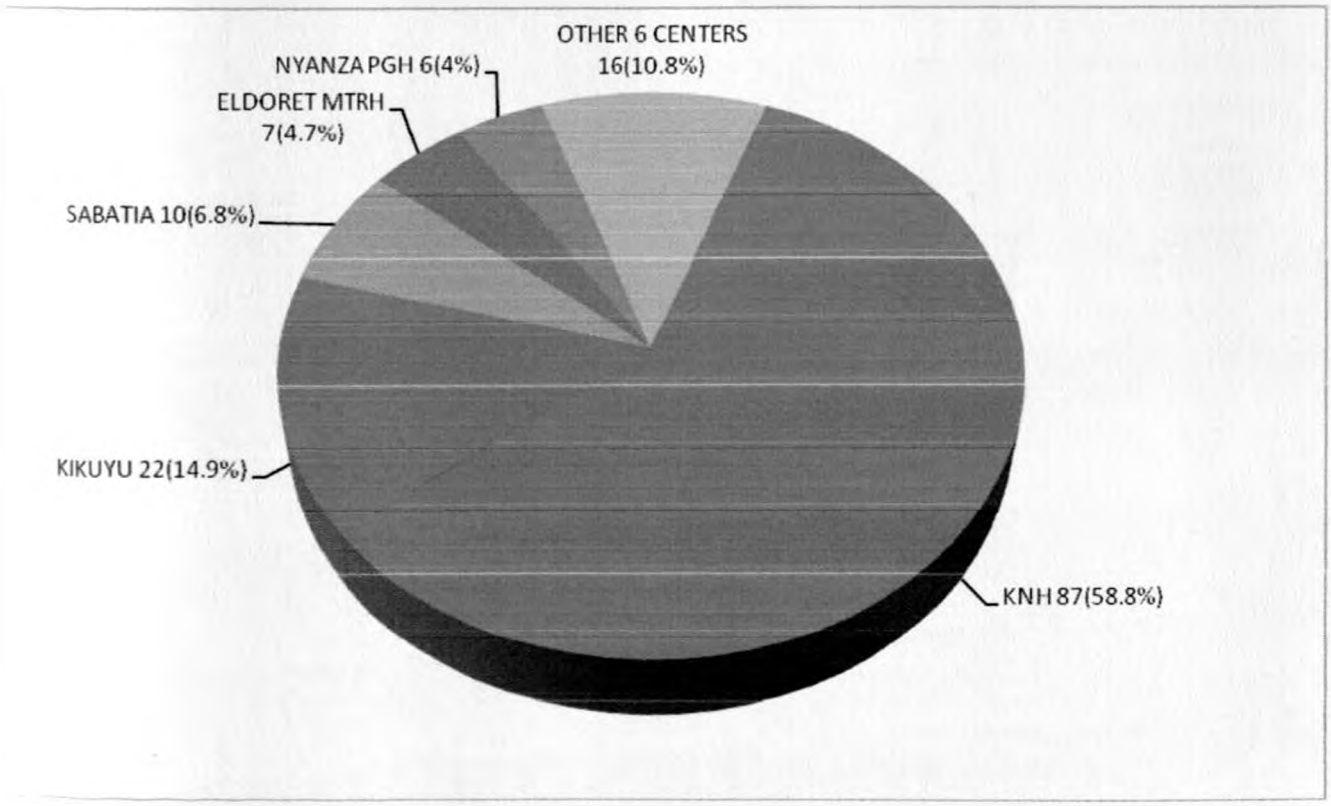
At 7 (31.8%) out of 22 centers, all the referred cases were lost.

Figure 4: Traced cases by province from which they were referred (n=148)



*Self referrals: 42 cases (at 9 centers) were treated at one center only without further referral.

Figure 5: Traced cases at specific final treatment centers (n=148)



*Other 6 centers were Litein, Tenwek, Kapenguria, Kitale, Coast PGH and Mombasa Lighthouse.

Table 2: Traced cases by Type of final treatment center (n=148)

Type of center	No of Centers	Cases	%
Teaching & Referral	2 (KNH, Eldoret MTRH)	94	63.5
Mission	5 (Kikuyu, Sabatia, Tenwek, Litein, Mombasa lighthouse)	41	27.7
Provincial General	2 (Coast PGH, Nyanza PGH)	8	5.4
District & Sub district	2 (Kitale DH, Kapenguria DH)	5	3.4
Total	**11**	**148**	**100**

*NGO: no cases were treated at the NGO-based Lions sight first Hospital.

A total of 16 cases were excluded from subsequent analysis comprising 3 missing files and 13 cases in which retinoblastoma was ruled out on histology. Of 139 cases that underwent histology, 126 cases {90.6% (95% CI 88.5-92.7)} were retinoblastoma and 13 cases (9.4%) were not.

In addition to 126 cases confirmed by histology, 6 cases (2 unilateral and 4 bilateral) that declined enucleation were included based on leukocoria and fundal mass diagnosed by an ophthalmologist. Therefore, 132 (89.1%) of 148 suspected cases were confirmed cases of retinoblastoma.

7.2 Distribution of retinoblastoma

Table 3: Distribution of cases by province of residence (n=132)

Province	No of Districts	Cases	%	Population < 5yr in 2007	% Population <5yr
Rift Valley	14	43	32.6	1,253,895	25.6
Central	7	26	19.7	375,224	7.7
Eastern	7	20	15.2	617,782	12.6
Nyanza	6	19	14.4	1,043,360	21.3
Western	4	11	8.3	603,767	12.3
Coast	4	6	4.5	429,639	8.8
North Eastern	3	4	3	214,214	4.4
Nairobi	1	2	1.5	356,020	7.3
Non-Kenyan	1	1	0.8	-	-
Total	**47**	**132**	**100**	**4,893,901**	**100**

After classifying by the district of residence on the date of presentation, the 132 cases resided in 47 districts in the 8 provinces of Kenya, except a Ugandan from Mbale district. (See Appendix X)

Table 4: Distribution of cases by Ethnicity (n=132)

		Unilateral	Bilateral	Total Cases	Percent %	% General Population
BANTU	1.Kikuyu	25	10	35	26.5	20.78
	2.Luhya	12	1	13	9.8	14.38
	3.Kamba	6	6	12	9.1	11.42
	4.Kisii	10	1	11	8.3	6.15
	5.Meru	3	2	5	3.8	5.07
	6.Mijikenda/Swahili	2	2	4	3	0.6
	7.Taita	1	0	1	0.8	0.95
	8.Embu	1	0	1	0.8	1.2
	Subtotal	**60**	**22**	**82**	**62.1**	**60.55**
CUSHITE	9.Somali	3	0	3	2.3	-
	10.Oromo	1	1	2	1.5	-
	Subtotal	**4**	**1**	**5**	**3.8**	**-**
NILOTE	11.Kalenjin	23	4	33	20.4	11.46
	12.Luo	6	4	10	7.6	12.38
	13.Maasai	2	0	2	1.5	1.76
	14.Samburu	0	2	2	1.5	0.5
	15.Turkana	2	0	2	1.5	1.52
	Subtotal	**33**	**10**	**43**	**32.5**	**27.62**
OTHER	16.Non Kenyan	1	1	2	1.5	-
	Total	**98**	**34**	**132**	**100**	

There was no statistically significant association between ethnicity and bilaterality (p=0.874).The cases constituted 15 broad ethnic subgroups except a Ugandan and a Somali citizen (Dadaab).

Table 5: Age-Sex distribution of Cases at presentation (n=132)

Age in months (range 2 to 96)	Male	Female	Total	Percent
< 6	6	3	9	6.8
6 to 12	8	8	16	12.1
13 – 18	6	1	7	5.3
19 – 24	16	6	21	15.9
25 – 30	5	8	13	9.8
31 – 36	13	11	25	18.9
37 – 42	4	4	8	6.1
43 – 48	9	5	14	10.6
49 – 54	1	2	3	2.3
55 – 60	5	0	5	3.8
60 +	6	5	11	8.3
Totals	**79** (59.8%)	**53** (40.2%)	**132**	**100**
Mean= **33.46** (SD 20.8) months				
Total population < 5yrs in 2007	**2,397,833** (49%)	**2,496,068** (51%)	**4,893,901**	

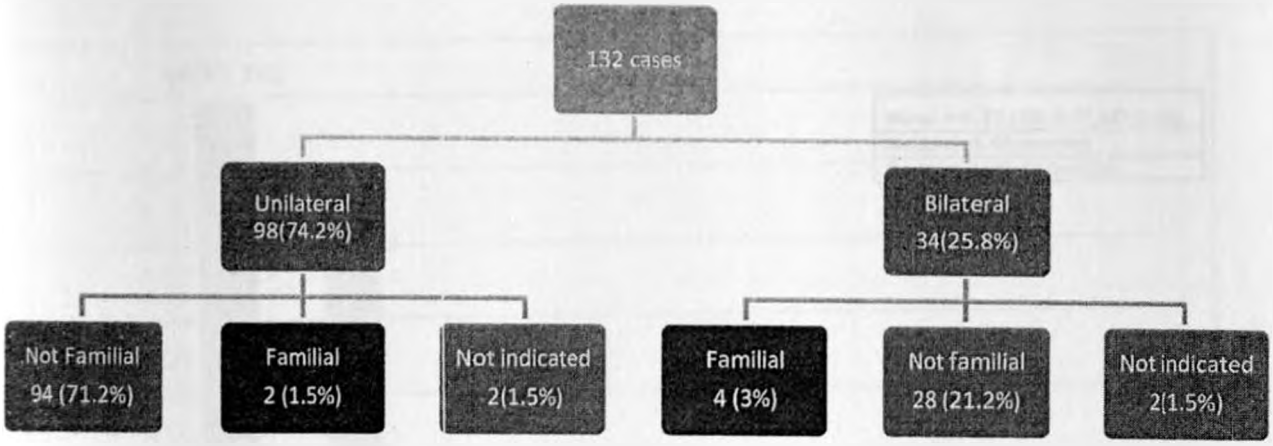
The male to female ratio was 1.49:1 for traced cases and 1.23:1 for lost cases compared to 0.96:1 for children less than 5 years of age in the general population in 2007.There was a statistically significant difference in the proportions between male and female patients (p=0.016).

Table 6: Distribution of cases by Age at presentation and bilaterality

Age in months	Unilateral	Bilateral	Total Cases	Percent
< 6	8	1	9	6.8
6 to 12	6	10	16	12.1
13 - 18	4	3	7	5.3
19 - 24	13	8	21	15.9
25 - 30	10	3	13	9.8
31 - 36	22	3	25	18.9
37 - 42	7	1	8	6.1
43 - 48	12	2	14	10.6
49 - 54	2	1	3	2.3
55 - 60	4	1	5	3.8
60 +	10	1	11	8.3
Total	**98(74.2%)**	**34(25.8%)**	**132**	**100**
Mean	35.9	26		

Patients with unilateral retinoblastoma were significantly older at presentation than those with bilateral disease (p=0.017).

Figure 6: Distribution by Family history



A positive family history was present in 6(4.5%) cases, of which 4 cases (66.7%) were bilateral. The mean age at presentation for familial (32.8months) and non-familial (33.1months) cases was similar.

Table 7: Association between bilaterality and Family history

	Family History		OR (95%CI)	P-value
	Yes	No		
Bilateral	4 (66.7%)	26 (22.2%)	7.0 (1.0 – 58.9)	0.031
Unilateral	2 (33.3%)	91 (77.8%)		

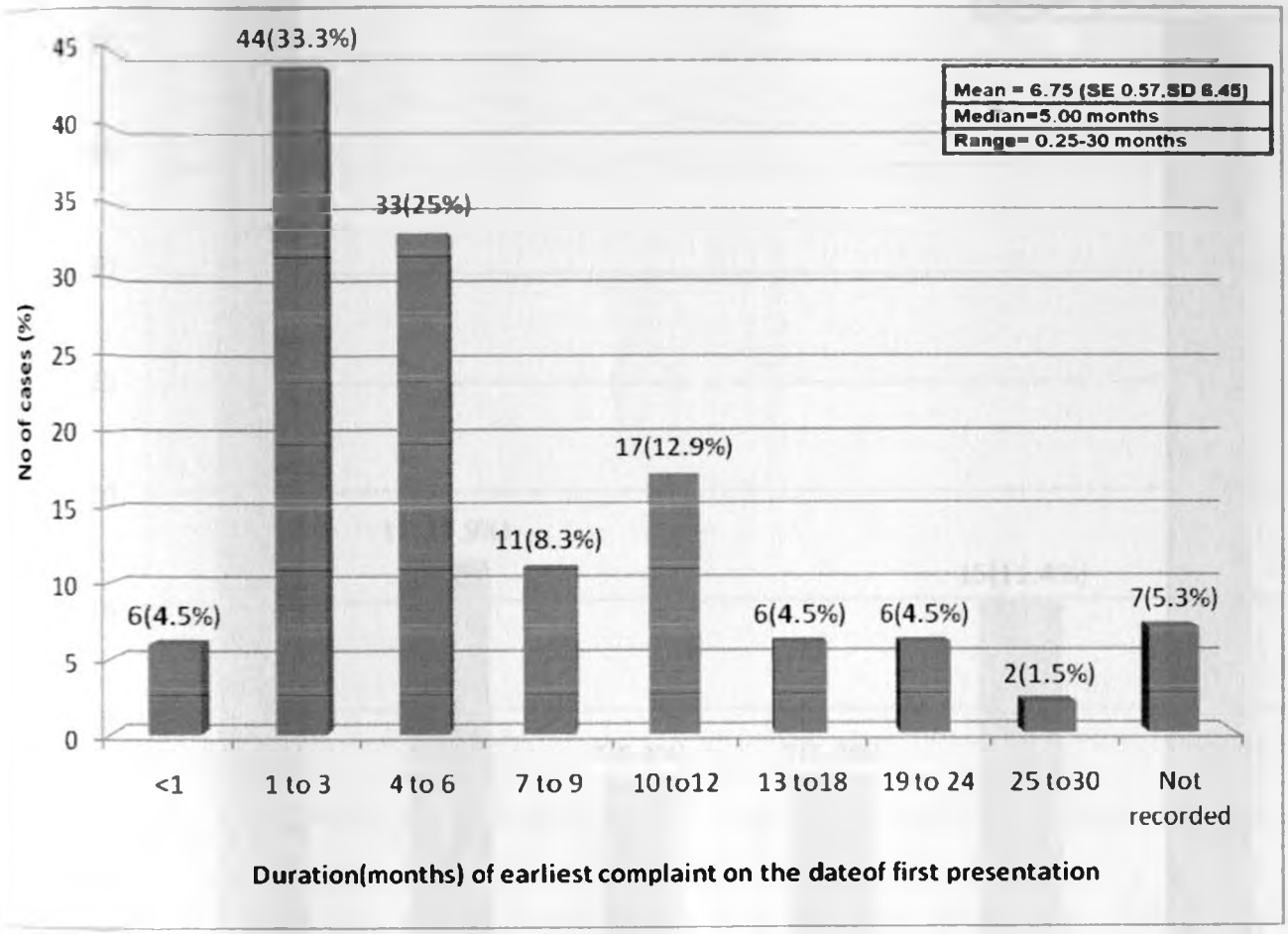
Patients with a positive family history were more likely to suffer bilateral than unilateral disease (p=0.031).

Table 8: Distribution by bilaterality and metastasis (n=132)

Final Diagnosis	**Cases**	**Percent %**
Unilateral	83	62.9 (95% CI 55.5-75.5)
Unilateral with metastasis	15	11.4 (95% CI 3.5-18.5)
Unilateral subtotal	**98**	
Bilateral	33	25 (95% CI 21.9-42.1)
Bilateral with metastasis	1	0.8 (95% CI 0.1-3.8)
Bilateral subtotal	**34**	
Total	**132**	**100**

7.3 Pattern of clinical presentation

Figure 7: Delay in first presentation (n=132)



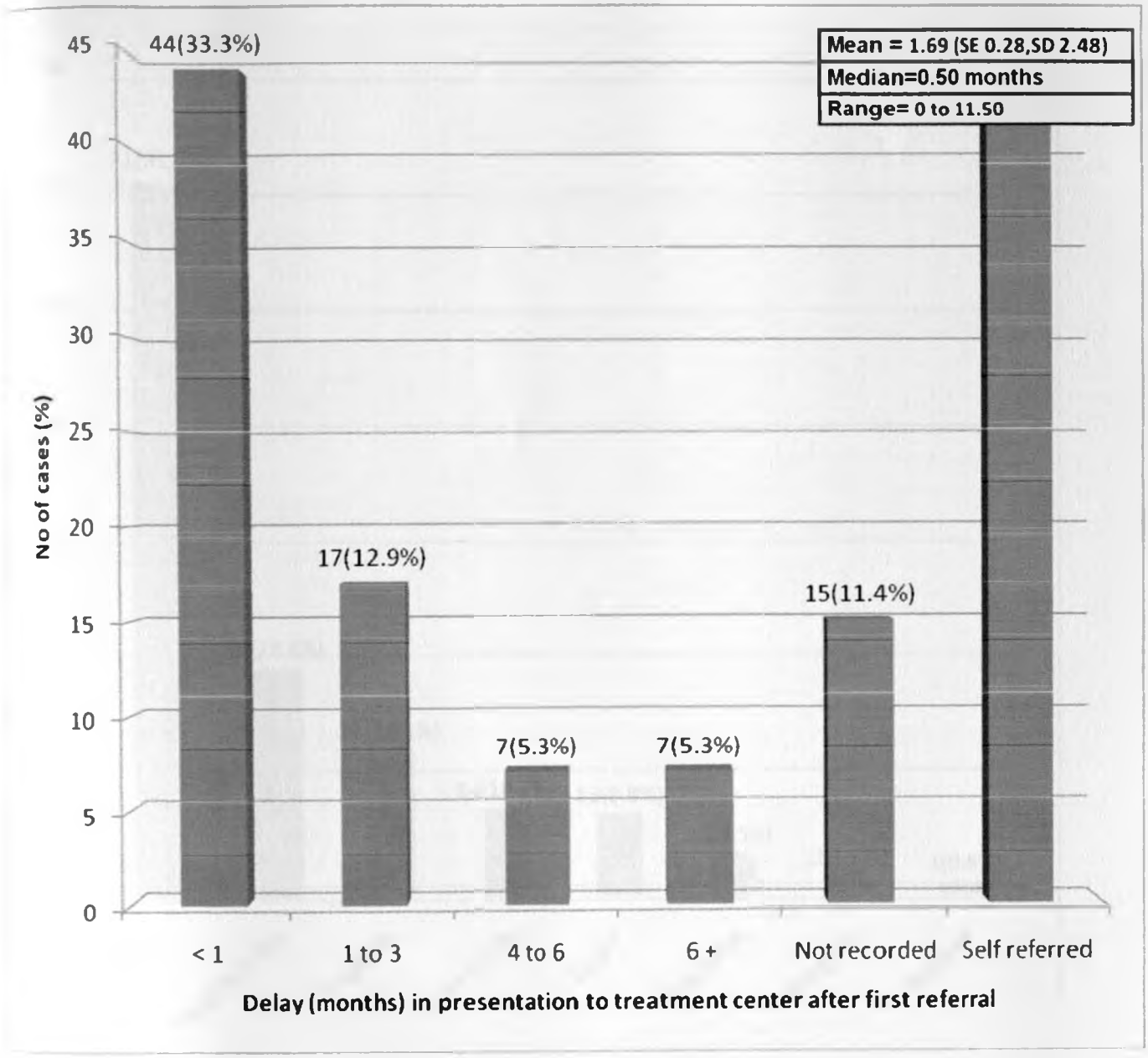
The reasons for delay in first presentation were not available. The mean delay in first presentation was significantly longer for patients who had metastasis at presentation than those who did not (p=0.014).

Table 9: Delay in first presentation by Province of residence (n=132)

	Non-Kenyan	Rift Valley	Central	Eastern	Western	North Eastern	Nyanza	Coast	Nairobi	Total
Missing details	0	4	1	1	0	0	1	0	0	7
No of cases	1	39	25	19	11	4	19	6	2	125
Total	**1**	**43**	**26**	**20**	**11**	**4**	**19**	**6**	**2**	**132**
Mean delay in months	**5.00**	**8.93**	**4.61**	**5.93**	**8.18**	**2.25**	**4.33**	**12.5**	**5.5**	**6.75**

The mean delay in first presentation varied by the province of residence (range 2.25-12.5 months) but the total number of cases by province varied (range 2 to 43).

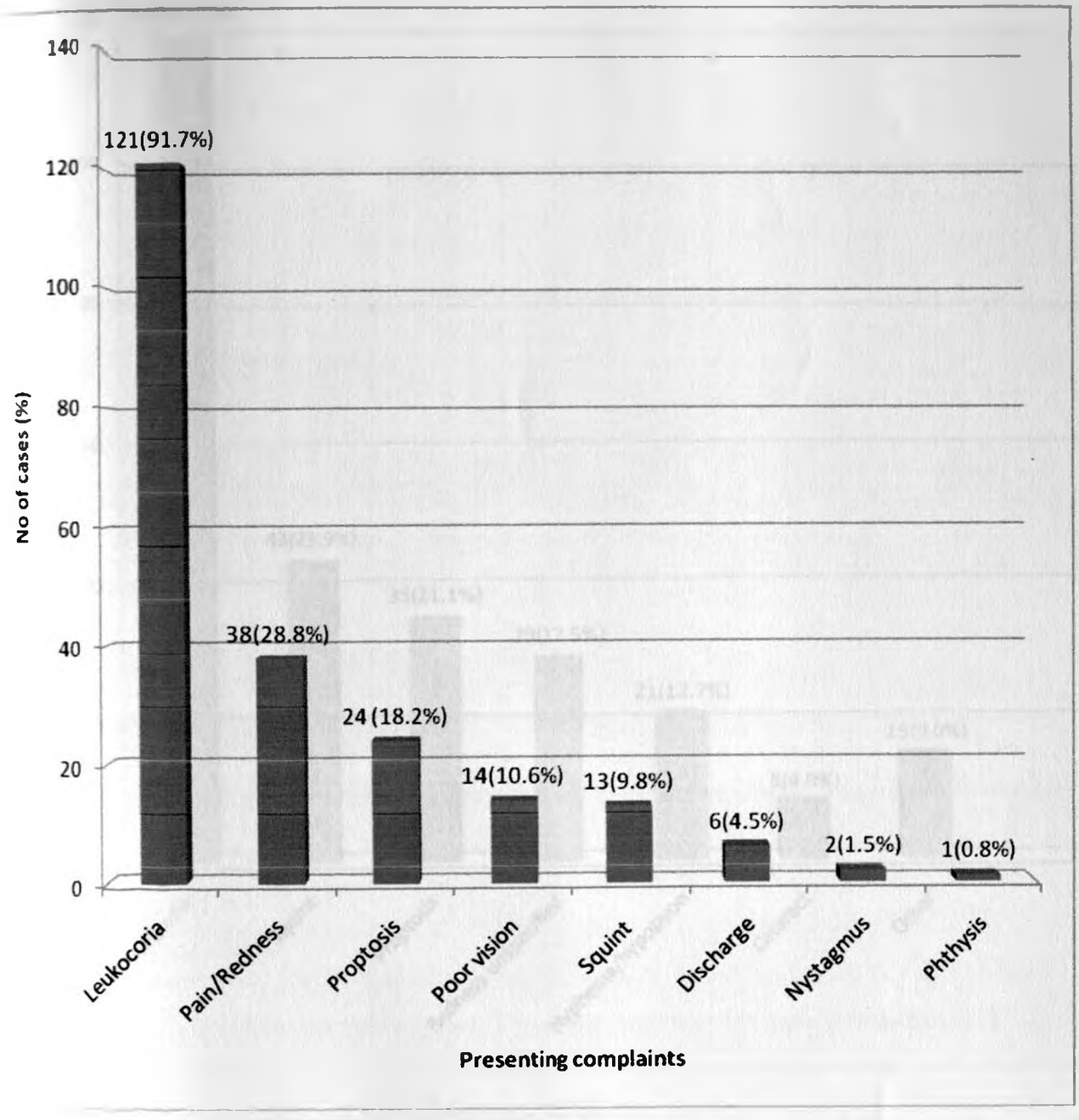
Figure 8: Delay in presentation after referral from first center (n=132)



The delay after referral was the duration from the date of referral at the center where the patient first presented to the date of presentation at the center where specific treatment for retinoblastoma was first administered.

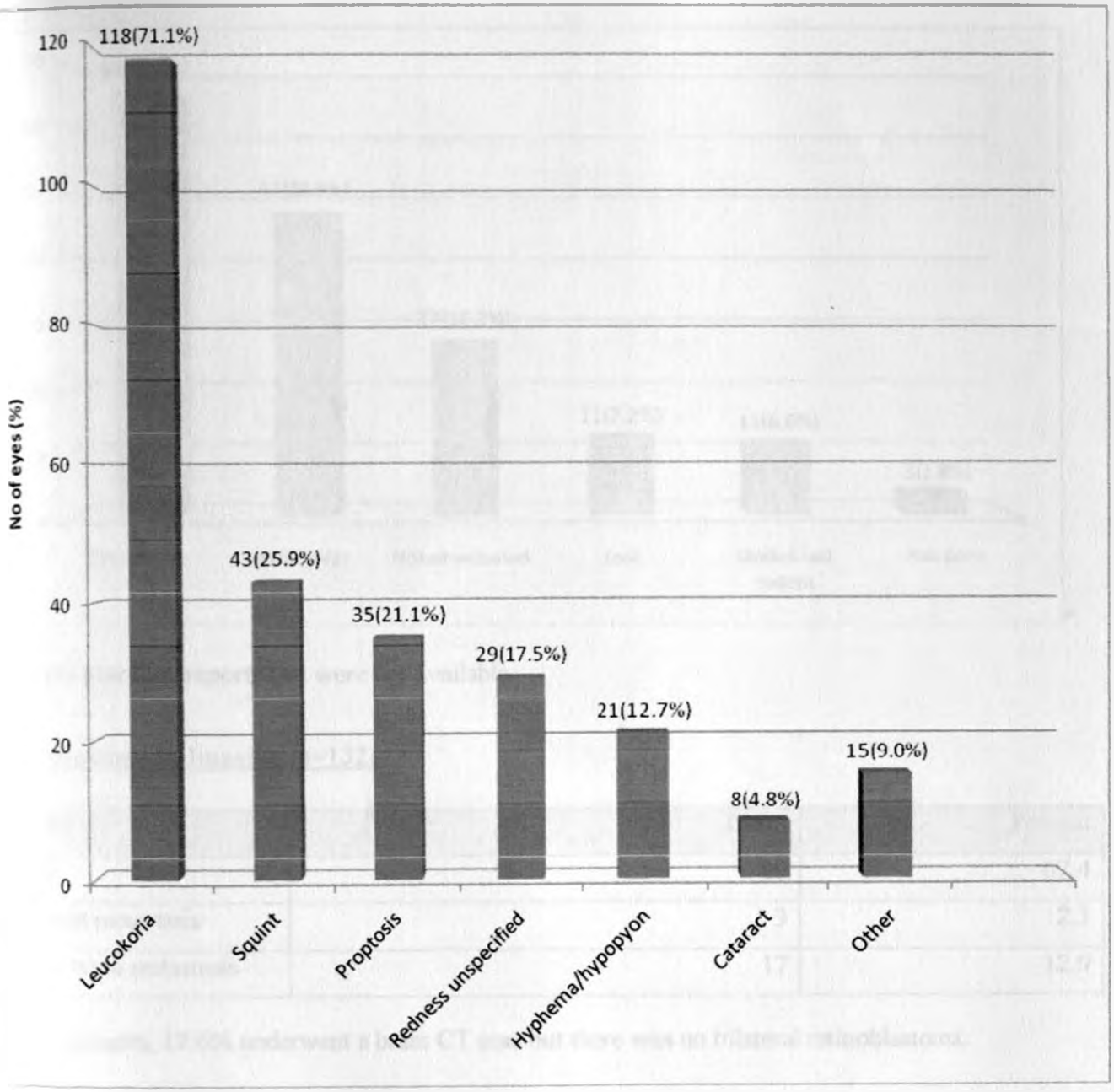
A total of 42 self referred cases were treated without further referral. Of 106 referred cases, 15 were excluded because the date of referral was missing. There were 75 referred cases.

gure 9: Presenting complaints of retinoblastoma cases (n=132 cases)



here was overlap of symptoms because patients presented with more than one complaint.

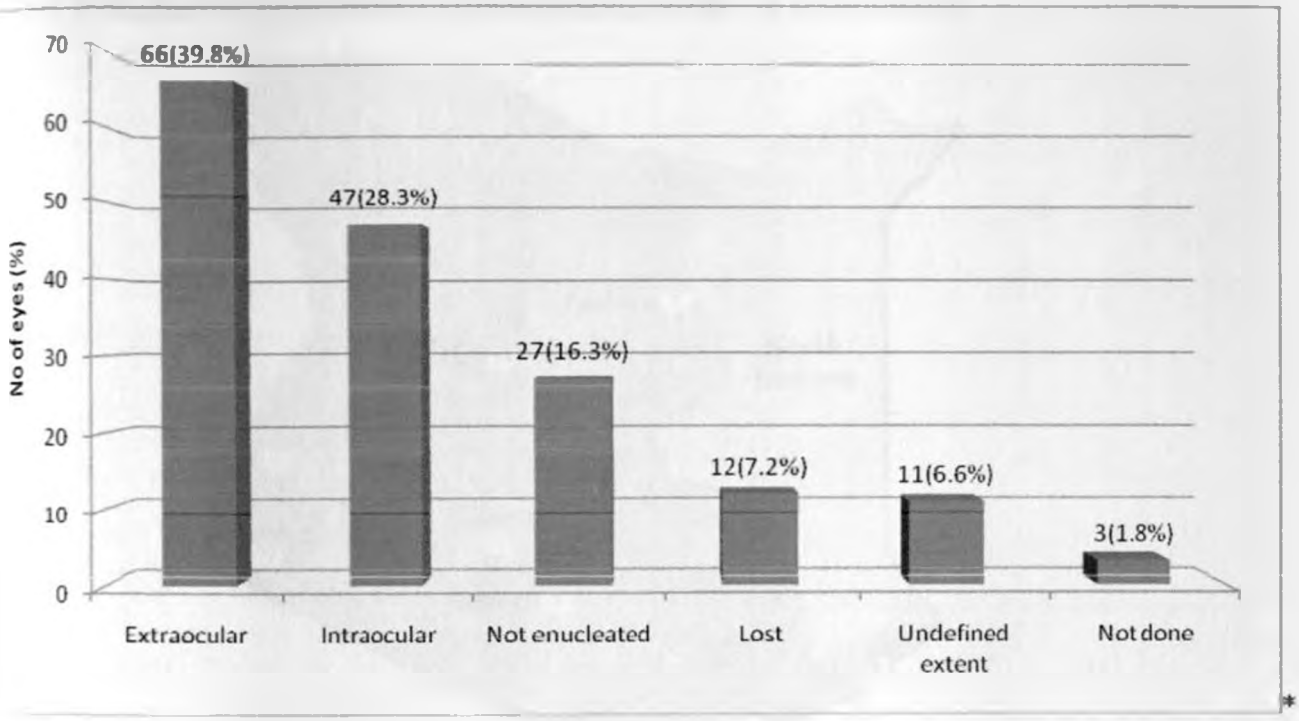
Figure 10: Examination findings in retinoblastoma cases (n= 166 eyes)



*Other findings in 15 eyes with retinoblastoma are buphthalmos (5), dilated pupil (3), necrotic cornea (2), nystagmus (2), rubeosis (1), phthysical eye (1) and retinal detachment (1).Iris rubeosis was found in the first affected eye of a bilateral case that presented after 12 months.

The 132 cases comprised of 166 affected eyes (87 right and 79 left).There was overlap of signs because many eyes had more than one finding on examination. Clinical evidence of metastasis at presentation was found in 22 of 132 cases (16.7%).

Figure 11: Histopathology findings (n=166 eyes)



Lost refers to histology reports that were not available.

Table 10: Findings on Imaging (n=132)

Investigation	Cases	Percent
Ultrasound	89	67.4
CT scan-Brain metastasis	3	2.3
CT scan-No brain metastasis	17	12.9

Of 34 bilateral cases, 17.6% underwent a brain CT scan but there was no trilateral retinoblastoma.

Table 11: Therapy received at eye care centers (n=132)

	Teaching & Referral	Mission	Provincial	District	Total	%
First Enucleation	64	45	9	8	126	95.5
Declined enucleation	0	5	0	1	6	4.5
Total	**64**	**50**	**9**	**9**	**132**	**100**
Chemotherapy	60	4	6	0	70	53.0
Cryotherapy or Laser	6	0	0	0	6	4.5
Radiotherapy	16	0	0	0	16	12.1

A total of 126 cases were treated but 6 cases declined enucleation and further treatment. Only 3 cases (2 unilateral and 1 bilateral) with advanced disease underwent palliative chemotherapy. All 6 cases (4.5%) that received laser or cryotherapy were treated at KNH. At the time of data collection, 21 of 132 cases (16%) had died and the mean duration between diagnosis and death was 7.2 (range 0.25-25.5) months.

7.4 Incidence of retinoblastoma in 2007

Figure 12: New cases of confirmed retinoblastoma in 2007 in Kenya(n=57)

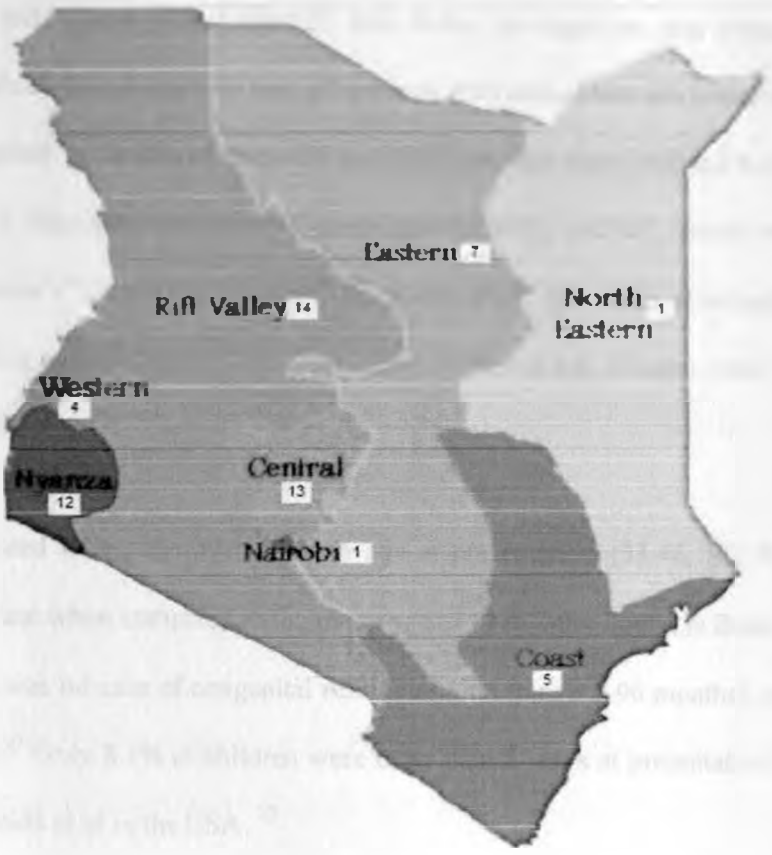


Table 12: New cases of retinoblastoma in 2007 by province

POPULATIONS PROJECTIONS PER PROVINCE : Kenya's Growth Rate 3.8% Source CBS 1999 Census										
			New cases of retinoblastoma in 2007							
	Children<5yr	Live births	Traced cases			Lost cases			Traced + Lost	
PROVINCE	TOTAL	TOTAL	TOTAL	%	< 5yr	TOTAL	%	< 5yr	<5yr	TOTAL
Nairobi	356,020	112,562	1	1.8	1	1	3.3	1	2	2
Central	375,224	125,068	13	22.8	13	6	20.0	6	19	19
Coast	429,639	128,712	5	8.8	4	1	3.3	1	5	6
Eastern	617,782	215,031	7	12.3	7	6	20.0	4	13	13
North Eastern	214,214	40,304	1	1.8	1	0	0.0	0	1	1
Nyanza	1,043,360	227,820	12	21.1	10	8	26.7	6	18	20
R. Valley	1,253,895	374,370	14	24.6	12	4	13.3	4	16	18
Western	603,767	206,660	4	7.0	3	4	13.3	3	7	8
Overall Total	4,893,901	1,430,527	57	100	51	30	100	25	81	87

Of 148 traced cases, 132 (89%,CI 86.1-91.9) were confirmed to be retinoblastoma of which 57 were new cases in 2007.Of 58 cases lost after referral, 30 were new cases in 2007 of which 27 (89%) were presumed to be the proportion of confirmed cases. Considering the 84 cases, the incidence was **1:17,030 live births** in 2007 which is compared to other countries in Appendix IX

8.DISCUSSION

In 2007, there was an estimated population of 34,652,581 in Kenya of which 14.1% (4,893,901) were less than 5 years old. There were 1,430,527 live births. In-migration was presumably equal to out-migration. In this study it was assumed that, all patients with retinoblastoma presented to health facilities, patients who presented to facilities which did not offer eye care were referred to eye care facilities, all eye health workers diagnosed and referred cases appropriately, and all records were registered at the health facilities. From 1st January 2006 to 31st December 2007, 206 cases of retinoblastoma presented to 46 (61.3%) of 75 eye care facilities in the 8 provinces of Kenya but 58 cases were lost after referral and 16 cases were excluded.

Of the 132 confirmed cases, the overall mean age at presentation (33.46, SD 20.8 months) suggests patients presented late when compared to the mean age of 12 months found in Britain by Goddard et al.[58] In our study, there was no case of congenital retinoblastoma (range 2-96 months), which Abramson et al reported to be rare.[27] Only 8.3% of children were older than 5 years at presentation which was similar to 8.5% found by Shields et al in the USA. [22]

Although equal sex distribution of retinoblastoma was reported in most countries such as the Netherlands,[7] USA[9,14] and Malawi,[19] males were significantly more affected than females in our study (p=0.016). Despite there being a larger proportion of girls among children less than 5 years of age in Kenya, the male to female ratio was 1.5:1 for the confirmed cases and 1.2:1 for cases lost after referral(**Table 5**). Of 147 cases in Mumbai, Balkrishna et al found a male to female ratio of 1.4:1 which may have been due to a higher proportion of boys in the Indian population of children.[15] The male preponderance in our study may suggest that either boys were preferentially taken to hospital or that they were more affected.

There were 74.2% unilateral and 25.8% bilateral cases which was similar to findings at KNH[21, 26] In Mexico, Leal et al found 73% unilateral and 27% bilateral cases.[23] In our study, the mean age at presentation was 35.9 and 26 months for unilateral and bilateral cases respectively (p=0.017) which was

similar to findings at KNH.[21, 26] In Mexico, the mean age at presentation was 30 and 18 months respectively.[23] In Britain, the mean age at presentation was 18 and 5 months respectively.[58] therefore, compared to Britain and Mexico, patients in Kenya presented late.

A positive family history was found in 6(4.5%) of 132 cases compared to 12% in Britain [3] and 10.6% of 955 cases in the Netherlands.[7]Of 6 familial cases, most (66.7%) were bilateral. Patients with a positive family history suffered more bilateral than unilateral disease (p=0.031). The mean age at presentation for familial (32.8 months) and non-familial (33.1 months) cases was similar unlike in the USA where all familial cases had presented by 28 months.[29] Although pathological and clinical staging was not routinely documented at eye care centers in Kenya, histology showed most (67%) familial cases had extraocular extension unlike in Netherlands where 56% of familial cases presented early in group I of the Reese-Ellsworth classification.[28] This suggests that familial cases in Kenya presented unusually late.

Each case was classified by the district of residence as recorded on the date of first presentation, irrespective of new administrative changes. The confirmed cases resided in 47 districts within the 8 provinces of Kenya, except 1 resident of Mbale district in Uganda. The largest proportion resided in Bomet, Kiambu and Kisii districts which are also densely populated. (Appendix X) The distribution by province was proportional to the number of children less than 5 years old in the respective provinces but a disproportionately large number of cases resided in Central province. (Table 3) The proximity of this province to referral centers in Nairobi may have enabled more patients to easily access these facilities.

There are 42 ethnic communities in Kenya comprising Bantus, Nilotes and Cushites. The cases constituted 15 broad ethnic subgroups which were distributed in proportion to their size in the general population but there were 2 non-Kenyans. (Table 4) There were no ethnic differences in the frequency of unilateral and bilateral cases unlike in the Indian population where differences were apparent.[15] Ethnic groups may have had different health seeking patterns and cultural practices that influenced presentation by region but further social studies are necessary. In Uzbekistan, a higher incidence was found among the Tartars who practice consanguineous marriage.[12]

The mean delay in first presentation (6.75 months) was longer compared to Britain (0.5 months).[58] The shortest delay (0.25 months) was seen in 3 children aged 8, 10 and 27 months who presented with pain, squint and leukocoria respectively which suggests it is possible for patients in Kenya to present early. The longest delay (30 months) was found in a child from a nomadic community who ignored leukocoria and presented because of proptosis which illustrates the need for public education. Patients with a long delay in first presentation were more likely to have metastasis than those who presented earlier ($p=0.014$). Despite the variable number of cases by region, the longest mean delay in first presentation (12.5 months) was found in Coast province **(Table 9)**.

The mean delay after referral was longer (1.69 months) compared to Britain (2 weeks).[58] This suggests patients in Kenya did not seek further treatment promptly. A 2 year old child whose parents declined enucleation presented after 11.5 months with leukocoria in the better eye. The reasons for late presentation could not be assessed in our study. However, in a prospective review of 52 patients at KNH, Kimani et al found the main reason for delay in the first presentation to be ignorance rather than financial constraints, and the main reason for delay after referral was mismanagement at the first center followed by ignorance, distance and financial constraints. [26]

We found the most common presenting complaint was leukocoria in 121 of 132 cases (91.7%) but clinical evidence of metastasis was found in 22 cases (16.7%) due to late presentation. At KNH, Kimani et al found leukocoria as a complaint in 77% of 52 cases. [26] In our study, the commonest sign was leukocoria in 71% of 166 eyes compared to 56% in the USA[39] and 80% of 92 eyes in Korea.[40] Corey et al found orbital cellulitis in 5% of cases in USA[42] but this finding was not specified at centers in Kenya and may have been broadly classified as red eye (Figure 9).

Most (67.4%) cases underwent ultrasonography but this service was available in very few facilities. Only 15.2% of cases underwent a brain CT scan of which 17.6% were bilateral cases. It was not surprising that there was no case of trilateral retinoblastoma because Amoaku et al found the condition to be rare[24] and few cases underwent brain CT scan which is required for diagnosis. Of 166 affected eyes, histology

showed tumour was extraocular in most eyes (39.8% compared to 28.3% for intraocular tumour) which suggests most cases presented late, by which time the tumor had already spread (Figure 11).

Almost half of the cases (48.5%) were enucleated at the first center and most (58.8%) cases were eventually treated at KNH. Of 70 cases (53%) that received chemotherapy, few (14.3%) were treated at church-based and provincial hospitals while 85.7% were treated at 2 teaching and referral hospitals. All the 6 cases (4.5%) that underwent local therapy (laser[51] or cryotherapy[52]) and 16 cases (12.1%) that underwent radiotherapy were treated at KNH (Table 11). The availability of additional treatment modalities resulted in a large proportion of cases being treated at KNH where the 3-year survival was 26.6%.[55] A total of 21 cases (16%) had died by the time of data collection. The mean duration between diagnosis and death was 7.2 months. One child was enucleated but the parents declined chemotherapy and 6 cases (4.5%) declined surgery. This illustrates poor uptake of services despite availability.

Of 206 cases, 58(28.2%) were not found at the centers to which they had been referred, or any other eye care center. The largest proportion of lost cases (25.9%) was found in Nyanza province at 2 centers-Homa Bay and Kisii (Figure 3).Because there was no ophthalmologist in Homa Bay, all cases diagnosed by the ophthalmic clinical officer were referred to the nearest ophthalmologist at Kisii district hospital. The cases were not found at the Nyanza provincial hospital in Kisumu which was the nearest alternative center. Homa Bay, Kisii and Kisumu are geographically close to each other but 9 of 10 cases were lost after referral. The patient's relatives may have ignored medical advice but further investigation is necessary. At 7 centers, all the 15 referred cases were lost. Of these, patients at the border towns of Busia and Moyale may have preferentially sought treatment in Uganda (Tororo) and Ethiopia respectively due to proximity. However, other 5 centers further away from the borders also lost all the referred cases (See map Appendix VIII).This implies other factors were at play that requires detailed investigation.

Although Central province is the nearest to the national referral hospital (KNH) in Nairobi, 19% of referred cases were lost which suggests distance was not the only explanation for lost cases. In the arid North Eastern province where very few cases (3.4%) were lost after referral and only 1 center reported cases, this may have been due to poor health seeking behavior in the resident communities so that very

few cases attended hospital, if at all. It is possible that the patient's relatives ignored medical advice or socio-economic constraints prevented them from accessing further treatment but this warrants further investigations.

In our study, 148 cases were successfully traced to 38 centers at which they were finally treated but 28.4% cases were treated without further referral. Of 106 referred cases, most (56.6%) were sent from district and sub-district hospitals probably because these centers were the most numerous. Only 63.5% of cases were finally treated at the 2 teaching and referral hospitals (Table 2) which suggests previous studies conducted at KNH did not necessarily represent the country.[21,25,26] The Rift valley province is the largest and attended 15.5% cases at 14 centers but most cases (21.6%) were referred from Central province (7 centers) probably due to its proximity to facilities in Nairobi where KNH and Kikuyu eye unit treated 73.6% cases.(Figure 4).

On histology, 13 (11%) of 148 traced cases were not retinoblastoma. Of these, 8(61.5%) had endophthalmitis, 2(15.4%) had Coat's disease and the rest were single cases of PHPV, non-specific granuloma and rhabdomyosarcoma. In France, Vahedi et al found 78(16%) of 486 clinically suspected cases were not retinoblastoma on histology; of these 78 cases, 25% had Coats disease, 30% had congenital lesions and the rest were other tumours, harmartomas, and inflammation but there was no case of ROP and very few had PHPV.[44] Of 139 suspected cases that underwent histology in our study, 126 cases (90.6%, CI 88.5-92.7) were found to be retinoblastoma which demonstrates the accuracy of a clinical diagnosis. However, 6 (4.5%) of 132 confirmed cases that declined enucleation were diagnosed using clinical findings by an ophthalmologist. These 4 unilateral and 2 bilateral cases had at least one eye with leukocoria and fundal mass. Similarly, 8 of 147 cases (5.4%) diagnosed by clinical findings alone were included in the register-based study in Mumbai.[15]

The incidence by standard annual analysis was 1:17,030 live births in 2007 (**Table 12**) but may be an underestimate because the number of cases that did not present to hospital was not known. This was similar to incidence found in other countries (Appendix IX). Because incidence by birth cohort analysis was more accurate in the Northern Europe, it is recommended in future studies on retinoblastoma.[4]

Findings of this study provide important baseline characteristics on retinoblastoma in Kenya. A Ministry of health, the health management information system reported 378 cases of retinoblaston 2007 which was an overestimate because of erratic reporting and double-counting of revisits and c referred cases.

Study Limitations

The greatest challenge in this study was tracking of the cases that were lost after referral. At most p facilities, patients retained their outpatient records during visits and they could not be contacted bec telephone and address details were not routinely recorded in the clinical registers. Complete details c not be obtained. However, only 3 files were missing and clinical data was incomplete in a few cases.

Secondly, different systems of record keeping may have affected the retrieval rate; at 2 center computer system was upgraded during the period under review. Thirdly, estimates of the ge population in 2007 were based on a growth rate of 3.8% determined in the 1999 census (Appendix This 8-year period may have witnessed significant alterations in the national demographic character which will become apparent only after the next Kenya national census in August 2009.

9. CONCLUSIONS

1. A significant proportion of cases were lost after referral, especially in Nyanza province.

2. The cases presented late which resulted in the advanced stage of disease found at the time of diagnosis. Leukocoria was the most common clinical presentation of retinoblastoma.

3. There was a male preponderance among the confirmed cases.

4. Bilateral cases presented at a significantly younger age than unilateral cases and a positive family history was found in 4.5% cases.

5. Most cases resided in the Rift Valley province but a disproportionately large number of cases were referred from the Central province. There were no ethnic differences in the frequency of retinoblastoma.

6. The incidence of retinoblastoma in Kenya was comparable to other countries.

10. RECOMMENDATIONS

1. Public Education through mass media (e.g leukocoria and squint on children's photographs), screening (red reflex test for leukocoria) by maternal and child health workers and screening of familial cases at first contact and up to the age of 5 years.

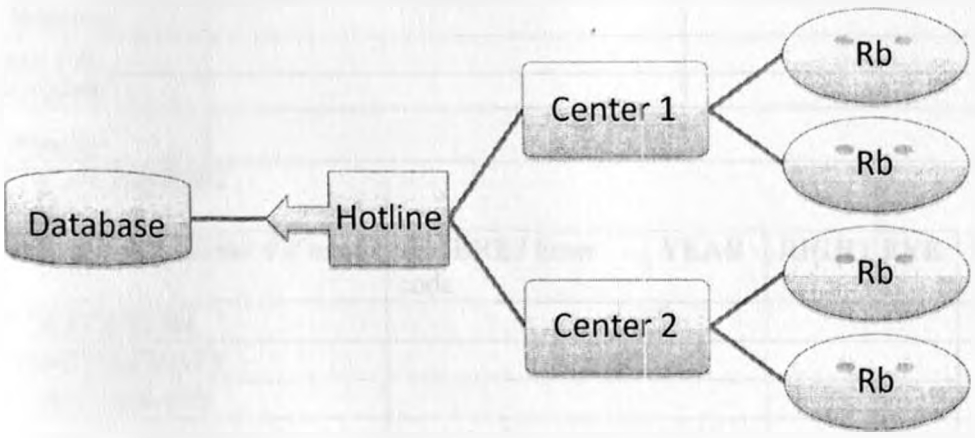
2. Enforce mandatory registration of patient telephone contacts in clinical registers at all centers and equip regional centers with the capacity to treat patients at first contact.

3. Improve record-keeping and documentation by implementing predesigned data forms at eye care facilities and introduce validation checks in the eye health management information system.

4. Further research to investigate the lost cases after referral, factors influencing uptake of services and determinants of the regional distribution of retinoblastoma.

5. Establish a National retinoblastoma hotline and registry coordinated by a workgroup (**Figure 13**). Prospective registration of data in the pre-designed form (Appendix I) and database will ensure accurate records in future through register-based studies.

Figure 13 Proposed model of the retinoblastoma (Rb) registry for the workgroup



APPENDIX

Questionnaire

THE PATTERN OF RETINOBLASTOMA IN KENYA: 2006-2007

A. *HOSPITAL DETAILS: Enter details in block letters*

1. Form Serial No: _____ Contact person:_____ Phone:_____
2. Hospital code: ☐☐ Name:_____
3. Who diagnosed? *Tick one* (1) Ophthalmologist (2) OCO (3) Other-specify:_____
4. Referred from ☐☐ Name:_____ Date: ___/___/___ *(N/A if Not Referral)*

B. *PATIENT DETAILS: Enter details in block letters*

1. Date of first presentation at center A2:___/___/___(dd/mm/yy)
2. Patient File No: _____
3. Patient Name: 1st_____ 2nd_____ 3rd _____
4. Phone/Address: _____
5. District of Residence: Code___Name:_____
6. Ethnicity *or Nationality if non-Kenyan*_____
7. Age at presentation:_____Months
8. Sex: *Tick one* (1) **Male** (2) **Female**

C. *PRESENTING COMPLAINTS: Enter duration of complaint in Months on Date of Presentation*

	COMPLAINT	DURATION IN MONTHS RIGHT EYE	DURATION IN MONTHS LEFT EYE
C1	Leukocoria		
C2	Squint		
C3	Proptosis		
C4	Pain / Redness		
C5	Shrunken Eye		
C6	Not Recorded		
C7	Other-Specify		

D. *PAST MEDICAL HISTORY*

	PROCEDURE (*Enter 0 if none*)	WHERE? Enter code	YEAR	RIGHT EYE	LEFT EYE
D1	ENUCLEATION				
D2	CHEMOTHERAPY				
D3	RADIOTHERAPY				
D4	OTHER –specify				

E. *FAMILY HISTORY:* Is there a Positive family history of Retinoblastoma? *(Tick one only)*

1. **Yes.**_____ 2. **No.**_____3. **Not Recorded**_____

F. *EXAMINATION:*

Code: 1.Yes 2.No 3. Not Recorded

	FINDING	RIGHT EYE	LEFT EYE
F1	VISUAL ACUITY: Was the eye at least able to follow light?		
F2	PROPTOSIS: Was there exophthalmos?		
F3	SQUINT: Was a squint present?		
F4	RED EYE: Was the conjunctiva injected?		
F5	ANT CHAMBER: Was there hypopyon or hyphema?		
F6	IRIS: Was there rubeosis?		
F7	PUPIL REFLEX: Was there white reflex?		
F8	LENS: Was there a cataract?		
F9	FUNDUS-Was the tumour visible?		
F10	OTHER ocular findings–specify		
F11	Systemic: Was there evidence of metastasis?		

*G. **INVESTIGATIONS**: Circle one code only*

	INVESTIGATION	RIGHT EYE	LEFT EYE
G1	ULTRASOUND: *1.Positive 2. Negative 3.Not done 4.Indefinite*		
G2	CT SCAN: *1.Orbital 2.Brain metastasis 3.Not done 4.Indefinite*		
G3	HISTOLOGY: *1.Intraocular 2.Extraocular 3.Undefined 4.Not RB 5.Not done 6.Lost*		
G4	OTHER-specify		

*H. **FINAL DIAGNOSIS**: Tick one only*

1. Unilateral RE **2.** Unilateral LE **3.** Bilateral **4.** Trilateral **5.**Metastatic **6.**Other_____

*I. **OUTCOME OF HOSPITALIZATION**: Circle one option and enter the details:*

1. Referred on Date:___/___/___to Code:___ _____Hospital
2. Treatment:(1)Enucleation (2)Chemotherapy (3)Local/focal (4)Radiotherapy (5) Declined (6)Other
3. Date of Death:_____/___/2007

*J. **DATE OF LAST FOLLOW UP**:* ___/_____/___.

Remarks:_____

..... **The End**.....

- If Referred, enter the Cross referral of form serial No: _____
- (1) New case 2007 **(2)** Existing Case diagnosed before 2007
- (1)Confirmed **(2)**Unconfinned **(3)**Other (not-retinoblastoma) **(4)**Lost to follow up

Correspondence: (contacts of researcher)

II. Institutional Consent Form

INSTITUTIONAL CONSENT FORM

Title of Project: A 2-year Retrospective Study of the Incidence and Pattern of Retinoblastoma in Kenya

Researcher: Dr. Joseph M Nyamori, University of Nairobi and Ministry of Health

I confirm that:

1. I have read the information sheet (study abstract) for the above research and I have had the opportunity to ask questions.
2. I understand the participation of my institution(s) is voluntary and necessary in fulfillment of the national study to establish **The Pattern of Retinoblastoma in Kenya**. I understand that sections of relevant records of the patients in my health institution(s) will be looked at by responsible individuals where it is relevant to the research. I give permission for these individual(s) to access the records.
3. I accept that my institution will take part in the above study

Faithfully,

Name: _____

Signature & Title: _____

Date: _____

Institution Name: _____

III. KNH Ethical Approval

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along. Ngong Rd.
P.O. Box 20723, Nairobi
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi
Email: KNHplan@Ken.Healthnet.org

26th November 2008

Ref: KNH/UON-ERC/ A/118

Dr. Joseph M. Nyamori
Dept. of Ophthalmology
School of Medicine
University of Nairobi

Dear Dr. Nyamori

RESEARCH PROPOSAL: "A 2-YEAR RETROSPECTIVE STUDY ON THE PATTERN OF RETINOBLASTOMA IN KENYA" (P246/09/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above revised research proposal for the period 26th November 2008 –25th November 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF. A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Ophthalmology, UON
Supervisors: Dr. Kahaki Kimani, Dept.of Ophthalmology, UON
Dr. Margaret W. Njuguna, Dept.of Ophthalmology, UON

IV.Authorization from the Ministry of Health

MINISTRY OF MEDICAL SERVICES
OFFICE OF THE DIRECTOR OF MEDICAL SERVICES

Telegrams "MINHEALTH", Nairobi
Telephone Nairobi 2717077
Fax: 2713234
When replying please quote

AFYA HOUSE
CATHEDRAL ROAD
P O Box 30016
NAIROBI

MMS/ADM/3/8 VOL.X/13

5th January, 2009

Dr. Joseph M. Nyamori
Department of Ophthalmology
School of Medicine
University of Nairobi

Dear Dr. Nyamori

REF: AUTHORITY TO CONDUCT RESEARCH STUDY TITLED "PATTERN OF RETINOBLASTOMA IN KENYA – A RETROSPECTIVE STUDY BY UON"

Your letter dated 8th December, 2008 refers.

The Ministry has received and granted authority for you to conduct the above study in all the hospitals with eye clinics in Kenya.

We wish you a fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

Dr. Francis Kimani
DIRECTOR MEDICAL SERVICES

V.Feedback form (Data Control Register)

Retinoblastoma cases from Jan 2006 to Dec 2007

Name of facility	Patient Name	File No	Date seen	Age	Sex	Diagnosis Right or Left	Admitted?	Is file at hospital?	Referred where to?	Date of data collection	Contact person
	1										
	2										
	3										

VI.Kenya Population Projections Report 2007

POPULATIONS PROJECTIONS PER PROVINCE: Kenya's Growth Rate 3.8% Source CBS 1999 Census							
			TOTAL	Children			Live births
	PROVINCE	G.Rate (%)	2007	M < 5yrs	F < 5yrs	TOTAL<5yr	TOTAL
1	Nairobi	3.6	2,940,911	187 074	168,946	356,020	112,562
2	Central	3.1	4,076,631	180 506	194,718	375,224	125,068
3	Coast	3.9	3,042,675	194 587	235,052	429,639	128,712
4	Eastern	3.6	5,206,592	322 064	295,718	617,782	215,031
5	North Eastern	2.7	1,603,281	94,330	119,884	214,214	40,304
6	Nyanza	4.1	5,021,695	465 928	577,432	1,043,360	227,820
7	R. Valley	4.1	8,746,094	635 600	618,295	1,253,895	374,370
8	Western	4.5	4,014,702	317 744	286,023	603,767	206,660
	Overall Projection	3.8	34,652,581	2,397,833	2,496,068	4,893,901	1,430,527

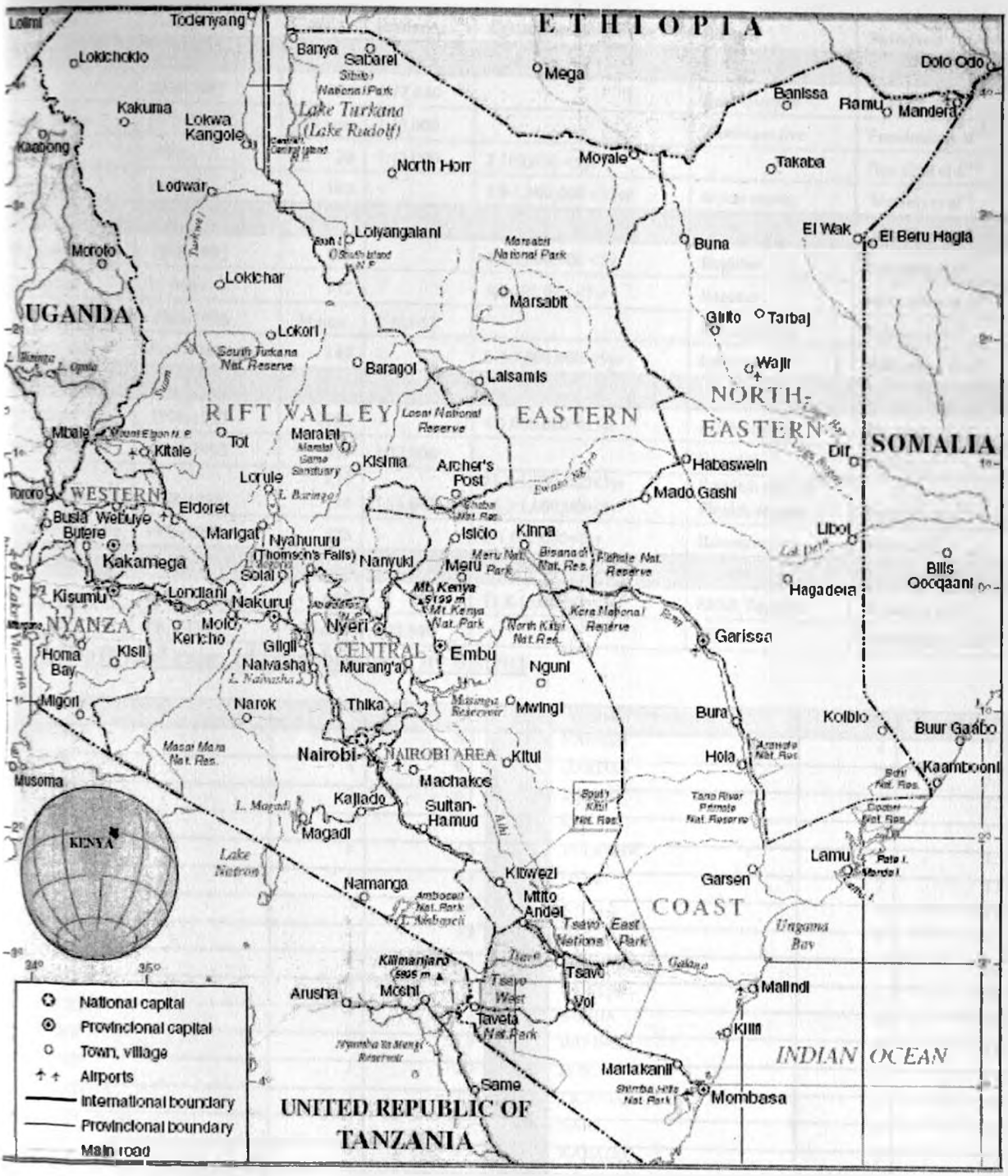
VII.Health information system: Retinoblastoma cases in 2007

MINISTRY OF HEALTH, DIVISION OF OPHTHALMIC SERVICES ANNUAL REPORT FOR THE YEAR 2007
(EXTRACT: RETINOBLASTOMA CASES ONLY)

Centers with no data reported (months reported=0) are included with a "?" prefix . RTB= Retinoblastoma

	EYE FACILITY	MONTHS	< 5 YRS	RTB	NO	EYE CENTER	MONTHS	< 5 YRS	RTB
	COAST PROVINCE					RIFT VALLEY PROVINCE			
1	COAST PGH	9	619	7	40	KAJIADO	11	81	0
2	LIGHT HOUSE	12	825	3	41	LOITOKTOK	11	253	0
3	PWANI LIONS	12	219	0	42	NAKURU PGH	12	1138	9
4	KWALE DISTRICT EYE CENTER	9	798	4	43	NAIVASHA	9	409	1
5	MOI VOI	8	246	0	44	KAPKATET	11	2055	0
6	HOLA	2	2	0	45	LITEIN	12	521	95
7	MALINDI	7	123	1	46	KERICHO	10	0	10
8	TAWFIQ	1	13	0	47	KAPSABET	12	656	0
9	? MSAMBWENI	-	-	0	48	NANYUKI	10	530	0
10	? PORT REITZ	-	-	0	49	MARALAL	11	1060	4
11	? KILIFI	-	-	0	50	KABARNET	12	246	1
	EASTERN PROVINCE				51	ITEN	10	38	3
12	MAKUENI	12	390	0	52	NAROK	10	785	0
13	MWINGI	12	270	12	53	KAPCHEROP	3	51	0
14	EMBU PGH	11	0	0	54	ELDORET MTRH	3	0	2
15	CHUKA	10	0	0	55	UASIN GISHU DH	4	284	0
16	MERU	11	0	1	56	KITALE	12	1607	13
17	NYAMBENE	12	197	1	57	KAPENGURIA	12	2409	10
18	ISIOLO	12	1109	0	58	LODWAR	12	130	0
19	MARSABIT	7	344	0	59	KOIBATEK	11	155	8
20	MOYALE	10	24	7	60	AMREF KAJIADO	11	0	0
21	MACHAKOS	12	1679	0	61	NANDI HILLS	5	223	1
22	KITUI	11	1482	0	62	NYAHURURU	12	0	2
23	KANGUNDO	7	387	0	63	? TENWEK			
24	CHOGORIA	10	128	1		WESTERN PROVINCE			
	NORTH EASTERN PROVINCE				64	SABATIA	12	564	5
25	MANDERA	10	144	1	65	KAKAMEGA	10	276	1
26	GARISSA	4	147	0	66	BUNGOMA	8	0	1
27	WAJIR	8	70	0	67	WEBUYE	8	406	1
	CENTRAL PROVINCE				68	BUSIA	11	383	2
28	KIKUYU	12	4702	41		NYANZA PROVINCE			
29	THIKA	11	1383	8	69	NYANZA PGH	11	626	25
30	KERUGOYA	9	1315	0	70	KISII	12	1128	7
31	NYERI PGH	11	848	13	71	HOMA BAY	11	115	9
32	KARATINA	12	524	5	72	NYAMIRA	12	0	3
33	OL KALAU	10	1222	1	73	SIAYA	5	61	0
34	MURANGA	4	217	0	74	MIGORI	7	0	0
35	? KIAMBU					OTHER (enquiries)			
	NAIROBI PROVINCE				*75	Aga khan University Hosp	0	0	0
36	MBAGATHI	12	1344	5		TOTALS		41879	378
37	LORESHO	9	1352	2					
38	KENYATTA. N. HOSP	10	3128	49					
39	SIGHT BY WINGS	12	150	2					

VIII. Map of Kenya



IX. World Incidence of Retinoblastoma compared to Kenya

Population	Time period	Cases	Incidence	Age adjusted incidence	Design	Reference
AFRICA						
Kenya	*2006-2007*	*132*	*1:17,030*		*Retrospective*	*Present study*
South Africa	1955-75	80 new	1:10,000		Retrospective	Freedman et al[17]
Malawi	1975	20	1:10,000	2:100,000 <5yr		Ben Ezra et al[19]
Namibia	1983-88	163	-	5.8:1,000,000 <15yr	6-year survey	Wessels et al[18]
ASIA						
Singapore	1968-1995	125	-	4.8:1,000,000 <5yr	Register	Sao-bing et al[11]
Uzbekistan	21 years	972	-	5.8:100,000 <5yr	Register	Mouratova et al[12]
Japan	1965-1986	34 new	1:16,053		Retrospective	Takano et al[13]
Mumbai-India	1986-1998	147	-	8.2:1,000,000 <5yr	Register	Balkrishna et al[15]
EUROPE						
Many countries	1978-1997	2283	-	4:1,000,000 <15yr	AICS register	Mc Arthy et al[6]
Netherlands	1862-1995	955	1:17,000		Register	Moll et al[7]
North Europe	1958-1998	291 174	1:16,642	11.8:1,000,000<5yr 11.2:1,000,000<5yr	Swedish register Finnish register	Seregard et al[4]
New South Wales	1975-2001	128	-	8:1,000,000<6yr	Retrospective	Azar et al[8]
AMERICA						
USA	1974-2004	658	-	11.8:1,000,000<5yr	SEER Register	Broaddus et al[9]
USA	1969-1971	70 new	1;18,000		SEER	Pendergrass et al[14]

X. Confirmed cases of retinoblastoma by district

No	District of Residence	Cases	Percent	No	District of Residence	Cases	Percent
1	BOMET	11	8.3	24	NAIROBI	2	1.5
2	KISII	8	6.1	26	GARISSA	2	1.5
3	KIAMBU	8	6.1	27	MIGORI	2	1.5
4	MURANGA	6	4.5	28	KITUI	2	1.5
5	WEST POKOT	6	4.5	29	TURKANA	2	1.5
6	MACHAKOS	5	3.8	30	NYERI	2	1.5
7	MAKUENI	5	3.8	31	KWALE	2	1.5
8	NAKURU	5	3.8	32	NAROK	2	1.5
9	KAKAMEGA	4	3	33	SAMBURU	1	0.8
10	VIHIGA	4	3	34	LAIKIPIA	1	0.8
11	KISUMU	4	3	35	GUCHA	1	0.8
12	THIKA	4	3	36	BARINGO	1	0.8
13	NANDI	3	2.3	37	BUSIA	1	0.8
14	MARSABIT	3	2.3	38	TIGANIA	1	0.8
15	UASIN GISHU	3	2.3	39	ISIOLO	1	0.8
16	MARAKWET	3	2.3	40	KAJIADO	1	0.8
17	SIAYA	3	2.3	41	KERICHO	1	0.8
18	KIRINYAGA	3	2.3	42	WAJIR	1	0.8
19	TRANS NZOIA	3	2.3	43	TAITA TAVETA	1	0.8
20	MERU	2	1.5	44	MARAGUA	1	0.8
21	MERU NORTH	2	1.5	45	UGANDA-MBALE	1	0.8
22	BUNGOMA	2	1.5	46	BONDO	1	0.8
23	MALINDI	2	1.5	47	LAMU	1	0.8
24	NYANDARUA	2	1.5		**Total**	**132**	**100**

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