Retinoblastoma-Demographic Features, Clinical Presentations, Treatment Modalities and Outcomes - In a Tertiary Care Centre

- A Prospective Descriptive Study

Dissertation submitted for
MS (Branch III) Ophthalmology

THE TAMIL NADU DR. M.G.R MEDICAL UNIVERSITY
CHENNAI

March 2006

CERTIFICATE

Certified that this dissertation entitled **"Retinoblastoma- Demographic Features, Clinical Presentations, Treatment Modalities and Outcomes - In a Tertiary Care Centre"** submitted for MS (Branch III) Ophthalmology, The Tamil Nadu Dr.M.G.R.Medical University, March 2006 is the bonafide work done by **Dr.S.PREETHI**, under our supervision and guidance in the Retina and Vitreous Services of Aravind Eye Hospital and Post Graduate Institute of Ophthalmology, Madurai during her residency period from April 2003 to March 2006.

DR. R. KIM
Chief, Retina and Vitreous services
Aravind Eye Hospital
Madurai.

DR. M. SRINIVASAN
Director
Aravind Eye Hospital
Madurai.

ACKNOWLEDGEMENT

I acknowledge with sincere thanks all the people without whom this thesis could not have been a success.

I express my sincere thanks to **Dr. G. Venkatasamy**, Chairman, **Dr. P. Namperumalsamy,** Vice-Chairman, **Dr. M. Srinivasan**, Director and **Dr. G. Natchiar**, Director, HRD whose untiring dedication to the prevention of needless blindness in this community has inspired and will continue to inspire innumerable young ophthalmologists like me.

My sincere and heartfelt gratitude to my guide **Dr. R. Kim**, Chief of Retina and Vitreous Services, Aravind Eye Hospital for his unfailing support and critical evaluation of my work. I am grateful to **Dr. Usha Kim**, Chief Orbit and Oculoplasty services, Aravind Eye Hospital for her constant encouragement, advice and support without which this work would not have been completed

I am also indebted to **Dr. N.V. Prajna**, Director, Residency programme for his constant support during my residency programme.

My sincere thanks to **Dr. Hadi,** whose help was invaluable in completion of this thesis.

I will forever remain indebted and acknowledge my sincere thanks to all my study patients without whom this work could not have been possible.

My special thanks to the paramedical staff of the orbit clinic, and the library staff for their untiring support.

I would like to thank my husband, my parents, my grand parents and brother for their unwavering support. I remain grateful to my friends and colleagues for their support at all times.

I thank God for making this all happen.

CONTENTS

PART TWO

Introduction

Retinoblastoma is the most common primary intraocular malignancy of infancy and childhood[1]. It is the second most common intraocular malignant tumour of all age groups next to choroidal melanoma. It is the tenth most common cancer in childhood in US and accounts for 3% of all childhood cancers[2]. Retinoblastoma has cumulative life time incidence of 1:18000 to 30,000 live births world wide[3]. Indian studies have shown the incidence of the tumour in India as 1:15000 live births (Viswananth et al).

Retinoblastoma is a highly malignant tumour that arises from the neuroectodermal cells (most commonly from the nuclear layers of retina) that are destined to become retinal photoreceptors. Retinoblastoma represents the phenotypic expression of an abnormal or absent tumour suppressor gene known as retinoblastoma gene RB1 the first tumour suppressor gene to be identified [20].

Retinoblastoma most often presents in early child hood as leucokoria or white reflex. The manner of intra ocular presentation, extraocular extension, pattern of metastases and recurrence, ocular complications and associated malignancies makes diagnosis of retinoblastoma one of the most challenging problems of paediatric ophthalmology. To ensure appropriate therapy retinoblastoma must be differentiated from a host of benign lesions that simulate it. The diagnosis must be established rapidly to permit maximum ocular salvage and to minimize tumour associated mortality.

Prior to this century, retinoblastoma was a uniformly fatal disease[4].With the advances in diagnosis and treatment, survival have raised from 30% in 1930s to nearly 95% in 1990s in most developed countries[5].

Recent advanced in our understanding of retinoblastoma have led to trials of new treatment modalities aimed at decreasing morbidity and continuing excellent survival.

RETINOBLASTOMA IN INDIA

India is one of the countries that have the largest numbers of individuals affected with retinoblastoma. World wide **t**he incidence of retinoblastoma has been reported to be 1 in 18,000 live births. In India, which has the highest number of babies born in the world, 1,500 children are born every year with retinoblastoma.

This high number of cases found in India gives an opportunity for us to study these cases and to evaluate the efficacy and outcome of different treatment modalities available. Amongst problem facing in treating these cases, unawareness, illiteracy, poverty, cost and lack of compliance are issues to be tackled.

PURPOSE OF THE STUDY

Only few studies about Retinoblastoma have been published from India. Of the few studies only 4 studies have studied the demographic pattern, modes of presentation, clinical features of retinoblastoma, problems and perspectives

in diagnosis and treatment, survival of retinoblastoma cases in India [64, 65, 66, 67]. The studies have been from western and northern India. The probable reason for having such a few studies could be because of availability of treatment modality for retinoblastoma in only few places in India.

The Aravind Eye Care System is one of the few tertiary eye care centers in India that has all facilities for diagnosis and treatment of Retinoblastoma and the hospital is also involved in research on its various aspects. The hospital acts is one of the main referral hospital in south India. A prospective study conducted in cases of Retinoblastoma treated in this hospital would give a good idea about demography, main mode of presentation, clinical features, acceptance and response to treatment of the cases in this part of the country and would help us in proposing new strategies or strengthening existing ones for earlier diagnosis and opting better treatment methods in treatment of Retinoblastoma.

Review of Literature

The first description of a tumor resembling retinoblastoma was by Peter Pawius of Amsterdam[6]. He wrote of a malignancy invading the orbit, the temporal region, and the cranium, a picture now strongly suggestive of untreated retinoblastoma. The tumor was described to be filled with a "substance similar to brain tissue mixed with thick blood and like crushed stone."

In 1805, William Hey coined the term fungus naematodes, which he used to describe a fungating mass affecting the globe of the eye and destroying its internal organization In 1809, the Scottish surgeon James Wardrop pieced together the random isolated facts and observations of previous authors. Despite not having a microscope at his disposal, his meticulous dissection and astute interpretations of some of these eyes led him to conclude that in most instances the tumor arose from the retina. Wardrop documented the extension of the tumor to the optic nerve and brain[7]. Later, he described metastasis to different parts of the body.

In 1836, Langenbech, Robin, and Nystin of Paris confirmed by microscopic studies that the tumor definitely arose from the retina.

In 1864, Virchow named it a glioma of the retina, supporting glial cells as the cell of origin of the tumor[6]

In 1891, Flexner of Johns Hopkins was first to notice rosettes within the tumor. A few years later in 1897, Wintersteiner concurred with Flexner and

proposed the name neuroepithelioma noting its resemblance to rods and cones and traced one tumor to the photoreceptor cell layer[6]. Presently, their names are attached to these rosettes..

Most cells comprising the tumor histologically resembled the cells of an undifferentiated retina of the embryo called retinoblasts. This resemblance prompted Veorhoff[8] to coin the term retinoblastoma, which later was adopted by the American Ophthalmological Society in 1926 as a general term for this entity.

In 1970, Tso and colleagues established that the tumor arises from photoreceptor precursors[9]

Retinoblastoma was one of the prototypic models demonstrating the genetic etiology of cancer. Though it was recognized as a genetic problem in beginning of this century ,the ideas that were significant to understanding this cancer came in 1970.In early 1970s Knudson[10] used knowledge about the clinical presentation of retinoblastoma and the number of cell divisions in human retina to develop a “two hit” mutational model. The Knudson’s hypothesis was eventually proved correct with discovery of the RB 1 gene.

In 1980, the gene causing retinoblastoma was identified by a research group in Boston.

Exciting discoveries have occurred in the past decade regarding the molecular genetic basis for this disease. The tumor suppressor RB gene has

now been cloned and there exists a potential for prevention and other treatment advances arising from these discoveries. The most difficult problem posed in treatment of the tumors will probably be solved only by molecular genetics approaches.

EVOLUTION OF TREATMENT FOR RETINOBLASTOMA

Prior to this century retinoblastoma was a uniformly fatal disease. The development of ophthalmoscope, general anesthesia and surgical enucleation improved prognosis so that survival rate exceeded 90% in most developed countries[5]. The initial treatment in the 19th century was enucleation. Though it was a life saving procedure, in many cases it eliminated any chance of vision in the affected eye and it was associated with usual problems of anophthalmic socket.

The radiation therapy was advocated in early part of 19th century ,but the first long term survivor after radiation therapy was a patient treated by Verhoeff in 1921 at the Massachusetts Eye and Ear infirmary[11]. The modern Era of radiation therapy was introduced by Reese and colleagues in the 1930s and 1940s[12].The external beam Radiotherapy(EBRT) allowed salvage of many eyes ,some with useful vision, however a number of potentially serious problems were subsequently recognized to be associated with EBRT –some being dry eye symptoms, radiation cataract and radiation retinopathy, facial cosmetic deformity and most importantly a number of malignant secondary

neoplasm in the field of radiation[13]. With the use of radioactive plaque brachytherapy, laser photocoagulation and cryotherapy many problems associated with enucleation and EBRT were alleviated.

In 1990's a modality termed "Chemoreduction" evolved. Different chemotherapeutic regimens are being used. In 1990's a combination of four drugs became the standard treatment for bigger tumours. Modalities frequently used for tumour consolidation include diode laser hyperthermia, cryotherapy and plaque brachytherapy.

The familial nature of retinoblastoma was first reported in the early 19th century[14].The most exciting current work on retinoblastoma has been on genetics and has had revolutionary implications for the understanding of the genetics of the malignant neoplasm in general. And with all the recent understanding about retinoblastoma and evolution of the new classification, use of chemotherapy with local therapy, **the management of eyes with Retinoblastoma, should have become a multidisciplinary approach**. This approach involving ophthalmologist with experience in ocular oncology, a radiation oncologist, a paediatric oncologist, a genetician, a neuroradiologist will enable us to have consistently excellent treatment outcomes in the future.

Epidemiology

INCIDENCE

Retinoblastoma though is the most common primary intraocular malignancy of childhood, is a relatively rare form of child hood cancer.

Earlier studies have shown the incidence of retinoblastoma ranging from 1 in 1400 live births to 1 in 34,000 live birth depending on the country[3]

It is estimated that around 350 new cases occur in United States every year. A more commonly used estimate is 11 cases per million children younger than 5 yrs or 1/18000 child birth[1]

The incidence in India is reported to be 1:15000 live birth (Viswanath et al)

RACE

There seems to be no racial predilection for retinoblastoma[15]. Retinoblastoma does appear to occur more commonly in poor patients world wide. Preliminary evidence suggest that the reason for this predilection is that the presence of HPV sequence in the RB tumour tissue may play a role in development of sporadic retinoblastoma[16]

SEX

Studies show that there appears to be no significant difference in the incidence of retinoblastoma by sex for children aged 0-14 yrs of age.

AGE

Retinoblastoma is diagnosed at an average of 18 months with 90% diagnosed before the patient reach 5 yrs of age.

Children who are affected bilaterally are diagnosed at an average age of 13 months, while patients with unilateral retinoblastoma are diagnosed at an average of 24 months of age[17]

When a known family history of retinoblastoma exists, patients with bilateral retinoblastoma are diagnosed at an average of 11 months.

Retinoblastoma is known to present with atypical symptoms in older patients studies show that clinical and histopathologic features were atypical in 47% and 21% respectively in the retinoblastoma patients who presented after the age of 5yrs[18]

Few cases of retinoblastoma in adults (aged 20 yrs and older) have been reported in the literature. Some have proposed that these lesions arise from a previously existing retinocytoma that underwent malignant transformation.

Genetics in Pathogenesis of Retinoblastoma

Retinoblastoma (Rb) occurs as a result of mutational inactivation of the Rb gene, which along with other genetic events allows the tumour to overcome the cellular safe guards against neoplastic transformation.

Retinoblastoma occurs both in hereditary and non hereditary form. Even though less than 10% of new retinoblastoma patients have a positive family history, 30-40% of new patients will have the hereditary or germ line form of disease due to sporadic germline mutations. Hereditary retinoblastoma is characterised by autosomal dominat inheritance (phenotype), a high risk of multiple bilateral tumors, a life long predispositions to cancer throughout the body. Non hereditary retinoblastoma occurs in 60-70% of case and usually consists of unifocal retinal tumours and no increased risk of other cancers[21].

The retinoblastoma gene (Rb 1 gene) on chromosome 13q14 is the first human **cancer suppressor gene** to be completely characterized. The RB1 locus contains 27 exons ranging in size from 31 to 1,889 base pairs[23]. The 26 introns vary in size from 80 to 71,712 base pairs. The retinoblastoma gene product is a 928 amino acid phosphoprotein whose normal function is to suppress cell growth. The activity of the protein is regulated by phosphorylation[27].When the retinoblastoma protein is phosphorylated, it is inactive. With phosphorylation, it is able to repress DNA transcription and prevent cell division[22] Two normal copies of the retinoblastoma gene are present in most human cells. Their function is to limit growth of the cell. **Only one normal copy of the protein is**

needed to accomplish this function. The process of phosphorylation is controlled by a cell-cycle-dependent kinase[23] .Retinoblastoma is unique in that all cases are thought to involve the same initiating genetic event –the **biallelic mutational inactivation** of the Rb gene.

Knudson's "two hit hypotheses" points out that retinoblastoma occur when both the copies of Rb gene are mutationally inactivated in the same developing retinoblast.

In the hereditary form, one Rb mutation is already present in germline so only one subsequent mutation is needed. The "second hit" that inactivates the other copy of the Rb occurs frequently enough during retinal development that multiple tumours often occurs, because the inherited mutations are present through out the body, cancers are more likely to occur in other tissues, in contrast non hereditary Rb occurs only in the unlikely event that somatic mutations occur in both alleles of the Rb gene in the same retinoblast.

Most RB1 germline mutations are minute deletional defects, duplications, or point mutations that are detectable by molecular (DNA) analysis[24,25]. Larger abnormalities are demonstrable by chromosome (cytogenetic) analysis or by a combination of both methods. Regarding the genetic events in the pathogenesis of retinoblastoma, the initiating genetic event as mentioned above is the bi allelic inactivation of the Rb gene. Several other chromosomal abnormalities are found with high frequency in retinoblastoma.

Growth Patterns, Presentation and Diagnosis of Retinoblastoma

Retinoblastoma arises from a multipotent precursor cell that could develop into almost any type of inner or outer retinal cell. Intraocularly it exhibits a variety of growth patterns. The classic description of the **GROWTH PATTERNS** is as below.

ENDOPHYTIC GROWTH

Endophytic growth occurs when the tumor breaks through the internal limiting membrane and has an ophthalmic appearance of a white-to-yellow mass showing either no surface vessels or small irregular tumor vessels. This growth pattern typically is associated with vitreous seeding wherein small fragments of tissue become separated from the main tumor. In some instances, vitreous seeding may be extensive allowing tumor cells to be visible as spheroid masses floating in the vitreous and anterior chamber, simulating endophthalmitis or iridocyclitis, and obscuring the primary mass. Secondary deposits or seeding of tumor cells into other areas of the retina may be confused with multicentric tumors.

EXOPHYTIC GROWTH

Exophytic growth occurs in the subretinal space. This growth pattern often is associated with subretinal fluid accumulation and retinal detachment. The tumor cells may infiltrate through the Bruch membrane into the choroid and then invade either blood vessels or ciliary nerves or vessels. Retinal vessels are noted to increase in caliber and tortuosity as they overlie the mass.

DIFFUSE INFILTRATING GROWTH

This is a rare subtype comprising 1.5% of all retinoblastoma. It is characterized by a relatively flat infiltration of the retina by tumor cells but without a discrete tumor mass. The obvious white mass seen in typical retinoblastoma rarely occurs. It grows slowly compared with typical retinoblastoma.

PRESENTATION AND DIAGNOSIS OF RETINOBLASTOMA

Retinoblastoma begins early, and most of the cases with a previous family history are detected on examination early in infancy. The average **age** at diagnosis in patients who have not been examined for positive family history is 15 months for **bilateral** retinoblastoma and 24 months for **unilateral** retinoblastoma[17]. Most of the patients present by 3 yrs and presentation is rare after 5 years. Of all retinoblastoma 30% are bilateral and 70% unilateral. Because the tumour is not always bilaterally expressed in a patient who carries genetic abnormality, some unilateral retinoblastomas are familial. Thus 40% retinoblastomas are familial and 60% non familial.

The modes of presentations are variable and must be understood for the timely diagnosis of the disease.

The most frequent mode of presentation is **leukocoria 56%**[28]. **Strabismus** is the next most frequent mode of presentation **24%, Defective**

vision in **8%** cases and reinforces the need for a careful dilated fundus examination in all the patients with strabismus and defective vision on their initial visit to ophthalmologist[26]. Other modes of presentation are much less common[27]. Retinoblastoma can cause secondary changes in the eye, including **glaucoma**, **retinal detachment,** and **inflammation secondary to tumor necrosis. Pseudouveitis,** with a red eye and pain associated **hypopyon** and **hyphaema**, is a rare presentation. .Probably one mode of presentation causing the most difficulty in diagnosis being **Orbital inflammation** [26,27] mimicking orbital cellulitis, it may occurs in eyes with necrotic tumors and does not necessarily imply extraocular extension. **Proptosis** is a more common presenting symptom in most underdeveloped countries. The prognosis is clearly unfavourable for these patients. It is also rare for a patient to present with distant metastases. The tumour tends to **metastasize** late and usually presents some local ophthalmologic signs long before it metastasize. Finally in rare cases a pinealoblastoma, thought to be a retinoblastoma in pineal body, so called **trilateral retinoblastoma**[28] may be the initial presentation.

PROTOCOL FOR DIAGNOSIS IN CASE SUSPECTED AS RETINOBLASTOMA

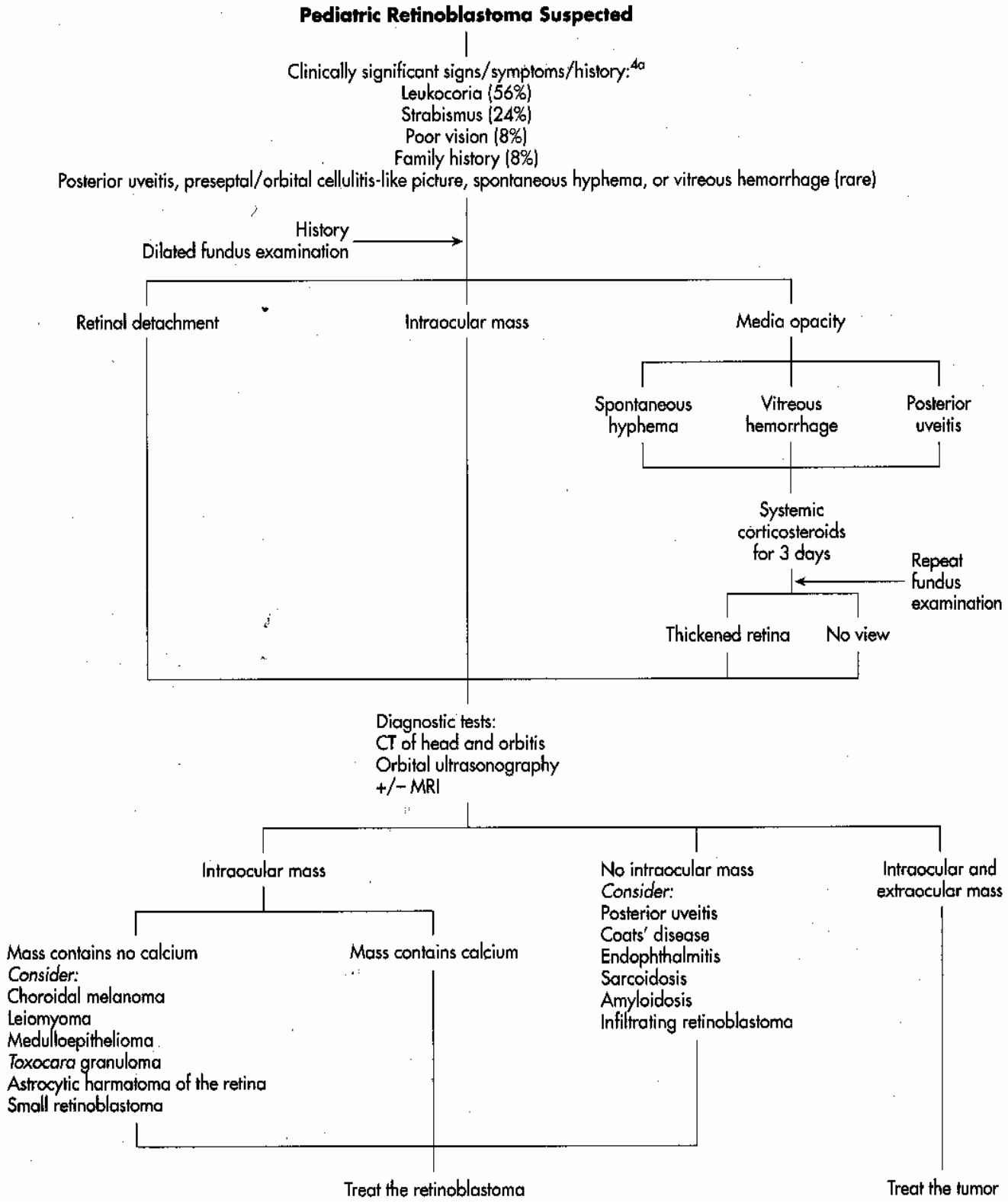
A flow chart has been proposed to be useful in the evaluation of a child in whom retinoblastoma is suspected[29]. The diagnostic work up in a child with suspected retinoblastoma has two purposes:

1. To confirm and solidify the diagnosis of retinoblastoma and

2. To confirm that the tumour is confined to the eye.

The work up of a child with suspected retinoblastoma should begin with a careful extensive history taking including recording of patient information, chief complaints, history of presenting illness, past history, antenatal, natal, post natal , developmental, immunization, diet history and previous family history of eye tumours or enucleation or any malignancy in childhood. The history taking should be followed by physical examination by a paediatrician, a detailed ocular examination by an ophthalmologist. The infant should have a complete eye examination including determining the visual acuity and dilated fundus examination. If diagnosis of retinoblastoma is fairly certain, the patient should be promptly scheduled for an imaging study and a staging examination under anaesthesia.

The most helpful diagnostic tools in order, are, CT, ultrasonography and if the CT is equivocal, MRI.


Pediatric Retinoblastoma Suspected
Clinically significant signs/symptoms/history:[4a]
Leukocoria (56%)
Strabismus (24%)
Poor vision (8%)
Family history (8%)
Posterior uveitis, preseptal/orbital cellulitis-like picture, spontaneous hyphema, or vitreous hemorrhage (rare)
History
Dilated fundus examination
Retinal detachment
Intraocular mass
Media opacity
Spontaneous hyphema
Vitreous hemorrhage
Posterior uveitis
Systemic corticosteroids for 3 days
Repeat fundus examination
Thickened retina
No view
Diagnostic tests:
CT of head and orbitis
Orbital ultrasonography
+/− MRI
Intraocular mass
No intraocular mass
Consider:
Posterior uveitis
Coats' disease
Endophthalmitis
Sarcoidosis
Amyloidosis
Infiltrating retinoblastoma
Intraocular and extraocular mass
Mass contains no calcium
Consider:
Choroidal melanoma
Leiomyoma
Medulloepithelioma
Toxocara granuloma
Astrocytic harmatoma of the retina
Small retinoblastoma
Mass contains calcium
Treat the retinoblastoma
Treat the tumor

DIFFERENTIAL DIAGNOSIS

The three most common causes for pseudoretinoblastoma were persistant hyperplastic primary vitreous (28%), coats disease (16%), and presumed ocular toxocariasis(16%). The differential diagnosis of retinoblastoma is mostly the differential diagnosis of leukokoria. Most of these can be ruled out on clinical grounds but some create difficulty in diagnosis. To make the process of diagnosis easier the following diseases can be categorized by presenting feature:

Diseases presenting with leukocoria	Diseases mimicking as exophytic tumor	Diseases mimicking as endophytic tumor
❖ Persistent hyperplastic primary vitreous ❖ Congenital Cataract ❖ Cicatricial retinopathy of prematurity ❖ Toxocariasis ❖ Coloboma of choroid and optic disc ❖ Uveitis ❖ Pseudogliomas ❖ Coats disease ❖ Late stage vitreous hemorrhage ❖ Retinal dysplasia ❖ Medulloepitheliomas, ❖ Tumors other than retinoblastoma and Retinal detachments	❖ Coats disease ❖ Toxocariasis ❖ Choroiditis ❖ Exudative retinitis ❖ Choroidal hemangioma ❖ Angiomatosis retinae ❖ Retinal pigment epithelium proliferation	❖ Retinal hamartomas ❖ Astrocytomas ❖ Myelinated nerve fibers ❖ Retinochoroiditis ❖ Metastatic endophthalmitis

Diagnostic Imaging

As soon as the ocular examination reveals classic findings of retinoblastoma imaging of the ocular structure, orbit and brain is warranted. The result of both the investigations-- the imaging studies and the staging examination under anesthesia together help in formulating the treatment plan.

Imaging of the retinoblastoma patient has several intended functions:

1) To confirm the clinical and ophthalmoscopic suspicion of the tumour

2) To evaluate for retrobulbar spread

3) To search for intracranial metastases

4) To exclude a second intraocular tumour in both the affected eye and the contralateral eye.

Ultrasonography (USG)-B Scan, Computerized tomography (CT) and, and Magnetic Resonance Imaging (MRI) are the most useful imaging techniques in evaluation of these lesions. Although MRI may be useful when it is difficult to distinguish between retinoblastoma and simulating lesions or when there is a question of optic nerve invasion, MRI is not as specific as CT because of its lack of sensitivity in detecting calcification[30].

MAGNETIC RESONANCE IMAGING (MRI)

MRI may be beneficial in estimating the degree of differentiation of retinoblastomas but is not as specific as computerized tomography because of its lack of sensitivity in detecting calcification.

Studies show that on **T1-weighted images**, the tumors usually appears **slightly or moderately hyperintense** than the surrounding normal vitreous but, on **T2-weighted images**, retinoblastoma tumors demonstrate **very low intensity** compared to vitreous. Calcification is more pronounced on T2 sequences and appears as low signals in all sequences. Prominient enhancement is seen after Gd-DTPA administration.

MRI also is useful in identifying any associated hemorrhagic or exudative retinal detachment. This is seen as a localized subretinal area of higher signal intensity compared to vitreous on both T1- and T2-weighted sequences. The MRI scan can demonstrate **infiltrative spread along the intracanalicular and cisternal portions of the optic nerve, subarachnoid seeding, and involvement of the brain**[37] and is far superior to CT in this aspect. It is especially useful in determining extraocular spread after radiation and chemotherapy.

CRANIAL AND ORBITAL COMPUTERIZED TOMOGRAPHY (CT)

The value of CT in diagnosing retinoblastoma has been well documented.[32] CT with its high sensitivity for calcification is the procedure of choice for diagnosis of calcification .The usual CT appearance of retinoblastoma is that of a **calcified mass within the globe.** The mass, which may be of any size, arises from the retina, but the borders may be ill defined making the retinal origin unclear. **Calcification** seen in 95% of these tumours

may be large,small single or multiple. Enhancement is usually seen after contrast administration in CT scan. As Haik et al[33] pointed out, calcification can occur in any of the retinoblastoma-simulating lesion where significant ocular disruption or phthisis is eveident, but this is dystrophic calcification usually deposited along the lines of normal structures.

ULTRASONOGRAPHY (USG)

The USG is the next best diagnostic confirmatory test. In 1973 Coleman[34] reported on the reliability of ultrasound in tumour diagnosis. The tumour and calcification can be diagnosed by ultra sonography; however the accuracy of Ultrasonography for this condition is only 80%[35].

USG may be helpful in distinguishing retinoblastomas from non neoplastic conditions[36]. Echographically retinoblastomas may have a smooth, dome shape, but more typically have a very irregular configuration. **The internal reflectivity can vary according to the degree of calcification**. Non calcified tumours demonstrate low to medium reflectivity, where as calcium produces extremely high internal reflectivity. The calcium may be quite dense and located throughout the lesion or confined to a small foci**.. Demonstration of calcium is important in the diagnosis of retinoblastoma.** These eyes are usually of normal size or larger. Consequently, their axial length measurement can often help in differentiating a case of retinoblastoma from other causes of leukocoria that presents with small globe. Echography is also important for

monitoring the size of retinoblastomas that have been treated with radiation or alternative methods of therapy. In most instances these tumours that recur or continue to grow after treatment tend to exhibit low to medium internal reflectivity and do not show calcification.

Studies show histopathology as being superior to echography in detecting Optic nervehead invasion,extra ocular extension and presence of calcification[37,38]

The 3DUS allows for analysis of the acquired and stored volumes. Rotation and sectioning of this volume allows the discovery of new oblique and coronal views. The ability to retrospectively analyse the (scanned and stored) ocular volume will facilitate patient care, teaching, tumour volume analysis and tele medicine[39].

X-RAY STUDIES

In areas of the world where ultrasonography and computerized tomography are not available, x-ray studies may be the only means of identifying intraocular calcium in patients with opaque media.

FLUORESCEIN ANGIOGRAPHY

Angiography is not necessary for making a diagnosis of retinoblastoma. Angiography may be of value if the diagnosis of recurrent retinoblastoma in a previously treated lesion is uncertain in which case an active retinoblastoma will leak, stain with fluorescein and accumulate the dye[40]

Examination under Anaesthesia, Lab Investigations and Histopathologic Features

LAB INVESTIGATIONS

Blood counts, electrolyte determination, Blood Haemoglobin values are useful to assess general condition of patient before subjecting to any procedure under general anaesthesia.

The tests like routine bone marrow aspiration and biopsy as well as lumbar puncture are not necessary in new patients with retinoblastoma when there are no other signs that the tumour has spread outside the eye. However they may play a role if extraocular, metastatic or locally recurrent retinoblastoma is suspected.

In cases in which there is clear evidence of tumour outside the eye, a full metastatic work up should be carried out and It should ideally include bone scan in addition to search for tumour cells in bone marrow and CSF.A whole body CT should be carried out and many times an MRI is helpful.

Bone marrow analysis and CSF analysis are also done before administering the chemotherapy regimen. Hemoglobin estimation, Blood grouping, Blood counts, liver function tests, Kidney function tests, and Blood electrolytes help in assessing the patient’s general health before the patients are subjected to chemotherapy. A periodic repeat of these tests before administering each cycle in chemotherapy regime and after the completion of chemotherapy enables to find out the systemic adverse effects of drugs and alter the therapy or adjust drug dosage accordingly.

Blood specimens should be taken not only from the patient but also from the parents and any siblings for DNA analysis, which could aid in genetic counseling.

Assays of aqueous humor enzyme levels could offer useful information to patients with suspected retinoblastoma. Lactate dehydrogenase (LDH) is a glycolytic enzyme that uses glucose as an energy source. It is present in high concentrations within metabolically active cells. Normally, its concentration in serum and aqueous humor is low and the ratio of aqueous humor to serum LDH is less than 1.0 in patients with ocular disease other than retinoblastoma. However, aqueous humor for eyes with retinoblastoma exhibits increased LDH activity expressed as an aqueous humor/LDH ratio of greater than 1.0

STAGING EXAMINATION UNDER ANAESTHESIA

It is important to carry out a careful classification and staging examination under anesthesia before treatment.

The examination should include evaluation of anterior segment, the iris, and the vitreous cavity. A good documentation of the findings with appropriate drawings should be made. Retinal drawings should be made of both the eyes with the location of lesion indicated. Wide angle retinal photography is extremely useful in the documentation of the eye findings. The height of each lesion can be estimated clinically .B scan Ultrasonography can be used to

document the dimensions of the tumour and demonstrate calcification within the tumour. Comparison diagrams and follow up images are useful in assessing response to treatment and planning further treatment.

HISTOPATHOLOGICAL FEATURES

The classic histologic findings of retinoblastoma are Flexner-Wintersteiner rosettes and less commonly fleurettes. A Homer-Wright rosette can be encountered, but they also are seen in other neuroblastic tumors.

Considerable variability exists in the histologic features. Some neoplasms display marked necrosis and prominent foci of calcification. Few show areas of glial differentiation.

Note: In an enucleated eye that is being prepared for gross examination and fixation for histopathologic examination, it is essential that adequate fixation is attained (fixation usually is complete within 48 h). Thorough fixation is especially important for eyes removed for retinoblastoma because the tumor is friable and may be spilled into the uvea or outside of the eye when the eye is sectioned, thereby confusing the assessment of the confinement of tumor to the interior of the eye (a feature that is important for the assessment of survival

Staging of Retinoblastoma

An ideal Classification and staging system of retinoblastoma should be (1).Simple and easy to use, (2).Reliable, (3).Capable of predicting the likelihood of successful treatment of new cases.

The Essen Classification system did not receive widespread usage. The Reese-Ellsworth classification system was the most useful system when external beam radiation (EBR) was the standard of treatment for eye salvage.

Now that chemotherapy has become a better option than radiation and more patients are subjected to chemotherapy schedules, this classification system is not as predictive of outcome and survival. A Linn Murphree and colleagues have developed (and are in the process of refining) a new classification system[75, 76, 15]

REESE-ELLSWORTH CLASSIFICATION

This system was originally developed in 1950s to predict the survivability of eye following EBRT. This was developed just as indirect ophthalmoscope was being introduced into clinical practice. Anterior lesions which can be easily treated now with cryotherapy or radioactive plaque, cause the eye to be classified as more advanced stage using the Reese Ellsworth classification. Also vitreous seeding of any amount places the eye in group 5b with the poorest prognosis.

Nevertheless the Reese Ellsworth Classification has been used by most groups throughout the world for more than 30 yrs.

Group 1- very favourable

a) Solitary tumor, <4DD in size at or behind the equator

b) Multiple tumors <4DD in size behind the equator

Group 2- favourable

a) Solitary tumor, 4-10 DD in size, at or behind the equator

b) Multiple tumors 4-10DD in size behind the equator

Group 3 - doubtful

a) Any lesion anterior to the equator

b) Solitary tumor, larger than 10DD in size, behind the equator

Group 4 - unfavourable

a) Multiple tumours, some larger than 10DD

b) Any lesion extending to the ora serrata.

Group 5 – very unfavourable

a) Massive tumors involving >1/2 the retina

b) Vitreous seeding

NEWLY PROPOSED CLASSIFICATION FOR INTRAOCULAR RETINOBLASTOMA [15, 75, 76]

With the introduction of primary neoadjuvant chemotherapy (chemoreduction) as the initial management method, the Reese Ellsworth system fails to be helpful clinically.

The following is a proposed system based on the likelihood of salvaging the eye when chemotherapy is used as the primary treatment of the intraocular malignancy.

Group A

Advantageous location & size disease. **Avoids** significant morbidity & vision loss. One or more intraretinal tumours ***3mm*** or less in greatest diameter; none touching the optic nerve or impinging on the foveal avascular zone. **No** vitreous seeding or subretinal fluid.

Group B

Brachytherapy-eligible disease. Solitary Rb ***outside zone 1*** with a basal diameter no longer than***10mm*** OR multiple, closely spaced, smaller tumors confined to a single retinal area no greater than 10mm in diameter. **No** diffuse vitreous seeding or ***significant*** RD

Localized vitreous seeding is allowed no greater than 2 mm from the surface of the tumor. ***Significant RD*** is defined as an area of detachment equal to or greater than the retinal area occupied by the tumor. ***Extraretinal Rb*** defines the disease extending beyond the retina & vitreous

Group C

Confined disease of a size requiring chemotherapy. One or more intraretinal or endophytic tumors, none exceeding 15mm in greatest basal

diameter. **No** local or diffuse vitreous seeding or *significant* RD. Small tumors (<3mm) touching the optic nerve or involving the fovea.

Group D

Dispersed, disseminated, or diffuse intraocular disease. Vitreous seeding or **significant retinal detachment,** or both, may be present. The total volume of the tumour does not exceed half the volume of the eye. **No** detectable extraretinal disease except for vitreous involvement. Potential for useful vision.

Group E-- for Enucleation

Extraretinal retinoblastoma or the presence of intraocular tumor volume greater than half the volume of the eye. Primary **enucleation** recommended. Anterior segment disease, glaucoma, hyphema, total detachment with fixed retinal folds

Group *F*

Future risk from containment failure. Neuroimaging or histological evidence of increased risk for metastatic disease (massive choroidal involvement and/or tumor in the optic nerve posterior to the lamina cribrosa).

Treatment Modalities, Treatment Methods and Techniques

Treatment approach for retinoblastoma has gradually changed over past five years The treatment guidelines based on the proposed new classification is as follows:

Group A

Local treatment only; cryotherapy for peripheral disease, direct laser photocoagulation for posterior disease

Group B

Primary Brachytherapy (single site). If multiple brachytherapy sites are needed, downclassify to intraocular group C. If brachytherapy is not available treat like group C.

Group C

Three-drug chemoreduction (primary neoadjuvant chemotherapy) + local consolidation (crytherapy, laser, or plaque). Lens-sparing EBR consolidation for tumors that have minimal response to chemotherapy. If age <1yr, consider plaque.

Group D

Four drug chemoreduction (primary neoadjuvant chemotherapy) *with* **prechemotherapy cryodisruption** + **whole eye consolidation** (whole eye EBR or intensified chemotherapy). ***Primary enucleation for unilateral group D***

Group E

Primary enucleation in unilateral cases and in failure of conservative management in bilateral cases.

Group F

Adjuvant chemotherapy before and/or after enucleation. Add orbital radiation therapy if there is direct extension to the orbit or tumor extends to cut end of the optic nerve

SPECIAL CASE MANANGEMENT:

1.Retinoma: regular observation [41]

2.Unilateral Retinoblastoma: According to retinoblastoma study group Group D Unilateral cases Enucleation. and Group E Unilateral --Enucleation. Unilateral Group C –three or four drug chemotherapy[42]

3. Bilateral Symmetric Retinoblastoma :

a. Bilateral group A- Cryotherapy and laser photocoagulation if away from fovea,if close to fovea and optic disc down regulate to Group C and start chemoreduction

b. Bilateral group B –rare presentation-Primary brachytherapy in each eye appropriate. If not available down regulate to Group C and start chemoreduction.

c. Bilateral group C –more common presentation- Chemoreduction is appropriate.

d. Bilateral group D four drug chemotherapy with Carboplatin, Etoposide, Vincristine and Cyclosporine A as primary treatment followed by local consolidation with cryo or laser.

4. Bilateral Asymmetric Retinoblastoma

If worse eye is group E enucleation is scheduled for that eye.

If the group E eye also has optic nerve invasion and the other is Group C or higher and requires chemotherapy ,enucleation for the Group E eye is delayed until after at least three cycles of chemotherapy. This way the subsequent enucleation is uncomplicated and the orbital healing was good[43]

In Group D disease in one eye and associated with Groups A to C in the second eye, if choice is made to salvage the group D eye, the treatment intensity should be aimed towards the Group D eye and local therapy to other eye should be delayed till the chemoreduction has its effect in the fellow eye.

5 Vitreous Seeding

Vitreous seeding is a contraindication to photocoagulation and a relative contra indication to cryotherapy.

It has been found that even with treatment with quadruple chemotherapy for diffuse vitreous seeding, massive recurrence occurred in 70% of eyes treated[44].The presence of vitreous seeding in unilateral retinoblastoma is a

reason to enucleate. In bilateral cases with vitreous seed, eye preservation therapy becomes essential. Recent studies have shown local therapy using intra vitreal injections of Melphalan combined with ocular hyperthermia can preserve about 50% of the eye balls with vitreous seeding[45,46]

Another new approach is currently being investigated (Kishi Et al)-They attempted vitreous surgery with perfusion of anticancer drugs into vitreous to kill tumour cells during the procedure[45]

6. Diffuse infiltrating retinoblastoma- Enucleation

7. Retrolaminar Optic nerve involvement and choroidal involvement

6-12 months of adjuvant chemotherapy is essential to prevent metastatic disease.

8. Orbital Extension: Systemic chemotherapy and orbital radiotherapy

9. Metastases: Suspect metastases when advanced tumour size, and or anterior segment involved (Rubeosis iridis, Ectropion uvea, Tumour hypopyon) - Invasion of optic nerve past lamina[27].High dose chemotherapy with Cyclophosphomide, Vincristine, Doxorubicicn and Palliative radiotherapy if symptomatic local disease is present.

10.Trilateral retinoblastoma - systemic and intrathecal chemotherapy and craniospinal EBRT[47]. Stephen Nelson et al showed the following therapy for trilateral retinoblastoma to be successful .Chemotherapy initiated with intra venous administration of cyclophosphamide (750 mg/m2) on day 1.

Then intrathecal chemotherapy is administered using guarded lumbar puncture and after extracting 1ml of Cerebro Spinal Fluid. The Intrathecal chemotherapy regimen which is given is Injection Cytarabine (14mg),Inj Methotrexate (7mg), Inj Hydrocortisone (7mg).Subsequent therapy,consisting of Cyclophosphamide and Vincristine administerd monthly and Methotrexate / Hydrocortisone / Cytarabine administered intrathecally at two month interval was given at the same dosage for 24 courses with resolution of the pineal enhancing mass. A custom made body cast can be used for delivering cranio spinal radiotherapy.

TREATMENT METHODS AND TECHNIQUES

1. CRYOTHERAPY [48,49]

It was first introduced by Lincoff in 1967 [15]

Indication [49]

1. Small tumors confined to sensory retina, (less than 3-4 dd) not located at vitreous base, no vitreous seeds.

2. If tumour is anterior to equator –transconjuctival approach.

3. If tumour is posterior to equator –Through incision on conjuctiva. (curved cryo probe is used)

Procedure(4)

- Tumor visualized by I/O, elevated on the tip of the probe

- Freeze at -90 degree C until tumor + surrounding retina incorporated in the iceball, rendering the tumor margins indistinct.
- Thaw for 1 min before reapplying freeze
- Repeat the same procedure in the same location twice more. Totally tumour treated three times per session for as long as 3-4min per freeze.
- Two such cycles to be given at 1 month interval
- End point –No viable or visible tumour remains, patient is left with a white chorioretinal scar.
- Good effectivity with few less serious complications[15]

Complications

Transisent sub conjuctival edema, lid edema, and Vitreous hemorrhage and transisent Retinal detachments.

2. LASER [48, 49, 50, 51,52]

Laser photocoagulation is typically not used with chemoreduction because it causes vascular coagulation and might minimize chemotherapy delivery to tumours. Thus use of laser coagulation in retinoblastoma has decreased in recent years[53]

Indications[54]

1. Children not treated with chemoreduction protocol

2. Tumors < 4.5 mm base diameter/2.5mm thickness

3. Tumour posterior to the equator,

4. No vitreous seeds

5. No SRF

- Laser is delivered through indirect ophthalmoscope laser photocoagulation system.
- Treatment directed to limit the spread of tumour and specifically coagulate all blood supply to tumour with argon or diode laser.
- Special care not to treat tumour directly because it might induce rupture of internal limiting membrane and then seeding of tumour in vitreous cavity.

Two to Three sessions at one month intervals necessary for complete regression[15]. Efficacy –With proper case selection 70% tumour control, 30% recurrence[15]

Complications

Transient serous retinal detachment, visually significant retinal vascular occlusion, Retinal traction, Retinal hole and Pre retinal fibrosis are the complications of the procedures.

3. TRANSPUPILLARY THERMOTHERAPY [15]

It was first used by Lagendijik in 1982 was treatment of retinoblastoma.

Mechanism of action:Laser beam directly aimed at tumour and thermal effect leads to direct apoptosis of tumour cells.

Indication

1. Viable tumour within the retina or subretinal space with less than 1mm overlying sub retinal fluid.
2. Large tumours and vitreous seeding from the tumour are criteria for exclusion for this treatment.

Procedure

Thermal energy delivered from a 810 nm infra red ophthalmic laser with modification to laser hardware and software.

Techniques

1. Murphee et al[55] – paediatric laser gonioscopy and an adapter on an aperating room microscope that delivers a Transpupillary 3.0mm spot of radiation. Power 350-1500 mW and treated for one minute.

2. Adaptor on indirect ophthalmoscope and a 20 D lens delivers a Transpupillary 1.6 mm spot of radiation, the power being 350-1500 mW and treatment performed in approximately one minute.

3. Radiation delivered transconjuctivally via a diopexy probe.One minute of treatment using a hand held adaptor which delivers a 1mm spot of radiation, power being 500-1500mW.

THERMOCHEMOTHERAPY (TCT) [49,15]

- Heat is synergistic with Carboplatin in the destruction of RB cells
- Heating the tumour doubles the amount of Carboplatin bound to tumour DNA

Procedure

- One hour infusion of Carboplatin 18.7 mg / kg/ dose
- Day 0 – Within 2 hours of completion of infusion –diode laser hyperthermia(810 nm infra red ophthalmic laser)
- Day 8 – A new laser treatment not preceded by Carboplatin, with identical parameters
- Three such cycles to be given at 28 day intervals
- Spot size (depending on tumour size) 0.8 – 1.2 mm
- Power (depending on tumour size)

  <2 DD – 300 mW

  3.4 DD – 450 mW

  >4 DD 600 – 700 mW
- Therapy considered adequate when there is whitening of the tumour and surrounding retina
- A small amount of hemorrhage is acceptable. If significant edema noticed, laser energy is too much

- End point- Tumour typically regress to flat pale scars that are less than 2mm.

Complications

Focal iris atrophy (36%), focal paraxial lens opacity(24%), sector optic disc atrophy(24%), retinal traction(2%), optic disc edema(5%), retinal vascular occlusion(2%), serious retinal detachment(2%) and corneal edema (1%)[15]

Follow up

- Re-examine at 3 weeks – locally treat edge recurrence and residual small tumours
- If tumour is in posterior pole laser photocoagulation is done.
- If tumour is anterior to the equator cryotherapy is given.
- Re-examine at 3 weekly intervals until 3 consecutive examinations show complete regression
- Re-examine 3 monthly for at least 1 year

Studies have shown that TTT alone is sufficient for tumours 1.5DD or smaller in diameter, and 64% tumours required only one session[15]

4. BRACHYTHERAPY

Episcleral brachytherapy was pioneered in 1933 by Henry Stallard [15]

Indications

1. Reese Ellsorth IV a or less

2. Tumours between 4 and 10 dd in size (Group B new classification)

3. Large tumours >10dd and tumours involving macula are contra indications for this therapy.

Procedure

Under GA, in operating room, gold shields of Iodine 125 (currently most used radioactive plaque) plaque designed to match the size of the lesion is attached to the sclera over the tumour.

Dose

Primary Brachytherapy- 4000-4500 cGy to the apex of the tumour at a rate of approximately 1,000 cGy per day.

Chemotherapy → brachytherapy (20Gy)

Plaque is by second operation 3-5 days later, depending on isotope and size of the tumour.(Ruthenium can also be used instead of iodine)

Complications

Side effects from brachytherapy for retinoblastoma are rare.

Optic neuropathy and radiation retinopathy have been reported. Cataracts can occur after some years and often do not require surgery.

5. ENUCLEATION

First published in 1809 as a successful approach to treating intraocular retinoblastoma, enucleation continues to be main stay of treatment for patients

with advanced intraocular disease. Patients are also considered for enucleation if they have failed all other forms of treatment, or if they have active tumour and cannot be followed[56].Greater than 99% of patients with unilateral retinoblastoma without microscopic or macroscopic extraocular disease are cured by enucleation[15]. In all centers Enucleation for children is performed under GA

Special precautions

Avoid undue handling of muscles,avoid perforation of the globe.

Avoid optic nerve snare to crush the nerve, use 9-10 ml of Xylocaine with adrenaline around the optic nerve before sectioning the nerve (to avoid bleeding and prevent micrometastases).

Use minimally curved scissors and cut as long a section of the optic nerve as possible.

Preferable to use orbital implants after enucleation for better cosmetic prosthesis

Complications

Most Common complication of enucleation are hemorrhage and infection. Hemorrhage is best controlled during surgery by firm digital and if necessary, thrombin soaked patties, Flo Seal, or Avitene (bovine collagen).Post operative ecchymosis usually subsides with use of a pressure patch and ice

compresses. Infection is rare, those patients who develop recurrent infection of the socket are managed effectively by topical antibiotic therapy.

Follow up

Follow up done for determining other eye status and general status of the individual and to detect metastases.

CT – scan taken – 6 monthly for 1year.

EUA done 3 monthly for 18 months, yearly for 3 years

6. EXTERNAL BEAM RADIOTHERAPY (EBRT)

External Beam Radiotherapy has fallen out of favour in many centres now due to increased risk of development of additional non ocular cancers in survivors of germinal retinoblastoma.

When EBRT is administered the dose prescribed to retinal target volume ranges from 4200 to 4600 cGy. The dose is administered in 180-200 cGy daily fractions, five times per week.

Complications

Other than the most dreaded long term complication of additional non ocular malignancies, patients experience skin erythema,radiation cataract,Facial and temporal bone hypoplasia.

7. CHEMOREDUCTION PLUS SEQUENTIAL AGGRESSIVE LOCAL THERAPY (SALT)[49,51,57,58]

Efforts to treat intraocular retinoblastoma with chemotherapy began with Kupfer in 1950s.Currently chemotherapy is an area of active clinical and basic science research and in past decade it has emerged as a important globe sparing treatment.

Indications

1. For patients who have visual potential in eyes containing tumour which are too large to treat with focal methods. Chemoreduction is used to shrink the tumour so that other focal methods can be administered after words. Group C & D tumours in new classification.

2. As potential single modality eye preserving treatment for patients of any age with advanced unilateral or bilateral retinoblastoma. Permanent responses are rarely observed in these cases[15]

3. As a palliative treatment for preventing or containing metastases in advanced diseases.

The recommended chemotherapeutic regimen varies at different institutions. Regime preferred by Shields et al[53] : Three drug regimen : Carboplatin, Vincristine And Etoposide (CEV). The regimen is given for six consequtive cycles on a monthly basis. Focal therapy is included to individual tumours at cycle 2 or cycle 3 after adequate tumour reduction and subretinal

fluid resolution are achieved. Focal therapy is then performed at each chemoreduction cycle upto cycle 6.It has been shown that ocular salvage has been improved with addition of chemoreduction to treatment regimen[59].

CEV protocol

	Carboplatin	Etoposide	Vincristine
Day 0	*	*	*
Day 1	-	*	-
Day 7 & 14	-	-	*

Dosage for primary neoadjuvant chemotherapy, If Group C – 3 to 4 cycles, If Group D – 7 to 9 cycles.

Dosage of Drugs

Vincristine 1.5 mg / m2 (0.05 mg / kg, 36 months), Etoposide 150 mg /m2 (5mg/kg <36 months), Carboplatin 560 mg/m2 (18.6 mg/kg <36months).

Patients <10 kg dosed mg / kg. All infants <6 months of age at diagnosis decrease drug dosage by 25% first course and escalate to 100% if tolerated on second and subsequent courses. 6 such cycles are to be given monthly.

Adjuvant therapy is to be started after cycle 2, EUA done to assess the response and residual tumor and the mode of therapy is selected to depend upon, tumor location, tumor size, small localized seed, and diffuse seeds.

The various adjuvant therapy methods available are Photocoagulation, cryo for smaller tumours, Thermotherapy within 4 hours of the chemoreduction

dose, EBRT for larger tumours > 12 mm base or diffuse seeds, Enucleation for extensively involved eyes (for unilateral group D)

Follow Up

Follow up advised to be for every month after each cycle of chemoreduction. Three monthly till 1 year – adjuvant treatment as required at the time of EUA. Six monthly thereafter

Subconjuctival Carboplatin for retinoblastoma

Local delivery of chemoreduction for intraocular retinoblastoma is aimed so that the eye benefits from treatment and systemic side effects avoided. Studies in animal models showing ability of carboplatin to penetrate sclera and reach vitreous cavity allowing for effective doses in eye with minimal toxicity shows subconjuctival carboplatin[54] as most useful for treatment of vitreous seeds .Presently subconjuctival chemoreduction is combined with three agent intravenous chemoreduction protocol for children with advanced disease to achieve local chemotherapy boost in ocular region[53]

POST TREATMENT FOLLOW UP

The challenge to an ophthalmologist following patients treated with retinoblastoma is to be able to determine clinically the first sign of recurrent disease. The pattern of regression of the tumour varies, to a certain degree, with the treatment method.

For local treatment methods, cryotherapy and photocoagulation, anything less than a flat pigmented scar is unacceptable. Regression pattern after radiation have been reviewed by Abramson et al[60].

Regression pattern after treatment

Type 1 - calcification only

Type 2 - fish flesh, transluscent appearance

Type 3 - type1+type2

Type 4 - flat white scleral scar

Pretreatment volume of the tumour correlated with the long term regression patterns.

The pattern of regression seen with the triple drug systemic chemotherapy for the treatment of group D disease generally shows type 3 regression pattern. The lesion must generally be treated with another method or else the risk of recurrence at edge of previous lesion is relatively high. The same observation exists for Group C and larger tumours[62]

Need for long term follow up has to be stressed for evaluating the recurrence of tumour in treated cases, to detect metastatic spread of disease, for visual and social rehabilitation and assessing long term survival of the patients.

Aim and Objectives

AIM

To study the demographic features, clinical presentations, treatment modalities and outcomes in patients with retinoblastoma in a tertiary care centre.

OBJECTIVES

1. To study the demographic features of patients with retinoblastoma.
2. To study the various modes of presentation of patients with retinoblastoma.
3. To study the tumour characters in eyes with retinoblastoma.
4. To study the different treatment modalities for retinoblastoma (including local ophthalmic therapy, chemotherapy, surgery) and outcomes of eyes with retinoblastoma, following treatment.

Materials and Methods

A Prospective and Descriptive study was carried out in newly diagnosed patients with intraocular retinoblastoma who were identified at the Aravind Eye Hospital, Madurai. India.

Patients eligible for consideration were all newly diagnosed cases of unilateral, bilateral or trilateral retinoblastoma who presented between January 2004 and May 2005. All other cases of retinoblastoma previously treated elsewhere, or review patients who were subsequently subjected to chemotherapy during the follow up were excluded from the study.

The patients who presented for the first time were examined in the "Retinoblastoma Clinic" and were subjected to a detailed medical and ophthalmologic history taking including age, complaints at presentation, duration of symptom, antenatal, natal, postnatal, diet, immunization & family history including pedigree charting.

Assessment of visual acuity was done whenever possible either by ability to pick up cake decoration, ability to fix & follow light or visual acuity by SG chart (Scheridan Gardner Chart) in pre school and school going children.

This was followed by diffuse torch light examination, slit lamp examination whenever possible of anterior segment to look for hyphaema, hypopyon, pupillary reaction, secondary glaucoma and other signs of anterior segment involvement. Indirect ophthalmoscopy using 20D lens of the dilated fundus was done to diagnose tumour mass, retinal detachment, vitreous

hemorrhage, vitreous seeding, signs of optic nerve head involvement. The diagnosis was confirmed using Ultrasound B Scan. In patients whom diagnosis could not be ascertained or to look for optic nerve infiltration & intracranial extent, a CT Scan Brain and Orbit (Plain and Contrast) was performed. In most of the patients, since they were children and could not cooperate for detailed examination of anterior and posterior segment in the outpatient department, a staging examination under anesthesia was performed and all anterior and posterior segment finding and character of the tumour were confirmed and noted. The patients eyes were staged according to the “Newly proposed classification for Intraocular Retinoblastoma”.

General physical examination was done in all patients to assess general health detect a signs of metastatic disease.

Good general and genetic counseling was given for the family regarding the disease and the stage of the disease in their child, need for treatment, regular follow up in the treatment. Any interventional procedure was performed after a written informed consent from parent or guardian.

According to the staging of the eye with retinoblastoma, the eye was subjected to either or combination of local therapy, chemotherapy, radiotherapy, surgery. According to the location and size of the tumour Local therapy given was either or combination of cryotherapy, transpupillary thermotherapy, and laser barrage around the tumour.

The need for chemotherapy in individual cases was assessed in accordance to their stage of the eye after staging by New Classification of Retinoblastoma. In any patient requiring chemotherapy, a complete hematological examination, examination of peripheral smear, bone marrow examination, CSF analysis, Liver Function Test (LFT), USG abdomen and chest X-ray were done to determine the general condition of the patient, ability to withstand chemotherapy and detect distant metastases.

The liver function test and blood investigations were repeated before commencing each cycle of chemotherapy, to assess the adverse effect of chemotherapy and to determine the general body condition and fitness for that chemotherapy cycle.

Most of the cases subjected to chemotherapy received three cycles of triple drug regimen,(Vincristine 0.05mg/kg body weight as Intravenous (IV) in 100ml Normal Saline(NS) on the first day, Etoposide 5mg/kg body weight in 100 ml NS as IV infusion over 2 hrs on first day and same dose in 500ml RL on 2^{nd} day, Carboplatin 16.7mg/kg body weight in 500ml Ringer lactate as IV infusion over 2 hrs) on day 1 and day 5.On each day, premedication with BD dose of Inj.Emset, Inj.Ranitidine and Inj.decadran was given before giving chemotherapy drugs. Three such cycles were given at interval of one month. In two cases where regression of tumour was not observed with triple drug regimen a quadruple regimen including administration of Cyclosporine A was

administered. Intrathecal chemotherapy in addition to systemic chemotherapy with VEC (6 cycles) was administered for one case of trilateral retinoblastoma and one case with suprachiasmatic extension of the tumour.

All cases unilateral, bilateral & trilateral retinoblastoma subjected to chemotherapy were advised every month follow up till the chemotherapy completion. EUA was performed during the chemotherapy cycles and during the follow up after chemotherapy to assess need for and deliver the local ophthalmic treatment and assess the response of tumour to treatment.

The final response of the retinoblastoma to treatment was noted at EUA performed one month following completion of planned chemotherapy cycles. Patient was then advised regular follow up every month for the next 3 months and every 3 months for next 6 months and ever 6 months for next one year.

The well being of the patients, the status of the normal eye or the treated existing eye is noticed in every follow up visits. Appropriate rehabilitation like cosmetic artificial shell for the enucleated eye was provided for the patient.

Tables and Charts

Table 1

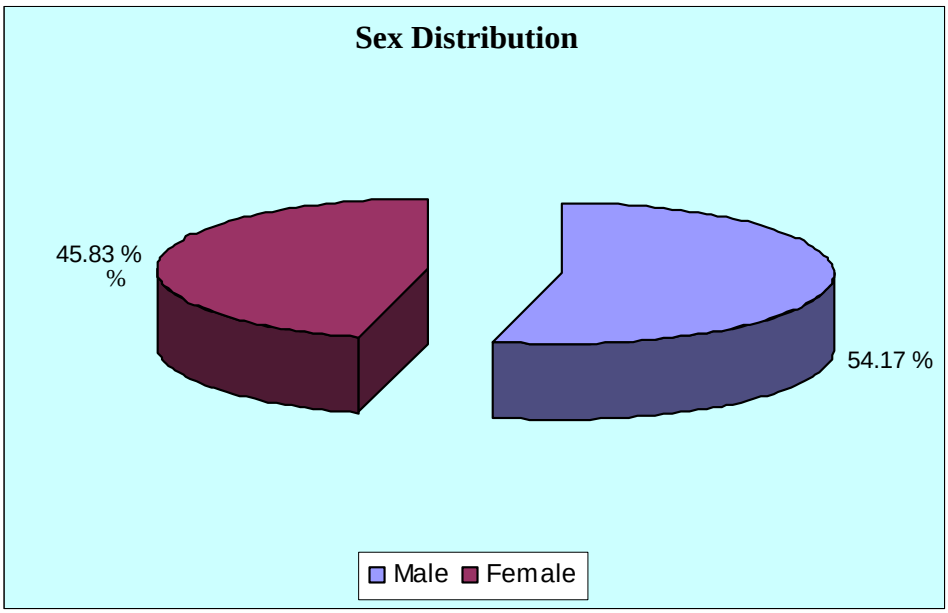
Patient Demographics

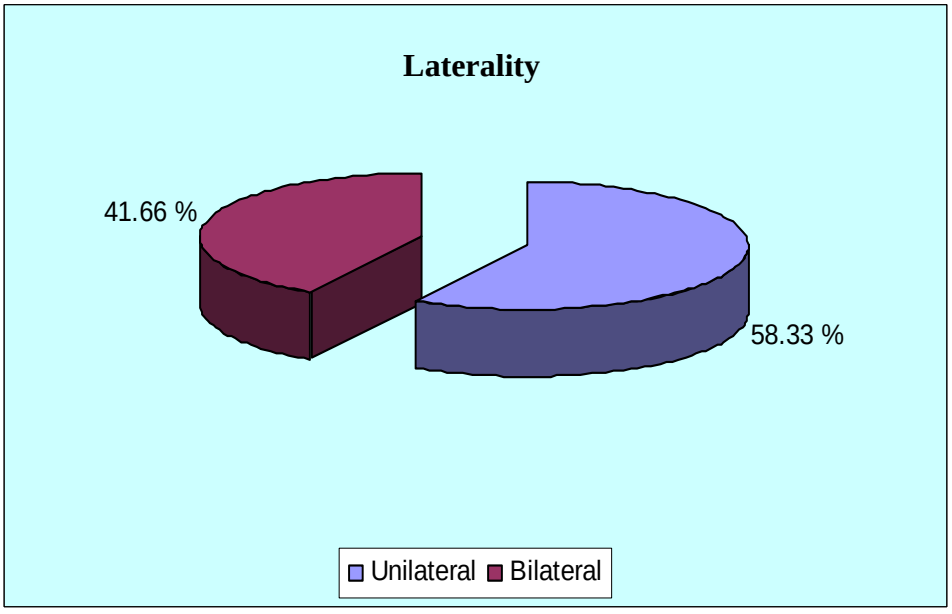
S.No.	Particulars	No	Percentage
1.	Patients	48	
2.	Eyes	68	
3.	Sex : Male Female	 26 22	 54.17% 45.83%
4.	Laterality: Unilateral Bilateral	 28 20	 58.33% 41.66%
5.	Mean age : Unilateral - 28 Months (Range - 80 days to 72 Months) Bilateral - 22.31 Months (Range - 13 days to 96 Months) Trilateral - 24 Months		

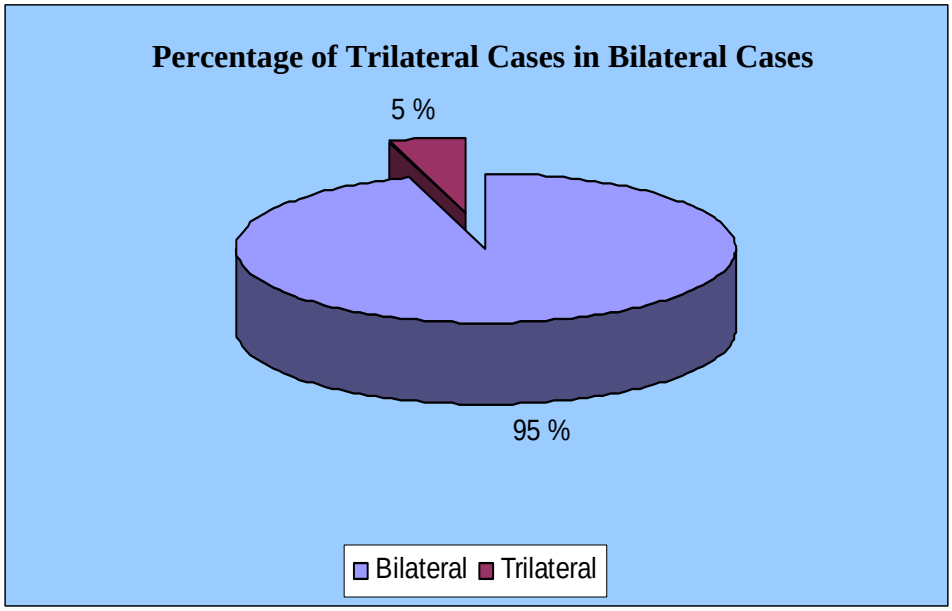
Table 2

Modes of 1st Presentation

S.No.	Particulars	No	Percentage
1.	Leukocoria	32	66.66%
2.	Secondary glaucoma	11	22.91%
3.	Squint	6	12.50%
4.	Proptosis	3	6.25%
5.	Vitreous hemorrhage	1	2.08%
6.	Hyphaema	1	2.08%
7.	Hypopyon	1	2.08%
8.	Defective vision	11	22.91%
9.	No specific complaints	3	6.25%


Sex Distribution
45.83 %
%
54.17 %
Male
Female


Laterality
41.66 %
58.33 %
Unilateral
Bilateral


Percentage of Trilateral Cases in Bilateral Cases
5 %
95 %
Bilateral
Trilateral

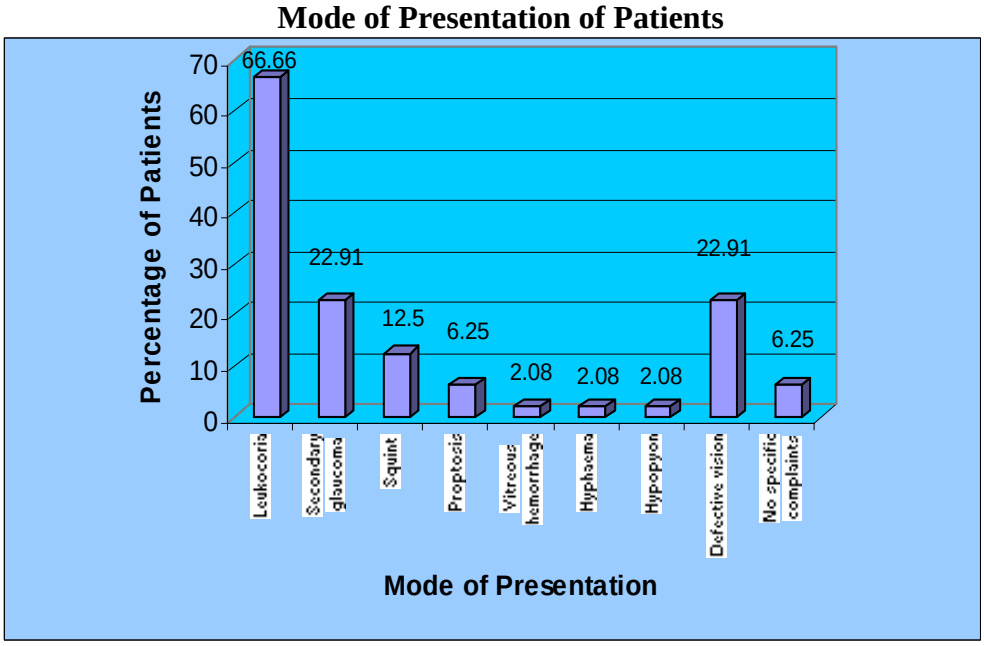

Mode of Presentation of Patients
Percentage of Patients
70
60
50
40
30
20
10
0
66.66
22.91
12.5
6.25
2.08
2.08
2.08
22.91
6.25
Leukocoria
Secondary glaucoma
Squint
Proptosis
Vitreous hemorrhage
Hyphaema
Hypopyon
Defective vision
No specific complaints
Mode of Presentation

Table 3

Eye Involved

S.No.	Particulars	No	Percentage
1.	Eye :		
	RE	33	48.53
	LE	35	51.47
2.	Laterality :		
	Unilateral	28	58.33
	Bilateral	20	41.66
	Trilateral	1	

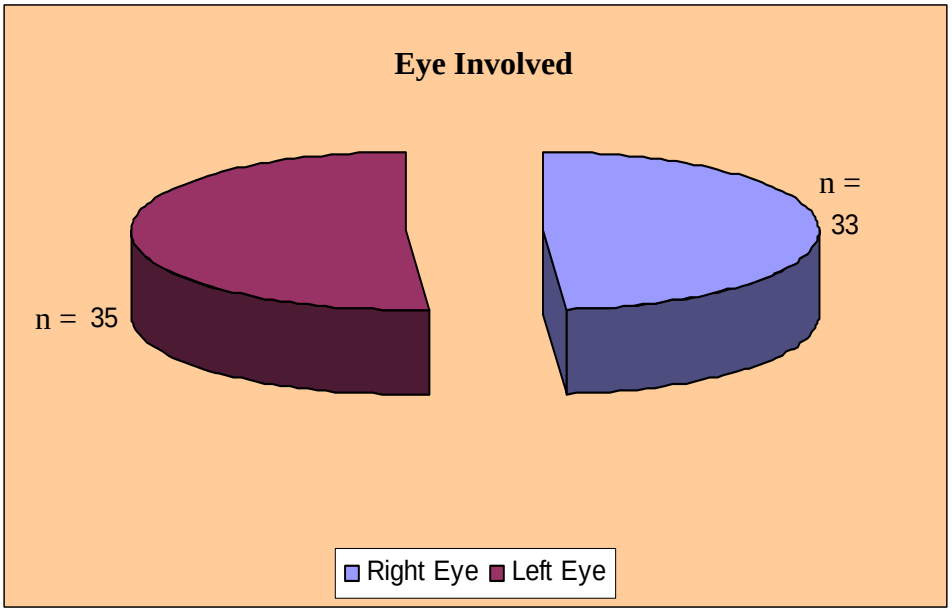


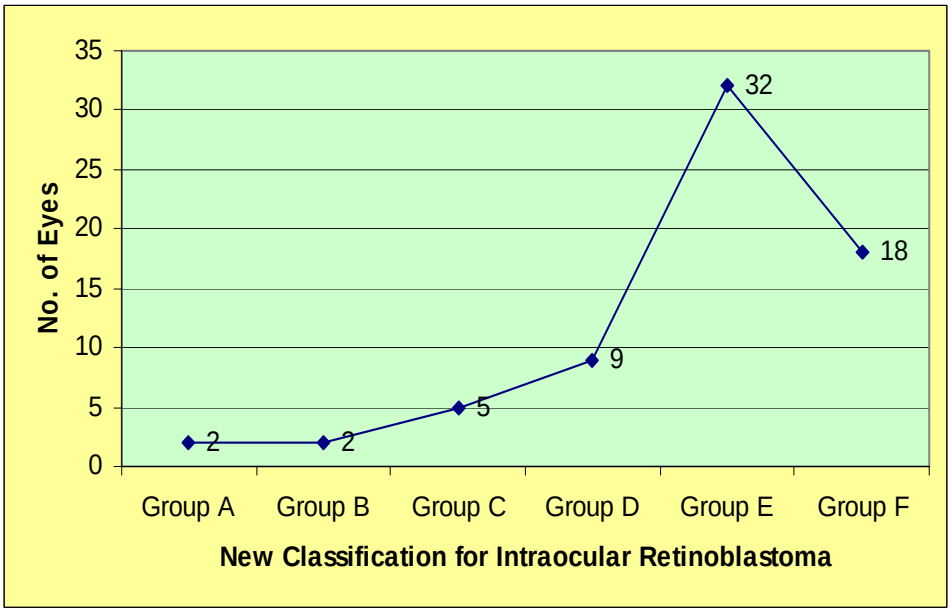
Table 4

Staging

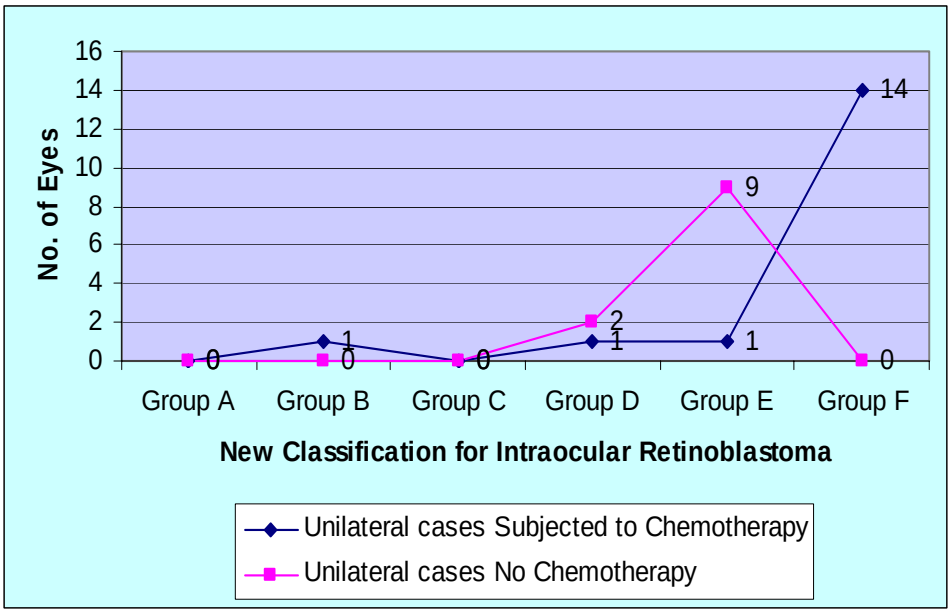
According to the "Newly proposed classification of Intraocular retinoblastoma".

S.No.	Stage	Total no. of eyes	Unilateral cases		Bilateral cases
			Subjected to Chemotherapy	No Chemotherapy	
1.	Group A	2	0	0	2
2.	Group B	2	1	0	1
3.	Group C	5	0	0	5
4.	Group D	9	1	2	6
5.	Group E	32	1	9	22
6.	Group F	18	14	0	4
Total		68	17	11	40

Total Cases



Unilateral Cases



Bilateral Cases

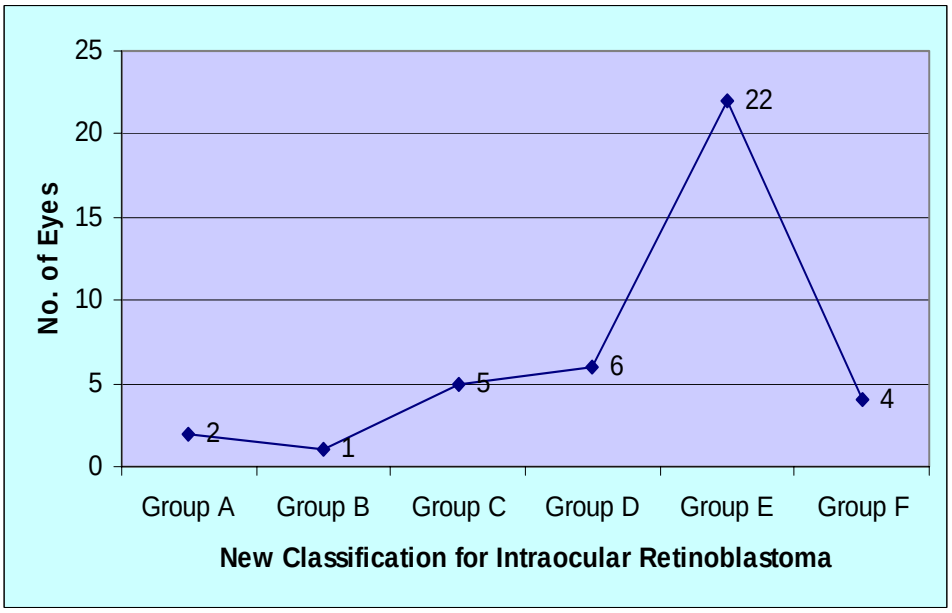


Table 5

Nature of Presentation of Tumour Mass

S.No.	Particulars	No	Percentage
1.	Single tumour mass	46	67.64%
2.	Multiple tumour mass	16	23.52%
3.	Retinal Detachment	26	38.23%
4.	Vitreous Hemorrhage	17	25.00%
5.	Vitreous seeding	11	16.17%
6.	Optic Nerve Infiltration	17	25.00%
7.	Orbital metastases	5	7.35%
8.	Choroidal metastases	7	10.29%
9.	Calcification	48	70.59%
10.	Retinal seeding	3	4.41%

Nature of Presentation of Tumour Mass

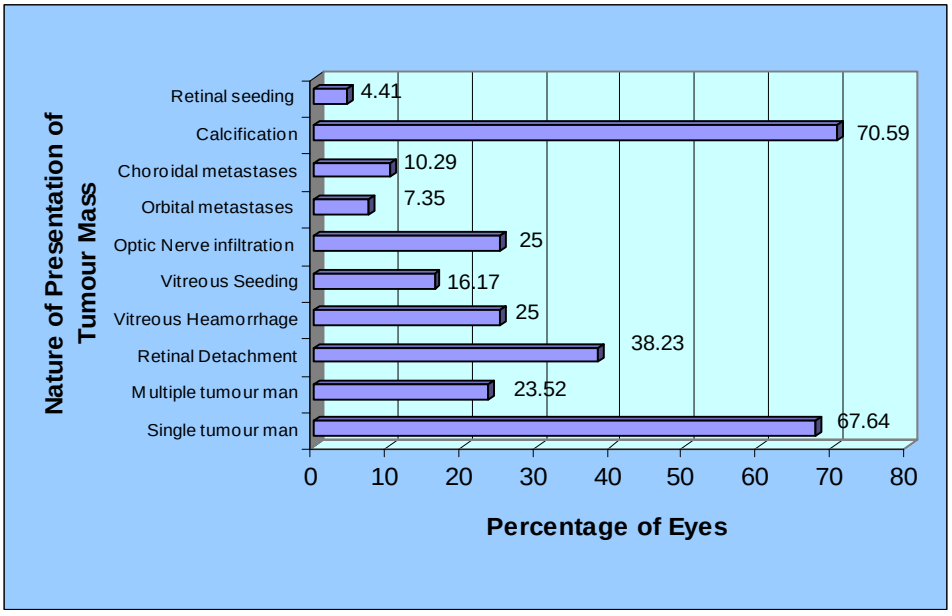
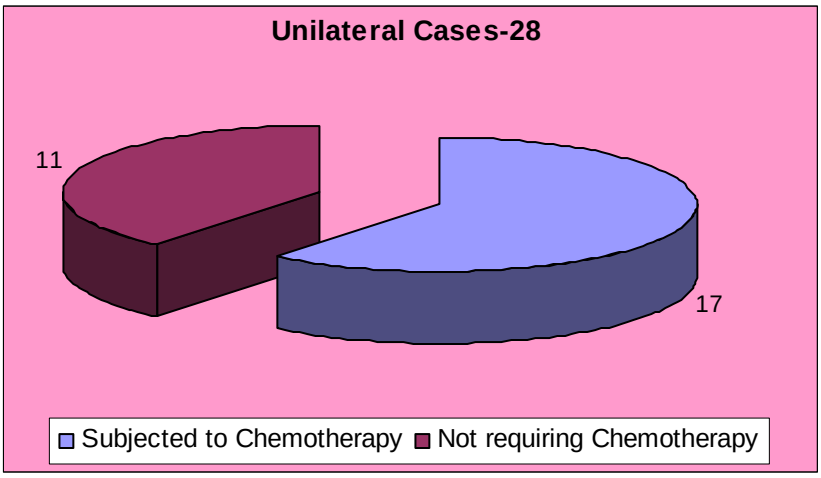


Table 6

Percentage of cases requiring chemotherapy

S.No.	Particulars	Total no. of cases	No subjected to Chemotherapy	Percentage
1.	Total number of cases	48	36	75.00%
2.	Unilateral	28	17	60.71%
3.	Bilateral	19	18	94.74%
4.	Trilateral	1	1	100.00%



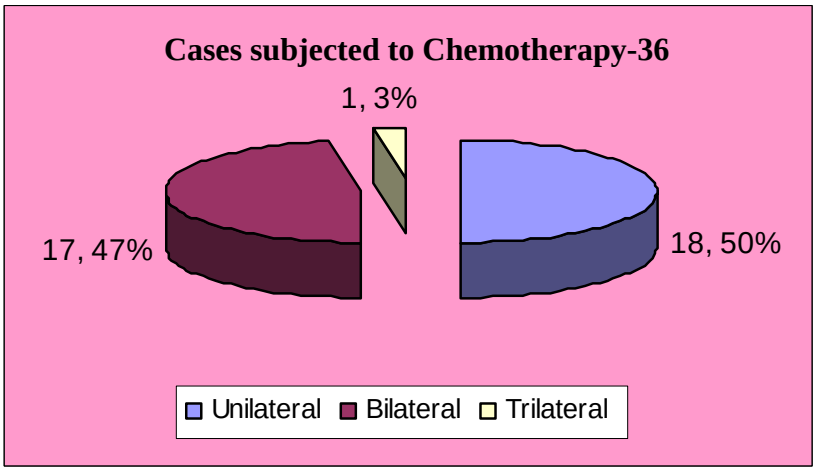


Table 7

Treatment Modalities

S.No.	Particulars	No of Eyes Treated	Percentage
1.	Enucleation	45	66.18%
	Unilateral	26	92.86%
	Bilateral	21	65.62%
2.	Exentration	2	2.94%
3.	Chemotherapy	36	75.00%
4.	EBRT	8	16.67%
5.	Focal Therapy	7	10.29%

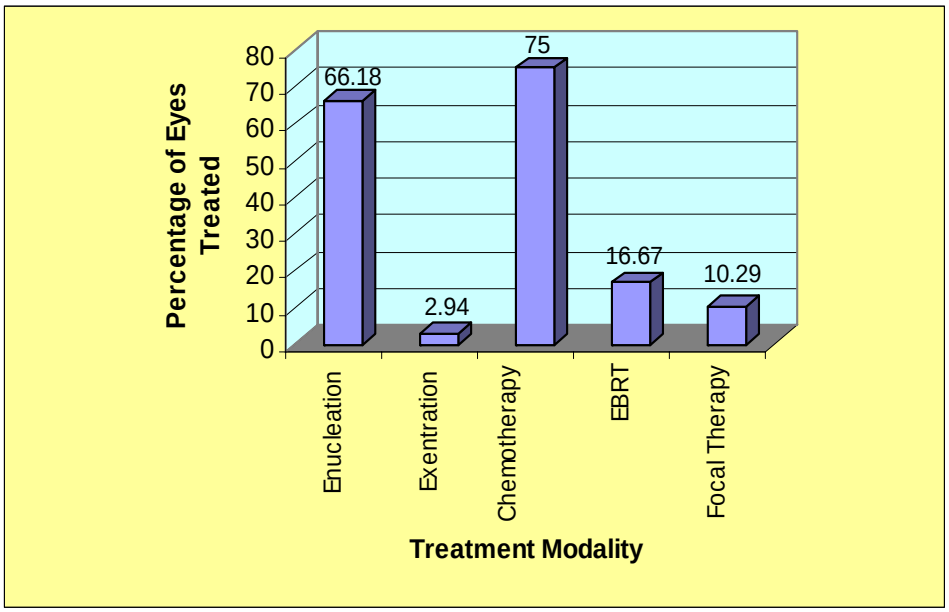


Table 8

Character of Retinoblastoma which regressed following Chemotherapy

S.No.	New Classification	Laser Treatment	Cryo therapy	TTT	No. of Tumours	Additional Information
1.	B	A	A		1	
2.	A	A	A		1	RB with Suprachiasmal extension EBRT given
3.	C	A	A		2	EBRT given
4.	D	A	A		4	EBRT given
5.	D	A	A		2	
6.	D	A	A		2	
7.	A	A			3	
8.	C	A		A	2	
9.	C				4	Only Chemotherapy
10.	D				3	Only Chemotherapy
11.	D	A		A	4	Quadruple Therapy

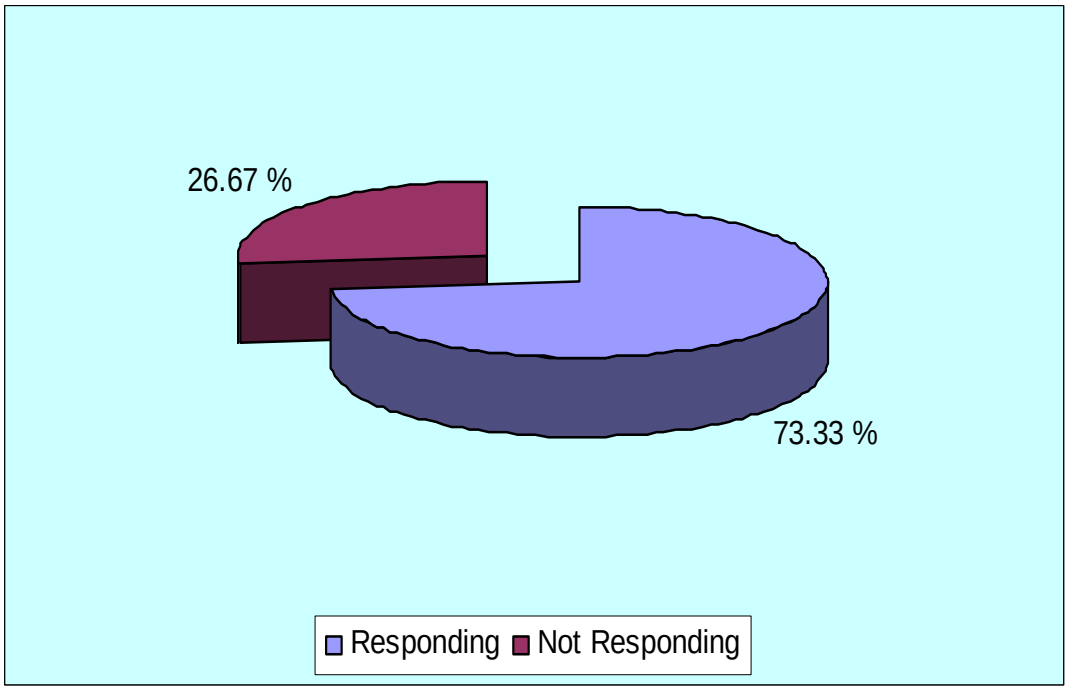
A - Administered

Table 9

Character of Tumour not responding to Chemotherapy

S.No.	New Classification	Laser Treatment	Cryo	TTT	No. of Tumours	Additional features
1.	E	G		G	1	RD, Vitreous Seeding (VS)
2.	D				1	No response to quadruple regiment
3.	E				1	Total RD
4.	E				1	Total RD, VS

Response of Tumour to Chemoreduction and Local Therapy



Results

Our studies included 68 eyes of 48 patients with retinoblastoma. Out of these 48 patients, 26 were male and 22 were female (Male Female Ratio was 1.18:1). 28 of them had Unilateral (58.33%), 20 of them had Bilateral (41.66%) and 1 out of the 20 bilateral cases had trilateral retinoblastoma at the time of presentation (5%).

The mean age at presentation of Retinoblastoma was 27.54 months(Unilateral cases Mean 28.0 months(mo), Median 24 mo, and for bilateral cases mean 22.31 mo, median 21 mo).One patient of trilateral retinoblastoma was 2 yrs at presentation. The earliest age at presentation was 13 days and highest age of presentation was 8 years. 89.58% of cases were diagnosed before 5 years of age and 27.08% before 1 year of age.

The mode of 1st presentation was leukocoria in 32 patient(66.66%), Secondary glaucoma in 11 (22.91%), Squint in 6(12.50%), Proptosis in 3(6.25%), Vitreous hemorrhage in 1(2.08%), Hyphaema in 1(2.08%), Hypopyon in 1(2.08%), Defective vision in 11 patients(22.91%) and no specific complaints in 3 cases(6.25%).

Of the 68 eyes with retinoblastoma, 33 were right eye and 35 were left eye. According to the Newly proposed classification, the number of eyes belonging to Group A was 2, Group B was 2, Group C was 5, Group D was 9, Group E was 32 and Group F was 18.

46 eyes (67.64%) had single tumour mass, 16 eyes (23.52%) had multiple tumour mass, 26 eyes (38.23%) had significant retinal detachment, 17 eyes (25.00%) had vitreous hemorrhage, 11 eyes (16.17%) had vitreous seeding, 17 eyes (25.00%) had optic nerve involvement, 5 eyes had orbital metastases, 7 eyes (10.29%) had choroidal metastases, (7.35%) 48 eyes (70.59) had calcification , 3 eyes (4.41%) had retinal seeding.

Of the 28 unilateral cases, 28 eyes with retinoblastoma, 26 eyes were treated by enucleation, of these 2 eyes belonged to Group D, 10 eyes belonged to Group E and 14 eyes belonged to Group F category when classified on basis of Newly proposed classification of intraocular retinoblastoma. Of the 14 eyes belonging to Group F, all of them were subjected to Triple drug chemotherapy with Vincristine, Etoposide & carboplatin combination for preventing metastases.

One eye belonging to Group D intraocular retinoblastoma was subjected to globe salvaging chemotherapy but patient did not follow up.

One eye belonging to Group B was subjected to glove salvaging chemotherapy and the tumour showed complete regression at end of completion of chemotherapy and in subsequent follow up.

One eye belonging to Group E was given S.C Carboplatin in to the socket following enucleation for preventing orbital metastases.

One eye belonging to Group E category was given S.C carboplatin in to the socket following enucleation, but subsequently developed intraorbital mass which was advised excision biopsy but patient did not follow up.

One eye belonging to Group F was given S.C carboplatin in to the socket following enucleation to prevent orbital metastases in addition to triple drug.

Of the 20 cases of bilateral retinoblastoma and one cases of trilateral retinoblastoma of the 20 bilateral cases, one eye with the higher grade of retinoblastoma was treated by enucleated. Of the enucleated eyes 16 eyes were Group E, One eye Group F. Two eyes belonging to Group F underwent lid spacing exentration.

In one case, in which the other eye was Group B retinoblastoma, the tumour was treated with only two episodes of TTT and showed complete regressed in the subsequent visit.

In remaining 18 bilateral cases all were subjected to chemotherapy for globe salvage of the other eye, 14 eyes followed up till the end of required number of chemotherapy cycles and out of which total 10 eyes showed complete regression of the tumor (71.42%). 5 eyes showed complete regression with chemotherapy and local therapy {Group D 2 cases, Group A 2 case, Group C 1 case}.

2 eyes {both eyes were Group C according to new classification} showed complete regression with only 3 drug chemotherapy.

2 eyes showed complete regression with 3 drug chemotherapy and EBRT + local therapy {Group C one eye in which other eye had shown optic nerve infiltration Group F, the other eye was group D}

1 eye belonging to Group D regressed with quadruple therapy + Local TTT.

4 eyes did not show regression of the tumour mass –Three of them were Group E and 1 Group D which failed to regress despite use of Quadruple chemotherapy regimen.

4 eyes did not follow up – 3 were Group E, 1 was Group D.

In one bilateral case, an 8 year old female child with suprachiasmal spread of the retinoblastoma, the child underwent lid sparing exentration of Right eye and it was treated with Intrathecal Chemotherapy, triple drug systemic chemotherapy and EBRT for orbit & craniospinal irradiation as per the regimen proposed by Stephen Nelson et al. The patient showed complete regression of Group A tumour in the other eye and the regression of supra sellar tumour. But patient subsequently after 5 month of completion of Chemotherapy developed knee pain and patient was suspected to have developed Osteogenic Sarcoma and referred to higher centre for management. Patient failed to follow up after that

One patient with trilateral retinoblastoma was given intrathecal Chemotherapy, and one cycle of triple drug regimen, but failed to follow up after the first cycle.

Over all 26 Unilateral, 18 eyes in bilateral retinoblastoma & 1 eye in trilateral retinoblastoma required Enucleation. Overall 45 eyes - 66.18% of eyes required treatment by enucleation.

- 92.85% of unilateral cases required enucleation.
- 2/20 bilateral case required exentration (10%).

1 out of 20 bilateral cases were trilateral cases (5%).

36 out of 48 patients - 75% needed chemotherapy

11 out of 15 eyes with tumour subjected to appropriate systemic chemotherapy for globe salvage regressed completely. (73.33%)

8 Cases needed EBRT for treatment of tumour (16.66%)

7 eyes received focal therapy - 10.29%

Overall follow up rate among patients with retinoblastoma subjected to chemotherapy 69.44% (11 patients failed to follow up - 5 bilateral cases, 6 unilateral cases).

Overall follow Up rate for acceptance of treatment in patients with retinoblastoma 72.91% (13 patients did not accept treatment).

Discussion

Demographic features

In our study The average age at presentation was 27.54 months (Unilateral cases – 28 months, bilateral cases 22.31 months). The median age at presentation was 24 months (24 months in unilateral cases and 21 months in bilateral cases). The minimum age at presentation was thirteen days and maximum age was 8 years. 89.58% were diagnosed below 5 years of age and 27.08% before age of 1 year 58.33% had unilateral diseases & 41.67% had bilateral disease, 10%of the bilateral cases had bilateral disease. Male female ratio was 1.18:1.

In Tamboli series[3] 95% of cases of Retinoblastoma were diagnosed before age of 5 years and 40% diagnosed before 1 year.

Shields et al[62] in a review of 1,196 eyes with Retinoblastoma which presented between 1974-2001, reports, median age in months (Mean, Range) as 15(22,1-550), male to female ratio as 1.04:1, 53% of cases being unilateral, 47% being bilateral, 51% right eyes and 49% left eye,

S.P.Dhir et al[63] in 1980 in analysis of 47 cases of Retinoblastoma which presented between 1972 and 1976, reported minimum age at presentation 6 months and maximum age 7 years. The average age at presentation was 48 months, male female ratio was 1:1.474, 60% of the eyes were unilateral and 40% were bilateral.

Sahu S et al[63] in a study in 1998 about Clinical and Epidemiological character of Retinoblastoma reported the median age at presentation as 42 months (3.5years) (42 months for unilateral and 12 months for bilateral), male female ratio as 1.4 : 1, **74.5% of eyes were advanced stage diseases (Reese – Ellsworth Grade IV and V)**.

The age at presentation in our study in slightly more (9 months) higher when compared to studies from western literature, but much less (18-21 months lesser than studies from India published before). The number of cases which presented to us before 1 year of age in lesser than in western studies

Clinical presentation

In our study the classification of the eyes with retinoblastoma was done only according to the **Newly proposed classification for retinoblastoma**.

Reese-Ellsworth classification system for intraocular retinoblastoma was designed to help predict which eyes would most likely be salvaged after primary external beam radiotherapy. Anterior lesions, which can now be easily recognized and treated with cryotherapy or radio active plaque, cause the eye to be classified in a more advanced stage when using Reese-Ellsworth classification. Also local vitreous seeding of any amount places the eye in Group 5b with poorest prognosis. With combination of chemoreduction and local therapy, vitreous seeding, a frequent finding of large tumours is

successfully treated in almost 75% of cases. Studies have shown erratic correlation of the Reese-Ellsworth classification with treatment success following chemoreduction[74] and more than 10 yrs ago itself Bob-Ellsworth discussed the fact that Reese –Ellsworth was out of date and should be revised.(R.M.Ellsworth, personal communication , Nyon, Switzerland, 1987).

Since chemoreduction and all local therapy for treatment of retinoblastoma were available in our set up and eyes could be mananged with appropriate combination of methods available, eyes with tumour were classified on basis of New classification.

In our study, Leukocoria (66.66%) was the most common mode of presentation, followed by defective vision (22.91%), secondary glaucoma (22.91%), squint (12.50%) and proptosis in (6.25%). According to New classification 86.76% of eyes in our study, had advanced stage disease (Group D to Group F).

In study by **SP Dhir et al[63]** in India (1980) of 47 eyes with Retinoblastoma, proptosis was the most common mode of presentation 68% followed by 17% being white reflex and squint 6.1%.

In **western literature**, almost all series of retinoblastoma, Leucokoria has been the most common presenting sign, strabismus the next most frequent mode of presentation[71,72] and other presentations as with glaucoma, defective vision, orbital cellulites etc as less common presentation[73].

Barret G.Haik et al[73], in an analysis of 250 cases 11% had positive family history, 56% had white reflex, 20% had strabismus, 7% had glaucoma, Poor Vision in 5 %, no complaints in 3%, orbital cellulites in 3%, Hyphaema in 1%.

Most common mode of presentation in our study is leukocoria similar to those reported in western literature, percentage presenting with defective vision is second highest and is higher than reported in western literature. Percentage presenting with strabismus is markedly lower than in western reports. Percentage of glaucoma, proptosis, and hyphema is higher in our study.

When compared to previous Indian study in 1980 the presentation as proptosis has definitely decreased, indicating that compared to a decade before, the disease is being diagnosed at an earlier stage in India. The percentage of eyes presenting in advanced stage of disease in our study is still slightly higher than that in the western population. This data in our study indicates that in India, probably due to increasing literacy among population making them avail medical care earlier, higher degree of suspicion in medical population to look for the disease, and availability of modalities to diagnose and treat diseases earlier, efficiently and appropriately, the disease is being diagnosed earlier than it was a decade before, and further improvement in above said factors and institution of screening for Retinoblastoma will help us diagnose and treat Retinoblastoma in par with the western world.

Treatment modalities for Retinoblastoma :

Abramson, MD et al[15] and **Carol C.Shields MD et al**[65] have described the various treatment modalities available for Retinoblastoma including the recent and emerging developments in management. The modalities of treatment being, enucleation for retinoblastoma that fills most of the eyes and especially when tumour invasion into the optic nerve or choroids is suspected. External beam radiotherapy as an important method of treating less advanced retinoblastoma especially when there is disease vitreous or subretinal seeding plaque radiotherapy, for small and medium sized RB, Cryotherapy & photocoagulation as providing good control of selected small tumour. Thermotherapy, the newest focal treatment method fro retinoblastoma and the combination of thermotherapy and chemotherapy providing satisfactory tumour control & the need for further study & follow up to determine fully the safety & applicability of periocular administration of carboplatin & other potential agents.

In our study, therapy was instituted as per individual case requirement. Unilateral cases 92.5% were in advanced stage and so were enucleated. We had the diseased eyes enucleated because studies[70] have shown chemo reduction combined with local ophthalmic therapy less effective in RE group 4 & more so in RE group 5 with or without vitreous seeds. In bilateral cases 100% of them

presented with at least one eye or in few cases both stage disease (New classification D to F).

In bilateral cases, one eye with advanced disease stage was enucleated & in one case exentrated, for the previous reports mentioning of poor tumour response in them & also in a view to decrease the tumour load when the salvage of patient's other eye was attempted by chemo reduction and local ophthalmic therapy. Histopathlogical examination of the enucleated eye enabled us having a definite histopathological diagnosis of retinoblastoma and to know the status of optic nerve and choroids since infiltration into either warrants a more aggressive & compulsory systems therapy. By decreasing the tumour load, the total number of cycles of chemotherapy administered could be decreased & thus adverse effect of chemotherapy can be decreased. We thus after enucleation of the eye with advanced disease, administered only 3 drug regimen (VEC) for only 3 cycles in majority of cases in a view that Indian children general health might not tolerate a higher cumulative dose, and in minimum 3 months follow up of tumour which regressed there were no recurrence. External beam radiotherapy was administered in only 8 cases as an adjunctive method for chemoreduction..

Most studies of chemoreduction for retinoblastoma since 1996 have utilized Vincristine, carboplatin Etoposide or Teniposide[66,67,68,69,70]. The choice

of agents as well as number & frequency of cycles had been varying currently at different institution update.

In a pilot study of 20 patients, **Shields et al**[69] found that two cycles of VEC was sufficient to promote regression in all 54 tumours studied in 31 eyes. Further follow up revealed that six cycles of chemotherapy decreased the vitreous seed recurrences.

Debra L Fried man, Bruce Himelstern, Carol L shields et al[71] in a study of 75 eyes of 47 children, patients were treated with a six cycle protocol of VEC regimen along with local chemotherapy methods given during monthly or bimonthly ophthalmic regimen. Under GA and they reported that used of chemoreduction with local ophthalmic patients with eyes in RE group 1 to 3 and that the therapy was less effective for group 4 & group 5 patients.

In our study only 15 eyes of 15 patients were available for assessing the response of retinoblastoma to chemoreduction & local ophthalmic since 45 eyes were enucleated (26 unilateral, 17 eyes of bilateral cases), 2 eyes underwent exentration & 5 eyes could not be assessed since the 5 patients did not follow up, one eye showed total tumour regression with cryotherapy and laser barrage.

Of the 15 eyes which received total course of chemotherapy and local therapy with or without EBRT as planned – 11 eyes showed total regression of tumour (73.33%) & follow up of minimum 3months and maximum 15 months showed no recurrence. One of these patient required quadruple regimen

including Cylosporin A & 3 patient received EBRT in addition to chemoreduction & local therapy. One patient of bilateral retinoblastoma with suprachiasmal extension of the tumour treated with one dose of intrathecal chemotherapy and 6 cycles of VEC regimen, showed complete regression of the Group A tumour in the other eye and the suprasellar tumour. 3 patient received EBRT in addition to chemoreduction & local therapy. In 2 patients tumour regressed only with chemotherapy. None of these eyes which showed regression had Retinal detachment, Vitreous seeding, Vitreous Hemorrhage at presentation.

In eyes subjected to chemoreduction and local of ophthalmic therapy, enucleation could thus be avoided in 73.33% of cases, and both enucleation & EBRT could be avoided in 53.33% of cases subjected to Chemoreduction and local opthalmic therapy.

The 3 eyes which did not show regression had Retinal detachment, 2 had vitreous seeding & one eye did not respond in spite of quadruple regimen.

Overall follow up among patients subjected to chemotherapy is 69.44%. Over all acceptance to treatment was 72.91%.

In our study, the initial experience of administering chemoreduction and adjuvant local ophthalmic therapy for treatment of retinoblastoma, showed good regression of tumour in 73.33% of cases and is an encouraging result. Since most of the tumour presented in advanced stages Group E and Group F

and needed enucleation not many eyes were available to assess response of the tumour subjected to chemoreduction and adjuvant therapy.

There were no adverse effect of chemotherapy in our study and drugs could be safely administered.

Our study was limited by time, a long term follow up and recruitment of more eyes for treatment will enable us analyse and compare our results following therapy to other major studies from western literature which have assessed response to chemotherapy. This will help us in formulating and standardizing a protocol for treatment of retinoblastoma in an Indian tertiary care set up.

Conclusions

1. Our study showed presenting age to be slightly higher than in western literature(The mean age at presentation was 27.54 months (Unilateral cases – 28 months, Bilateral cases 22.31 months).
2. In our study the number of cases that presented to us before the age of 1 year was lesser when compared to the western literature. (27.08% diagnosed before age of 1 year).
3. Male Female Ratio (1.18:1), Percentage of unilateral (58.33%) and bilateral retinoblastoma (41.67%), in our study was similar to previous reports from western world.
4. Percentage of trilateral retinoblastoma (5%) among the bilateral ones in our study was similar to previous reports.
5. Leucokoria(66.66%) was the commonest mode of presentation in our study similar to other studies. But mode of presentation with defective vision(22.91%), glaucoma(22.91%), proptosis(6.25%) were higher in our study compared to western literature. Presentation as strabismus (12.50%) was much lesser in our study.
6. Percentage of cases (86.76%) presenting in advanced stage of disease were higher.
7. The response to attempt to salvage eyes using chemoreduction & local therapy with three cycle VEC regimen seems promising (regression of tumour in 73.33%). Even group D tumours have shown regression

completely after chemoreduction, local therapy and EBRT (EBRT was required is one out of 5 Group D cases which showed regression of tumour).

8. Retinal detachment, vitreous seedings and vitreous hemorrhage at presentation could be taken as indicators for poor prognosis for tumour regression.
9. A long term follow up is necessary to assess the long term survival of these patients, and also to diagnose the recurrence of tumour if any in these patients and to decide if more number of cycles of chemotherapy has to be administered.
10. Follow up of patients and acceptance to treatment is low (below 75%) and should be improved.
11. Emphasis on early screening & diagnosis is advised to enhance prognosis and quality of life in these patients.
12. All the treatment modalities for retinoblastoma available in western countries can be made available in tertiary eye care centre in India. Chemotherapy including triple regimen (VEC), Quadruple regimen in resistant tumour, Intrathecal chemotherapy for trilateral retinoblastoma can be safely administered in a tertiary eye care centre & response can be assessed. With the early diagnosis, application of chemo reduction &

local therapy the percentage of Enucleation and EBRT, morbidity and mortality of patients can be decreased.

13. There is a necessity to create a national registry to understand the actual impact of retinoblastoma in our country, treatment modalities should be standardized so that every centre can offer best available treatment at lower cost for patient.
14. A multi centered clinical study in India is necessary to evaluate clinical presentation, response of chemoreduction, local therapy in retinoblastoma in India.

Bibliography

1. Shields JA, Shields CL, Atlas of Intraocular Tumors. Philadelphia: Lippincott, Williams & Wilkins; 1999: 207-232.
2. Gattag et al. Childhood cancer survival in Europe & the United States. Cancer – 2002; 95(8): 1767-72
3. Tamboli A, Podgor MJ, Horm JN. The incidence of retinoblastoma in the United States: 1974 through 1985. Arch Ophthalmol 1990; 108(1): 128-32.
4. Albert DM. Historic review of retinoblastoma, Ophthalmology 1987; 94: 654-662.
5. Bishop JO, Madson EC. Retinoblastoma: Review of current status. Surv. Ophthalmol. 1975; 19: 342-366.
6. Duke elder S, Dobree JH; System of ophthalmology: Vol X disease of the Retina. St.Louis, CV Mosby, 1967, P 672.
7. Albert DM, Robinson N: Wardrop lecture, 1974. James wardrop : A brief review of his life & contribution. Tram Ophthalmol Soc Uk 94: 892-908, 1974.
8. Zimmerman LE: Retinoblastoma & retinocytoma. In spencer WH (Ed): Ophthalmic Pathology. Philadelpha, WB Saunders, 1985, P.1292.
9. Tsu.MOM, Zimmerman Le, Fine BS: The nature of retinoblastoma I.. Photoreceptor differentiation: A Clinical & Histologic study. Am.J.Ophthalmol 69: 339-350, 1970.

10. Knudson AG Jr.Mutation & Cancer : Statistical study of retinoblastoma. Proc. Nati. Acad Sci USA. 1971; 68: 820-823.
11. Albert DM et al: Development of additional primary tumors after 62 years in the first patient with retinoblastoma cured by radiation therapy. Am J Ophthalmol 97: 189-196, 1984.
12. Reese AB, Merriam GR Jr, Martin HE : Treatment of bilateral retinoblastoma by irradiation and surgery : Report on 15 year results. Am J Ophthalmol 32: 175-190, 1999.
13. Murphee LA. Molecular genetics of retinoblastoma. Ophthalmol clin N America 1995; 8: 155-166.
14. Ellsworth R M: The Practical Management of Retinoblastoma Trans Am. Ophthalmol Soc 67: 463-534, 1969.
15. D and H, Abramson, MD, FACS, AMY.C Schefler, MD ;Update on Retinoblastoma - Retina - 2004, Volume 24. Number 6:828.
16. Orjuela M et al. Presence of HPV in tumour tissue from children with retinoblastoma: an alternative mechanism for tumour development. Clin cancer Res 2000; 6(10): 4010-6.
17. Abramson DH, et al: Retinoblastoma: Survival, age at detection and comparison 1914-1958, 1958-1983. J. Paediatric Ophthalmol Strabismus 22: 246-250, 1985.

18. Karcioglu,Zeynel A et al; Retinoblastoma in older children. J AAPOS 2002 Feb; 6(1) : 26 - 32.
19. Derkinder en DJ, Kotenjw et al; Parental age in sporadic hereditary retinoblastoma. Am J. Ophthalmol. 1990 Dec 15; 110(6) : 605-9.
20. Bookstem R, Lee Ey et al. Human retinoblastoma susceptibility gene: Genomic organisation and Analysis of heterozygous intragenic deletion mutants. Proe Natt Acad Sci USA 1988; 85: 2210-2214.
21. Hamel PA, Gill RM, Philips RA et al. Region controlling hyperphosphorylation and conformation of retinoblastoma gene product are independent of domains required for transcriptional repression. Oncogene 1992; 7: 693-701.
22. Zamanian M, La Thangue NB. Adenovirus Ela prevents the Retinoblastoma gene product from repressing the activity of a cellular transcription factor. EMBO J. 1992; 11: 2603-2610.
23. HU QJ, Lees JA et al. The retinoblastoma protein physically associates with the human Cd c2 Kinase. Mol bior. 1992; 12: 971-980.
24. Murphree Al, Munier FL. Retinoblastoma In: Ryan SJ, ed. Retina. 2nd ed. St. Louis, Mo: CV Mosby; 1994:571-626.
25. Paul T Finger, M.D et al. Risk factors for Metastasis in Retinoblastoma. Survey of Opthalmol Vol 47. Number 1. Jan-Feb 2002.

26. Abramson DM, Frank CM, Susman M, et al. Presenting signs of retinoblastoma J. Pediatric 1998; 130: 505-508.
27. Haik Ba, Siediechi et al: Documented delays in diagnosis of retinoblastoma. Ann. Ophthalmol 17: 731-732, 1985.
28. Kingston JE, Plowman PN : Ectopic intracranial retinoblastoma in childhood. Br.J.Ophthalmol 69:742-748, 1985.
29. Murphee Al and Cibis, GW : Retinoblastoma. In cibis, GW, Tongue AC and Stass bern, Ml, eds : Decision making in Paediatric Ophthalmology, st.louis, 1993, Mosby.
30. Benham OU, E. Burger J and TSO Mo: Magnetic resonance imaging in retinoblastoma and retinocytoma; a case report, J.Paediatric Ophthalmol strabismus 26: 276-280, 1989.
31. Schulman JA, Peyman GA et al : The use of magnetic resonance imaging in the evaluation of retinoblastoma J.Paediatic Ophthalmol Strabismus 23: 144-147, 1986.
32. Zimmerman RA and Bilaniuk LT: Computed tomography in the evaluation of patients with bilateral retinoblastoma, J Comput Assist Tomogr 3: 251-257, 1979.
33. Haik BG, Saint Lows L, Abramon DM et al: Computed tomography of the nonrhegmatogenous retinal detachment in the pediatric patient. Ophthalmology 92: 1133-1142, 1985.

34. Coleman DJ: Reliability of ocular tumor diagnosis with Ultrasound; Tr, Am Acad. Ophthalmol otol 77: 677-686, 1973.
35. Shields JA, Shields CL: Intraocular Tumours. Lippincott Williams & Wilkins, Philadelphia, 1999.
36. Shields JA, Micheison JB, et al : B.Scan Ultrasonography in diagnosis of a typical retinoblastoma. Can J. Ophthalmol 11: 42-51, 1976.
37. Ann Ophthalmol 1981 May: 13(5) 535-8 which pathologic characteristics influence echographic patterns and Retinoblastoma Basta LL, Israel CW et al.
38. Roth, Daniel B Scott et al, “Echography of retinoblastoma: histopathologic correlation and serial evaluation after globe –conserving radiotherapy or chemotherapy”, Journal of pediatric ophthalmology and strabismus 2001,May June;38(3):136-43
39. Finger,PT, Khoobeki A, et al. Three dimensional ultrasound of Retinoblastoma: Initial experience .British Journal of Ophthalmology 2002, Oct; 86(10):1136-1138.
40. Wetzig PC, Jepson CN: Flourescene photography in the differential diagnosis of Retinoblastoma .Am J Opthalmol 61:341-343,1966.
41. Eagle, RJ, Shields, JA et al : Malignant transformation of spontaneously regressed retinoblastoma retinoma / retinocytoma variant, Ophthalmology 96: 1389-1395, 1989.

42. Shields JA, Shields CL : Changing Concepts the management of retinoblastoma, Ophthalmic Surg 21: 72-76, 1990.
43. Atchaneeyasakul L Rao, NA, Reynolds, CP, Nelson MV et al; Residual viable retinoblastoma in Reese Ellsworth Group 5 eyes treated with multiagent chemotherapy with and without cyclosporine A. Arch Ophthalmol 1998 (submitted).
44. Atchaneeyasahul L Rew, NA et al : Clinical efficacy of multiagent chemotherapy plus high dose cyclosporine A in Reese Ellsworth group 5b intraocular retinoblasma, Arch Ophthalmol 1998.
45. Kishi et al; Japanese journal of clinical oncology 33: 601-607, 2003. Eye preservation treatment of retinoblastoma with vitreous seedings.
46. Kaneko A - Teach us about current treatment of retinoblastoma : Atarashii Ganka 1996; 13: 229-33 (Japanese).
47. Nelson SC, Friedman HS et al : Successful therapy for bilateral retinoblastoma, Am J Ophthalmol 114: 23-29, 1992.
48,49. Gallie BL, Budnig A, De Boer G et al. Chemotherapy with Focal treatment can cure intraocular retinoblastoma without radiotherapy : Arch Ophthalmol 1996; 114: 1321-1328.
50. Shields CL, Shields JA et al. Treatment of retinoblastoma with indirect ophthalmoscope laser photocoagulation. J.Paediatr. Ophthalmol and Strabismus. 1995; 32: 317-322.

51. Murpee AC et al. Chemotherapy plus local therapy in the management of intraocular retinoblastoma Arch Ophthalmol 1996; 714: 48-356.
52. Abramson DH. Servodido CA, Nissen M - Treatment of retinoblastoma with the trausceleral diode laser. Am J Ophthalmol 1998 ; 126(5) : 733-735.
53. Carol L. Shields, Jerry A, Shields et al. Continuing challenges in management of retinoblastoma with chemotherapy. Retina 2004 volume 24, Number 6, P.No. : 851-862.
54. Shields CL, Shields JA, Kirachi. Treatment of retinoblastoma with indirect ophthalmoscope laser photocoagulation. J. Paediatric Ophthalmol Strabismus 1995; 32: 317-322.
55. Abramson DM, Ellsworth RM, Hark B G. Cobalt Plaque in advanced retinoblastoma. Retina 1983; 3:12-15.
56. Gallie BL, Troung T, Heon E et al. Retinoblastoma ABC classification survey. In: 11th international retinoblastoma symposium 2003;
57. Shields CL, De Potter P, Himelstein BP, Chemotherapy in the initial management of intraocular retinoblastoma. Arch Ophthalmol 1996; 114: 1330-1338.
58. Shields CL, Shields JA, Needle M et al. Combined chemotherapy and adjuvant therapy for intraocular Retinoblastoma Ophthalmology 1997; 104: 2101-2111.

59. Abramson DM, Frank CM, Dunkel IJ. A phase I/II study of sub conjunctival carboplatin for Intraocular Retinoblastoma Ophthalmology 1999; 106: 1947-1950.
60. Abramson DM, Gerold CM et al : Radiation regression patterns in treated retinoblastoma.
61. Atehaneeyasahul, A Linn Murphres – Retinoblastoma volume one, chapter 23, page no. 547, Retina book, Basic Science & inherited retinal diseases.
62. John A Epstein, MD., Carol l. Shields al. Trends in management of Retinoblastoma : Evaluation of 1,196 consecutive eyes during 1974 to 2001, Jour of Paediatirc ophthalmol & strabismus 140, July- Aug 2004, 196- 203.
63. Dhir SP, Jain IS et al, survival of retinoblastoma cases in North India IJO 1980 Jul 28(2) : 97- 100
64. Sahu s et al, Retinoblastoma problem and perspectives from India. Paediat Hematol Oncol 1998, Nov – Dec, 15(6): 501 -8.
65. Carol L. shields, MD; Jelly A shields, MD; Recent – development I the management of Retinoblastoma. J. Peadatric Ophthalmol Strabismus 1999 ; 36- 8 – 18.

66. Gallie BL, Budnig A, DeBoel G, et al.Chemotherapy with focal therapy can cure intraocular retinoblastoma without radiotherapy. Arch ophthalmol 1996 114 (11) 1321 -8.
67. Green wald MJ, Strauss LC.Treatment of intraocular Retinoblastoma with Carboplatin and Etoposide therapy ophthalmology 1996; 103(12): 1996 -97
68. Shields Cr, De Potter et al. Chemoreduction in the initial management intraocular retinoblastoma . Arch ophthalmol 1996; 114(11): 330- 8.
69. Shields Cr, Shields JA et al combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. Ophthalmology 1997; 104 (2) : 2101-11.
70. Friedman DL, Himelstein B, Shields Cr et al. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma J. Clinical on co 2000; 18(!) 12-7.
71. Ellsworth RM:The Practical management of retinoblastoma.Trans Am Ophthalmol Soc 67:463-534,1969.
72. Shields JA, Augsburger JJ: Current approaches to diagnoses and management of retinoblastoma. Surv Ophthalmol 25:347-372, 1981.
73. .Haik BG, Ellsworth et al: Documented delays in the diagnosis of retinoblastoma, Ann opthalmol 17:731-732, 1985.

74. Carol.L.Shields,MD, Arman Mashayekhi,MD et al: Practical approach to management of Retinoblastoma. Arch Opthalmol Vol 122, May 2004,P.No 729-735.
75. Xu K,Rosenwaks Z,Beaverson K, Cholst I, Veeck L, Abramson DH, preimplantation genetic diagnosis for retinoblastoma :the first reported live born. Am J Ophthalmol 2004; 137(1):18-23.
76. A.Linn Murphee, La – Ongsri Atchaneeyasakul. Retinoblastoma In:Ryan SJ,ed. RETINA (3rd Ed) , Pg No: 513-570.

RETINOBLASTOMA-Prospective analysis - Detailed Case Sheet

1. Name: *(kindly take clinical photo,Gross Eye*
2. MR NO: *specimen photo,HPE slide photo,Recording of fundus picture during EUA every visit)*
3. Date of first visit ----------
4. .Age _____(mention if in days/months / yrs)
5. Date of birth _____(mm/dd/yy)
6. Sex
7.Address:

8.Presenting illness (kindly encircle the appropriate entity)

Symptoms	**Right eye**		**Left eye**	
1.White reflex	Y	N	Y	N
2.Duration of white reflex in days and months	___d/__m		__d/__m	
3.Squinting	Y	N	Y	N
4.Pain	Y	N	Y	N
5.Redness	Y	N	Y	N
6.Swelling of eye	Y	N	Y	N
7.Dimness of vision	Y	N	Y	N
8.Others(please specify) esp Trauma,pet animals				

9.Past History:

1.Similar illness in same eye	Y	N
2.Similar illness in the other eye	Y	N
3.Treatment offered elsewhere /AEH	Y	N

(if yes specify what

	Right eye		**left eye**	
1.Laser	Y	N	Y	N
2.Cryo	Y	N	Y	N
3.EBRT/plaque	Y	N	Y	N
4.Chemotherapy	Y	N	Y	N
5.Enucleation	Y	N	Y	N

4.any other major hospitalization requiring illness in the past(specify) .

10.Antenatal History:

1.Full term delivery Y N
2.Normal delivery / caesarean section
3.H/o fever in mother during gestation (specify what and which month and treatment if any) _____
4.other drug use in gestation,radiation if any

11.Family history

(if yes specify which eye and which member: mother,father,sibling,distant relative) of squinting,white reflex,proptosis,death due to ocular cause,enucleation, diagnosed ocular tumour,retinoblastoma,other cancers

(Family tree) O----□

EXAMINATION

12.General systemic examination

1.obvious congenital anomaly

2.lymphadenopathy (region if present ---preauricular ,post auricular, submandibular deepcervical ,.any other group(specify)

3.hepatospleenomegaly Y N

4.skeletal system

5.CVS

6.RS

13.*Ocular examination*		***Right eye***		***Left eye***	
1.vision		---		---	
2.leukokoria		Y	N	Y	N
3.proptosis		Y	N	Y	N
4.orbital cellulites		Y	N	Y	N
5.cornea cloudy		Y	N	Y	N
6.Anterior chamber					
	a.hyphaema	y	n	y	n
	b.hypopyon	y	n	y	n
	c.exudates	y	n	y	n
	d.Depth (mention shallow or deep)				
7.Iris a. colour pattern(normal/heterochromia)			---		---
b.Neovascularisation.			---		---
8.lens			---		---
9.Extra ocular movements {F-full;R-restricted)			---		---
10.Pupils(specify)	Ectropion uvea	y	n	y	n
	size(mm)	---		---	
	shape	---		---	
	reaction-direct	---		---	
	indirect	---		---	

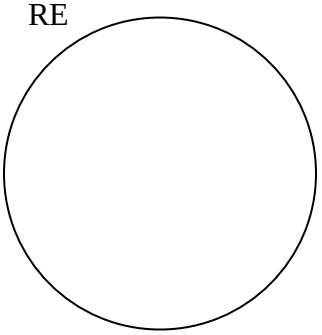
13.Fundus Findings:Kindly mention glow,posterior pole as seen in direct opthalmoscope,I/O whenever possible, Retinal detachment if any.

14.Fundus **Examination under anesthesia**

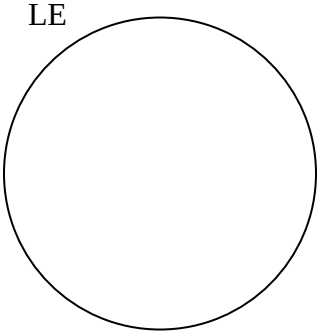
	RE	LE
a.Corneal diameter in mm	----------	----------
b.IOP (by schiotz in mmhg)	----------	----------

13B.FUNDUS PICTURE (examination under anesthesia)

RE

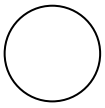


LE



c.Tumour mass	y/n	y/n
b.Number of tumours seen		
.		
c.Type of mass		
1.endophytic	y/n	y/n
2.exophytic	y/n	y/n
d.Tumour overlying optic nerve head	y/n	y/n
e.Mass overlying Macula	y/n	y/n
f.Vitreous seeding	y/n	y/n
g.Vitreous hemorrhage	y/n	y/n
h.Retinal detachment (Mention if significant or not)	y/n	y/n
i.no view	y/n	y/n

14.

Radiological methods	Axia Length Of globe in mm	Type of growth (endo-phytic/ Exo-phytic)	Dia-meters Of mass  In mms	Reflectivity From inside globe indicating	Calcification Yes/no %of tumour occupied	Optic Nerve & Nerve head	VH	RD	VS
1.USG--RE									
2.USG--LE									

VH-Vitreous hemorrhage,VS-Vitreous seeding,RD-Retinal detachment(specify type,extent)

15. CT findings(if done)-axial length of globe,dimensions,calcification,optic nerve involvement, brain mets)

16. MRI findings (if done)

17.Structures/features in CT MRI

1.optic chiasma
2.pituitary fossa
3.pineal gland
4.Brain Parenchyma

18.**Provisional diagnosis** with staging according to "New classification for intraocular Retinoblastoma "

19.Management: **RE** **LE**

1.Enucleation
2.Enucleation status(mention appropriate choices)
a.Primary b.Pre chemotherapy
c.Post chemotherapy d.Pre radiotherapy
ePost radiotherapy
3.Chemotherapy
4.Indication for chemotherapy
a.Vision salvage,b.Globe salvage
c.ONH invasion,choroidal invasion
(life saving-To contain metastasis)
d.Metastatic RB-Palliative)
5.Total no of cycles given
(till end of chemotherapy or last follow up date)
6.Regimen used (triple/Quadrple)
7.Total number of follow up
8.Total number of additional local therapy given
9.Tumour response
A.(regression pattern) –which cycle
B.Degree of regression
10.Adverse effect of chemotherapy
11.Post chemotherapy enucleation or EBRT
12.Local recurrance or distant metastases

20.Histopathology reports in enucleated eye

GROSS:

1.Type of Growth endophytic/exophytic
2.calcification yes/no extent in terms of tumour size ----
3.Necrosis. yes/no

MICROSCOPIC

1.Differentiation Well differentiated/undifferentiated
2.Choroidal invasion(kindly Grade if present) ---yes/no
3.Optic nerve infiltration yes/no

21.B.Details of Chemotherapy:

1.MRD NO:---------- 2.Age in months----- 3.Weight in kg----------

Items	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
1.***Pre chemotherapy investigations*** TC,DC,ESR, Hb,Blood GROUP, USG Abdomen, CSF analysis, SGPT,SGOT,ALP, other +report if any.						
2.Carboplatin						
3.Vincristine						
4.Etoposide						
5.Cyclosprorine A						
6.a.Tumour response b.Additional local treatment given c.follow up adviced d.adverse effects						

Additional Points if Any:

ANTI –CANCER MEDICATIONS

Cyclosporin A

- Cyclic polypeptide that acts as an immunosuppressant drug.It inhibits early cellular response to antigenic and regulatory stimuli (cyclophilins), mainly in helper T – cells
- Onset of action : within 12 hours
- Duration of action : upto 72 hrs

Adverse effects

- Nephrotoxicity, Hypertension, Tremor, Seizures
- Increased incidence of infection, Gingival hyperplasia, Hirsutism
- Flushing, Paraesthesias, Tinnitus, Headache
- Gynaecosmastia, conjunctivitis

Dose:

- 33 mg / kg/ dose intravenous over 3 hours—5-6 mg/kg

Preparations:

- Immusol (Dabur) 50 ml solution – 100 mg/ml Rs 3860
- Sandimmune (Novartis) 1 ml – amp – 250 mg / ml Rs 123

Carboplatin

- A platinum coordination compound, produces predominantly interstrand DNA cross links causing equivalent lesions and biological

effects.inhibits both DNA and RNA synthesis.Binds to proteins an dother compounds containing SH group.Cytotoxicity can occur at any stage of cell cyclebut cell is most vulnerable to action of these drugs in G1 and S phase.

- Duration of action : Terminal half life 5 days

Adverse effects :

- Vomiting, Thrombocytopenia, Raised alkaline phosphatase, Abnormally decreased serum electrolyte, Pain, Asthenia

- Aluminium and mannitol can react with carboplatin. So do not use needs or I.V sets containing aluminium parts that my come in contact with carboplatin

Dose **:** 560 mg / m2/ dose or **18.7 mg / kg/dose intravenous over 1 hour in 100 ml normal saline**

Preparation:

- Neocarb Inj. (biological E) 45 ml vial – 450 mg Rs1800
- Carbotinal inj (Neon) 45 ml vial – 450 mg Rs 2650

Etoposide

- It inhibits DNA synthesis and is most active against cells in the late S and G2 phases of the cell cycle. Binding of drugs to enzyme-DNA

complex results in persistence of transient cleavable form of complex and, thus, renders it susceptible to irreversible double strand breaks.

- Duration of action : 3-19 hours

Dose – 150 mg/m2/dose or 5 mg/kg/dose intravenous over one hour in 100 ml normal saline

Adverse effects

- Nausea,Vomiting,Diarrhoea
- Allergic reactionsFever
- Hypotension
- Bone marrow depression, Peripheral neuropathy
- Jaundice,Bronchospasm,Bleding and myelo suppression.
- Preparations : Etosid (Cipla) 5 ml vial – 100 mg / 5 ml Rs 190
- Fytosid (Dubar) 5 ml vial 100 mg / 5 ml Rs 193

Vincristine

- Avince alkaloid,Cycle specific and phase specific, which blocks mitosis in metaphase.Binds to icrotubular protein,tubulin,GTP dependent.Blocks the ability of tublin to polymerise to form microtubules ,which leads to rapid cytotoxic effects and cell destruction.
- **Onset of action** : 15-30 mins
- **Duration of action** : 19-155 hours

- Special precautions in case of radiation therapy and concurrent vaccination
- Cytocristin (Vincristine sulph – 1 mg, mannitol 100 mg, methylparaben 0-13%
- Prophyparaben 0.0.2% contain mannitol which can interact with cisplatin should be given through separate IV line)

Dose : 1.5 mg/m2 (0.05 mg / kg/ dose – bolus IV for children younger than 36 months and maximum dose 2mg)

Preparations :

- Cytocristin (Cipla) 1 mg inj Rs 45
- Biocristin (Biochem) 1 ml inj. Rs 54

Adverse effects

- Local reaction (extravasation)
- Constipation, Paralytic ileus
- Alopecia
- Jaw pain
- Bone marrow depression, Peripheral neuropathy
- Inappropriate ADH section
- Shortness of breath, Bronchospasm

PROFORMA

Name : _____

MRNo :

Age in months :

Sex : ☐ [1 - Male ; 2 - Female]

Eye Involved : ☐ [1 - RE ; 2 - LE ; 3 - BE]

Staging of eye according to New classification : RE ☐ LE ☐ [A,B,C,D,E,F]

Mode of presentation in patients : ☐ , ☐ , ☐

[1 - Leucokoria ; 2 - Glaucoma ; 3 - Squint ; 4 - Proptosis ;
5 - Vitreous hemorrhage ; 6 - Hyphaema ; 7 - Hypopyon ;
8 - Defective vision ; 9 - No specific complaints]

Tumour features : ☐ , ☐ , ☐

[1 - Single tumour mass; 2 - Multiple tumour mass; 3 - RD;
4 - VH; 5 - VS; 6 – Optic Nerve infiltration;
7 - Orbital metatases ; 8 - Choroidal metatases ;
9 - Calcification; 10 - Retinal seedings]

Treatment administered : ☐ RE ☐ LE

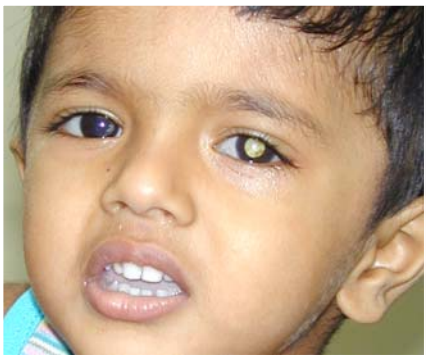
[1 – Enucleation ; 2 – Chemotherapy ; 3 – EBRT
4 – Local therapy; 5 – Excentration]

Chemotherapy status : ☐ [1 – Subjected to chemotherapy ;
2 – Not subjected to chemotherapy]

Follow up : ☐ [1 – Completed Follow up ; 2 – No Follow up]

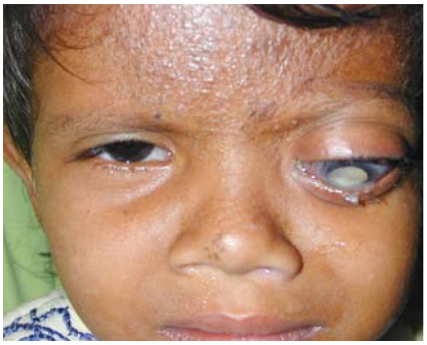
Tumour regression : ☐ [1 – Yes ; 2 No]

MODES OF PRESENTATION



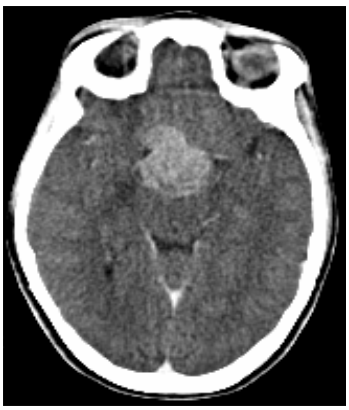
Leukocoria

Orbital Cellulitis



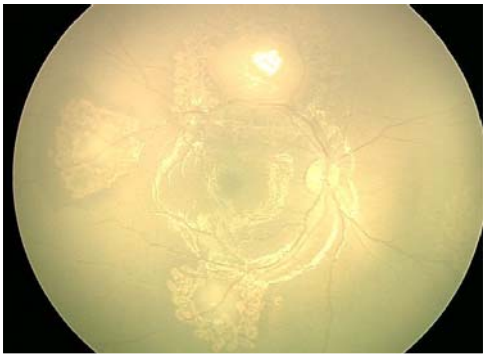
Proptosis

Glaucoma

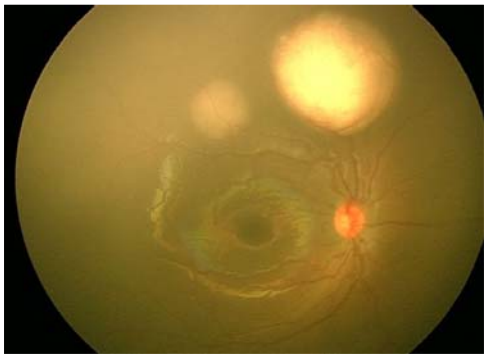


Retinoblastoma with Suprachiasmal Metastes

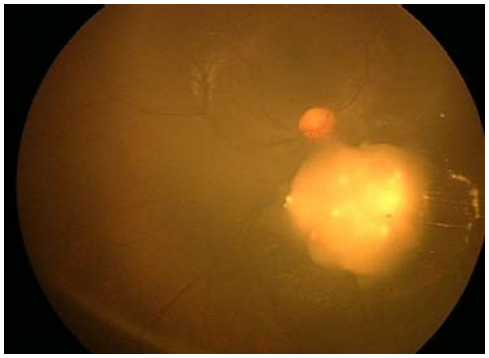
STAGING ACCORDING TO “NEW CLASSIFICATION”



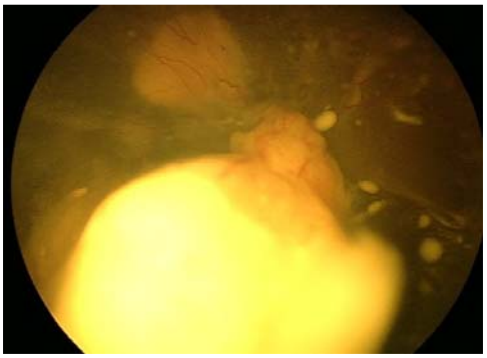
→ **GROUP A**



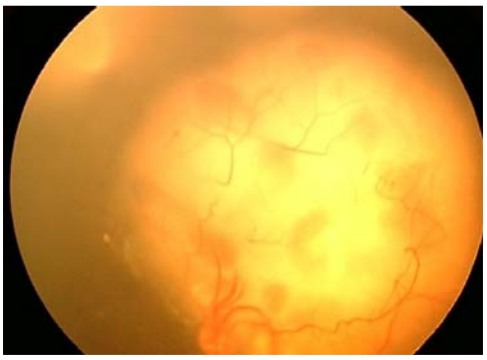
GROUP B ←



→ **GROUP C**

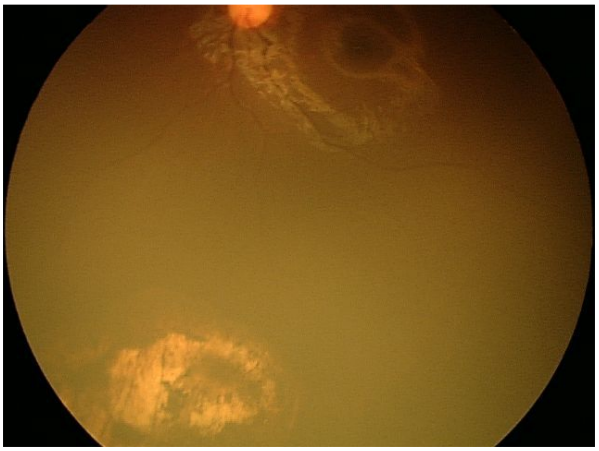


GROUP D ←



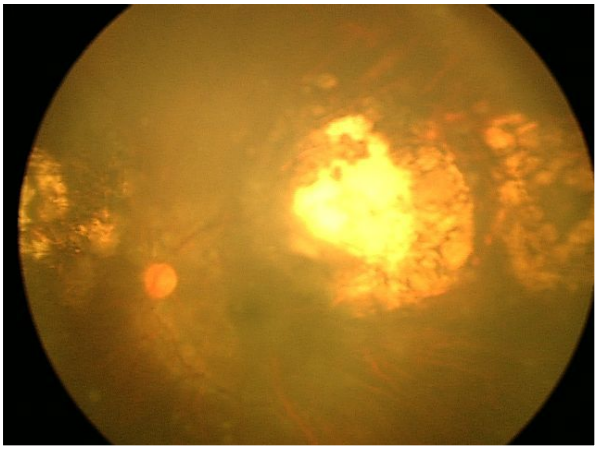
→ **GROUP E**

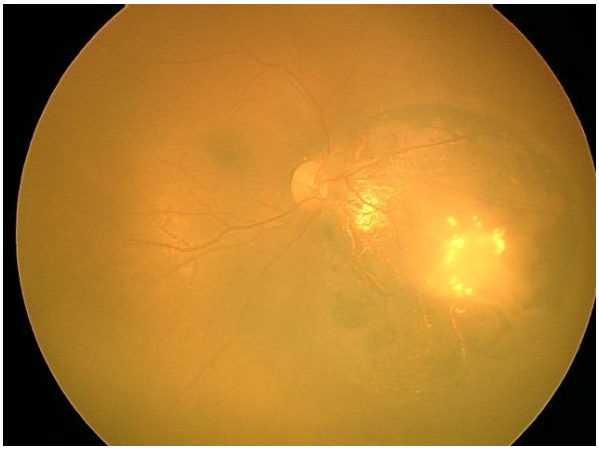
POST TREATMENT FUNDUS PHOTOGRAPH



GROUP A CRYOTHERAPY

GROUP A PHOTOCOAGULATION

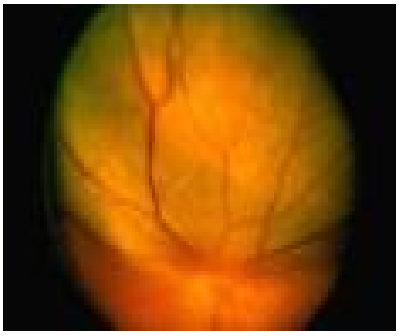




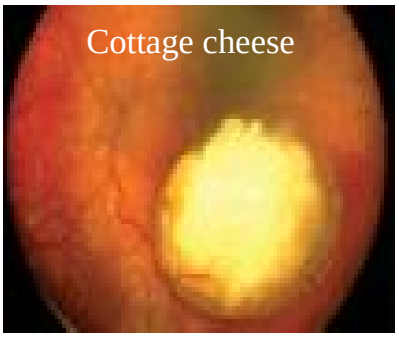
GROUP C CHEMOTHERAPY WITH THERMOTHERAPY

EFFECT OF CHEMOTHERAPY

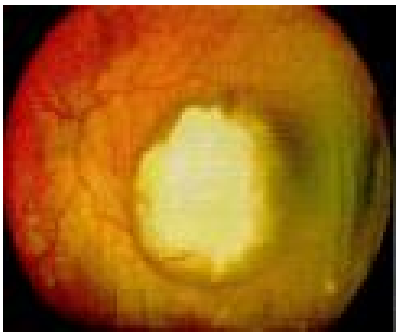
DAY 1



AFTER 3 CYCLES

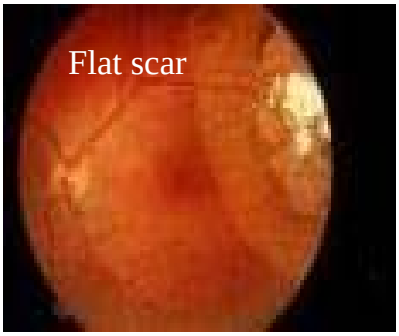


AFTER 4 CYCLES



AFTER 5 CYCLES

AFTER 6 CYCLES



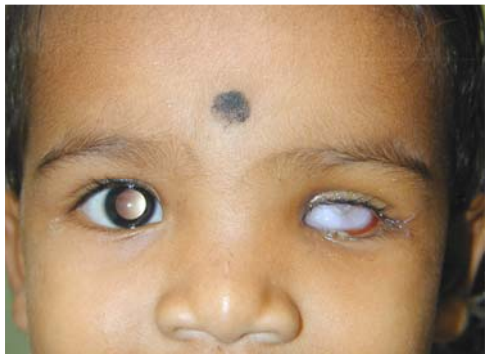
AFTER 8 MONTHS REVIEW

BILATERAL RB

Prior To Treatment

Enucleated Left Eye

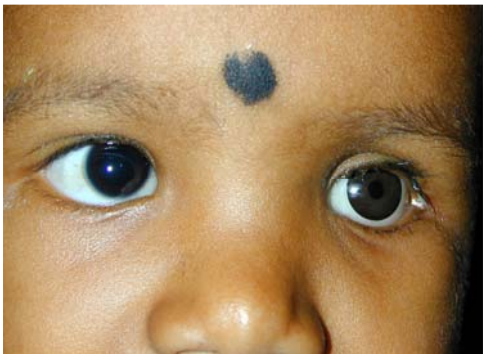
Gross Pathology



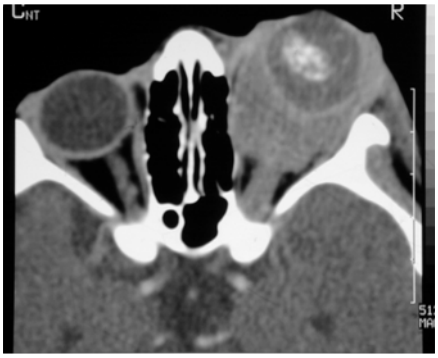
Before Chemotherapy

After Chemotherapy

Left Eye Artificial Eye

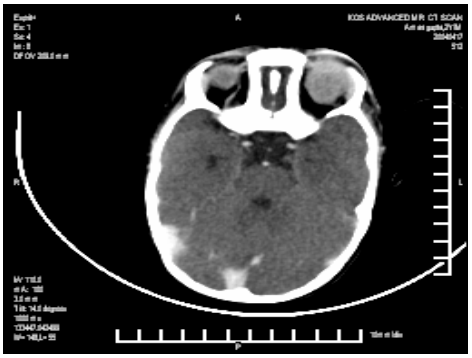


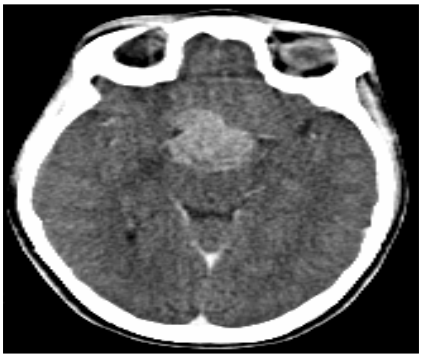
CT Scan Pictures showing Retinoblastoma



RB with
Orbital Involvement

Bilateral RB with
Meningeal Metastasis

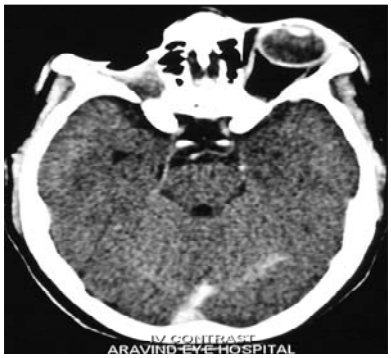




Bilateral RB with
Suprachiasmal Metastasis

Pre Treatment

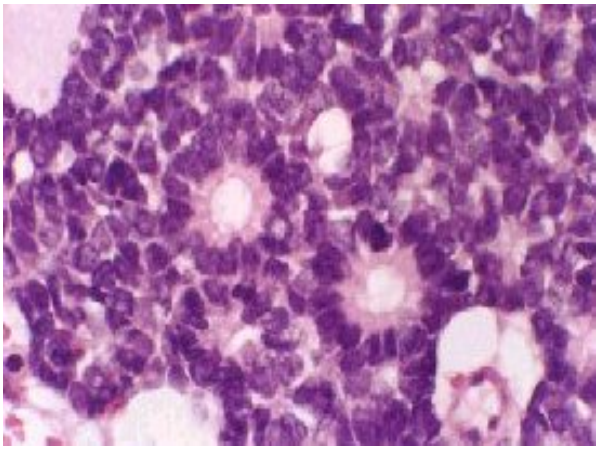
Post Treatment

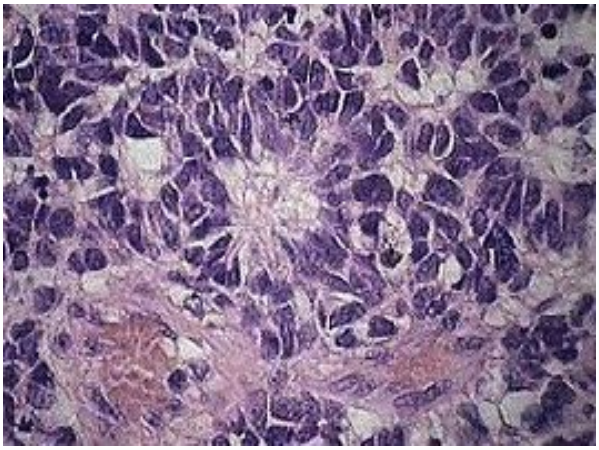


HISTOPATHOLOGY

Gross Specimen

Flexner wintersteiner rosettes





Homer Wright rosettes