HISTOPATHOLOGICAL CORRELATION WITH OUTCOME IN RETINOBLASTOMA

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CERTIFICATE

This is to certify that the dissertation entitled "**HISTOPATHOLOGICAL CORRELATION WITH OUTCOME IN RETINOBLASTOMA**" is a bonafide work done by **Dr**.**MANGALESHWARI.M** under our guidance and supervision in the Orbit, Oculoplasty, Ocular oncology and Ocular prosthetic department of Aravind Eye Hospital and Postgraduate Institute of Ophthalmology, Madurai during the period of his postgraduate training in Ophthalmology for May 2017 – May 2020.

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DECLARATION

I, **Dr.MANGALESHWARI M** hereby declare that this dissertation entitled, **"HISTOPATHOLOGICAL CORRELATION WITH OUTCOME IN RETINOBLASTOMA"** is being submitted in partial fulfillment for the award of **M.S. Ophthalmology (Branch III) degree** by the **The Tamil Nadu Dr M.G.R. Medical University** in the examination to be held in May 2020. I declare that this dissertation is my original work and has not formed the basis for the award any other degree or diploma awarded to me previously

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1.1 INTRODUCTION

Retinoblastoma is an intraocular malignancy of childhood and found to be the most common tumor of this age, and its incidence ranges from 1 in 15,000 to 1 in 18,000 live births(1) .The origin is thought to be either a precursor cone photoreceptor cell or may be a multipotent retinoblast(2)., The first two years of birth is the most common period of presentation of retinoblastoma, but presentation in older age has also been noted. Retinoblastoma has not shown any gender difference, the probability is found to be equal on both sexes. Of the 100 cases 25 to 30 cases are showing bilateral presentation (3). The age of presentation depends on the laterality, bilateral cases presents ealier (around 12 months) , compared to unilateral cases which is usually around 24 months, average age of presentation is about 18 months.

Bilateral cases present at an younger age, while sporadic unilateral disease presents around 30 to 36 months of age .There are an estimated 5000 new cases worldwide annually, with India contributing to 1500–2000 cases.(4)

IMPORTANCE OF HISTOPATHOLOGICAL ANALYSIS

Histopathological analysis and evaluation of the high risk factors helps in effective planning of management and categorize the patient who are expected to have metastasis in future, thereby the chance of early detection and treatment is possible in such cases. Early detection and treatment is very important in decreasing the mortality due to retinoblastoma. Mortality due to ocular retinoblastoma is less , recent advances has dramatically decreased the mortality. But the survivors of retinoblastoma suffer secondary malignancy due to genetic predisposition due to RB1 mutation or due to radiotherapy treatment.

Hereditary variety of retinoblastoma has a tendency of transformation of a intracranial neuroblastic tumor into malignancy, especially in pinealoblastoma (cases of bilateral retinoblastoma with pinealoblastoma is referred to as ‘‘trilateral’’retinoblastoma).(6)

PURPOSE OF STUDY

India is one of the countries to have largest incidence of retinoblastoma, it is estimated over 1500 children are born annually with retinoblastoma. Though such high incidence are prevalent , not many studies are done regarding the histopathological analysis of risk factors.

The important reason could be because of few center having the treatment modality and histopathological analysis setup together.

"Aravind Eye Care" system is one of the few tertiary eye care center in India having all facilities , and I was fortunate enough to be a part of it. In our institution , the treatment was basically targeted to save the life of child first then to salvage the eye and last is to save vision. The recent advances like external beam radiotherapy and chemoreduction has increased the chance of salvaging the eye and decreased the need of enucleation. Focal therapy for small tumors like cryotherapy, photocoagulation and plaque brachytherapy allows targeted treatment of small tumours and salvage of vision. Advances in radiological field like ultrasonography, computed tomography and magnetic resonance imaging has helped in early and accurate non-invasive diagnosis of the tumor.

The newer technologies for the genetic mutation identification has changed the mode of treatment from external beam radiotherapy to chemoreduction, (7,8) as the initial mode of treatment, the chemoreduction usage has improved the regression of the tumor and its scar thus improving the vision, (9-13), after enucleation, the eye should be subjected to high risk factors analysis histopathologically(14), based on the reports adjuvant chemotherapy can be extended to decrease the incidence of metastasis(15), standardized management of retinoblastoma (16-18), and appropriate and

maximum management of orbital retinoblastoma (19,20) using a collective multimodal treatment , has decreased the necessity of enucleation and improved the vision recovery.

1.2 REVIEW OF LITREATURE

Pawius described retinoblastoma as early as in 1597, he described the tumor substance to be " brain tissue mixed with blood, having appearance of crushed stone".

In 1809, Sottish surgeon James Wardrop described this presentation as fungus haenatodes, and advised enucleation as the initial treatment modality. In 1836, Langenbech, Robin and Nystin of Paris stated that the tumor definitely arose from the retina and confirmed it by microscopic evaluation.

The retinoblastoma features was analysed in a descriptive manner after the discovery of ophthalmoloscope in the year 1851. In the beginning it was called as glioma as it was thought to arise from glial cells in retina, by Virchow (1864). As it had rosettes in its histopathological picture ,Flexner(1891) and Wintersteiner (1897) thought it as neuroepithelioma (5), Verhoeff adopted the term retinoblastoma, which was officially agreed by American Ophthalmological society in 1926.

In 1970, Tso and colleagues stated the genetic etiology of cancer,they stated the tumor arises from photoreceptor precursors Retinoblastoma was one of the prototypic models. Till early 1970s this problem was thought as a genetic problem. In early 1970s Knudson explained the famous theory of the “Two Hit” hypothesis in the development of retinoblastoma. After the discovery of RB1 gene, his theory was confimed practically beyond doubt.

Later , in 1980, the gene for development of retinoblastoma was identified by a group in Boston. Still several studies based on the molecular genetics of retinoblastoma is under research. In future the treatment of retinoblastoma may be totally dependent on these basis.

1.3 CLINICAL MANIFESTATION

The most common presenting sign of retinoblastoma is “ Leucoria “, which is a whitish reflex seen through the pupil while torch is shined or during a flash photography. It is accidentally noted in otherwise normal child mostly. This sign is actually a late feature, seen only after tumor has grown in large size, hence vision or eye salvage at this point is not possible.

The most common presentation of retinoblastoma is Leucocoria (white reflex in center of pupil) which is seen about 56% of cases (21), the second most common clinical feature is strabismus (20%), other presenting

features are not uncommon, they are red painful eye (7%), poor vision (5%), rare presenting feature of orbital cellulitis, Unilateral mydriasis 2%,Heterochromia iridis 1%,Hyphema 1%(21).

The presentation time and feature is dependent on the site of tumor in retina. It presents as a white fluffy mass, early tumour can be identified with indirect ophthalmoscopy examination . If tumour involves macula , then it can present as strabismus or decreased visual acuity

Tumour presents in three different patterns(22)

ENDOPHYTIC – The tumor grows into the vitreous cavity, it is seen as yellowish white mass, later vitreous seeds may occur. Retinal vessels is not usually seen upon the tumor.

EXOPHYTIC – In this variety of tumor , it grows blow the retina , in the subretinal space and retinal vessels seen over it, redinal detachment is common.

DIFFUSE INFILTRATIVE- This type of tumor grows diffusely in retina, hence a separate mass is uasully not seen, and it is the most difficult variety to diagnose, hence identified late.

Other signs , such as proptosis, diffuse orbital cellulitis is usually seen in the later or advanced period of tumor, which may be secondary to orbital or optic nerve invasion (22), mainly the breach of lamina cribrosa is considered as a highrisk factor of histopathology for metastasis. Orbital invasion are usually seen through the sclera emissary vein . distant metastasis can occur to brain, skull ,long bones and draining lymphnodes. Rarely unusual presentation such as pseudohypopyon, vitreous hemorrhage, phthisis bulbi, hyphema and preseptal cellulitis may be the presenting clinical feature.

DIAGNOSIS OF RETINOBLASTOMA

A good and complete clinical grading along with careful evaluation of all the details, aided by ultrasonography B-scan can comfirm the diagnose of the retinoblastoma (22). Other radiological investigations such as Computed tomography and magnetic resonance imaging takes an important part in diagnosis of difficult and atypical presentation, and also in situations of extraocular and intracranial spread in suspected (22). A case of retinoblastoma or a suspicion of retinoblastoma in child always warrant the need of extensive ophthalmic evaluation and a thorough dilated fundus examination with 360 degree sclera indendation for peripheral retina under general anaesthesia.(22), the anterior segment evaluation is very important

and evaluation of the intraocular pressure is mandatory, also see for any neovascularization, pseudohypopyon, hyphema, and signs of inflammation(22). Visualization of retinoblastoma in indirect ophthalmoscope is diagnostic in most cases (around 90%). Recent advances such as Retcam (wide angle fundus camera) aids in diagnosis as well as monitoring the therapy of retinoblastoma .

Ultrasonography represents an irregular mass intraocularly with sites of intralesional calcification , which is represented by high internal reflectivity. Computed tomography helps to dectect extraocular extension and early detection of pinealoblastoma in case of trilateral retinoblastoma. Magnetic resonance imaging is highly useful in case of optic nerve invasion and intraocular extension.In smaller retinoblastoma minimally dilated feeder vessel can be seen in fluorescein angiography in arterial phase and hyperflourescence in the veins and late stages of FFA.

CLASSIFICATION OF RETINOBLASTOMA

Classification of retinoblastoma has two components, grouping and staging

GROUPING- done to know wether the organ can be salvaged

STAGING – done to know the survival and prognosis

The ***Reese Ellsworth classification*** mainly tells about the prognosis of patients who are treated with other modes of management excluding enucleation (23), The ***Reese Ellsworth*** classification was mainly pertaining to eyes treated with external beam radiotherapy, this was introduced before wide use of indirect ophthalmoscopy and focal measures for treatment of retinoblastoma.

Essen classification has addressed the problems of Reese ellsworth classification but the problem with this classification is its complexity. All the older classifications are not useful in finding tumors prognosis or response for chemoreduction, which is the most common method of treatment at present.

The new ***International Classification Of Intraocular Retinoblastoma*** is the most used classification as it is easier to correlate with the newer modalities of treatment. There are two parts of this classification .(24,25)

The new ***TNM classification*** by the American Joint Committee on Cancer and the Union Internationale Control Cancer (AJCC/UICC) is comprehensive and includes both clinical and histopathological aspects

Reese Ellsworth Classification has been used widely throughout the world for more than 30 yrs.

Group 1 - very favourable

a) Solitary tumour of size <4DD , at or behind the equator of retina

b) Multiple tumors of size <4DD behind the equator of retina

Group 2 - favourable

a) Solitary tumour of size 4-10DD at or behind the equator of retina

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

Group 3 - doubtful

a) Any tumor lesion of any size anterior to the equator of retina

b) Solitary tumour of size > 10DD , behind the equator of retina

Group 4 - unfavourable

a) Tumors of size larger than 10DD , multiple tumors

b) retinoblastoma extending to the ora serrata.

Group 5 - very unfavourable

a) Multiple tumors involving >1/2 the area of retina

b) Seeding of vitreous

INTERNATIONAL CLASSIFICATION FOR INTRAOCULAR RETINOBLASTOMA:

The treatment modalities that has changed the prognosis and salvage of eye and vision has introduced the newer classification of retinoblastoma into the following groups:

Group A – Very low risk :

1. Any tumor of size 3mm or less in its greatest diameter which is confined to retina.
2. Any tumor which located 3mm from fovea or 1.5 mm from optic disc

Group B – Low risk :

1. Tumors of any size, which is confined to retina or tumors that is not classified in group A.

2. Tumor of any size and location in retina with absence of any seeding in vitreous or sub retinal space.

Group C – Moderate risk : separate tumor with minimal seeding in focal subretinal space or vitreous

1. Tumors should be seperate.

2. Any new or old Subretinal fluid, with no gross seeding, which is involving atleast 1 quadrant of retina.

3. Any new or old local seeding of subretinal space , which is seen <5mm from the tumor.

4. Discrete tumors with focal vitreous tumor.

Group D – High risk : Diffuse retinal disease with a significant tumor seeding in vitreous and/or subretinal space.

1. Massive or diffuse tumors

2. Any new or old Subretinal fluid, with retinal detachment (may be total)

3. Diffuse seeding in subretinal space, such as tumour nodules or subretinal plaques .

4. Massive or diffuse seeding of vitreous , which may include “greasy” seeds or avascular masses or tumor

Group E – Very high risk : A very high risk and poor prognosis is anticipated if one or more of these features are present.

1. Any lens touching tumors

2. Diffuse infiltrating retinoblastoma

3. Any tumour which is anterior to anterior vitreous face, that shows involvement of ciliary body or anterior segment

4. Neovascular glaucoma

5. Phthisis bulbi

6. Aseptic orbital cellulitis

7. Opaque media due to haemorrhage

International Staging System for Retinoblastoma

Stage 0 No enucleation (unilateral or bilaterally may have intraocular disease)

Stage I Enucleation, resection of whole tumor

Stage II Enucleation, residual tumor, that is evident microscopically

Stage III Regional extension

A. Orbital disease

B.Extension to Preauricular and /or cervical lymph node

Stage IV Metastatic disease

A. Hematogenous spread

1. Single or focal lesion

2. Multiple or diffuse lesions

B. CNS metastasis

1. Prechiasmatic spread

2. CNS tumor

3. Leptomeningeal spread

1.4 MANAGEMENT OF RETINOBLASTOMA

The goal of treatment is to save the life of patient, which is primary and salvage of vision and eye are the secondary and tertiary goals in management of retinoblastoma.

The treatment of retinoblastoma has changed a lot today, it is not just ophthalmologist treating the patient, it needs multidisciplinary approach, where a team of doctors including, pediatric oncologist, ocular oncologist, radiational oncologist, ophthalmic oncopathologis play an important role. Treatment depends on the stage of tumor and associated high risk factors.

Therefore treatment of retinoblastoma is highly individualized depending on the stage of tumor, high risk characteristic, presenting age, one or both eye invovement, recovery of vision, other systemic disease, family and societal awareness, economic condition, follow –up and its overall prognosis.

Current Suggested Protocol

A. Any Intraocular tumor, Classified under Group A to C in international classification, Unilateral or Bilateral

1.Any tumor of size less than 3mm in greatest diameter and height which is located in non vision threatening area is treated with focal therapy (cryotherapy or transpupillary thermotherapy) alone.

2. Standard 6 cycles of chemoreduction and later by aggressive focal therapy for tumors of larger size and tumors that are visually significant.

3. Tumors of macular and juxtapapillary areas or the visual potential area, 6 cycle of chemotherapy is given, Focal therapy such as transpupillary thermotherapy or plaque brachytherapy for the residual tumor after 6 cycles.

4. For small residual tumor focal therapy is given , and for large residual tumor plaque brachytherapy/ external beam radiotherapy (>12 months age)

If the tumor is bilateral, and for unilateral enucleation is done .

B.International Classification of retinoblastoma Group D, Unilateral or Bilateral

1. Increased dose of chemotherapy with adjuvant aggressive focal therapy.

2. Periocular carboplatin for tumors with seeding of vitreous (20).

3.Primary enucleation in unilateral retinoblastoma , in eyes with nil or very guarded visual prognosis.

C. International Classification of retinoblastoma Group E, Unilateral or Bilateral

1. Enucleation done as initial management.

2. Histopathological for high risk factors evaluation.

D. Histopathological high risk factors, International Staging (Stage 2)

1.Primary systemic evaluation for spread of tumor

2 Adjuvant chemotherapy of standard 6 cycle

3.Adjuvant chemotherapy with high dose chemo and in sclera infiltration orbital external beam radiotherapy , extraocular extension, and optic nerve extension is present at the nerve transection.

E. Extraocular tumor, International Staging, Stage 3A

1.Systemic evaluation for spread (baseline investigation)

2. 3-6 cycles of high dose chemotherapy , which is followed by enucleation or extended enucleation,or focal therapy (external beam radiotherapy), and continued

12 cyclesof high dose chemotherapy .

F. Regional Lymph Node Metastasis, International Staging, Stage 3B

1. Systemic evaluation for metastasis (baseline evaluation)

2. High dose chemotherapy for 6 cycles with neck dissection, followed by the focal therapy (external beam radiotherapy), another12 cycles of high dose chemotherapy is continued.

G. Hematogenous or Central Nervous System spread, International Staging, (Stage 4)

1.After discussion with the family Palliative therapy can be advised

2. For hematogenous metastasis high dose chemotherapy with bone marrow rescue

3. For central nervous system metastasis ,high dose chemotherapy with intrathecal chemotherapy may be given.

1.5 GENETICS

In the new cases of retinoblastoma, 94% are of sporadic origin and only 6% are familial. Germline mutations is seen in maximum patients of bilateral retinoblastoma. 15% of unilateral sporadic cases are also said to have germline mutations in retinoblastoma and sporadic mutations in rest 85% of cases.

The two hit hypothesis proposed by knudson , in 1971 has brought an enlightment in the knowledge of retinoblastoma evaluation . He stated that, there must be two chromosomal mutations for a retinoblastoma to develop. The first hit in germinal mutation is seen in hereditary retinoblastoma , it is seen in all cells of the body, the second hit in the somatic cells of retina leading to retinoblastoma development. Since the mutation is present in all cells of body the hereditary mutations has tendency to develop non ocular tumors such as osteosarcoma., In unilateral cases of somatic mutations both the hit occur in the retina during the development of retina, hence the risk of developing second non ocular tumors is nil.

RB1 has 928 amino acids, which is of 110 kd nuclear protein, and it spans 180 kb and has 27 exons. This is a tumor suppressor gene which acts by regulating the cell cycle , by checking between the G1 phase and S phase entry. As already described in hereditary cases of retinoblastoma (40% of cases), one chromosome is already mutated in its germline , which is usually acquired from the parent, and every cell of the body has the same mutation and has the potential of developing tumor in any part . So if the hit occurs in eye it leads to retinoblastoma, in these patients non ocular malignancies can also develop in the absence of RB 1 function, for ex:

osteosarcoma, and these patients are highly susceptible for bilateral retinoblastoma.

Most RB1 germline mutations develop atleast 1 retinoblastoma (90%), and many develop 3 to 4 tumors. Long time survivors shows development of secondary non ocular tumors at a rate of 1% every year , such as osteosarcoma of the skull and long bones, soft tissue sarcomas, pinealoblastomas, cutaneous melanomas, brain tumors, Hodgkin disease, lung cancer, and breast cancer by gerline mutations,. In these patients , radiation exposure may cause secondary tumors in the exposed areas, hence external-beam radiation therapy is avoided in these patients, gives rise to the increased incidence of secondary malignancies in the irradiated area , hence this is drawback of such treatment . For those patients with germline RB1 mutations, carcinogenesis rate is high on exposure to any agent , or sunlight.

Famliy should be counseled if germline mutation is present, which is one of the the multidisciplinary management in retinoblastoma. It is found that there is a risk of 40% of the siblings to develop retinoblastoma and 40% of the children of the affected patient may develop retinoblastoma.

Patients with a negative family history usually presents with a unilateral retinoblastoma, in this type of sporadic mutations it is found that

1 % of siblings and 8 % of offspring may develop retinoblastoma. In cases of bilateral tumors with no fanily history there is a 6% risk in siblings and 40 % risk in offspring for developing retinoblastoma.

Other Genetic Events in Retinoblastoma

Retinomas or retinocytoma are milder forms of tumors found in RB1 mutations of germline in few patients. It is estimated about 1 % of incidence in retinoblastoma. These tumors are thought to be the representation of the benign variety of retinobastoma , but it is not yet fully understood wether it is truly benign or a regressed form of retinoblastoma. Though these tumors also has lost both the RB1 alleles , it requires further sequential events to get fully transformed to a malignant variety. These retinomas can also potentially transform to retinoblastoma in future in few patients hence it is important to consider significant to counsel the family and investigate them with the same clinical investigations and follow-up as for retinoblastoma. These retinomas also have both RB1 gene mutations , but they don't show any proliferation, aneuploidy or gene expression. This is the reason for it to be a benign variety , it requires further genetic events to convert a RB1– / – cell to a retinoblastoma cell. p16, an the pRb family member, p130, are senescence markers which are seen in retinoma and not in retinoblastoma.

1.6 HISTOPATHOLOGY OF RETINOBLASTOMA

Basophillic areas of tumour and calicification and eosinophillic areas of necrosis can be seen in low magnification.In differentiated tumors small round cells are seen poorly. These cells has large hyperchromatic nuclei with scanty cytoplasm. In tumors with well differentiation rosettes and flurettes are seen.Histopathologically there are 2 different types of rosettes which is characteristic of retinoblastoma, the Flexner-Wintersteiner rosettes, these have a central lumen with surrounding columnar cells, these are also seen in medulloepithelioma. Homer Wright rosettes is the other type which is made of a central neuromuscular tangle which is surrounded by columnar cells, these are also found in neuroblastomas, medulloepitheliomas and medulloblastomas. The pseudorosettes are tumor cells around the blood vessels , these are signs of bad or poor differemtiation. Flurettes are pear shaped tumor cells which has a memberane which is fenestrated by the eosinophilic processes. These Rosettes and fleurettes depicts that these tumor cells shows photoreceptor differentiation. The basophilic deposits, are formed by the tumor necrosis of DNA material ,can be seen along the walls of the lumen of the blood vessels.

1.7 TREATMENT MODALITIES IN RETINOBLASTOMA

The presentation of these tumors are usually at intraocular stage. Fast diagnosis and treatment of tumor is essential for salvage of life, if possible the vision. There are various modalities in treatment in retinoblastoma , focal therapy (like laser photocoagulation, trans scleral thermotherapy, plaque brachytherapy, cryotherapy ,transpupillary thermotherapy), systemic (chemotherapy) and local (external beam radiotherapy, enucleation). The focal measures are the treatment of choice for small tumors , local and systemic therapy are mostly used for advanced or large tumors.

Cryotherapy

This is focal treatment which is preferred for tumors of small size that arte located in peripheral or equator, size is usually 4mm of greatest diameter and 2 mm of thickness (2,11). The Triple freeze cryotherapy is done in interval of 4-6 weeks once, till the tumor regress . cryotherapy produces scar of retina which is usually larger than the tumor itself. May result in complication such as transient serous retinal detachment , small or large rhegmatous retinal detachment or only retinal tear. This procedure is found to be synergistic with chemotherapy when applied 2-3 hrs prior, as it increases the drug transport across blood retinal barrier. (13)

Laser photocoagulation

Laser photocoagulation is a type of focal therapy for tumors of size 4mm in diameter thickness of 2 mm (2,13), which is situated in periphery. It causes a decrease in blood supply by applying a 2 layered overlapping burns on tumor.

Transient serous retinal detachment, retinal vascular occlusion, retinal hole, retinal traction, and preretinal fibrosis may occur. when laser photocoagulation of tumor in the juxtapapillary area is done a large visual field defect may occur. It is less often used now-a-days , as it restricts blood flow to tumor, it reduces the chemo concentration in tumor.

Thermotherapy

In thermotherapy infrared radiation heat is applied on tumor at subphotocoagulation level to produce cell appoptosis ,(29).A slow and sustained temperature of 40-60 degree is attained , thus preventing the retinal vessel damage.

In the transpupillary thermotherapy procedure, infrared radiation comes from a semiconductor diode laser with a1300-micron spot size, by indirect ophthalmoscope system has been used. It may also be given transpupillary by an operating microscope or by a diopexy probe in transscleral route . The tumor is heated till it becomes subtle gray.This

procedure is good for small focal tumors of size 4mm in diameter and 2mm thick. In 85% of tumors a complete regression is expected in about 3-4 sessions (29). Complications of iris atrophy and paraxial lenticular opacity can be minimized by utilization of 1300-micron up to 5 minutes in one sitting done under indirect ophthalmoscope delivery system , some times retinal traction and serous retinal detachment may be seen on heavy thermotherapy, used as adjunct to chemotherapy. Cytotoxic effect of platinum analog occurs on heating in thermotherapy.

Plaque Brachytherapy

This is focal treatment modality , where we implant a radioactive material at the base of tumor, over the sclera and transsclerally irradiate(29). Iodine 125 and Ruthenium 106 are the most common radioactive materials used. This focal delivery of radition minimize the periorbital tissue damage and cosmetically better, as the retarded orbital bone growth in the area of irradiation which occurs with the external beam radiation ,are Its advantages. It has reduced risk of secondary malignant neoplasm due to shorter duration of treatment. Plaque brachytherapy is indicated in tumors < 8 mm thickness and < 16 mm in basal diameter . Primary or secondary usage of this therapy is warranted depending on the chemoresistance or acceptance. Mostly used as the secondary mode of

treatment in cases of tumor recurrence after chemotherapy or those which does not respond to external beam chemotherapy. Ultrasonography is used to measure the tumor size and place, as this procedure is most dependent on its size and plaque placement. The design of plaque is based on the measurements of the basal diameter, in tumors which are near to optic nerve, notched plaques are used to protect the optic nerve from damage. About 4000-5000 cGy of dose is given at the apex of retinoblastoma. The plaque is stitched to the sclera and left in same site for about 36-72 hrs depending on requirement. 90% of tumors regress in size and activity , gives good result. The common complications seen are radiation retinopathy or radiation papillopathy of the eye.

External Beam Radiotherapy

The external beam radiotherapy was the favourite modality of focal therapy in late 1900s for the management of moderately advanced retinoblastoma (.28,29). After the era of chemotherapy the usage of External beam radiotherapy has decreased tremendously. Now it is used only in eyes where other modalities of focal therapy has failed , or when chemotherapy is contraindicated(11). The beam of radiotherapy is delivered using linear accelerator (X-rays) or Cobalt 60 (gamma rays) from external. In this modality , the Linear accelerator with multibeam technique

(intensity-modulated radiotherapy), the image guided and stereotactic radiotherapy has a better and accurate mode of transmission of rays to the tumor and a better treatment outcome, with minimal damage to the normal ocular structures and less complication. The major and devastating complication of this modality is the bone stunting of orbit which is cosmetically unacceptable, radiation retinopathy ,dry eye, cataract and optic neuropathy. In hereditary variety of retinoblastoma these radiation can cause secondary malignancy. There is 30% risk of secondary malignancy in exposed patients against the 6% non-exposed group. The risk is found to be increased in children of less than 13 months age who undergo this treatment.

Enucleation

Enucleation is the final procedure or management for the advanced retinoblastoma which has a high tendency to spread. Until a few decades ago enucleation was considered as the only primary procedure for unilateral and worse eye bilateral retinoblastoma. But the idea has changed drastically after the chemotherapy , and other recent advances were vision saving and eye salvaging has come to play , thus by reducing the number of enucleation. But Enucleation still remains as the primary treatment in cases of advanced intraocular retinoblastoma with high risk feautures such

as new vessels of iris, neovascular glaucoma , tumor invasion of anterior chamber , secondary orbital inflammation with the necrotic tumor, tumor occupying more than 75% of vitreous volume and in tumors with vitreous haemorrhage or hyphema where the tumor features cannot be assessed .

Surgical technique

Enucleation is done under general anesthesia. To aid hemostasis and postoperative pain , a retrobulbar block of local anesthetic with epinephrine can be given .After proper verification of patient details, correct eye and procedure the surgery is done. A 360 degree limbal conjunctival peritomy is performed with Wescott scissors . Blunt dissection in the sub-Tenon's plane is done in each of the oblique quadrants. Each rectus muscle is isolated with a muscle hook, secured with suture, and cut at the level of insertion to the globe. Then oblique muscles are hooked and cut . Confirm the globe rotates freely, then the optic nerve is identified, and transected with enucleation scissors or snare wire. Clamp the optic nerve with a curved hemostat prior to transection for hemostasis. A long segment of the optic nerve is cut, particularly in case of intraocular malignancy where histologic examination of the optic nerve is essential. Further hemostasis is then achieved with pressure in the intraconal space or cautery of the optic nerve if required. An implant is then placed in the socket to replace

volume lost by the enucleated globe, and for cosmetic symmetry with the fellow socket. The formula axial length-2 mm is been used to provide for adequate replacement of implant for socket and decrease superior sulcus deformity and enophthalmos. In severe infection, we may not to place an implant at the time of enucleation and opt to place an implant in a second surgery. A two-layered closure of tenon and conjunctiva is carried out with absorbable sutures. Antibiotic ointment is applied,followed by a clear plastic conformer is placed over the closed conjunctiva, and finally a pressure patch is placed on the socket.

Implants

There are different types of implants that are utilized in an enucleation. Implants of appropriate size is determined intraoperatively ,by the size of the patient's orbit and based on the size of the implant necessary to achieve symmetry with the fellow eye. Implants are of 2 types porous or nonporous. Porous implants are those that allow for anchoring of the extraocular muscles with proliferation of fibrovascular tissues into implant . These include hydroxyapatite, proplast and porous polyethylene . Hydroxyapatite implants was introduced in 1989(31), as they have a rough surface, they are wrapped with material such as donor sclera, pericardium acellular dermis, or synthetic meshes . The extraocular

muscles is sutured to the wrapping material to enhance motility of implant. Porous polyethylene implants later came as alternative, as they have a smoother surface they do not require wrapping. As they have a smoother surface the extraocular muscle can be directly sutured to implant.(30)

Implants in which a hole is drilled into the implant is called pegged implant, where a peg can be placed that attaches to the prosthesis. Pegging is done six to twelve months postoperatively and allows for free motility of the prosthesis(30) . A study showed a comparitve analysis of pegged and non-pegged implants, in which pegged implants produce a statistically significant improvement in horizontal but not vertical motility.(32).

Special precautions for enucleation in a case of retinoblastoma

a. Manipulation of tissue should be minimal

b. Eye should not be perforated

c. Optic nerve stump should be long (atleast 15 cm)

d. The eye after enucleation should be evaluated for any visible extra ocular spread or optic nerve involvement

e. For genetic studies, fresh tissue to be harvested

f. Implant should be placed

g. if post operative radiation is planned, then avoid biointegrated implant.

Systemic Chemotherapy

The current management of tumor size reduction is by chemotherapy (33) Chemoreduction dose not cure the tumor but when added with other focal therapy it helps in faster reduction of tumor.The combined procedure has decreased the need for enucleation or external beam radiotherapy with minimal systemic toxicity. Chemoreduction and focal therapy combination is the common primary management of retinoblastoma as it has reduced the need of enucleation (34-37) . The most commonly used protocols are vincristine, etoposide and carboplatin in combination, for 6 cycles (8-11). Reese Ellsworth groups I-IV (or international classification Group C) provides Standard dose chemoreduction (11). In high dose chemoreduction, etoposide and carboplatin dose is increased, which is used in Reese Ellsworth group V (or international classification Group D or higher) tumors(11).

Chemotherapy regimen and standard doses for intraocular retinoblastoma

Day 1: combination chemotherapy of VEC regime (Vincristine , Etoposide and Carboplatin)

Day 2: Etoposide

Normal dose:

Duration and cycle - *(3 weekly and 6 cycles*)

Vincristine - 1.5 mg/m2 (0.05 mg/kg for

children less than 36 months of age , maximum dose upto 2mg)

Etoposide - 150 mg/m2 (5 mg/kg for children less than 36 months of age),

Carboplatin - 560 mg/m2 (18.6 mg/kg for children less than 36 months of age).

High-dose

Duration and cycle - 3 weekly, 6-12 cycles

Vincristine - 0.025 mg/Kg,

Etoposide - 12 mg/Kg,

Carboplatin - 28 mg/Kg.

Chemoreduction combined with local therapy, it is now possible to decreased the number of enucleation and salvage an eye and maximize residual vision . Chemoreduction in tumors without high risk factors like subretinal fluid or vitreous seeding has high success rates (7,8). Chemoreduction provides a good control of tumors in group I-IV eyes of Reese Ellsworth classification, a 10% patients may need external beam radiotherapy and 15% of patients may need enucleation at the end of 5 year follow up , due to treatment failure in chemotherapy. In group V eyes of

Reese Ellsworth classification 47% require external beam radiotherapy and enucleation in 46% at the end of 5 year (7,8).

Chemotherapy for selected eyes with unilateral retinoblastoma, With modified protocol that is used specifically for advanced retinoblastoma ,In Reese Ellsworth group I-III the eye preserving rates are 100% .90% and 75% in Reese Ellsworth group D and group E respectively. The common adverse effects and interactions of chemotherapeutic agents, which are myelosuppression, febrile episodes , non-specific gastrointestinal toxicity and neurotoxicity .

Periocular chemotherapy

Deep posterior sutenon injection of carboplatin can pass through the sclera and achieve therapeutic concentrations inside vitreous cavity of the affected eye , hence used in the management of retinoblastoma with vitreous seeds. But this modality is currently under trial. The treatment results have shown that periocular chemotherapy achieves about 70% eye preservation in cases with Reese Ellsworth group VB retinoblastoma (37).

Intraarterial chemotherapy

Although retinoblastoma chemotherapy protocols are considered safe, there is increased risk of secondary acute myelogenous leukemia. Intravitreal concentrated delivery of chemotherapy to the eye, and avoiding

high systemic concentrations seems ideal. But this local approach has not gained much importance because of fear of extraocular dissemination of retinoblastoma. The first attempt of Injecting a chemotherapeutic agent into the carotid artery was by Reese in 1957.

Recently the interventional radiologist catheterise the carotid artery, and inject melphalan. A balloon catheter was passed and inflated into the internal carotid artery occlude the artery thus allowing the medication to perfuse the eye bypassing the brain.

Follow-up Schedule

After the initial course of treatment the patient is advised to review after 3-6 weeks. In patients where additional chemotherapy is given , review is advised for once in 3 weeks during each course of chemoredyction. Those patients who are treated with focal therapy are advised to come after 4-8 weeks of treatment or until the tumor regresses completely.After the complete regression of the tumor , further review should be planned once in every 3 months for first year and once in 6 months for the next 3 years or until the child turns 6 years and every year from then onwards. This is the usual follow up schedule, this may be changed according to the systemic condition of the patient as well as the family co-operation for further visits.

Management of High Risk Retinoblastoma

In retinoblastoma , most deaths are due to systemic secondary metastasis which may have occurred even before the initial presentation. With the newer modalities and the multidisciplinary approach of retinoblastoma the life expectancy has drastically improved in the last 3 decades, studies says that above 90% survival rate in developed countries (38) has been noted, but death in developing countries is still high (about 50%) (39,40). The mortality can be decreased by earlier identification of high risk factors and adjuvant treatment for retinoblastoma.

1.8 High–Risk Factors

High risk factors that are clinically significant doesnot seems to strongly correlate with the mortality of patient. Several studies done recently has shown the importance of histopathological evaluation of the enucleated eye for risk of metastasis. This is a reliable source to predict and treat the patient earlier to prevent further spread which is very vital for the patient and adding of chemoreduction. Lot of studies have been done on this issue (39,41-49) .It is now generally agreed that massive choroidal infiltration (>3mm), optic nerve invasion especially retrolaminar , extrascleral spread and invasion of the tumor optic nerve resection margin

,any scleral infiltration, are the high risk factors that points out to increased risk of metastasis.

Histopathologically high-risk factors predictive of metastasis

• Tumor seeding in anterior chamber

• Iris infiltration of tumor cells

• Ciliary body infiltration of tumor cells

• Massive choroidal infiltration of tumor cells

• Invasion of tumor cells in the optic nerve lamina cribrosa

• Retrolaminar optic nerve invasion of tumor cells

• Invasion of optic nerve resection margin

• Infiltration of sclera

• Extension beyond sclera

Adjuvant Therapy

In 1970, research on the efficacy of chemoreduction to decrease the risk of Extraocular spread was done and revealed variable results and did not provided any firm recommendation(18). A recent study , with patients who had primary enucleation as the initial modality of treatment , used specific indicators of high risk histopathologic features for patient selection for treatment with a follow-up of atleast once in a year was

advised for the early diagnose of any metastatic spread (mean age of 9 months) (13,50). The incidence of metastasis was about 4% in patients who were treated with adjuvant therapy and 24% in those who did not. The study showed significant reduction in the chance of metastatic spraed in cases with any high-risk histopathologic features. In our hospital we usually give 6 cycles of a combination chemotherapy of carboplatin, etoposide and vincristine in recommended doses (similar to the standard dose used for chemoreduction of the intraocular retinoblastoma) in patients with histopathological high-risk characteristics. All patients with suspected high risk factors should receive additional chemotherapy for 12 weeks and if required an adjuvant therapy together.

Orbital Retinoblastoma

Orbital retinoblastoma is rare well developed nations and but it is not that uncommon in developing nations. A recent multi –center study done in a large scale at Mexico, about 18% had orbital retinoblastoma in the total 500 cases(52). A 36% of orbital retinoblastoma was seen in a study conducted at Taiwan, this study was done in 116 cases of retinoblastoma (53). The occurrence seems to be higher in Nepal (40%, 19 of 43), proptosis is seen as the most common presenting clinical feature in cases of orbital retinoblastoma (54).

Metastatic Retinoblastoma

Usually metastasis is not seen at the time of presentation, such scenario is very rare, hence it is not mandatory to perform staging investigations such as bone scans, bone marrow aspiration and lumbar puncture, to asses metastasis at the time of presentation. Metastasis is commonly seen in orbit as it is in close proximity, and the reginal lymphnodes draining it, distant spread is seen in central nervous system and also to bone and bone marrow. The usual time of occurrence is about an year after the diagnosis of retinoblastoma. The child is followed upto 5 years after the treatment and if no metastasis is seen till then, the patient is considered cured. The metastatic retinoblastoma is estimated to be lesser than 5 %, but it is the major etiology for the mortality in our country hence it is important to evaluate. The prognosis with the metastatic retinoblastoma is very poor, and extensive studies have supported the same. Our regular protocol of chemothereduction using vincristine, etoposide, doxorubicin, cyclophosphamide, and cisplatin along with radiation has got only minimal results . This has made the practioners to increase the regular dose of chemotherapy to a higher dose, since the benefit over weigh the demerits we consider it as initial management in these high risk cases.

CONCLUSION

There has been a vast and dramatic change in the management of retinoblastoma in the last few decades. The newer Specific genetic study have been able to make a good prenatal diagnosis of retinoblastoma which is better for the parents to decide and mentally be prepared for the outcome. The vision and eye salvage has increased in recent years by the earlier diagnosis of retinoblastoma and appropriate focal therapy. In cases with moderately advanced retinoblastoma ,chemotherapy is the first and the best line of management.

Intraocular retinoblastoma in which enucleation was the treatment a few decades ago. Periocular chemotherapy is newer additional useful technique in salvaging eyes with vitreous seeds. Efficacy, complications and safety of intraarterial and intravitreal chemotherapy and are being explored. Though , so many newer modalities has been described , enucleation still continues to be the initial management of treatment in unilateral advanced retinoblastoma. The histopathological evaluation of the enucleated eye for the high risk factors, and adjuvant therapy for those patients has brought down the incidence of metastasis.

The orbital retinoblastoma can have a good clearance with aggressive and appropriate multidisciplinary treatment. Future with

multimodal approach , genetic studies and targeted tissue drug delivery system can improve the eye and vision salvage.

PART TWO

2.1 AIM AND OBJECTIVES

AIM

To study the Histopathological correlation with outcomes in patients with retinoblastoma in a tertiary care centre.

OBJECTIVES

- To study the demographic features of patients with retinoblastoma.
- To analyse the presence of highrisk histological features.
  - Choroidal invasion
  - Optic nerve invasion
  - Anterior chamber, iris & ciliarybody invasion
  - Scleral invasion
  - Vitreous seeding
- To analyse risk of metastasis and morbidity in correlation with the histopathological classification.
- To find the correlation between clinical and histopathological highrisk factors

 To study the various modes of presentation of patients with retinoblastoma.

 To study the tumour characters in eyes with retinoblastoma.

 To study the different treatment modalities for retinoblastoma (including local ophthalmic therapy, chemotherapy, surgery) and outcomes of eyes with retinoblastoma following treatment.

2.2 MATERIALS AND METHODS

A prospective, observational study was carried out in patients with intraocular retinoblastoma who were identified at Aravind Eye Hospital, Madurai. India.

Patients eligible for consideration were all cases of retinoblastoma who underwent primary or secondary enucleation between January 2018 and June 2019. All other cases who underwent enucleation elsewhere and on followup treatment at Aravind Eye Hospital,Madurai were excluded.

The patients with clinical features of retinoblastoma ,were subjected to detailed medical and ophthalmologic history taking and examinations .A detailed examination by diffuse torch light and slit lamp examination was done to look for hyphaema, hypopyon, papillary reaction, secondary glaucoma and other signs of anterior segment involvement.

Indirect ophthalmoscopy using a 20 D lens for detailed dilated fundus was done to evaluate tumour mass, if any associated retinal detachment, vitreous seeding, vitreous haemorrhage, optic nerve head involvement are present. Ultrasound B-scan is used to confirm the diagnosis. In patients when the diagnosis is doubtful or to look for any optic nerve infiltration & intracranial extention , a MRI brain and orbit (T1 and T 2 weighted images) were done. Since most of the patients were children and could not cooperate for detailed examination of anterior and posterior segment, they were examined under general anesthesia after pediatric opinion. These patients eyes were staged according to the "Newly proposed classification for Intraocular Retinoblastoma.

A complete and detailed physical examination was done in all patients to assess for any metastasis, and general health . A detailed genetic counselling was given for the family regarding the nature and the stage of disease in their child, need for immediate treatment and regular follow up. The interventional procedure was performed only after obtaining 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. In this study we are considering group D and E eyes were enucleation is the prime mode of treatment with or without adjuvant chemotherapy .

The chemotherapy to individual cases was provided in accordance to their stage of the retinoblastoma, after staging by New Classification of Retinoblastoma. Before starting chemotherapy, a complete haematological, peripheral smear, bone marrow examination, CSF analysis, Liver function tests (LFT), USG abdomen and chest X-ray was done to evaluate the general condition of the patient, and ability to withstand chemotherapeutic effects and detect distant metastases.

The LFT and baseline investigation , pediatric review were done on regular basis for chemotherapy . Most cases received 6 cycles of chemotherapy of triple drug regimen (Vincristine 0.05 mg/Kg body weight as intravenous (IV) in 100ml Normal Saline (NS) on the first day, Etoposide 5mg/Kg body weight in 100ml NS as IV infusion over 2 hours on first day and same dose on 500 ml RL on 2nd day, Carboplatin 16.7 mg/Kg body weight in 500ml RL as IV infusion over 2 hours on day 1 and day 5). Six such cycles were given in 1 month interval each. On each cycle premeditation with BD dose of Inj.Emeset, Inj.Ranitidine along with Inj.Decadran 8mg was given. A quadruple regimen including administration of cyclosporine A was tried in resistant cases.

All cases EUA was performed during the course of chemotherapy cycles and assess the progression of tumour. Enucleation was planned as

primary treatment in accordance with the staging on presentation or secondary in response to the chemotherapy.

Patient was then advised follow up regularly, every month for next 3 months and every 3 months for next 6 months and every 6months for next one year or in between the regular schedule if required. On every follow up, well-being of the patients, the status of the enucleated socket and the other eye is noticed on every follow up visits. Appropriate Low Vision rehabilitation and cosmetic artificial shell for the enucleated eye was provided for the patient.

OUTCOME MEASURES

The outcomes were studied by correlating the high risk histopathological factors (as stated before) in the enucleated eye, with the outcome such as post-op recurrence in stump and distant metastasis in retinoblastoma .

STATISTICAL METHODS

The descriptive variables are given in mean (standard deviation) and frequency (percentage). Chi square test or Fisher's exact test were used to find any association between the categorical variables. The pictorial representation such as bar charts , pie charts and flow charts were drawn for few variables where and when needed. The P values < 0.05 was

considered as statistically significant. All these statistical analysis were done using statistical software STATA ver. 14 (Texas, USA).

2.3 TABLES AND CHARTS

PATIENT DEMOGRAPHICS

Total No. of Eyes : 50

Epidemiological Profile

TABLE 1 : Gender

Gender	n (%)
Male	25 (50.0)
Female	25 (50.0)
Total	50 (100)

CHART 1

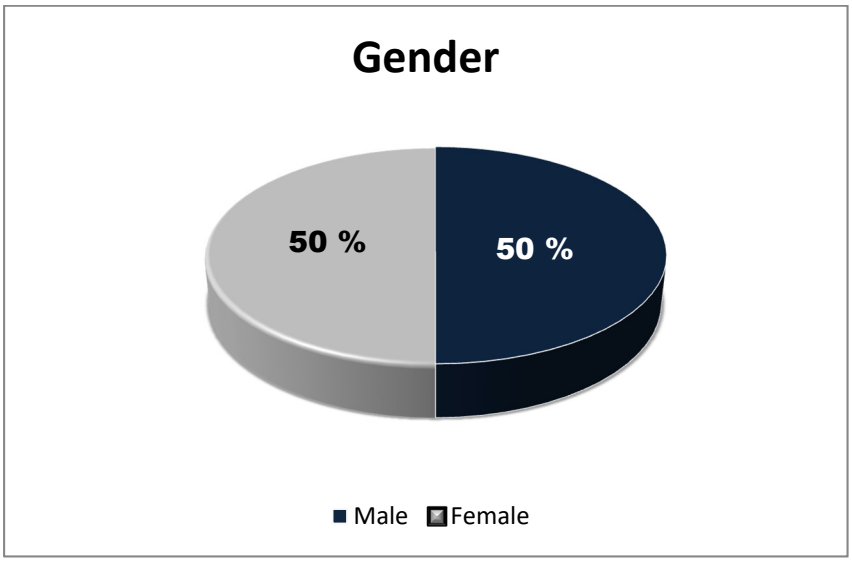


TABLE 2: Laterality

Eye	n (%)
RE	34 (68.0)
LE	16 (32.0)
Total	50 (100)

CHART 2

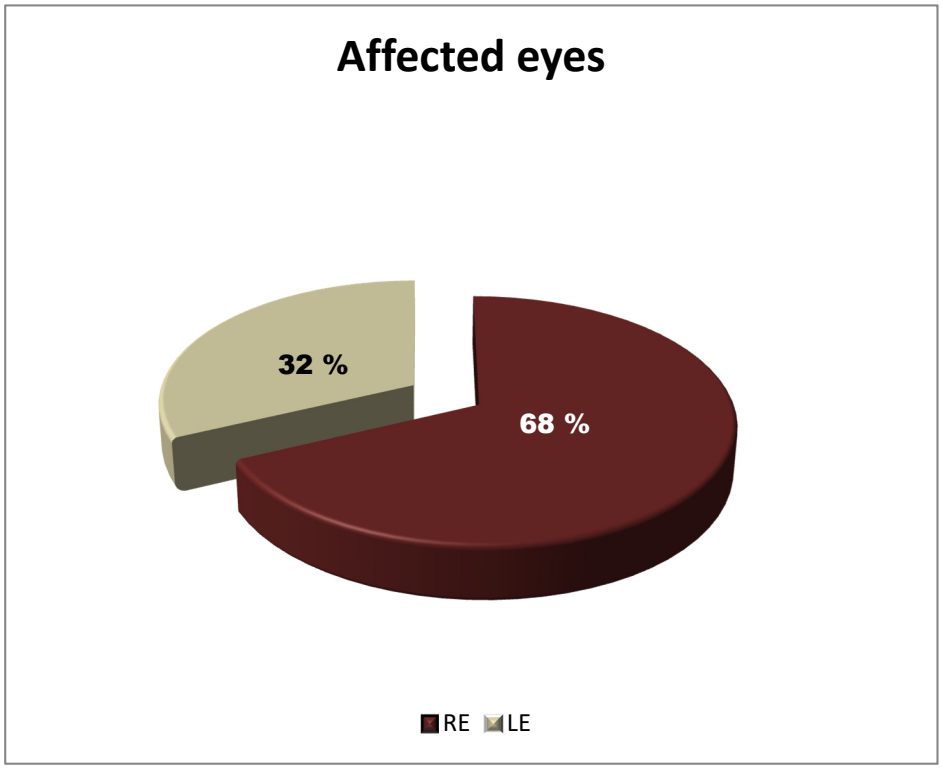


TABLE 3

Variable	n	Mean(SD)	Range		Median	IQR
			Min	Max		
Age in months	50	28.3 (17.67)	3	72	24	16 – 40

CLINICAL PROFILE

TABLE 4 : CHIEF COMPLAINTS:

CHIEF COMPLAINTS	N
Leucoria	47
Orbital cellulitis	5
Strabismus	8
Buphthalmos	3
Other complaints	6
Total*	69

*Some patients may have more than 1 diagnosis

CHART 3

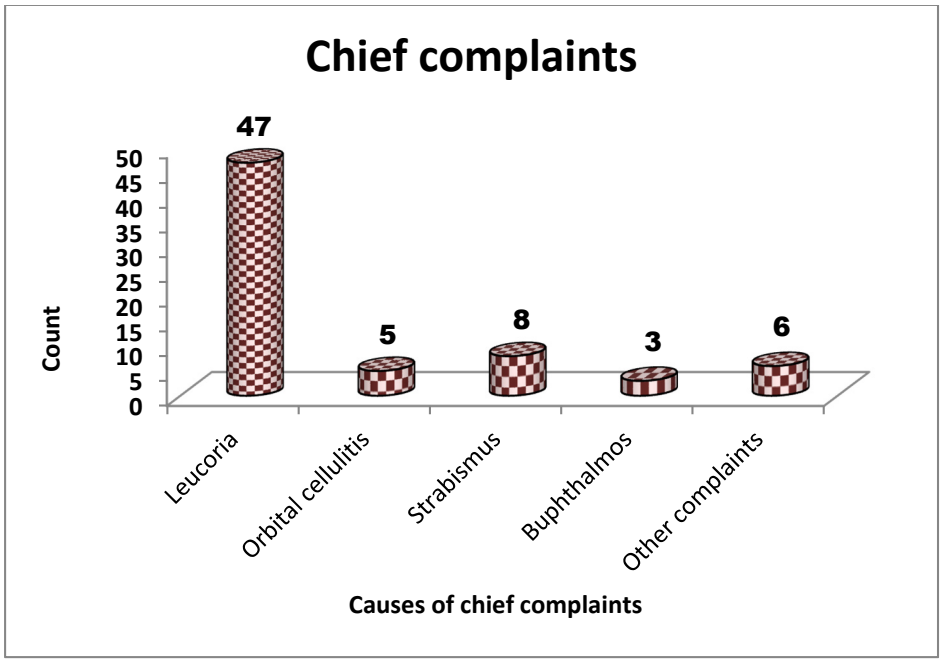


TABLE 5 :TYPE OF TUMOR FOCAL:

Tumor foci	n (%)
Multifocal	12 (24.0)
Unifocal	1 (2.0)
NA	37 (74.0)
Total	50 (100)

CHART 4

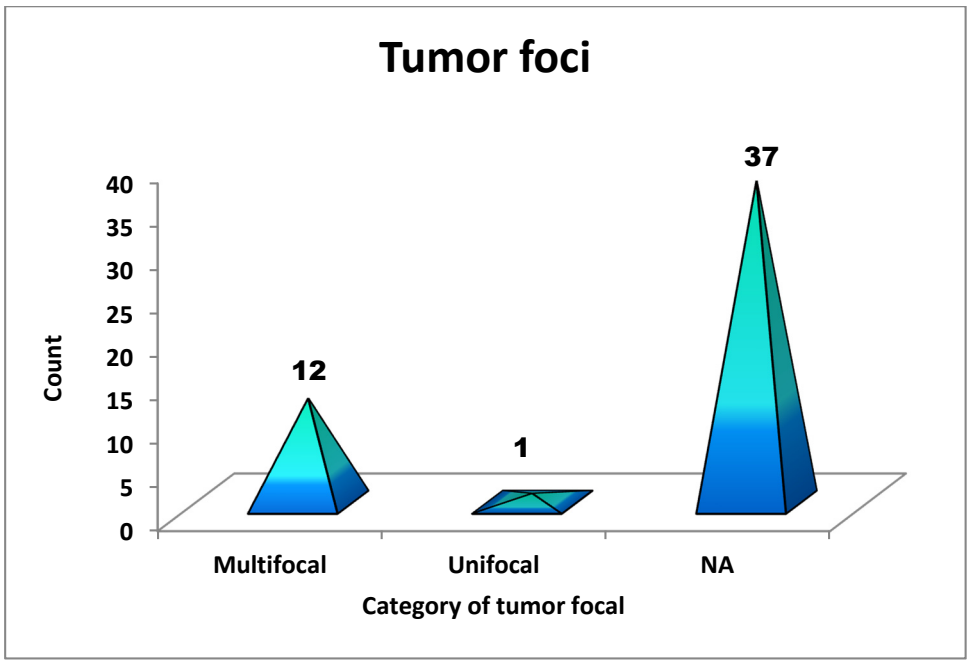


TABLE 6 :TYPE OF GROWTH

Growth	**n (%)**
Exophytic	3 (6.0)
Endophytic	39 (78.0)
Diffuse infiltrative	1 (2.0)
Mixed	7 (14.0)
Total	50 (100)

CHART 5

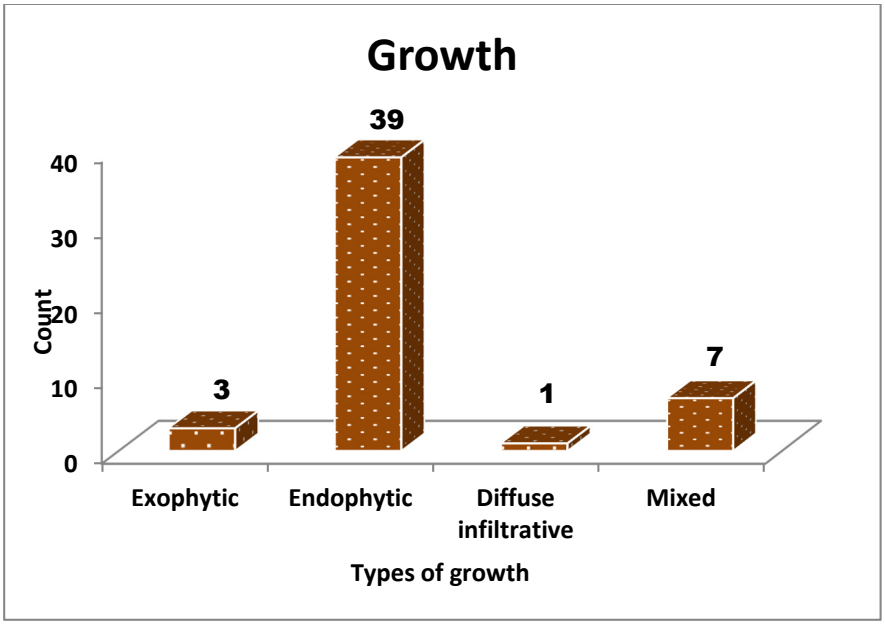


TABLE 7: OCULAR STRUCTURE INVOLVED:

Ocular structure involved	n
Anterior Chamber	9
Angle	7
Iris	8
Ciliarybody	4
Choroid	27
Optic nerve	33
Vitreous	35
Sclera	4
Extra Ocular	1
Anterior Chamber invasion	14
Iris /CB/Angle invasion	9
Scleral invasion	5
Extra Ocular 1	1
Total*	157

*Some patients may have more than 1 diagnosis

CHART 6

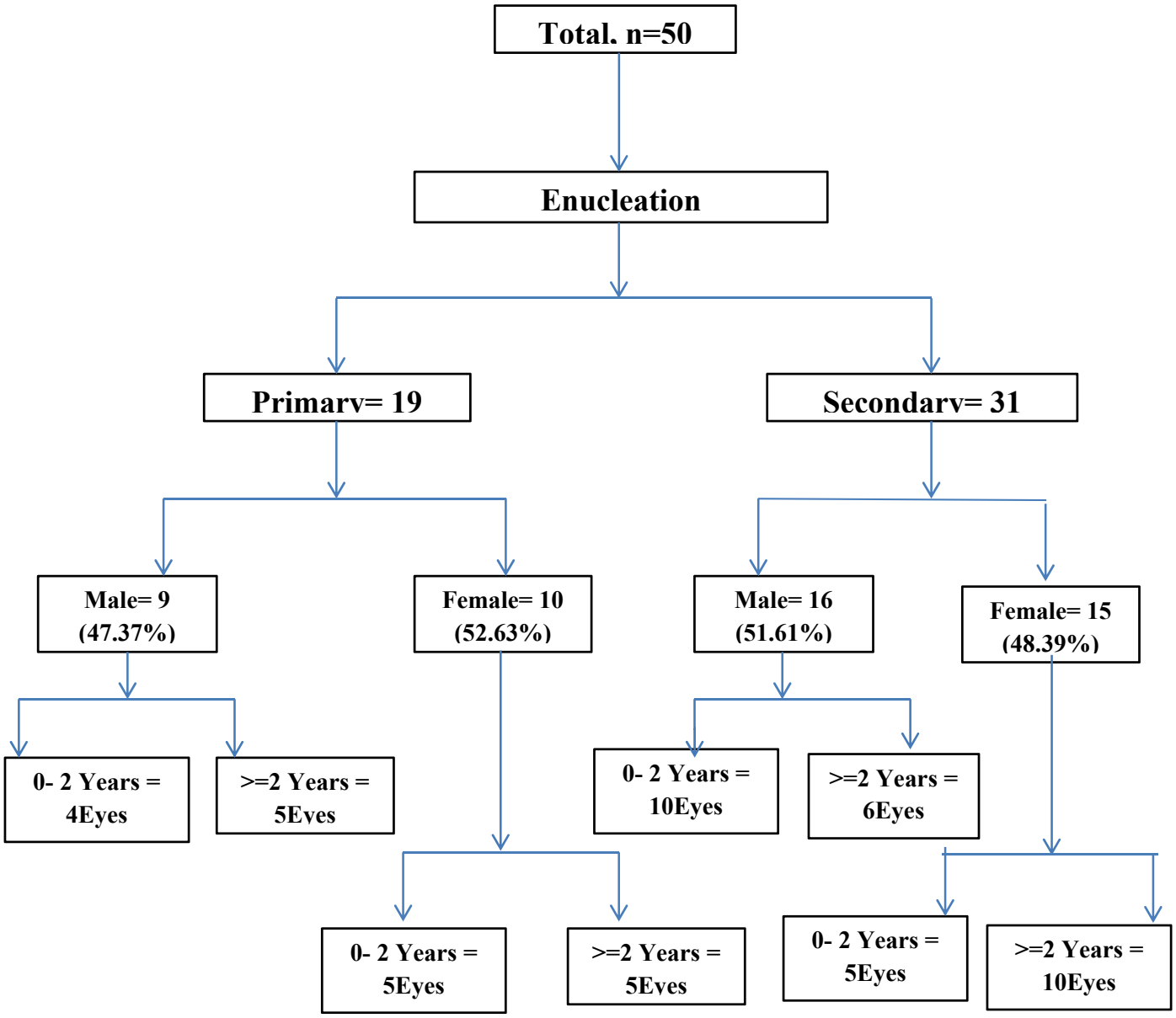

Total. n=50
Enucleation
Primarv= 19
Secondarv= 31
Male= 9 (47.37%)
Female= 10 (52.63%)
Male= 16 (51.61%)
Female= 15 (48.39%)
0- 2 Years = 4Eyes
>=2 Years = 5Eves
0- 2 Years = 10Eyes
>=2 Years = 6Eyes
0- 2 Years = 5Eyes
>=2 Years = 5Eves
0- 2 Years = 5Eyes
>=2 Years = 10Eyes

CHART 7

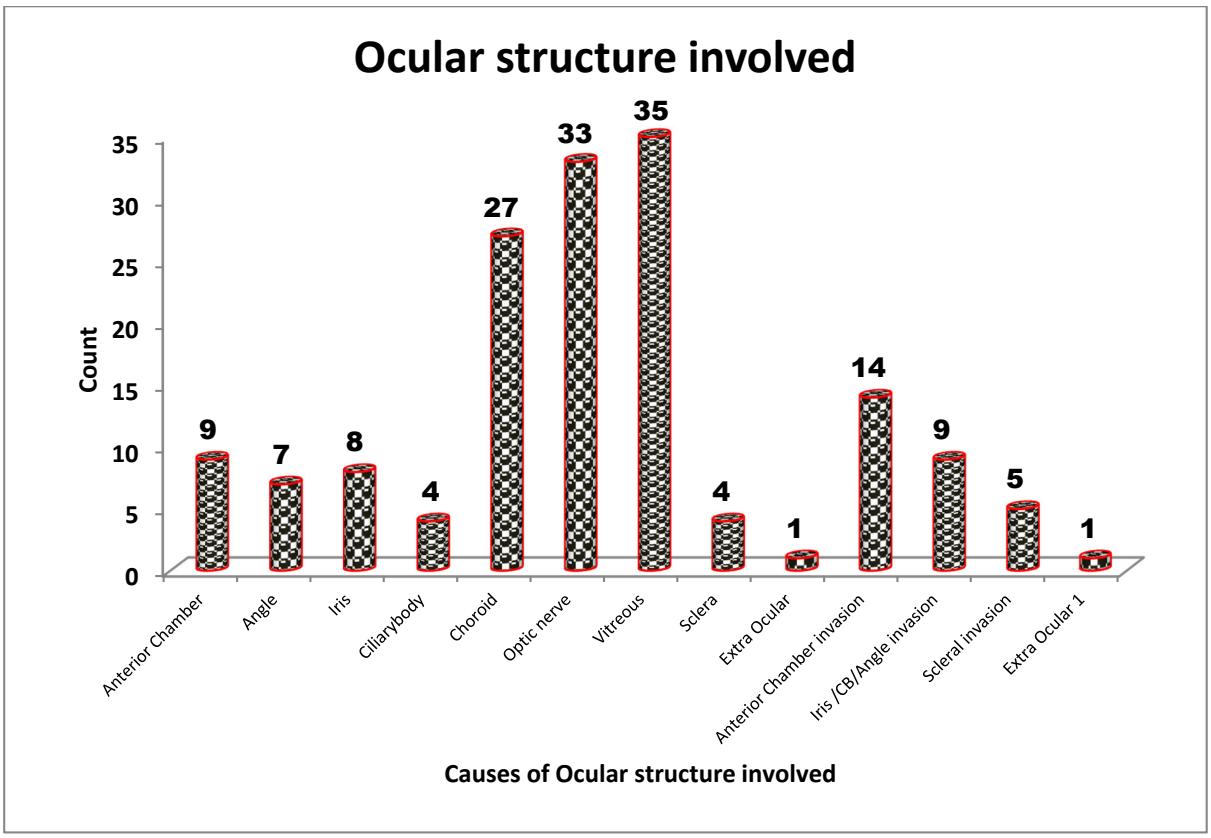


TABLE 8: TYPES OF TREATMENT:

Treatment	n (%)
Primary	19 (38.0)
Secondary	31 (62.0)
Total	50 (100)

CHART 8

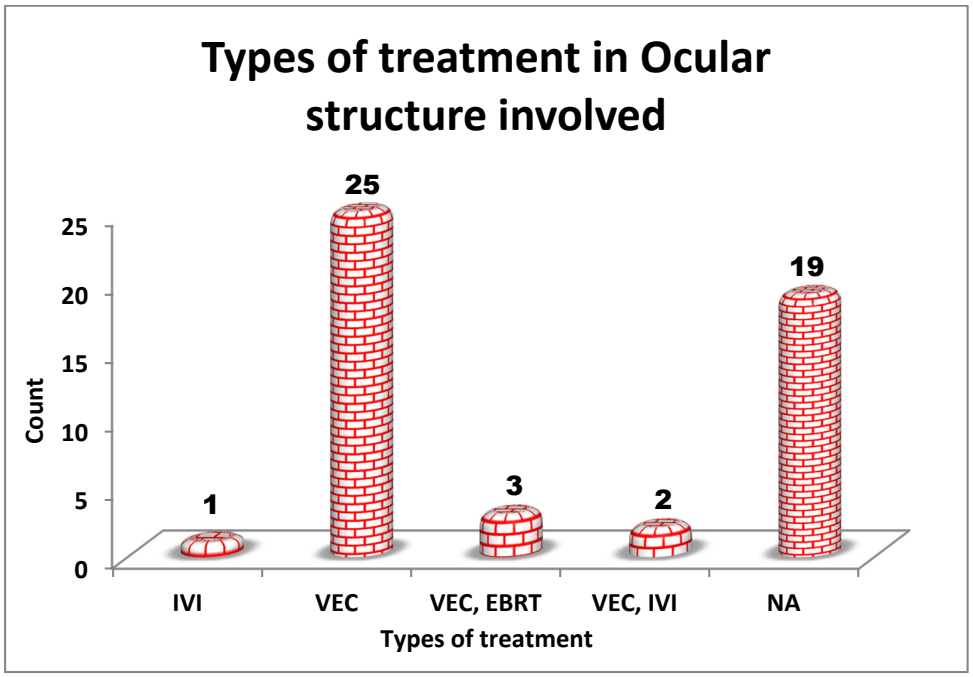


TABLE9 : FOR TYPES OF TREATMENT

Type	n (%)
IVI	1 (2.0)
VEC	25 (50.0)
VEC, EBRT	3 (6.0)
VEC, IVI	2 (4.0)
NA	19 (38.0)
Total	50 (100)

TABLE 10

Variable	n	Mean(SD)	Range		Median	IQR
			Min	Max		
Chemo duration in months at pre op	31	8.16 (11.93)	1	48	3	3 – 8

CHART 9

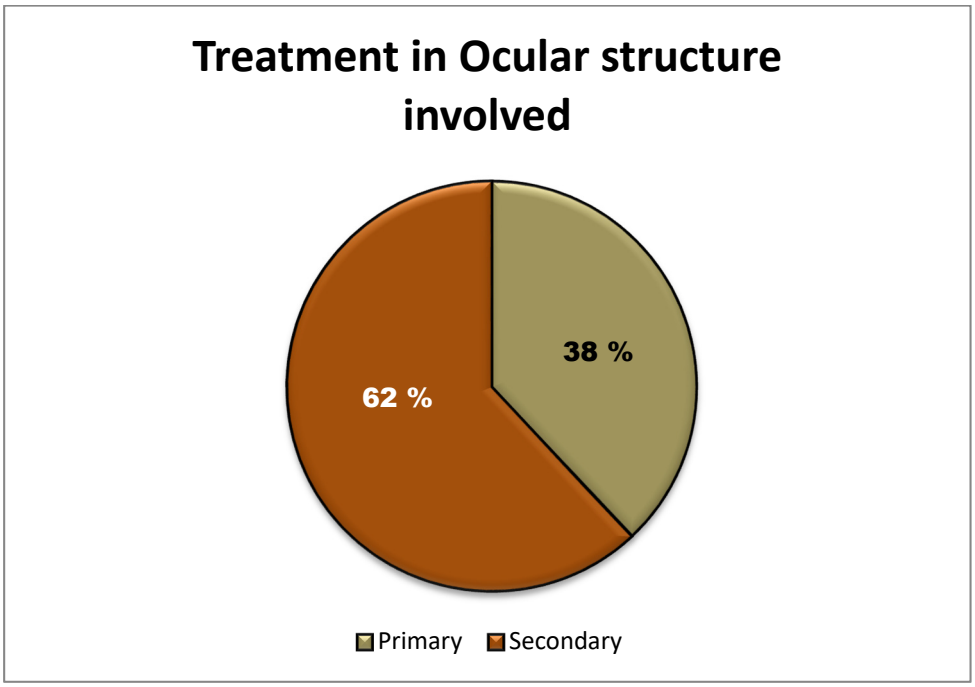
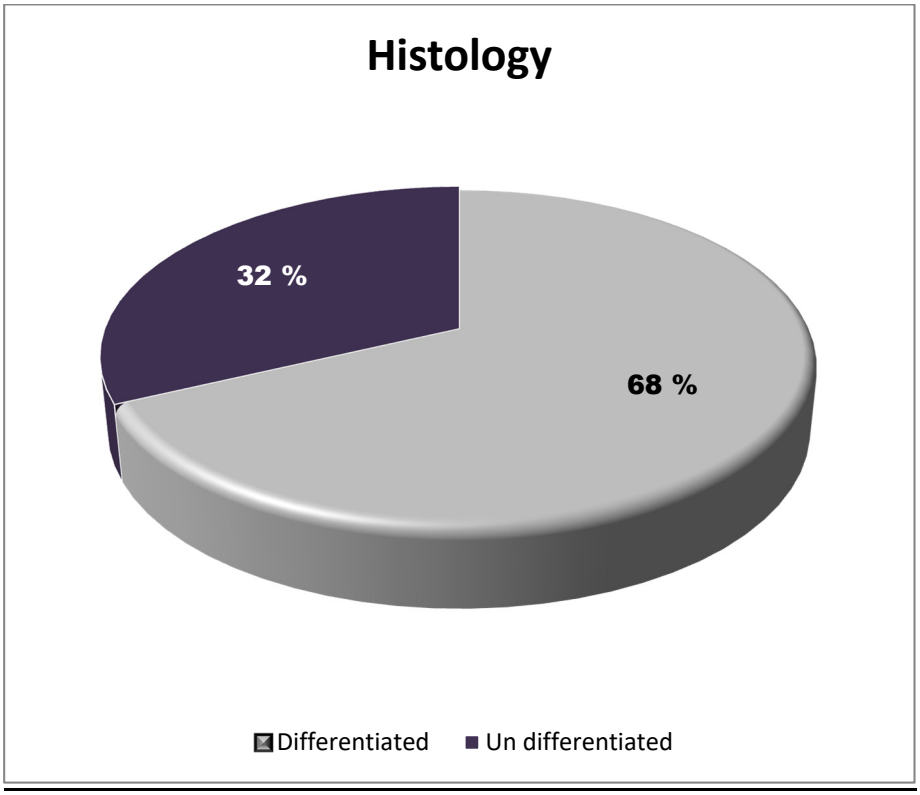


TABLE 11: HISTOLOGY

Histology	n (%)
Differentiated	34 (68.0)
Un differentiated	16 (32.0)
Total	50 (100)

CHART 10



TABLES 12 :OPTIC NERVE INVASION:

Optic Nerve Invasion	n (%)
Laminar	5 (10.0)
Prelaminar	18 (36.0)
Retrolaminar	13 (26.0)
Not identified	14 (28.0)
Total	50 (100)

CHART 11

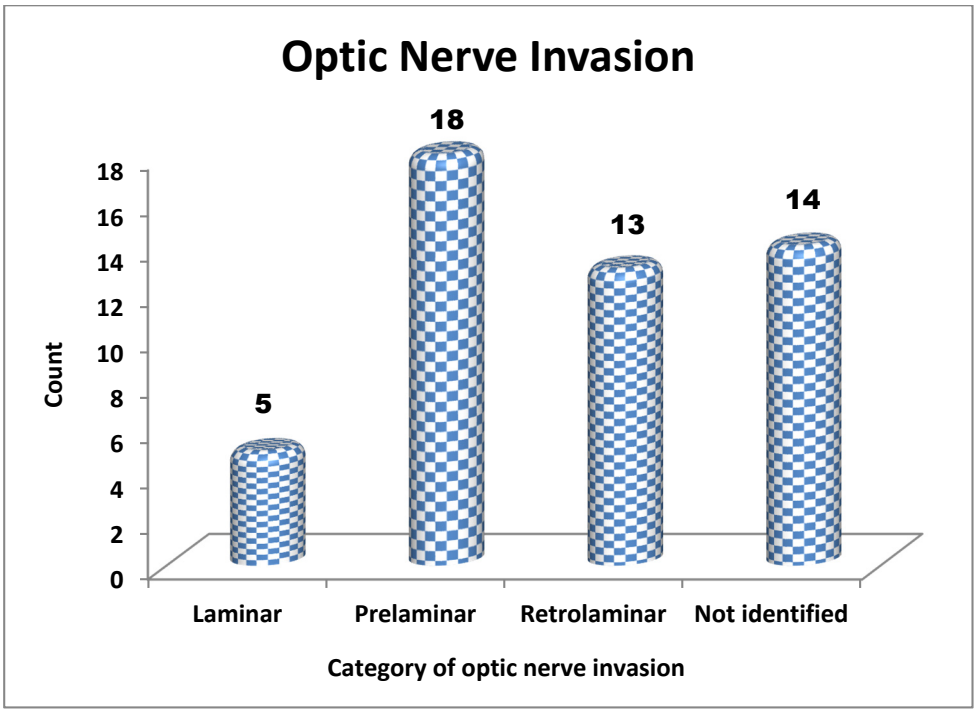
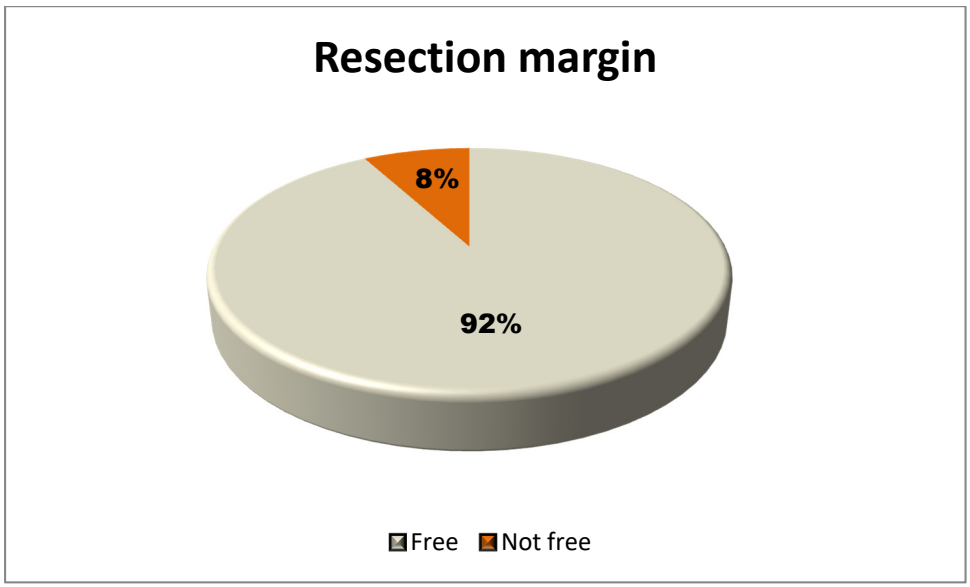


TABLE 13: RESECTION MARGIN:

Resection margin	n (%)
Free	46 (92.0)
Not free	4 (8.0)
Total	50 (100)

CHART 12



Flow chart of histopathological analysis

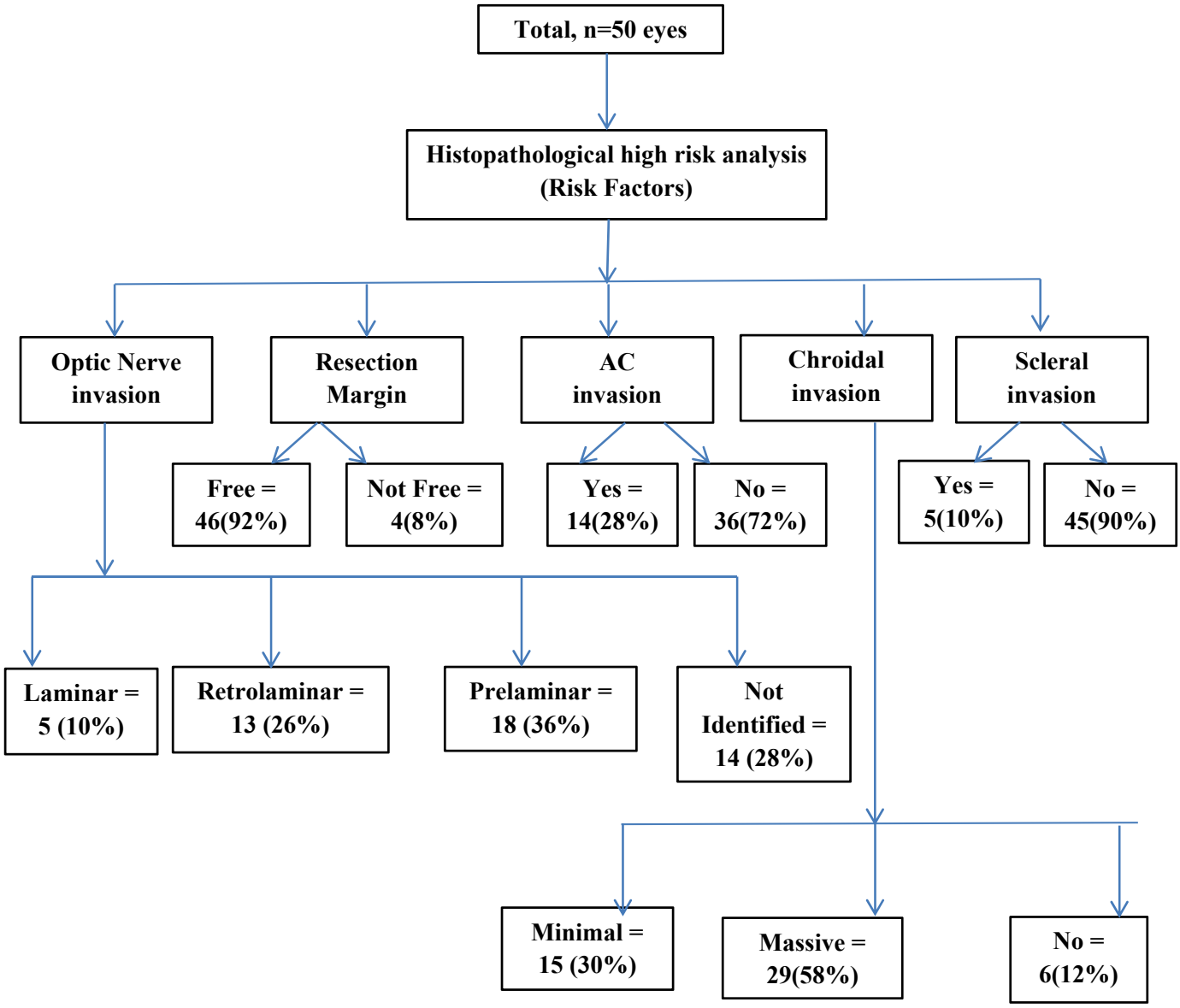


Table for association between Secondary Glaucoma vs Optic Nerve Invasion:

Secondary Glaucoma	Optic Nerve Invasion				Total (%)	p-value*
	Laminar (%)	Not Identified (%)	Prelaminar (%)	Retrolaminar (%)		
Yes	1 (0.3)	2 (0.8)	0 (1.1)	0 (0.8)	3 (3.0)	0.100
No	4 (4.7)	12 (13.2)	18 (16.9)	13 (12.2)	47 (47.0)	
Total (%)	5 (5.0)	14 (14.0)	18 (18.0)	13 (13.0)	50 (50.0)	

***Fisher exact test**

In the above table compared secondary glaucoma and optic nerve invasion. There was no association between secondary glaucoma and optic nerve invasion. So the association was not statistically significant. i.e., $p>0.05$

Table for association between Iris Neo vs Optic Nerve Invasion:

Iris Neo	Optic Nerve Invasion				Total (%)	p-value*
	Laminar (%)	Not Identified (%)	Prelaminar (%)	Retrolaminar (%)		
Yes	1 (0.5)	2 (1.4)	0 (1.8)	2 (1.3)	5 (5.0)	0.205
No	4 (4.5)	12 (12.6)	18 (16.2)	11 (11.7)	45 (45.0)	
Total (%)	5 (5.0)	14 (14.0)	18 (18.0)	13 (13.0)	50 (50.0)	

***Fisher exact test**

In the above table compared iris neo and optic nerve invasion. There was no association between iris neo and optic nerve invasion. So the association was not statistically significant. i.e., $p>0.05$.

Table for association between Secondary Glaucoma vs Resection Margin:

Secondary Glaucoma	Resection Margin		Total (%)	p-value*
	Free (%)	Not Free (%)		
Yes	3 (2.8)	0 (0.2)	3 (0.3)	>0.99
No	43 (43.2)	4 (3.8)	47 (47.0)	
Total (%)	46 (46.0)	4 (4.0)	50 (50.0)	

***Fisher exact test**

In the above table compared secondary glaucoma and resection margin. There was no association between secondary glaucoma and resection margin. So the association was not statistically significant. i.e., $p>0.05$.

Table for association between Iris Neo vs Resection Margin:

Iris Neo	Resection Margin		Total (%)	p-value*
	Free (%)	Not Free (%)		
Yes	5 (4.6)	0 (0.4)	5 (5.0)	>0.99
No	41 (41.4)	4 (3.6)	45 (45.0)	
Total (%)	46 (46.0)	4 (4.0)	50 (50.0)	

***Fisher exact test**

In the above table compared iris neo and resection margin. There was no association between iris neo and resection margin. So the association was not statistically significant. i.e., $p>0.05$

Table for association between Secondary Glaucoma vs Chroidal Invasion:

Secondary Glaucoma	Chroidal Invasion			Total (%)	p-value*
	Massive (%)	Minimal (%)	No (%)		
Yes	3 (1.7)	0 (0.9)	0 (0.4)	3 (3.0)	0.689
No	26 (27.3)	15 (14.1)	6 (5.6)	47 (47.0)	
Total (%)	29 (29.0)	15 (15.0)	6 (6.0)	50 (50.0)	

***Fisher exact test**

In the above table compared secondary glaucoma and chroidal invasion. There was no association between secondary glaucoma and chroidal invasion. So the association was not statistically significant. i.e., $p>0.05$

2.4 RESULT:

Our study included 50 eyes with retinoblastoma. Out of these 25(50%) were male and 25 (50%) were female (Table 1, chart 1). 34 (68%) of them had RE involvement and 16 (32%) of them had LE involvement at the time of presentation(Table , chart).

The mean age at enucleation of retinoblastoma was 28.3 months , SD 17.67 months. The minimum age of enucleation was 3 months and maximum age at enucleation 72 months.

Of the 50 eyes , the 47 presented with Leucoria, 8 presented with strabismus, 5 with orbital cellulitis , 3 with buphthalmos and 6 with other non specific complaints, some had more than 1 chief complaints at the time of presentation.

Of the 50 eyes, 7 had cataract, 5 had iris neovascularization and 3 had secondary glaucoma as secondary complication at the time of presentation. The tumor foci was not assessable in 37(74%), multifocal 12(24%),unifocal 1(2%). The type of growth was endophytic in 39(78%), mixed in 7 (14%), exophytic in 3 (6%) and diffuse infiltrative in 1 (2%).

Of the 50 eyes, vitreous involvement was in 35 eyes, optic nerve involvement was in 33 eyes, choroidal involvement in 27 eyes, anterior chamber and angle structure in 24 eyes, sclera invasion in 5 eyes and extraocular invasion in 1 eye. 19 (38%) eyes underwent primary

enucleation, and 31(62%) eyes underwent secondary enucleation . All the 31 eyes which was secondarly enucleated had chemotherapy prior to enucleation, the mean duration of chemotherapy was 8.16 months with a standard deviation of 11.93. The minimum duration being 1 month and maximum duration was 48 months.

The histological analysis of these 50 eyes revealed differentiated tumor in 34(68%) eyes, and undifferentiated tumor in 16 (32%) eyes. Optic nerve (ON) invasion was present in 36 eyes out of which 18(36%) was prelaminar, 13(26%) was retrolaminar and 5(10%) was laminar and ON invasion was not identified in14 eyes . The resection margin of the ON was free in 46(92%) eyes and not free in 4(8%) eyes. Choroidal invasion was massive in 29 (58%)eyes ,minimal in 15(30%)eyes and not involved in 6(12%) eyes. In post op 1 month followup orbital extension was present in 3(6%) and absent in 47(94%) eyes.

2.4 DISCUSSION

In our study, age of patients ranges from 3 to 72 months. The mean age of enucleation in retinoblastoma was 28.3 months. This is similar to the study of Yacoub A Yousef et al (54). Same findings were found from the Indian studies . A recent study published by Gupta et al revealed a mean age of presentation to be 29.74 months (55).

In our study, the ratio of male to female is 1 (25 males-50% and 25 females-50%). A few studies have demonstrated a male preponderance (56). A study by Azar et al showed no significant difference (57) , Mukhopadyaya et al did a study , which showed Female preponderance (58)

Leukocoria was found as most common presentation in our study. It was seen in 47 cases. Several studies worldwide have found similar observation (60). In many studies done in India, leucocoria was found to be the common presenting feature. Strabismus was the second most common feature in

our study which was seen in 8 cases. The importance of strabismus has been postulated by Abramson et al, another study by Balasubramanya et al had proptosis as second most common clinical presentation, (59,60).

Though leucocoria is the most common presenting feature, it signifies a large tumour to produce the white reflex which usually happens in the end stage of disease. Thus awareness has to be created among the family and public for the early screening for little eye changes.

Other presentations of retinoblastoma may be atypical that are included in our study were, secondary glaucoma, iris neovascularisation, pseudohypopyon, and cataract was also seen in few cases.

In our study we had taken 50 eyes of advanced retinoblastoma (Group D and Group E) , of which are 19 eyes were enucleated primarily and 31 eyes were enucleated secondarily after chemotherapy failure to reduce the tumor. Of which histology of 34 eyes were differentiated and 16 eyes were undifferentiated. 19 eyes showed multifocal tumor, 1 eye showed unifocal , and was not assessable in 30 eyes. The high risk histological factors were analysed, optic nerve invasion was found in 36 eyes and absent in 14 eyes. Resection margin of optic nerve was free in 46 eyes and not free in 4 eyes. Choroidal invasion was massive in 29 eyes, minimal in 15 eyes and absent in 6 eyes.

Out of 50 eyes , 3 eyes had orbital extension they were treated with extended chemotherapy cycle. 3 patients expired due to metastasis .

2.5 SUMMARY

A total of 50 eyes of retinoblastoma were enucleated and their histopathological studied , all patients who were enucleated in the study period of 1 year and 6 months, were evaluated for the demographics, clinical features, type of presentation and enucleation, histological high risk features.

1. Our study showed the mean age of enucleation was 28.3 months

2. In our study minimum age of enucleation was done in 3 months and maximium age was 72 months

3. Male : Female ratio was 1

4. Leucocoria (94%) was the most common clinical feature at the time of presentation in our study, followed by strabismus (16%).

5. All cases with nil visual prognosis or tumors not responding to medical therapy were enucleated.

6. Optic nerve invasion, choroidal invasion, optic nerve resection margin invasion , extraocular invasion were consider as high risk histological feature and associated with a bad outcome.

7. A long term follow up for atleast 5 years in post enucleated cases is mandatory to assess the long term survival , recurrence and metastasis in these patients.

8. We strictly emphasis the early screening and appropriate management to enhance prognosis , decrease the mortality and improve the quality of life in these patients.

9. All enucleation of retinoblastoma should be done in an eye center which is functioning with active pathology lab, so that all enucleated specimens reach the lab and evaluated for high risk features, with which further adjuvant therapy and follow up can be framed. This will segregate patients who need extra and intensive care and helps in early rehabilitation .

10. It is necessary to create a national registry for retinoblastoma to know the actual number of cases in our country, with which treatment modalities can be standardized ,thus early treatment renders good recovery and rehabilitation.

2.6 CONCLUSION :

1. From our study we came to know that with the advancements in retinoblastoma , early diagnosis and treatment modalities had improved the prognosis of vision , globe and life salvage.
2. It is important to create awareness in public and family members regarding the disease so that early presentation of the case to the treating center is possible. The prompt referral by the primary treating physician in case of suspicion is mandatory.
3. Retinoblastoma requires a multimodal approach of treatment which invoves radiological imaging, pediatric evaluation, appropriate treatment by oncologist and ophthalmologist .
4. Histopathological evaluation of all enucleated specimens are mandatory to determine the risk of metastasis and to schedule the adjuvant chemotherapy accordingly.

CLINICAL FEATURES

Figure 1 : White reflex-Leukocoria

Figure 2: Strabismus

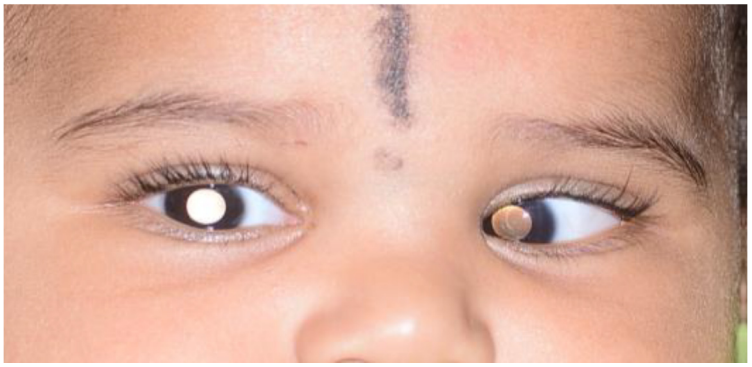


Figure 3: Proptosis

EXAMINATION UNDER ANESTHESIA

Figure 4 : unifocal RB

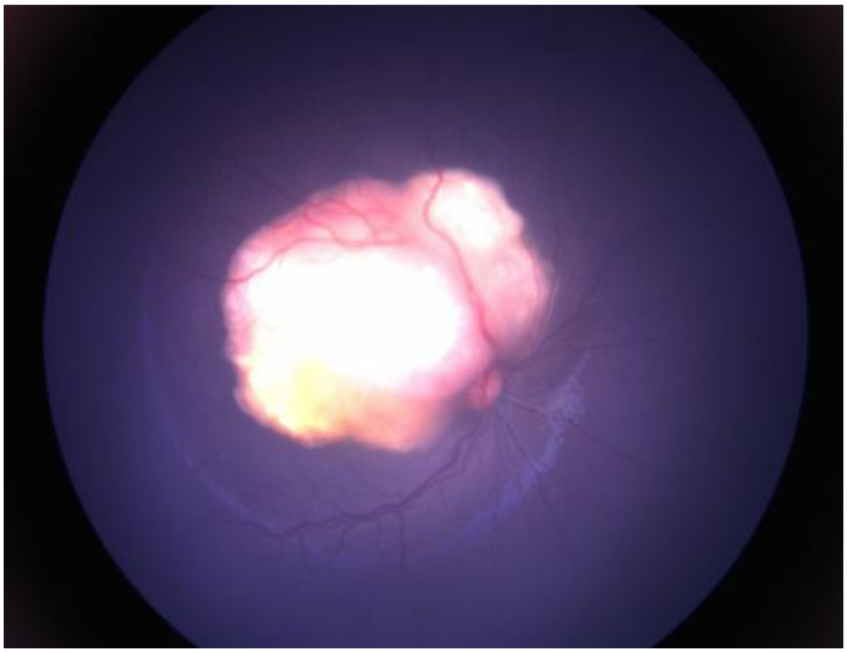
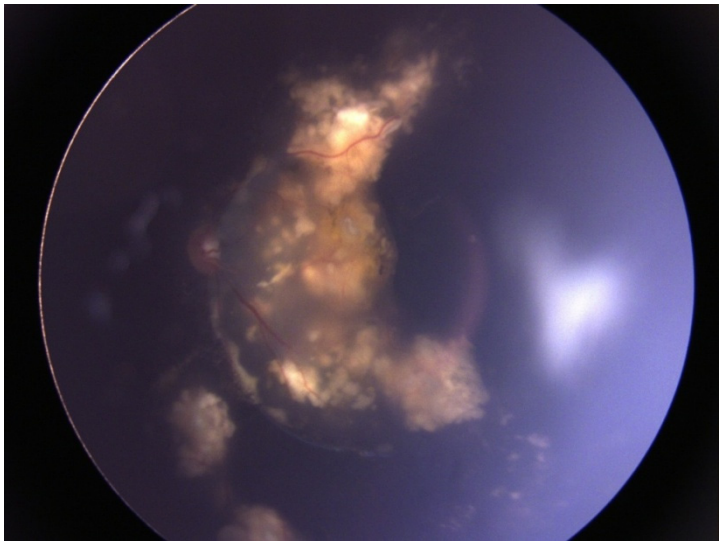


Figure 5: Multifocal RB



HISTOPATHOLOGY

Figure 6 : Poorly differentiated tumour

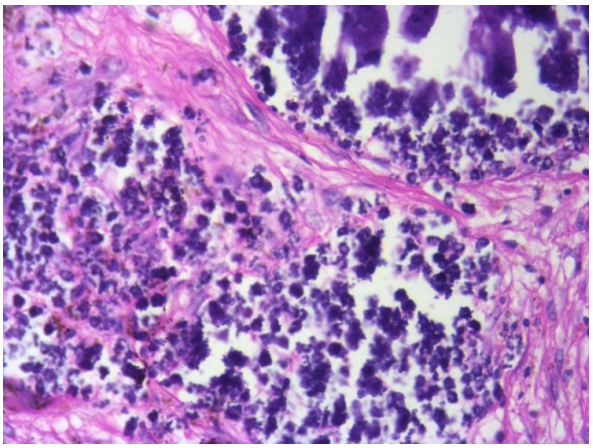


Figure 7 : Moderately differentiated tumour

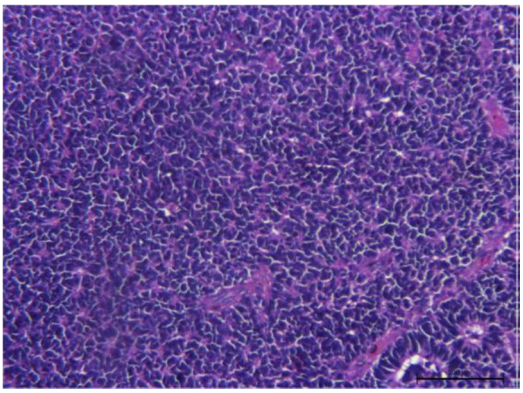


Figure 8: well differentiated tumor

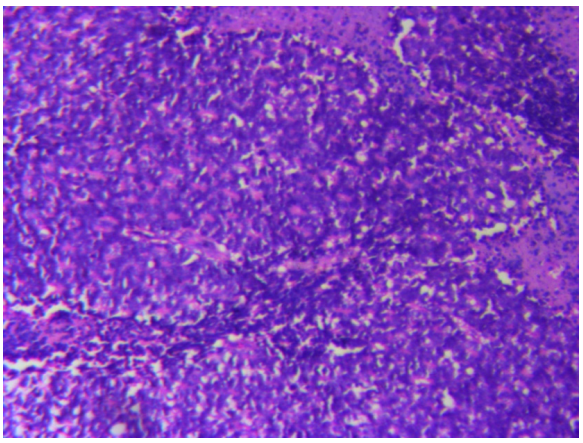


Figure 9 : Pre-enucleation (white reflex)

Figure 10 : post-enucleation

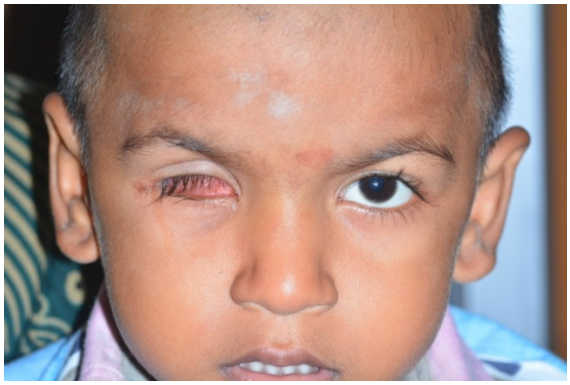
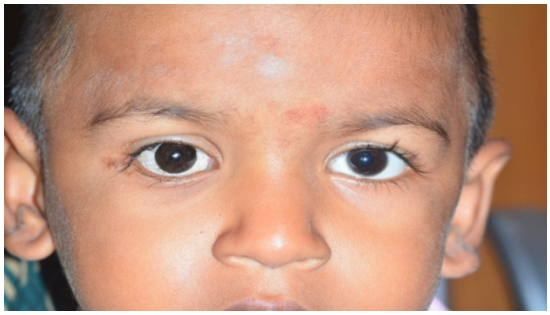


Figure 11 : with stock shell



RADIOLOGICAL IMAGING

Figure 12 : CT showing Retinobastoma

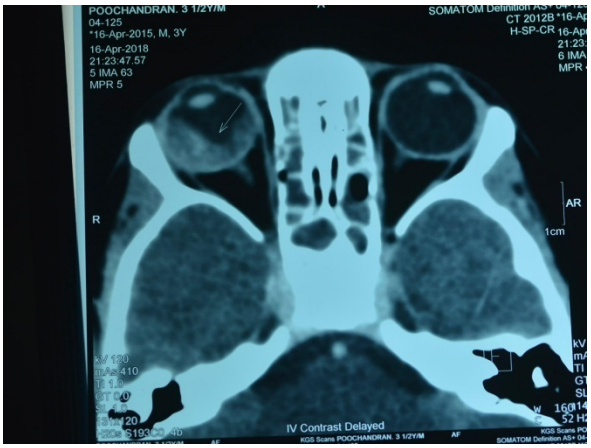
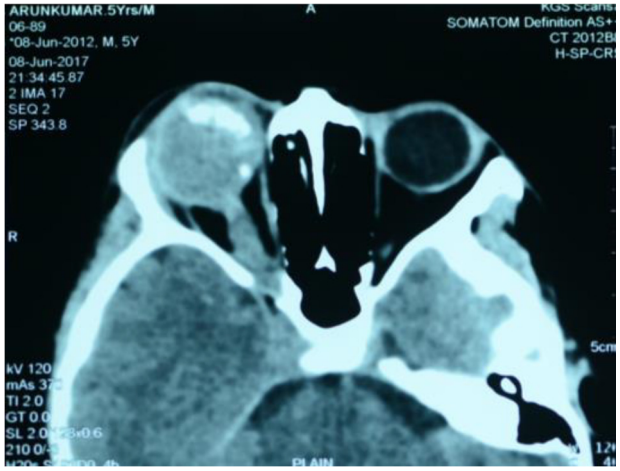


Figure 13 : MRI showing optic nerve infiltration



ANNEXURE

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ABBREVIATION

RB - Retinoblastoma

DD - Disc diameter

TNM - Tumour , Nodal , Metastasis

CGy - Centigray

VEC - Vincristine , Etoposide, Cyclophosphamide

20-D - 20- diopter

MRI - Magnetic Resonance Imaging

CSF - Cerebro Spinal Fluid

USG - Ultrasonography

EUA - Examination Under Anesthesia

SD - Standard Deviation

PROFORMA

Histopathological Correlation with Outcome in Retinoblastoma

Name : Date :

Date of Birth : Sex : ☐ M ☐ F

Date of Enucleation : Study no :

M.R.No : Affected eye : ☐ RE ☐ LE

Chief complaint

☐ Leucoria ☐ Strabismus

☐ Orbital cellutitis ☐ Buphthalmos

☐ Others, specify

Clinical features

Pseudohypopyon ☐ Y ☐ N Secondary Glaucoma ☐ Y ☐ N

Cataract ☐ Y ☐ N Iris neovascularization ☐ Y ☐ N

Clinical findings

Number of tumour foci

☐ Unifocal ☐ Multifocal ☐ Cannot be assesed

Growth type

☐ Exophytic ☐ Endophytic

☐ Diffuse infiltrative ☐ Mixed

Ocular structure involved

☐ Anterior chamber ☐ Choroid

☐ Angle ☐ Optic nerve

☐ Iris ☐ Vitreous

☐ Ciliary body ☐ Sclera

Extraocular ☐ Y ☐ N

Treatment Modalities

Type of Enucleation ☐ Primary ☐ Secondary

In secondary enucleation

Type of treatment : _____

Duration of treatment : _____

Histology

Retinoblastoma : ☐ Differentiated
☐ Undifferentiated

Number of tumour Foci : ☐ Unifocal
☐ Multifocal
☐ Cannot be assessed

Optic nerve invasion ☐ Present ☐ Not Identified

If present

1. **Degree of optic nerve involvement**
   ☐ Prelaminar ☐ Laminar ☐ Retrolaminar
2. **Optic nerve resection margin**
   ☐ Involved ☐ Not involved
3. **Anterior chamber invasion**
   ☐ Present ☐ Not identified
4. **Iris/Ciliary Body/Angle invasion**
   ☐ Present ☐ Not Identified
5. **Choroidal Invasion**
   ☐ Minimal (<3mm) ☐ Massive (≥ 3 mm)
6. **Scleral invasion**
   ☐ Present ☐ Not Identified
7. **Extraocular invasion**
   ☐ Present ☐ Not Identified

Report of Enucleation :

Informed Consent form to participate in a Study

Study Title: CLINICAL PROFILE, MANAGEMENT AND OUTCOMES IN PATIENTS WITH RETINOBLASTOMA

Protocol Number:

Subject's Name: _____Subject's Initials: _____

Subject ID No:_____

Date of Birth / Age: _____

		Please put initial in the box (Subject)
(i)	I confirm that I have understood the information about the study and procedures for the above study and have had the opportunity to ask questions and I received satisfactory answers to all of my questions. I have been given a copy of the informed consent form to take home	[ ]
(ii)	I understand that my child's participation in the study is voluntary and that I am free to withdraw my child at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]

IRB

ARAVIND MEDICAL RESEARCH FOUNDATION
Institutional Ethics Committee
(REGISTRATION NO. ECR/182/INST/TN/2013 DATED 20.04.2013)

To
Dr.MANGALESHWARI.M
MS Resident
Aravind Eye Hospital
Madurai

20th December 2017

Dear Dr. MANGALESHWARI,

Thesis Title: HISTOPATHOLOGICAL CORRELATION WITH OUTCOME IN RETINOBLASTOMA

IEC Code: IEC201800255

Thank you for submitting your thesis and seeking the approval from the ethics committee. The documents provided by you for consideration which include the thesis protocol and informed consent forms were reviewed for the research methodology and scientific content. The Ethical committee did not find any correction and has recommended the thesis to go ahead in the present form.

Thanking you

Yours Sincerely,

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
ARAVIND MEDICAL RESEARCH FOUNDATION
No.1, Anna Nagar, Madurai-625 020

Dr.R.Sharmila
Member Secretary
Institutional Ethics Committee

1, Anna Nagar, Madurai 625 020, Tamil Nadu, India; Phone: 0452-435 6550; Fax: 91-452-253 0984
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URKUND

Urkund Analysis Result

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Submitted By:	drmangalaeshwari@gmail.com
Significance:	12 %

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