Draft Consensus Document for Management of Retinoblastoma

Prepared as an outcome of ICMR's Subcommittee on Retinoblastoma

This draft of the consensus document has been formulated by ICMR's expert group and is available on website for seeking comments from wider section of scientific community for a period of 4 weeks from 1st Aug 2022 -28th August 2022.

Comments may be sent at oncoguidelinesphase2@gmail.com

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RETINOBLASTOMA: DRAFT ICMR GUIDELINES

INDEX

INTRODUCTION

Retinoblastoma (RB) is the most common malignant intraocular neoplasm in children. Although long-term survival has improved to well-over 90% with multimodality therapy in the developed world, it still causes fatalities in the low middle income countries (LMICs) because of delayed presentation (leading to advanced disease) and treatment abandonment.(1,2) The management of RB has evolved over the past few decades and brought about a paradigm change from enucleation being the primary modality of therapy to a more multimodality treatment strategy with an increased focus on globe preservation. The aim of RB therapy is not only to preserve life and the eye but also to optimize residual vision and lately to focus on decreasing second malignancies. Early diagnosis of RB with the disease contained within the eye is key to better survival.

INCIDENCE AND EPIDEMIOLOGY

Global incidence of Retinoblastoma

Retinoblastoma constitutes 2.5% to 4% of all pediatric cancers with 11% occurring in less than 1 year of age. (1,2) The age-adjusted incidence rates of RB in developed countries are 2 to 5 per million children (approximately 1:15,000 to 1:20,000 live births) (2,3) where RB is diagnosed early, in the intraocular stage, in over 90% of cases with the median age of diagnosis of unilateral and bilateral RB being 19 months and 8 months, respectively. (3) Contrary to this, in many of the LMICs children diagnosed with retinoblastoma present later with median age of presentation being 30 months (unilateral) and 14 months (bilateral), with one third of them having extra-ocular disease. (3–5)

Incidence of Retinoblastoma in India

The epidemiological data from India is available from the National Cancer Registry Program which includes data from both Population Based Cancer Registries (PBCRs) and Hospital Based

Cancer Registries (HBCRs). (6,7) The data regarding childhood cancers are predominantly from the HBCRs. The age standardised incidence rate in India is estimated to be 5.2 per million which equates to 1 in 11000 births. About 8000 children worldwide are diagnosed with RB each year with an estimated incidence in India being 1500 cases annually. (8) In India, as in many other LMICs, the median age of diagnosis of unilateral and bilateral RB is 30 months and 18-24 months, respectively. 63% of RB is diagnosed in the intra-ocular stage, with one-third presenting as locally advanced or metastatic disease. (3,4,7) Two thirds of the retinoblastoma children have unilateral disease. A positive family history of retinoblastoma is noted in only 5% of cases. (3,4)

India has a major burden of RB and the delay in diagnosis is attributed to socio-economic barriers, leading to a large proportion of advanced disease presentations resulting in poorer survival outcomes. (5,9,10) Patients in high income countries present with microscopic disease or disease identified on imaging. Patients in low and middle income countries additionally present with overt clinical disease occasionally presenting with large bulky cauliflower like growth. Lack of awareness, social taboo of enucleation, seeking alternative conservative treatment options, and poor accessibility to health care play a critical role in delayed diagnosis in LMICs. Around 20-40% patients present in advanced stage of the disease in LMICs as compared to less than 5% in developed countries. (11) Recent findings from global retinoblastoma study group revealed that the incidence of extraocular stage and metastasis at presentation was 49% and 19% in low income countries, respectively as compared to 1.5% and 0.3% in high income countries. (12) Incidence of extraocular RB varies from 9 to 27% in recently published studies from India. (13,14) Majority of the studies from developing nations have found a higher incidence in males, possibly because of the bias towards bringing male children for treatment. (9,13) The reason behind may be a bias as males are generally preferred for treatment. (13)

Scope for epidemiological research in retinoblastoma:

- Assess barriers to care with respect to early diagnosis and referral
- Population based cancer registry in childhood cancer including retinoblastoma
- Long term Cohort study of Retinoblastoma survivors
- Impact of community health worker (ASHA workers etc) screening of retinoblastoma in the community
- Correlation between HPV prevalence and Retinoblastoma
- Early screening program in familial retinoblastoma including children carrying germline mutation

GENETICS

Retinoblastoma is the first tumor where a genetic origin was identified. Retinoblastoma is caused by mutation in the *RB1* tumor suppressor gene at chromosome 13q14.2. Retinoblastoma occurs when both copies are lost or mutated.

Knudson proposed the two-hit hypothesis in 1971. (15) He stated that mutations in both copies of *RB1* gene are required for the development of Retinoblastoma. *RB1*, a tumor suppressor gene, is a regulator at the cell cycle checkpoint between G1 and entry into S phase. (16) The initial hit in hereditary retinoblastoma is a germline mutation, which is inherited and found in all cells of the body and the second hit occurs in the *RB1* allele of the retinal precursor cell (somatic mutation) that progress to form the tumor. The hereditary variant of Retinoblastoma also predisposes patients to second cancers like osteosarcoma, soft tissue sarcoma, and pineoblastoma (trilateral Retinoblastoma). (17)

In the ‘sporadic’ non-heritable form, the two hits occur in the retinal precursor cell (somatic mutations) and the mutation is confined only to the retinal cells.(18) Additional genetic events

predisposing to RB transformation include P53 pathway alterations like MDM2, MDM4 amplification, and epigenetic changes due to BCOR mutations and SYK upregulation. (19,20) *RB1* gene mutations have been associated with >95% of RB; however, there is a small subgroup of patients (2.7%) with RB with wild type *RB1* and who were found to have MYCN amplification. (21)

How can one find out if the patient's retinoblastoma is inherited?

When a child is diagnosed with retinoblastoma, it is important to determine if it is the heritable form or the non-heritable form of the disease. Unilateral tumors affect one eye and could be hereditary or sporadic retinoblastoma, whereas bilateral tumors which affect both eyes are of the hereditary subtype. It however must be emphasized that not all hereditary retinoblastomas are bilateral when they are found.

Bilateral or multifocal retinoblastoma is due to a germline *RB1* mutation that can be passed to the next generation. Heritable (germline) mutation in *RB1* gene usually affects about 90% of cases that develop retinoblastoma in early infancy, making genetic analysis an important aspect of management of the disease. 25% of germline retinoblastomas are acquired from a carrier parent (who was diagnosed with RB during childhood) and 75% germline retinoblastoma occur *denovo* during embryogenesis (no family history of retinoblastoma). In this situation, a new mutation that arose at random around the time of conception has ultimately led to the occurrence of retinoblastoma. In either situation, an *RB1* gene mutation can be found in all of the child's cells, including reproductive cells. Because the mutation is present in reproductive cells, there is a 50% possibility that the *RB1* mutation will be passed on to future generations, which is known as germline mutation. Forty percent of Retinoblastomas are of the hereditary (germline) subtype. The remaining 60% of children with retinoblastoma have a sporadic form of retinoblastoma that

cannot be inherited from generation to generation. Both *RB1* mutations are found only in the retinal cells in this patient.

Ninety-five percentage of individuals who have the *RB1* germline mutation develop retinoblastoma. As a result, parents of children who have hereditary retinoblastoma or any family history should be considered for genetic testing. It is also recommended that parents should also undergo a thorough ophthalmic evaluation to look for any evidence of previous retinoblastoma.

Is it important to screen for genes other than *RB1* gene?

In recent studies, fewer than 3% of the tumors have been found to be having MYCN amplification. These tumors are the ones that lack RB1 gene mutation. Is MYCN amplification the single genetic event that causes these tumors to become malignant, and do these tumors avoid the RB1 gene mutation? Is there a difference in pathology between these cancers? These questions remain unresolved, necessitating further research.

Is a child with retinoblastoma at risk of other related cancers?

Long-term side effects of radiation and chemotherapy may cause second malignancies in retinoblastoma patients. A child with hereditary retinoblastoma has an increased risk of acquiring malignancies other than those of the eye such as Pineoblastoma (a tumor in the pineal gland in the brain), osteosarcoma, soft tissue sarcomas, and melanoma. Second malignancy rates are greater in children treated for hereditary retinoblastoma than in people treated for sporadic retinoblastoma (cumulative incidence 36% vs 5% respectively) (22) suggesting a genetic vulnerability to a range of malignancies. Additionally, children with germline mutation of RB1 gene, who have received radiotherapy for treatment of retinoblastoma, have a significantly increased incidence of developing second malignancies compared to children who have not received radiotherapy (Cumulative lifetime incidence 38% Vs 21%) (23). Screening criteria are

recently advised to detect non-ocular malignancies at an early stage; however, the effectiveness of this screening has yet to be confirmed. Whole-body MRIs are also being studied to see if they can help persons with inherited retinoblastoma.

Is it necessary for the family of a child with retinoblastoma to have genetic testing?

All children with retinoblastoma should be considered for genetic counselling, screening and genetic testing where possible. Genetic counselors are available to meet with families to discuss the advantages, limitations, and risks of testing. They can also assist in the interpretation of test results.

In patients with unilateral disease, if enucleation has been performed then tumor DNA can be used for detecting the RB gene mutations. If mutation is identified then the same can be looked for in leucocytes DNA of peripheral blood or from DNA extracted from saliva of the patient. If one of the mutations is detected in the leukocyte DNA then the child has a germline RB which is heritable. If the mutation is not found in the leucocyte DNA, the possibility of it being heritable RB cannot be ruled out completely owing to the presence of low-level mosaicism. Future children of the proband must be screened for mutations identified in the tumour DNA, whereas other family members do not require genetic testing.

If a tumour sample is not available and no mutation is found in leukocyte DNA, there is still a 1% to 1.5% possibility of an undetected germline mutation. In such circumstances, the unaffected eye should be monitored until the child is five years old. The offspring of such youngsters should be monitored as well.

In bilateral or multifocal disease, germline mutation can be identified in the leucocyte DNA in the peripheral blood/saliva in 95% of children. If the mutation cannot be identified in peripheral

blood in a patient with bilateral disease and tumor DNA shows both mutations, low-level mosaicism is assumed and the proband's offspring is at risk of Retinoblastoma and needs surveillance. (24) If germline mutation is not identified by conventional methods and the patient has a positive family history, then linkage analysis can be used to clarify the mutation status of at-risk family members.

For DNA Analysis, blood specimens should not only be taken from the patient but also from the parents and any siblings, which could help with genetic counselling. If an *RB1* gene mutation is present in the blood, it is feasible to search for it in siblings of the patient, who may need to be evaluated for disease development. If an *RB1* gene mutation has been detected in the family, genetic testing can be done before conception. It can also be done during pregnancy or after the delivery of a child. (Figure 1)

A single genetic test is unlikely to detect all germline *RB1* gene mutations. It is necessary to combine various modalities such as DNA sequencing, FISH, MLPA, PCR, Methylation studies to increase the sensitivity of detection of *RB1* gene mutation to 90% to 95%. Although direct sequencing is commonly used to detect *RB1* mutations, it is not recommended for detecting low allelic-fraction variants. PCR can only be used to detect these types of variants when the mutations are already known. In many laboratories karyotyping and FISH are replaced by MLPA for detecting large *RB1* rearrangement, cytogenetic and subcytogenetic abnormalities.(25) There are various epigenetic processes linked to *RB1* gene such as microRNA regulation, DNA methylation, histone modification, and ATP-dependent chromatin reorganization. Inactivation of *RB1* gene results in rapid epigenetic dysregulation of cancer genes that contribute to retinoblastoma's critical cellular characteristics. For detecting all probable RB1 mutations, a combination of the aforementioned approaches is required. Next Generation Sequencing has

recently been introduced as a rapid and successful technique for identifying all changes in *RB1* genes, providing a number of advantages, including high sensitivity and cost-effectiveness. These techniques are not used in all laboratories to detect the *RB1* gene mutations.(25) If genetic testing cannot be done due to non-availability of facilities for these techniques, then siblings/parents need to be screened through EUA.

Is it important to have prenatal testing and preimplantation genetic testing for retinoblastoma?

Children with a family history of retinoblastoma and carrying the germline RB1 gene mutation are at risk of developing the tumor. Prenatal testing might be useful for parents to determine whether the pregnancy is affected by *RB1* gene mutation running in the family. Preimplantation genetic testing can be done before pregnancy or along with in-vitro fertilization (IVF). This gives an option to test the *RB1* gene mutation in embryo before it is implanted into the uterus. Similarly, prenatal testing can be done during pregnancy in two ways: chorionic villus sampling (CVS) which is during first trimester and prenatal amniocentesis which is done during second trimester or later. This provides parents the option of how to manage the pregnancy in case of the fetus carrying the *RB1*gene mutation.

More importantly examination of the eyes can be begun at birth and repeated EUA during the first years of life facilitates early detection the retinoblastoma which can be managed by less invasive interventions, consequently leading to a better visual outcome.(26)

What is the risk of retinoblastoma in siblings (of children with retinoblastoma) or future children?

Retinoblastoma is inherited as a Mendelian autosomal trait but with incomplete penetrance i.e. the likelihood of occurrence of the disease is 90% of those carrying it. Hence, all future children of a proband with heritable Retinoblastoma have a 45% chance of developing the malignancy and not 50%. Risks of Retinoblastoma for the proband's siblings depend on parental status. If a parent has a history of RB, retinoma, or positive genetic testing results, future offsprings have a 45% risk of RB. If neither parent's testing reveals the familial RB1 mutation, subsequent children have a 2% to 3% chance of inheriting the mutation due to undetectable low-level mosaicism in one of the parents. (27) Any unaffected child found to have a germline *RB1* mutation should be examined under anesthesia every 3 to 4 weeks until the age of 1 and then every 3 to 4 months until the age of 5 years. The following table illustrates the risk

Table 1: Probability of disease occurrence in subjects, offspring and siblings of carriers of *RB1* gene mutations

Subjects	**Probability of disease (%)**
Subjects with carriers of RB1 gene mutation	90
Offspring of patient with bilateral retinoblastoma	45
Sibling of patient (if either parent is affected)	45
Sibling of patient with bilateral disease (with parents unaffected)	2
Sibling of patient with unilateral disease (with parents unaffected)	1

(reference; requested permission from authors)

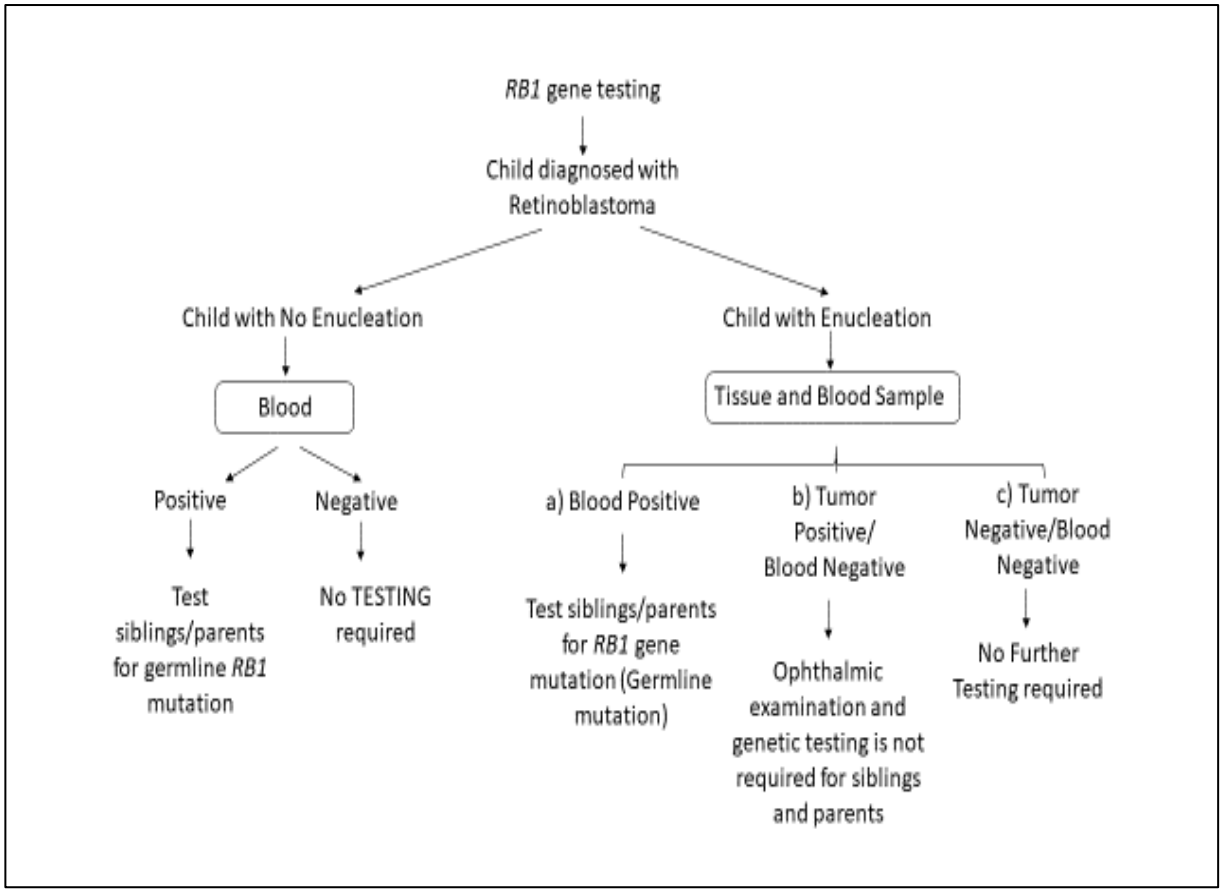


Figure 1: *RB1* Genetic testing

PATHOLOGY

Retinoblastoma arises from the sensory retina and grows initially into the intraocular compartments like choroid, vitreous, and anterior chamber. There are two growth patterns of RB, exophytic (away from vitreous) and endophytic (towards vitreous). Exophytic RB arising from outer layers of retina results in subretinal seeds and retinal detachment. Endophytic RB arising from the inner retinal layers causes vitreous seeding. Other types of growth patterns include mixed (both endophytic and exophytic growth) and diffuse infiltrating orbital pattern. Patients with tumors extending into the anterior chamber can present with white fluffy exudates in the anterior chamber. (28) When there is a delay in diagnosis, it spreads to extraocular compartments involving the orbit, optic nerve, regional lymph nodes and distant metastatic sites.

DIAGNOSIS AND WORKUP

Evaluation of a child with suspected retinoblastoma

Imaging in retinoblastoma

Most cases of retinoblastoma can be diagnosed based on clinical fundus evaluation and ultrasound. Indications for imaging in retinoblastoma are

a) Cases with diagnostic dilemma

b) To rule out extraocular extension in cases of

- Group E retinoblastoma
- Diffuse infiltrative retinoblastoma
- Group B-D retinoblastoma with tumour involving optic nerve head

c) Extraocular retinoblastoma for categorizing the type and extent of extraocular disease and CNS metastasis

d) In cases with bilateral intraocular retinoblastoma/familial disease/suspected or proven germline mutations to rule out possible concurrent pineoblastoma known as trilateral retinoblastoma. Histologically, these pineoblastomas show features similar to retinoblastoma differentiation like Flexner–Wintersteiner rosettes and fleurettes. Trilateral retinoblastoma occurs in 5–15% of children with germline mutations. (22,29) Besides the pineal region (pineoblastoma), these tumors may also occur in the suprasellar or parasellar regions. RBT can develop in both familial and sporadic forms of retinoblastoma, with a varied prevalence of 0.5-2% in unilateral RB cases and up to 6% in bilateral RB cases.

e) To look for brain malformations in patients with 13q deletion syndrome

f) To look for any orbital recurrence in suspected cases post enucleation.

Role of ultrasound (USG) in retinoblastoma

Ocular USG is usually the first imaging performed in a suspected case of retinoblastoma. In retinoblastoma, USG typically demonstrates an intraocular mass that is more echogenic than the vitreous, with characteristic fine calcifications seen as highly reflective foci with an acoustic shadowing.(30)

Presence of calcification helps in differentiating retinoblastoma from other intraocular mass lesions in the pediatric age group such as persistent hyperplastic primary vitreous (PHPV). Color Doppler can be useful for detecting and differentiating a vascularized intraocular mass in case of retinoblastoma that is associated with vitreous hemorrhage or effusion.

Ideal use: Ocular USG can be done in cases with suspected RB to

- detect intratumoral calcification and rule out other causes of leukocoria
- look for associated retinal detachment
- tumor growth pattern- endophytic exophytic or diffuse infiltrative
- look for presence of vitreous seeds
- Baseline measurement of tumor height and diameter and monitoring response to treatment

Essential use: It is an essential tool for baseline measurement of tumor height and diameter and monitoring response to treatment

MRI vs CT Scan in Retinoblastoma

Cases of diagnostic dilemma

MRI picks up soft tissue features of diseases mimicking retinoblastoma like PHPV, Coats' disease, FEVR and ROP, and therefore is more useful than CT scan in differentiating retinoblastoma from the other differentials of leukocoria. CT scan on the other hand is the best imaging modality for detection of intraocular calcifications and thus can aid in diagnosis in case of clinical dilemma. Reports from literature document a sensitivity of 81–96% for CT scan detection of calcifications in retinoblastoma, which is higher as compared to USG (≤92.5%). (31) Therefore, both MRI and CT can be used in cases of diagnostic dilemma. But due to inherent risk of radiation exposure, it should be avoided in bilateral retinoblastoma or those with known germline mutation. CT scan may be used in unilateral cases with diagnostic dilemma

Detecting extraocular extension and high-risk features of metastasis.

MRI is more sensitive and specific than CT for detection of tumor extent and metastatic risk factors like choroidal invasion, post laminar optic nerve invasion, anterior chamber iris invasion. MR imaging using high-resolution protocols is currently considered to be the most accurate and valuable tool in pre-treatment staging of retinoblastoma. **Thus, CEMRI is the modality of choice for retinoblastoma treatment.**

CONSENSUS STATEMENT: *There was debate amongst team members regarding the use of CT scan for ruling out extraocular extension in unilateral cases of retinoblastoma. It was agreed that availability of CEMRI facility may be limited in several areas of the country, also the facility of general anaesthesia may not be available at such limited Radiology centers. Thus, while MRI is the ideal imaging for picking up high risk features of metastasis (retrolaminar optic nerve enhancement, choroidal and anterior chamber invasion) in group E retinoblastoma and extraocular extension,* ***CT scan may be considered the essential imaging modality for ruling out extraocular extension in unilateral cases of retinoblastoma.***

Evidence Supporting the Use of MRI for the Identification of High Risk Disease

MRI can be used to prognosticate patients with orbital retinoblastoma. Radhakrishnan et al. reported the MRI findings at baseline and after three cycles of neoadjuvant VEC chemotherapy in 28 patients with IRSS stage III retinoblastoma. (32) They proposed a staging system based on the optic nerve thickness, contrast enhancement, and length of involvement on MRI. The proposed staging at baseline and after NACT could predict event-free survival (EFS) and overall survival (OS). The findings of Radhakrishnan et al. were confirmed in a study by Chawla et al. (33) They observed that combined thickening and enhancement of the optic nerve had a sensitivity, specificity, and accuracy of 100%, 82.4%, and 85%, respectively, in predicting post laminar optic nerve involvement. Presence of bilateral tumor (OR, 95% CI), tumor covering optic disc (OR, 95% CI), and tumor with ON enhancement (OR, 95% CI) increased the odds of having a histopathological posterior laminar optic nerve invasion. (34) Presence of isointense

signal of tumor on T2 weighted image excluded post laminar optic nerve invasion. Kim et al. compared CT and MRI preoperatively to predict optic nerve involvement in the enucleated specimen. (35) The study included 97 eyes, and among them, 30 eyes showed optic nerve involvement (laminar and retrolaminar) on histopathological examination. MRI significantly predicted histopathological optic nerve involvement compared to CT scan. The sensitivity, specificity, positive predictive value, and negative predictive value of CT scan and MRI to predict histopathological optic nerve involvement was 20%, 88.89%, 50%, and 66.67% and 40%, 93.55%, 66.67%, and 82.86% respectively. Another study compared CT and MRI to assess high-risk factors, including scleral, choroidal, anterior eye segment invasion, and postlaminar optic nerve invasion and observed that CT was inferior to MRI in identifying high-risk features in retinoblastoma. (36)

Intraocular tumor volume and size calculated using an MRI can predict massive choroidal involvement and PLONI in retinoblastoma. A retrospective study of 60 patients with retinoblastoma by Hiasat et al. showed that MRI done prior to enucleation was accurate in detecting prelaminar optic nerve invasion in the pathological specimen in 77% of patients, 56% for laminar invasion and 84% for postlaminar invasion, and 100% for optic cut edge invasion. (37) MRI detected Extrascleral extension in 96% of patients.

Abusayf et al. reported that MRI was less sensitive for diagnosing prelaminar and laminar optic nerve invasion (0.0 and 42.9%) compared to post-laminar invasion (88.9%) in retinoblastoma. (38) They recommended that if MRI shows evidence of PLONI, but the histopathology examination does not reveal PLONI then it is essential to obtain additional and deeper sections as usually PLONI is picked up when doing so.

A meta-analysis of 12 studies including 1240 patients and 1255 enucleated globes reported that MRI was an acceptable modality in detecting PLONI in patients with retinoblastoma. (39) The heterogeneity among studies was due to the variations in the MRI strength and protocols. Therefore, there is a need for developing standard MRI protocols for imaging optic nerve in retinoblastoma.

Table 2: Essential minimum MRI protocol *as advocated by the European Retinoblastoma Imaging Collaboration*

Requirements

Scanner and coils

3.0-T system combined with multichannel head coil Sequences (minimum requirements)

Orbits

Transaxial T2-W (slice thickness ≤ 2 mm) Eye(s) and optic nerve(s)

Unilateral advanced disease:

Precontrast T1-W; at least one plane: transaxial or sagittal oblique

T2-W; at least one plane: transaxial or sagittal oblique

Post Contrast T1-W, no FS; transaxial and oblique sagittal

Bilateral advanced disease: Postcontrast T1-W, no FS; sagittal oblique of both eyes in addition

Brain

Transaxial T2-W (slice thickness ≤ 4 mm)

Postcontrast T1-W (2D SE with slice thickness ≤ 3 mm or 3D

GRE ≤ 1 mm)

FS fat-saturation, SE spin-echo, GRE gradient-echo

Table 3: Checklist for parameters to be evaluated on MRI in a case of retinoblastoma
Orbit
Tumor characteristics
Tumor intensity relative to vitreous body (moderately high on T1-W and low on T2-W)
Laterality
Growth pattern
Tumor size and location in reference to optic nerve
Buphthalmia
Tumor extension
Optic nerve and meningeal sheath invasion
Ocular wall invasion (choroid and sclera)
Anterior chamber invasion/ enhancement
Ciliary body invasion
Extraocular extension
Brain
Pineoblastoma(pineal region)
Leptomeningeal metastases
Malformations

Does optic nerve uptake on PET scan predict outcome?

PET/CT scans are desirable but not essential for staging and response assessment in retinoblastoma. Radhakrishnan et al. evaluated the role of PET/CT in IRSS stage III retinoblastoma. (40) They observed

that optic nerve uptake at baseline on PET/CT and response after neoadjuvant chemotherapy are strong predictors of EFS and OS in IRSS stage III retinoblastoma.

When to do a biopsy?

Retinoblastoma diagnosis is based on clinical and imaging findings. However diffuse anterior infiltrative retinoblastoma which does not have any posterior segment mass is likely to be misdiagnosed and such cases may need fine needle aspiration biopsy. (41)

Role of Examination under Anaesthesia (EUA)

The aim of examination is to be able to grade the tumor according to ICRB classification that helps guide treatment and prognosis. The following points have to be noted

Table 4: Parameters to be noted on EUA		
1) Intraocular pressure with Perkins Tonometer.		
2) Corneal diameters		
3) Presence of scleral thinning and staphyloma		
4) Anterior chamber examination	a) Corneal haze b) Iris neovascularization c) Ectropion uveae d) Hyphema e) Pseudohypopyon f) Anterior chamber seeds	
5) Lens status	Clear/ cataractous	
6) Posterior segment evaluation on Indirect Ophthalmoscopy	a) Vitreous hemorrhage b) Tumor touching posterior lens surface c) Tumor filling more than half of globe, diffuse infiltration of retina with or without retinal detachment **(*Diffuse infiltrative morphology*)**	Tumor morphology should be noted as *i) Endophytic:* if it is growing into a vitreous cavity. *ii) Exophytic:* if it is growing into subretinal space and is associated with exudative Retinal detachment
Note: If any of the above findings is positive, the eye is graded as group E and planned for enucleation after excluding extraocular disease		
7) For Smaller tumours following details are to be *noted and documented either on a retinal diagram and preferably also on RETCAM*		

a) Tumour location	i) Posterior to equator ° Distance from macula ° Distance from ONH ii) Anterior to equator iii) Near ora-serrata	
b) Quadrant of location:	Supero-temporal Superonasal Inferotemporal Inferonasal	
c) Presence of vitreous seeds:	Focal/ diffuse Morphology ° Cloud ° Spheres ° Dust	If diffuse, number of quadrants involved
d) Presence of sub retinal seeds	Focal/diffuse	If diffuse, number of quadrants involved
e) Presence of retinal detachment	Focal/diffuse	If diffuse, number of quadrants involved
f) Tumour dimensions	Height and base diameter on Ultrasound.	

Role of metastatic workup in extraocular retinoblastoma

EORB has high incidence of lymph node metastasis, intra-cranial spread, leptomeningeal dissemination, or hematogenous spread. Magnetic resonance imaging (MRI) of orbits with the brain is recommended in all patients. If MRI orbit and brain cannot be performed, then a CT scan is desirable. A bone marrow aspiration and biopsy from the posterior superior iliac spine, lumbar puncture and a bone scan should be

done to rule out distant metastasis. Whole-body 18-fluorodeoxyglucose (18-FDG) positron emission tomography with computed tomography (PET/CT) is desirable but not mandatory. (42) Bone scan can be omitted if the patient has undergone a PET CT.

Future Research Area:

Role of tumor-derived DNA in the aqueous humor of retinoblastoma eyes to do genetic analysis

Cell-free DNA examination in aqueous humor (AH) of Rb eyes undergoing salvage therapy might be used as a surrogate tumor biopsy when Rb tissue is not available. With more research, this unique method may be used to diagnose Rb in the scenario of a diagnostic problem, as well as to see if particular chromosomal copy number variation profile characteristics or RB1 mutations are associated with prognosis or therapy response. While further research is needed, this surrogate biopsy has the potential to change the way we treat children with cancer. AH sampling and tumor biomarker analysis could provide novel clinical implications for Rb diagnosis, prognosis, and/or therapy.

STAGING AND CLASSIFICATION

Pathological Tumor, Node, Metastasis Classification

Staging system is an important factor in choosing treatment. There are multiple staging systems in retinoblastoma. Tumor, node, metastasis (TNM) classification is developed by the American Joint Commission on Cancer (AJCC) and the Union International Control Cancer. (43) TNM is a global system for describing the location and spread of cancer in the body of a patient. T stands for tumor size and any cancer spread into neighbouring tissue; N stands for cancer spread to nearby lymph nodes; and M stands for metastasis (spread of cancer to other parts of the body). This involves both intraocular and extraocular aspects in the same system.

Retinoblastoma is the first cancer in which the role of germline predisposition is recognised by incorporating stage category "H" into the AJCC classification. Recently, AJCC 2017 8th edition described the tumor, node, metastasis, heritable trait (TNMH) clinical (c) and pathological (p) staging system which is known to be the first evidence-based system for predicting overall prognosis of both eye(s) and patients. (44) This is a comprehensive AJCC retinoblastoma staging system that predicts both risk of metastasis and possibility of globe salvage.

Table 5: AJCC pathological classification (pTNM)

Primary tumor (pT)	
pTX	Primary tumor cannot be assessed
pTO	No evidence of primary tumor
pT1	Tumor confined to the eye with no optic nerve or choroidal invasion
pT2	Tumor with minimal invasion of optic nerve or choroid
pT2a	Tumor superficially invades optic nerve head, or tumor exhibits focal choroidal invasion but does not extend past lamina cribrosa
pT2b	Tumor superficially invades optic nerve head and tumor exhibits focal choroidal invasion but does not extend past lamina cribrosa
pT3	Tumor with significant optic nerve and/or choroidal invasion
pT3a	Tumor invades optic nerve past lamina cribrosa but not to surgical resection line, or tumor exhibits massive choroidal invasion
pT3b	Tumor invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion
pT4	Tumor invades optic nerve to surgical resection line or exhibits extra-ocular extension elsewhere

pT4a	Tumor invades optic nerve to resection line, but no extra-ocular extension identified
pT4b	Tumor invades optic nerve to resection line, and extra-ocular extension identified
Regional lymph nodes (pN)	
pNX	Regional lymph nodes cannot be assessed
pNO	No regional lymph node metastasis
pN1	Regional lymph node involvement (preauricular, cervical)
pN2	Distant lymph node involvement
Metastasis (pM)	
pMX	Presence of metastasis cannot be assessed
pM0	No distant metastasis
pM1	Metastasis to sites other than central nervous system
pM1a	Single lesion
pM1b	Multiple lesions
pM1c	Central nervous system metastasis
pM1d	Discrete masses without leptomeningeal and/or cerebrospinal fluid involvement
pM1e	Leptomeningeal and/or cerebrospinal fluid involvement

Table 6: AJCC cTNMH retinoblastoma staging

Primary tumor(cT)	
cTX	Unknown evidence of intraocular tumour
cTO	No evidence of intraocular tumor
cT1	Intraocular tumour(s) with subretinal fluid ≤5mm from the base of any tumour

	cT1a	Tumours ≤3mm and further than 1.5mm from the disc and fovea
	cT1b	Tumours >3mm or closer than 1.5mm to the disc and fovea
cT2		Intraocular tumour(s) with retinal detachment, vitreous seeding or subretinal seeding
	cT2a	Subretinal fluid >5mm from the base of any tumour
	cT2b	Tumours with vitreous seeding and/or subretinal seeding
cT3		Advanced intraocular tumour(s)
	cT3a	Phthisis or pre-phthisis bulbi
	cT3b	Tumour invasion of the pars plana, ciliary body, lens, zonules, iris or anterior chamber
	cT3c	Raised intraocular pressure with neovascularization and/or buphthalmos
	cT3d	Hyphema and/or massive vitreous haemorrhage
	cT3e	Aseptic orbital cellulitis
cT4		Extraocular tumour(s) involving the orbit, including the optic nerve
	cT4a	Radiological evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues
	cT4b	Extraocular tumour clinically evident with proptosis and orbital mass

Regional lymph nodes (cN)

cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph nodes involvement
cN1	Evidence of preauricular, submandibular, and cervical lymph node involvement

Distant metastasis (M)

cM0		No signs or symptoms of intracranial or distant metastasis
cM1		Distant metastasis without microscopic confirmation
	cM1a	Tumour(s) involving any distant site (*e.g.* bone marrow, liver) on clinical or radiological tests
	cM1b	Tumour involving the central nervous system on radiological imaging (not including trilateral retinoblastoma)
pM1		Distant metastasis with microscopic confirmation
	pM1a	Histopathological confirmation of tumour at any distant site (*e.g.* bone marrow, liver, or other)
	pM1b	Histopathological confirmation of tumour in the cerebrospinal fluid or central nervous system parenchyma
Heritable trait (H)		
HX		Unknown or insufficient evidence of a constitutional *RB1* gene mutation
H0		Normal*RB*1 alleles in blood tested with demonstrated high sensitivity assays
H1		Bilateral retinoblastoma, retinoblastoma with an intracranial central nervous system midline embryonic tumour (*e.g.* trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of constitutional *RB1* gene mutation

Table 7: International Retinoblastoma Staging System (IRSS)(45)

IRSS Stage	**Clinical Description**
0	Patient treated conservatively
I	Eye enucleated, completely resected histologically

IRSS Stage	Clinical Description
II	Eye enucleated, microscopic residual tumour (scleral involvement by tumor or retrolaminar optic nerve involvement by tumor)
III	Regional extension
a.	Overt orbital disease (clinical or radiological)
b.	Preauricular or cervical lymph node extension
IV	Metastatic disease
a.	Hematogenous metastasis (without central nervous system involvement) 1. Single lesion 2. Multiple lesions
b.	Central nervous system extension (with or without any other site of regional or metastatic disease) 1. Prechiasmatic lesion 2. Central nervous system mass 3. Leptomeningeal and cerebrospinal fluid disease

Intraocular Classification of Retinoblastoma

Currently, ICRB classification is the most commonly used scheme for grading of IORB worldover. However, there are two commonly used versions of this classification: published as ICRB from Philadelphia and IIRB/IIRC classification from Los Angeles. Most Indian studies have used ICRB (Philadelphia version)

It was discussed amongst the team members that Retinal detachment is not used as a criteria for grading in ICRB classification scheme. However, cases with retinal detachment have the potential of having subretinal seeds. Therefore, for tumors with RD, IIRC criteria of classification may be used: tumors with

RD less than 1 quadrant may be classified as group C and those with more than 1 quadrant of RD as group D. (CONSENSUS STATEMENT)

Table 8: **Intraocular Classification of Retinoblastoma (ICRB)**

Group	Intraocular Classification of Retinoblastoma (ICRB)
A	Tumor ≤ 3 mm (in basal diameter or height/ thickness)
B	Tumor > 3 mm (in basal diameter or height/ thickness) OR • Macular tumor located ≤3 mm from foveola • Juxta-papillary tumor located ≤1.5 mm from optic nerve head • Presence of limited subretinal fluid not extending beyond 3 mm from the tumor margin
C	Retinoblastoma with focal seeding: • Localised subretinal seeds (≤ 3 mm from tumour) • Localised vitreous seeds (≤ 3 mm from tumour) • Both localised subretinal and vitreous seeds
D	Retinoblastoma with diffuse seeding: • Subretinal seeds extending beyond 3 mm from tumour margin • Vitreous seeds extending beyond 3 mm from tumour margin • Both diffuse subretinal and vitreous seeds
E	•Retinoblastoma filling >50% globe OR retinoblastoma with • Neovascular glaucoma • Presence of opaque media from hyphema, or vitreous or subretinal haemorrhage •History of aseptic orbital cellulitis • Phthisis Bulbi • Imaging evidence of invasion of • Anterior chamber, choroid (>2 mm) sclera or postlaminar optic nerve.

Globe salvage rates expected for different groups of retinoblastomas

Table 9: Expected globe salvage rates for different groups of retinoblastoma

Author	**Grp A**	**Grp B**	**Grp C**	**Grp D**	**Grp E**
Shah et al	100%	100%	100%	29.4%	0%
Chawla et al	100%	94%	83%	54%	0%
Singh et al	100%	100%	91.7%	17.1%	0%

MANAGEMENT OF RETINOBLASTOMA

A search was performed in PUBMED and Google Scholar from inception to Feb 1, 2022, using the term "intraocular retinoblastoma," "unilateral retinoblastoma," "bilateral retinoblastoma", "retinoblastoma classification", "group D retinoblastoma", "TTT", "chemoreduction", "brachytherapy" "intraarterial chemotherapy" "extraocular retinoblastoma," "orbital retinoblastoma," "IRSS stage 3", "IRSS stage 4", "metastatic retinoblastoma," "retinoblastoma AND radiotherapy," and "retinoblastoma survivorship." The authors screened articles in the English language. Articles relevant to the guidelines were selected and reviewed by the authors.

The ideal management of retinoblastoma requires a multi-speciality team including ocular oncologist, pediatric oncologist, pathologist, radiologist, radiotherapist and interventional radiologist. Such multispecialty care is limited by availability in LMIC, further financial constraints of the patient that are typical to such countries further compromise the feasibility of ideal treatment as per world literature. The

NGOs play a crucial role in financial assistance, counselling and providing social support to ensure compliance and timely treatment. Retinoblastoma treatment outcomes from North America and Europe have shown paradigm changes in globe salvage and life salvage. However, in LMIC treatment still remains challenging. (46)

Table 10: Chemotherapy regimens used in retinoblastoma.

Chemotherapy Regimen	**Drugs and Doses**	**Frequency**
Intravenous (First-Line)		
VEC (standard dose carboplatin)	● Vincristine 0.05 mg/kg (Age ≥3 years: 1.5 mg/m^2), intravenous over 15 mins on day 1. The maximum dose is not to exceed 2 mg. ● Carboplatin 18.6 mg/kg (Age ≥3 years: 560 mg/m^2), intravenous over 60 mins on day 1. ● Etoposide 5 mg/kg (Age ≥3 years: 150 mg/m^2), intravenous over 60 mins on days 1 and 2.	every 3 weeks
VEC (high dose carboplatin)	● Vincristine 0.05 mg/kg (Age ≥3 years: 1.5 mg/m^2), intravenous over 15 mins on day 1. ● Carboplatin 25 mg/kg (Age ≥3 years: 750 mg/m^2), intravenous over 60 mins on day 1. ● Etoposide 5 mg/kg (Age ≥3 years: 150 mg/m^2), intravenous over 60 mins on days 1 and 2.	every 3 weeks
Intravenous (Orbital recurrence and prior VEC chemotherapy exposure)		
	● Ifosfamide 3 gm/m^2 over 3 hours intravenous infusion in normal saline on days 1 and 2.	every 3 weeks, up to 6 cycles

	• Mesna 900 mg/m^2 intravenous push at 0, 4, and 8 hours on days 1 and 2. • Adriamycin 25 mg/m^2 over 4 hours intravenous infusion in normal saline on days 1 and 2. • Vincristine 1.5 mg/m^2 slow intravenous push on day 1. The maximum dose is not to exceed 2 mg.	
	• Vincristine less than 12 months 0.05mg/kg slow intravenous push on day 1. More than 12 months, 1.5 mg/m^2 slow intravenous push on day 1. The maximum dose is not to exceed 2 mg. Course 1 to 11. • Intravenous Topotecan. 3 mg/m^2/day. Course 1, 2, 5, 8, and 11. • Intravenous Carboplatin. Area Under Curve 6.5 mg/ml/min on day 1. Course 3, 4, 6, 7, and 10. • Subconjunctival carboplatin 20mg/m^2 single dose. Course 5 and/or 8 and/or 11.	Each course administered once in 21 days
Intra-arterial		
Melphalan	Slow pulsatile infusion over 30 min • 0–2 years: 3 mg/30 cc • 2–5 years: 5 mg/30 cc • 4-5 years : 7.5 mg/30 cc	
Carboplatin	30 mg/30 cc slow pulsatile infusion over 30 min	
Topotecan	Slow pulsatile infusion over 30 min • 0–2 years: 0.5 mg/30 cc • ≥ 2 years: 1.0 mg/30 cc	

Intravitreal		
Melphalan	8–30 µg/0.1cc. Intravitreal injection through pars plana or clear corneal approach, cryotherapy to injection site. Eye should be jiggled to mix chemotherapy.	Every month
Methotrexate	400-800 µg/0.1cc. Intravitreal injection through pars plana or clear corneal approach, cryotherapy to injection site.	Twice weekly for a month, then weekly for a month and then monthly for a year.
Sub-tenon		
Carboplatin	20 mg/2 cc. Injection into subtenon's space, directly over sclera in area of tumour	

Table 11: RT recommendations, dose and target volume

Stage	Indication of RT	RT dose	Target volume
Group A-C	Previous failed chemotherapy and local therapy (If plaque brachytherapy not available or if multifocal disease)	36-45 Gy	Residual disease +5mm margin for CTV + 3-5 mm margin for PTV

Group D	Previous failed chemotherapy and local therapy	36-45	whole eye should be treated along with 5mm margin of optic nerve (anterior chamber can be spared if no vitreous seeding).
Group E	Extra-scleral extension and optic nerve cut end positive	40-45 Gy	Whole orbit Extend the CTV till optic chiasma if optic nerve cut end is positive
Orbital disease	All patients	40-45 Gy	Whole orbit
Preauricular and cervical lymph node metastasis	All patients	40-45 Gy	Proven/involved pre-auricular/cervical lymph nodes/entire LN chain –level of evidence-4 (No strong on target volume but it is recommended.
Bone metastasis	Palliative	8 Gy/1 fraction or 20 Gy in 5 fractions	Painful sites
Liver metastasis	Palliative	8 Gy/1 fraction or 20 Gy in 5 fractions	-

CNS metastasis	Palliative	Craniospinal irradiation (CSI) (23-36 Gy) or Whole brain radiotherapy (WBRT) 20 Gy in 5# or 30 Gy in 10#	CSI or WBRT

What are the minimum facilities needed for treatment of retinoblastoma?

A review of Literature on retinoblastoma from India shows that a significant percentage of retinoblastoma cases that present to tertiary eye care centers have advanced IO disease as compared to NA and Europe.(9,13) This points to a need for improving awareness at primary care level, amongst pediatricians, ophthalmologists, possibly teachers and **focussed screening practices** that may help pick this tumor early and improve globe salvage.(47) Notably retinoblastoma has a long clinical latent period before it presents with frank leucocoria. A simple distant direct ophthalmoscopy can pick up retinoblastoma in pediatric patients.(48) This can be exploited for early detection of retinoblastoma. A possible model of care for early detection of retinoblastoma at primary care level in the community is suggested in the text. (Table 18)

The preferred mode of treatment depends on the availability of expertise and infrastructural resources and hence varies in resource constrained countries as compared with developed countries. While ideally facility for all the treatments must be available at a hospital catering to management of retinoblastoma, **enucleation that remains the most common treatment for unilateral advanced intraocular retinoblastoma in LMIC** may be performed at centers that have minimum essential facilities for preoperative diagnosis and postoperative pathological assessment of the enucleated eye. (Table 12)

It is important to note that prescribing an early, prompt essential care can play a vital role in preventing delay in treatment and hence disease progression and thus improve life salvage. However, on the other hand an inadequate early treatment may produce more confusion in planning further treatment and increase risk of tumor recurrence and even death

Table 12: Where Can You Enucleate an Eye for Retinoblastoma?

	Personal	**Infrastructure**	**Need/ justification**
Ideal care facility	Oculoplastic Surgeon	Ophthalmic OPD, IPD and OT services	For retinoblastoma appropriate enucleation with orbital implant
	Radiologist	Radiodiagnosis services	For planning an adequate imaging and evaluation of case of advanced IORB
	Ocular Pathologist	Pathology services	For appropriate histopathological evaluation and an adequate reporting of enucleated eyes
	Medical Oncologist	Chemotherapy facility (Medical or Pediatric Oncology)	For providing adjuvant chemotherapy needs

Table 12: Where Can You Enucleate an Eye for Retinoblastoma?

	Personal	**Infrastructure**	**Need/ justification**
	Radiation Oncologist	Radiotherapy facility	For adjuvant EBRT when indicated
	Ocularist		Ocular prosthesis fitting
Essential care facility	Oculoplastic Surgeon	Ophthalmic OPD, IPD and OT services	For retinoblastoma appropriate enucleation with orbital implant
	Radiologist	Radiodiagnosis services	For planning an adequate imaging and evaluation of case of advanced IORB
	Ocular Pathologist	Pathology services	For appropriate histopathological evaluation and reporting of enucleated eyes
	Medical Oncologist	Chemotherapy facility (Medical or Pediatric Oncology)	For providing adjuvant chemotherapy needs
*OPTIONAL	Radiation Oncologist		

Table 12: Where Can You Enucleate an Eye for Retinoblastoma?			
	Personal	**Infrastructure**	**Need/ justification**
OPTIONAL	Ocularist		Ocular prosthesis fitting

**as debated and discussed amongst team members- Radiotherapy is required in very few cases after upfront enucleation for advanced IORB, radiotherapy facility may be therefore be an optional requirement for centers in order to practice enucleation for, however it is desirable that such facility maybe created at such centers.*

Only cases with **unilateral advanced intraocular retinoblastoma** group D / E eyes must be enucleated at such facilities. *Cases with bilateral disease or a family history must be referred to facilities competent to perform EUA and focal treatment.* Patients requiring small volume RT i.e in early stage of the disease or cervical/preauricular nodal irradiation should definitely be referred to super specialised centre.

Table 13: Where can you perform EUA/ carry out conservative treatment of retinoblastoma?		
Ideal care facility: For EUA and focal treatment measures should have following *in addition to facilities required for enucleation*		
Personal	*Equipment*	*Infrastructure*
*Trained ocular oncologist	RETCAM for fundus photos Ocular USG machine for tumor dimensions [$]	Plaque Brachytherapy facility chemotherapy facility Radiotherapy facility

	Equipment for delivering TTT Cryotherapy machine	Interventional radiology facility for IAC
Essential care Facility		
Personal	*Equipment*	*Infrastructure*
Trained ocular oncologist	Equipment for delivering TTT Cryotherapy machine	Chemotherapy facility Radiotherapy facility
Optional:	Handheld OCT	

$ after debate amongst the team members, consensus was reached that availability of USG may not be considered as an essential requirement for performing focal treatment for RB at a facility as the machine is limited by availability at many centers otherwise equipped for focal treatment of IORB.

Centers not having essential criteria for respective treatments must immediately refer patients to higher centers

Management of Intraocular Retinoblastoma

The treatment of intraocular retinoblastoma primarily depends on the intraocular tumor grading/ classification, presence of germline mutations, disease laterality, multifocality in case of unilateral disease, psychosocial situation of the family, compliance issues and existing institutional resources.(49,50)

Treatment modalities employed in management of intraocular retinoblastoma (IORB) comprise of-

1. Enucleation
2. Examination under anesthesia (EUA) for administering focal treatment to retinal tumor like cryotherapy, transpupillary thermotherapy (TTT) or laser photocoagulation and targeted treatment for vitreous seeds with intravitreal chemotherapy,
3. Systemic chemotherapy (IVC: intravenous chemotherapy or IAC: intraarterial chemotherapy) for reducing tumor volume (chemoreduction) or adjuvant treatment (IVC) in case of histopathological high risk factors after enucleation,
4. Plaque brachytherapy for residual/ recurrent retinal tumors
5. External beam radiotherapy (EBRT) for globe salvage in cases not responding to other treatment or microscopic residual disease (MRD) after enucleation.

There are few recent small case series showing better outcomes in advanced retinoblastoma retinoblastoma with multimodality treatment. (51,52)

Management of Unilateral Retinoblastoma

Most cases of unilateral retinoblastoma are sporadic, however 10-15% may have germ line mutations (GLM). UL RB with GLM has many unique aspects as compared with non GLM UL IORB:

a) These usually present at an early age and a surgery done at less than 6 months of age may not allow adequate sizing of orbital implant as majority of the orbital and ocular growth occurs in 1st 2 years of life. A smaller orbital implant will require a replacement with larger implant later on for an adequate cosmesis.
b) Also, there is risk of development of:

    i) Metachronous involvement of the other eye

    ii) Midline PNETS

Pointers of GLM in UL IORB are as follows

Age < 6 months

Multifocal disease

Family history

When a child presents at less than 6 months of age with IORB, there is a significant chance that the child is harboring GLM, which can be confirmed with Genetic testing. (53,54) Presence of family history and multifocal disease confirm the presence of GLM.

Table 14: Unilateral retinoblastoma presenting at less than 6 months of age- Management

Ideal	Genetic testing must be done to confirm GLM .	
	If no GLM is picked up:	They can be treated like unilateral RB presenting at older age.*
	If GLM is picked up:	Treat as for cases with confirmed GLM.
Essential	If genetic testing not available/ feasible: such cases must be **presumed to have GLM and treated accordingly**	

**Enucleation where indicated can either be delayed after discussing with parents to allow for orbital growth and chemotherapy may be given during this period/ upfront enucleation may be done followed by implant exchange at later age.*

Table 15: Protocol for UL IORB with Presumed/ Confirmed GLM

Recommendation		Evidence and consensus
Screening for midline PNETs		
	CE MRI orbit and Brain must be performed at presentation	There is level 3 evidence that screening on repeated imaging at 6 monthly intervals may help in early detection of midline PNET.(22,29,52) The need for repeat imaging for early detection was debated. As the treatment outcome of Midline PNET is very poor and early detection does not provide any prognostic advantage, it was agreed that there is no need for repeat imaging for early detection of same.
Close follow up for tumor in other eye (metachronous presentation)		
	Recommended follow up: 6 weekly follow up for 1st 6 months 3 monthly follow up for 1 year 4 monthly follow up for 1 year Annual follow up till 7 years of age	There is no guidance in literature regarding frequency of follow up for metachronous presentation, the following followup was agreed upon given that the*minimum latency reported was 30 days, maximum -2.5 Years.* (53)

Treatment Group E retinoblastoma		
Upfront enucleation	Must be done for Group E retinoblastoma with **high risk clinical or radiological features.**	There is level 3 evidence that presence of certain clinical features (longer lag time,older age at presentation, history of orbital cellulitis, and presence of hyphema, pseudohypopyon, staphyloma and bupthalmia (55) predict histological HRF. Radiological features predicting higher risk of systemic metastasis include • Invasion of anterior chamber, choroid (>2 mm), sclera and postlaminar optic nerve.
Secondary enucleation	May be done **in case of grp E eyes without high risk clinical or radiological features and age <6 months of age,** to delay enucleation beyond 6 months of age and the patient started on chemotherapy.	There is level 4 evidence that chemotherapy provides prophylaxis against midline PNETs (56) In view of the above advantage with chemotherapy and possible prophylaxis/ delay of metachronous involvement of other eye in addition to benefit of delayed enucleation allowing time for orbital and ocular growth - *consensus was made that delayed enucleation may be preferred in eyes with no clinical or radiological high risk features of RB and age less than*

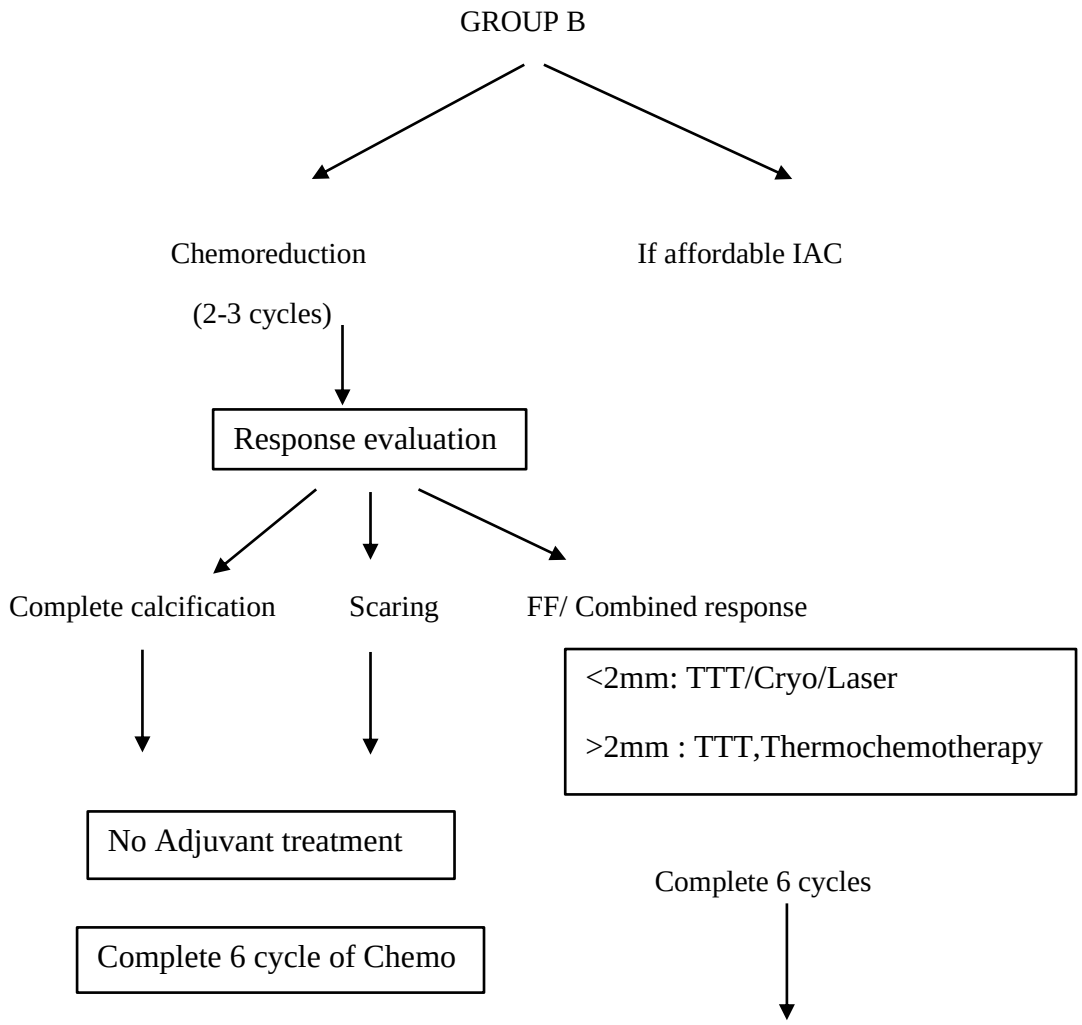
		6 months
Treatment Group B-D retinoblastoma		
	Intravenous chemotherapy is preferable to IAC	Consensus emerged due to possible benefits of intravenous chemotherapy as stated above
Adjuvant chemotherapy for high risk histological features.		
In patients undergoing upfront enucleation and histological HRF	6 cycles of adjuvant chemotherapy must be given	
In patients undergoing secondary enucleation	6 cycles of chemotherapy must be completed	
Chemotherapy protocol		
Adjuvant chemo for HRF	Standard 3 drug	*(chemotherapy protocols summarized in Table 10)*
Chemoreduction grp B-D	Standard 3 drug	
For delaying enucleation	2 drug	Since there is only level 4 evidence for this indication, -2 drug chemotherapy was agreed upon as a consensus chemo protocol in order to avoid leukemogenic chemotherapeutic agent etoposide.

Table 16: Management guide of unilateral retinoblastoma without GLM

	Upfront Enucleation	Chemotherapy (IVC/IAC)	Focal treatment
Ideal	-All group E* -Diffuse infiltrating retinoblastoma -Group D retinoblastoma, willing for enucleation *CONSENSUS: In view of poor globe salvage rate and vision salvage, long duration of treatment and high incidence of secondary enucleation* (50,57) *it was agreed that* ***ideal treatment for ul group D treated must be enucleation***	-ICRB groups B and C -Group D unwilling for enucleation *CONSENSUS: In view of low toxicity and easy availability and salvage rates as high as 100% in groups B and C (IVC) intravenous chemotherapy remains the ideal treatment for group B and C tumors* *Both IAC and IVC (LEVEL 3) will be ideal for group D depending on availability*	Retinal tumors with fish flesh or mixed pattern regression following 2 cycles of chemoreduction
**Group E eyes with severe Buphthalmia and a risk of globe rupture during upfront enucleation may be treated with chemotherapy prior to enucleation(58)*			

Essential	-Grp E with radiological or clinical high risk features -Diffuse infiltrating retinoblastoma	-ICRB groups B and C- IVC -Group D unwilling for enucleation -IVC		Retinal tumors with fish flesh or mixed pattern regression following 2 cycles of chemoreduction
Optional		-		Macular retinoblastoma

Fig 2: Flow chart for management of group B tumor



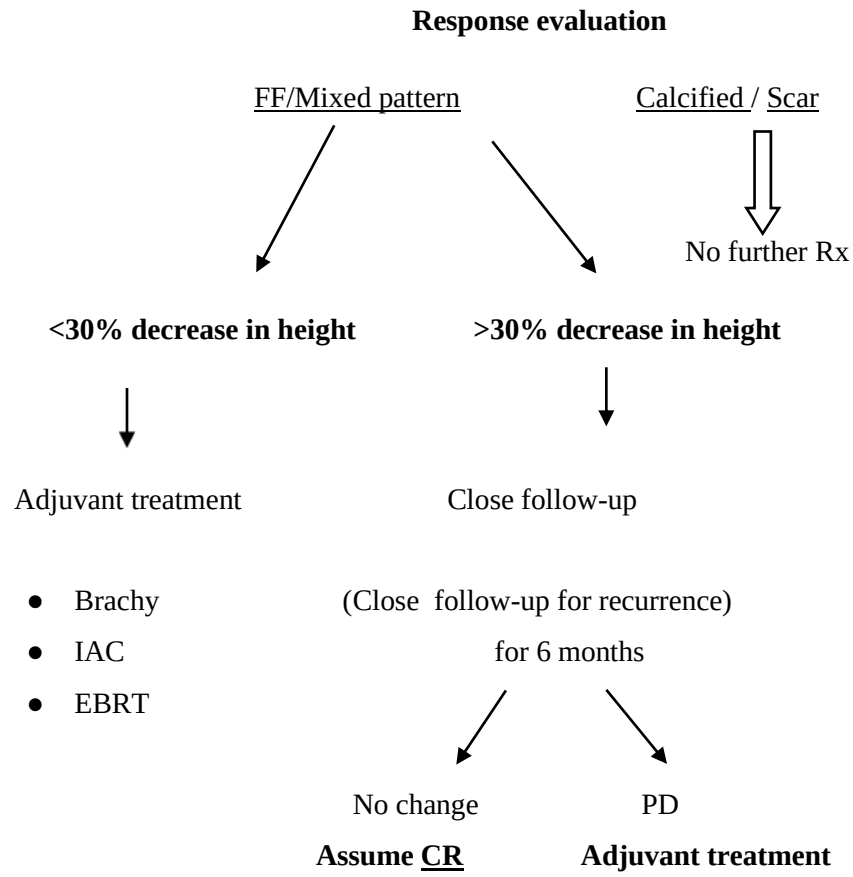
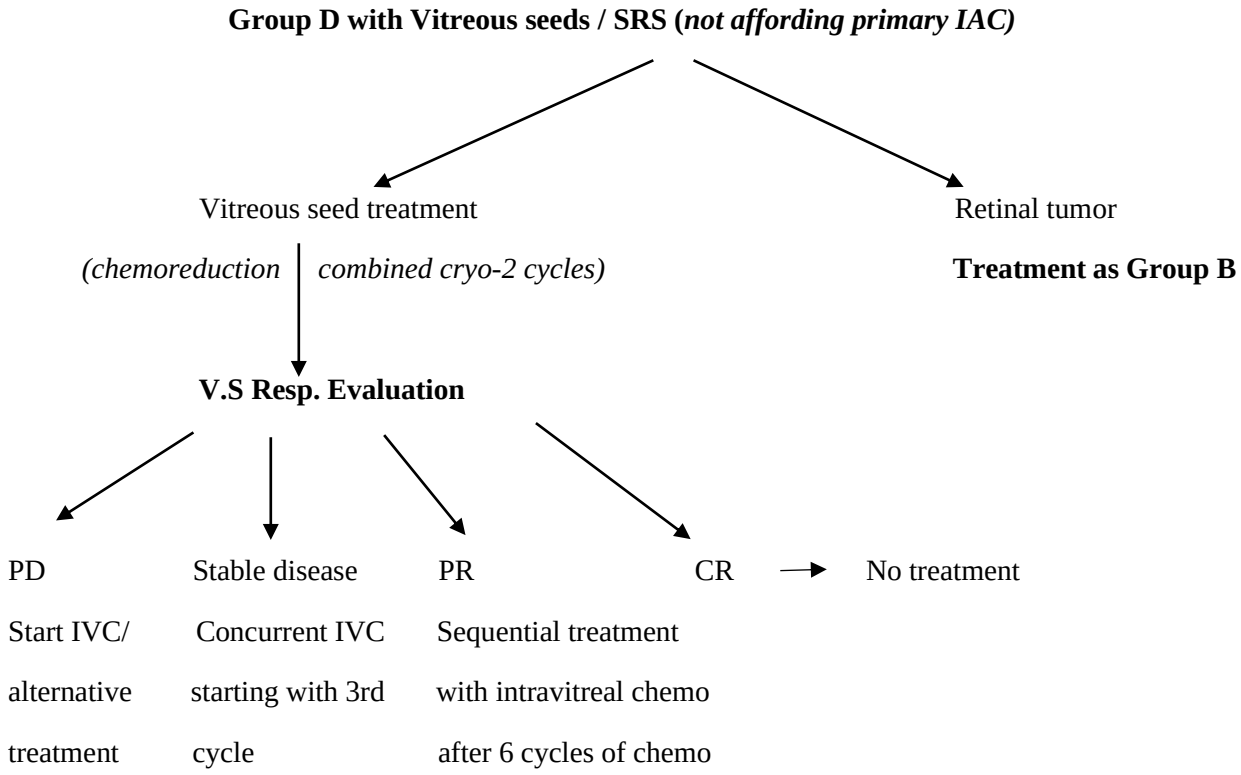


Figure 3: Flow chart for management of group D tumor



(Repeat IVC till 6 inj /till VS regress completed whichever occurs earlier)

CR: all seeds become refractile, calcified or disappear

PR:<30% seeds disappear, calcify or become refractile

Stable disease: >seeds disappear, calcify or become refractile

PD: increase in the number of seeds

What to do in case intraocular surgery is performed in an eye with unsuspected retinoblastoma?

The most common surgery that is done in unsuspected cases of retinoblastoma is pars plana vitrectomy (PPV). The most common preoperative misdiagnoses include vitreous hemorrhage, toxocariasis and endophthalmitis. (59,60) A delay in starting proper treatment is associated with poor prognosis.

Ideal: Immediate enucleation of the eye with subsequent chemotherapy and orbital radiation is imperative to avoid local recurrence and systemic metastases.(60)

Essential: Immediate enucleation with referral to a higher center for chemotherapy and orbital radiation

Which regression patterns need treatment with focal treatment methods?

Tumor regression patterns were originally described following radiotherapy.(61)

Table 17: Retinoblastoma-Tumor regression patterns

Type 0	Where the tumor disappears **without any retinal scar**
Type 1	is a completely calcified tumor that appears like **cottage cheese** (the most common regression pattern with EBRT)

Type 2	is an absolutely non-calcified mass or **the fish flesh regression**
Type 3	is partly calcified mass or **mixed pattern**
Type 4	is a flat **scar**

A completely calcified tumor (type 1) or a residual scar (type 4) have on histopathology proven to bear no active tumor and are considered as complete regression. But **tumors which have soft tissue/ fish flesh (type 2 or 3) areas need to be followed up closely and treated with focal treatment measures** with an aim to achieve complete regression and prevent recurrences. (61)

What focal method can be used for a partially regressed tumor?

The focal consolidation methods for treatment of retinoblastoma tumors include laser photocoagulation, (TTT) Transpupillary thermotherapy, cryotherapy and Brachytherapy.

Laser photocoagulation: can be used at centers where TTT is not available. This treatment coagulates the tumor using a 532 nm laser. Confluent spots are applied on the tumor and surrounding retina to produce whitish color change. It is effective in **small tumor less than 2 mm in height** and produces significant scarring of the retina and hence is avoided for macular tumors.

Transpupillary Thermotherapy is delivered using infrared diode laser (810 nm) delivered by transpupillary route using, most commonly, a laser adapted indirect ophthalmoscope and a 20-diopter (D) lens or an adaptor on the operating microscope and a wide-angle contact lens or a transscleral probe. Wide pupillary dilation is necessary.

Both tumors of posterior pole and those anterior to equator can be treated with TTT.

Small tumors i.e 3.0 mm or less in base and 2.0 mm or less in thicknesswith less than 1.0 mm of overlying subretinal fluid, in an eye with clear media can be treated with TTT upfront.

Larger tumors and those with presence of active vitreous seeds can be treated after chemoreduction, alone or in combination with chemotherapy, which is termed as **chemothermotherapy.**

Systemic chemotherapy is administered within 24 hours of the application of TTT and is preferred for larger tumors.

Treatment is provided so that a light gray-white appearance of the tumor is achieved at the end of the session.

Foveal-sparing thermotherapy is done so as to avoid the 1.5-mm area of the fovea and papillomacular bundle from the optic disc to the foveola in order to avoid vision loss in case of macular tumors.

Repeated treatments are given every 3-4 weeks till the tumor shows complete regression i.e calcification or scar formation.

In case of fish flesh regression in larger tumors one can stop treatment of the tumor if its dimensions are stable for 6 months after achieving maximum tumor regression.

Thermotherapy technique

Under general anesthesia, thermotherapy is applied using the largest spot size available to cover the tumor. The end point of treatment is a mild, light grayish color change of the tumor without associated vascular spasm or prompt whitening of the tumor. The treatment is initiated at a power of 200 mW and stepped up at 50 mW increments till the endpoint as described earlier is observed. Tumors near the optic disc and fovea and large in size (>6 mm are preferably treated with the operating microscope system. Tumors that were smaller or situated peripheral to the macula are treated with the indirect ophthalmoscope system.(62)

Complications of thermotherapy include focal iris atrophy, peripheral focal lens opacity, retinal traction, retinal vascular occlusion, and transient localized serous retinal detachment.

Cryotherapy

It is used primarily to treat small retinal tumors with/without focal sub retinal or preretinal seeds for tumors anterior to equator. Cryotherapy is useful for **tumors with base diameter up to 3.5 mm and thickness upto 2.0 mm**.(63)

Treatment is performed under indirect ophthalmoscopy. The cryotherapy probe is placed on the conjunctiva for anteriorly located lesions or can be placed directly on the sclera through a conjunctival

incision for lesions located posterior to equator. **A triple-freeze-thaw** technique is preferred. Cryotherapy is applied till the tumor apex and base is completely engulfed in the ice ball. Some ocular and eyelid inflammation is expected following cryotherapy and may need use of topical steroids and oral analgesics post-treatment. Exudative and rhegmatogenous retinal detachment may occur after extensive cryotherapy.

Table 18: Treatment guide for focal treatment for retinoblastoma

Tumor Location and Height	**TTT**	**laser Photocoagulation**	**Cryotherapy**	**Combination RX**
Anterior to Equator ≤ 2 mm	**yes**	**yes**	**yes**	**-**
> 2 mm	**After chemoreduction if tumor ≤ 2mm**			**if more than 2mm, TTT or chemoTTT**
Posterior to Equator Not Involving Macula ≤2mm	**yes**	**yes**	**No**	
>2mm	**After chemoreduction if tumor h ≤ 2mm**		**No**	**if > 2mm, TTT or chemoTTT**
Macular	**TTT/ chemoTTT after chemoreduction** -Spare fovea and papillomacular bundle if possible -Avoid Rx when other eye is enucleated			
Sub retinal seeds	**yes**	**yes**	**Focal SRS**	

**Focal treatment is given only to fish-flesh areas of type II and III regression. No need to treat calcified tumors and scars*

When to stop treating a retinal tumor?

On baseline evaluation during EUA, a single target tumor should be identified and measured whenever possible; its apical height and basal dimension should be noted using B-scan ultrasonography.

As per **standard imaging protocol**, one should measure the tumor from the inner sclera to the tumor apex (thus excluding the scleral thickness); in case of associated subretinal fluid, the tumor only should be measured without the overlying retina. (64,65)

At each EUA, the apical height and base of the target tumor should be re-measured.

As the tumour shrinks with chemotherapy, its dimensions (height and base diameter) achieve a minimum value usually after 2-3 cycles of chemotherapy. This minimum dimension of tumor is important to assess any subsequent increase in tumor size and hence tumor progression. (66) When evaluating the tumor response, a single response (CR, PR, SD or PD) must be given for the overall disease status in the eye. The individual retinal, vitreous seed and subretinal seed tumor response can be categorized as described in Tables 19,20 and 21. (67)

Table 19: Response criteria for retinal tumors

Complete response (CR)	Types 0, I, or IV regression or **Types II or III regression that are clinical stable** on fundus photography *and* ultrasound imaging for ≥6 months after cessation of Rx. **Further therapy not indicated.**
Partial response (PR):	**Decrease tumor height by ≥30%** from baseline for Types II or III regression and **clinically stable on fundus photography for <6 months.** **Local consolidation therapy can be ongoing**
Stable disease (SD):	Decrease in apical tumor height by <30% from baseline with lack of/**minimal regression** also seen on fundus photography or increase in apical tumor height by <30% from baseline. Consolidation therapy is ongoing or limited. **Persistent disease may be present**

Progressive disease (PD):	**Increase in tumor measurements by ≥30%** from tumor nadir in at least one dimension, that is, height and/or base, and/or **Appearance of new lesions.** **Recurrent disease,** defined as a new secondary growth at any location occurring after >**2 event-free months** following completion of first- or second-line therapies.

Ultrasound findings and clinical photographs must be always be considered together in assessing response

A calcified retinal tumor may appear larger on B-scan ultrasonography as compared to baseline measurements, especially if there was subretinal fluid and/or confluent seeding at diagnosis, thus a clinical photograph will rule out any tumor progression in such cases.

There may be a recurrence on a calcified tumor that may not be picked up on usg however will be seen on indirect ophthalmoscopy. Thus, both modalities are imperative in assessing the response.(67)

Vitreous seed regression patterns have been described by previous studies as follows (67,68)

Type 0 (No seed remnant)

Type I (Calcified and/or refractile seeds)

Type II (Amorphous, pigmented/ non-pigmented, mostly non-spherical residual seeds)

Type III (Combination of I and II)

Further the morphology of vitreous seeds can be like dust, spheres or clouds.

The response criteria has been defined as follows based on type of regression pattern.

Table 20: Response criteria for vitreous seeds

- CR: **Types 0/ I regression**

  OR

  Types II or III regression with clinical stability on fundus photography for ≥6 months.

  (*Further therapy not indicated)*

- PR: **Unequivocal improvement** in seeding with **Types II or III regression** and clinical stability for <6 months on fundus photography
- SD: Neither improvement nor progression of seeding.
- PD: **Unequivocal progression** of seeding (increase in number/ density of seeds),

  or

  conversion from dust to spheres

  or

  new preretinal tumors.

Morphology of the partially regressed vitreous seeds should be noted in order to prognosticate globe salvage. Studies have reported that ***residual spherical seeds are associated with significantly increased rates of relapse as compared to dust/ calcified seeds***.(69–71)

Table 21: Response criteria for subretinal seeds
• CR: **Disappearance of all subretinal fluid and visible subretinal seeds,** OR calcification of all subretinal seeds for ≥6 months. • PR: Unequivocal improvement in subretinal seeding (decreased number/ density) without complete calcification, and decreased subretinal fluid. • SD: Neither unequivocal improvement nor progression of subretinal seeding. • PD: Unequivocal progression of subretinal seeding (increase in number or density) and/or **increased subretinal fluid**.

How to treat vitreous seeds?

Focal vitreous seeds respond well to chemoreduction and undergo complete regression in more than 90% cases, without any adjuvant treatment. However **diffuse vitreous seeds** will usually require adjuvant treatment in the form of subtenon chemotherapy, intravitreal chemotherapy (ivc) or intra arterial chemotherapy (IAC). Subtenon chemotherapy has mostly been replaced with intravitreal chemotherapy. In LMIC, use of IAC is limited by its availability and cost. This is reflected by very few reports on use of IAC from South East Asia. Thus ,ivc is the preferred initial treatment for vitreous seeds in India. The treatment guide for diffuse vitreous seeds is summarized in the flowchart for treatment of Group D RB.

The most frequently used drugs for intravitreal chemotherapy (ivc) are melphalan and topotecan, used independently or in combination. The dosage recommended for melphalan or topotecan is 20-30 μg in 0.05 to 0.1 ml volume. Response is directly related to vitreous seed morphology and hence modified accordingly. (68) Vitreous seed clouds require higher dose as compared to vitreous seed dust or spheres.

This may be repeated every 1-4 weeks.The ideal interval between two intravitreal injections for achieving maximum tumoricidal effect is not yet known.

Intravitreal injection with melphalan (20-30 μg) is reported to cause retinal toxicity that manifests clinically as salt and pepper retinopathy and a diminution of ERG responses. This toxicity is found to be more in patients with greater ocular pigmentation and when combined with IAC such that the duration between the two treatments is less than 1 week. Most retinal toxicity is manifested within a week and remains stable thereafter.

Topotecan is the second common drug used for ivc. Studies report no significant decrease in ERG amplitude in patients who receive topotecan (20-30 μg) alone.(72) In view of a level III evidence of greater toxicity with Melphalan in eyes with greater ocular pigmentation, **topotecan may be preferred in Indian eyes.** However, there is only one Indian study to support this suggestion. (72) This study reported no ocular complications with topotecan and a final visual acuity of >6/60 in 75% of the salvaged eyes.

Combination therapy: Eyes that have failed to show response with melphalan have been reported to show complete response to combination treatment with injection of melphalan and topotecan. (73) Also studies report that combined ivc achieves vitreous seed control with notably fewer injections (median 2) than monotherapy

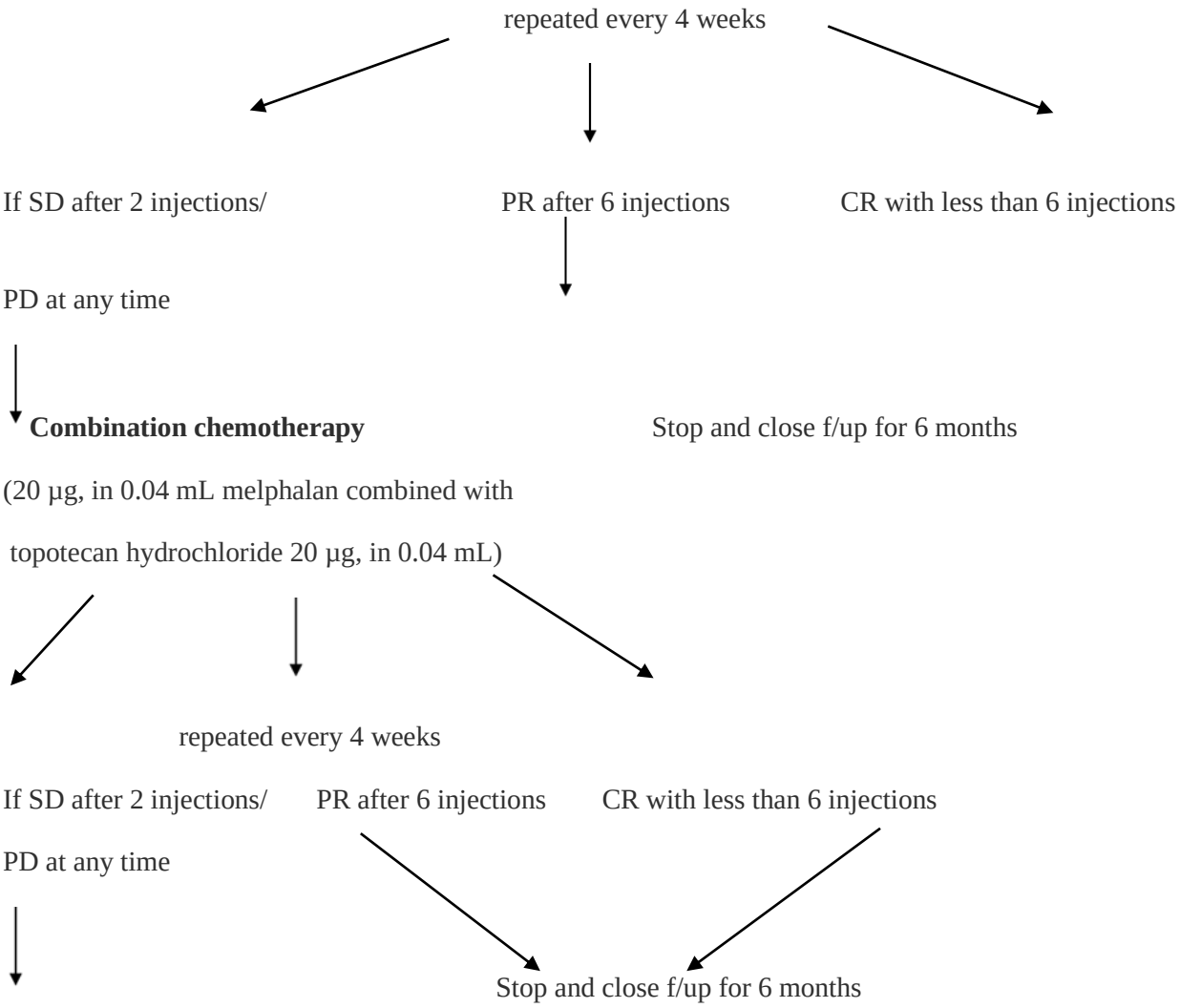
When to stop:

Injections can be repeated at 1-4 weeks intervals till complete regression, that is till vitreous seeds completely calcify, become refractile or disappear. The maximum number of injections that may be given without significant toxicity is unclear from previous studies. But studies show that greater cumulative number of injections cause greater toxicity and may lead to globe salvage without vision salvage.

Since there are no studies deliberating the maximum number of injections, a consensus was based on level 3 evidence from literature to guide ivc treatment.

Consensus Guide for intravitreal chemotherapy

Monotherapy with Topotecan/ Melphalan (Dosage:20-30 µg in 0.05 to 0.1 ml volume) for residual vitreous seeds after chemoreduction (topotecan preferable)



What to do if there is a macular tumor?

Gombos et al found that retinoblastoma has a greater likelihood to respond to systemic chemotherapy if it is macular in location (84 %). (74)

Treatment of macular retinoblastoma is particularly tricky as focal treatment carries a risk of foveal damage and vision loss. Some centers prefer not to use thermotherapy for macular tumors in order to preserve the best possible visual outcome for the patient and adjuvant treatment is given only after chemotherapy has failed. (74,75) On the other hand, Schefler et al reported 20/80 or better vision a majority (57%) of the patients treated with chemotherapy plus aggressive repetitive foveal laser treatments despite direct laser application to the fovea.(76) They concluded that the application of repetitive lasers appeared to have no negative consequences for visual outcomes. In another study comparing outcomes in macular retinoblastoma, authors reported that treatment of macular retinoblastoma with chemoreduction alone provides control of 65% while chemoreduction and adjuvant foveal-sparing thermotherapy provides tumor control of 83% by 4 years.(77) **Consideration should be given to avoiding foveal focal treatment, especially if both eyes are involved.**

Flow Chart for Management of Macular RB

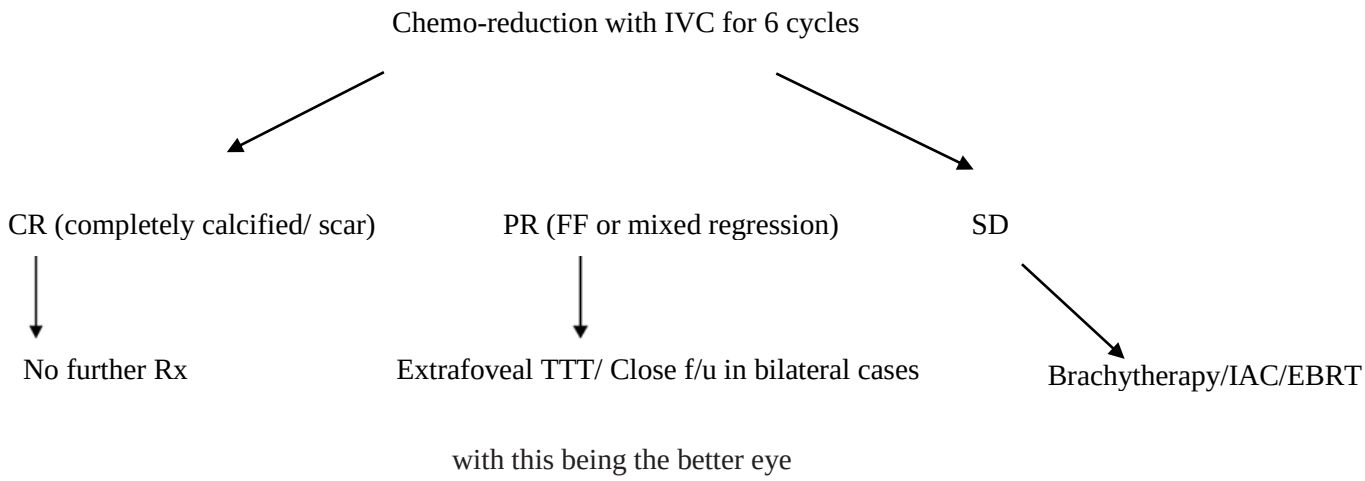


Figure 4: Flow Chart for Management of Macular RB

What to do if there is a tumor involving the optic nerve head?

Eyes with group B to D retinoblastoma and tumor covering the optic nerve head are at increased risk of extraocular extension into the optic nerve. Such eyes must be evaluated on MRI for any optic nerve invasion on MRI. There is sparse literature specifically evaluating outcomes in this subgroup of retinoblastoma eyes. (78) Chemoreduction with 2-3 cycles may cause tumor regression away from the optic nerve head in majority of cases allowing focal treatment of tumor. However, **if the tumour still covers the optic nerve head following 3 cycles of chemotherapy, the eye must be enucleated.**

How to treat a recurrent tumor?

Recurrent disease is defined as a new secondary growth at any location occurring after >2 event-free months following completion of first- or second-line therapies.

Table 22: Treatment Guideline for recurrent Tumor				
Type	Characteristic	Size	Treatment	If no response to first Rx
Retinal tumor recurrence	**Edge recurrence**/ recurrence over a scar* *(usually single)*	≤2 mm >2mm	ICG enhanced TTT(79,80)/ Cryotherapy Chemoreduction f/b TTT or cryotherapy	Brachytherapy if no response
	Recurrence over calcified tumor	-	IAC/ enucleation	
	From subretinal seeds or vitreous seed implantation*(usually multiple)*	≤2 mm >2mm	TTT/ cryotherapy Chemoreduction 2 cycles f/b TTT or cryotherapy	IAC/EBRT/Enucleation (*Brachytherapy usually not feasible due to multiple lesions)*
Vitreous seed recurrence			intravitreal chemo #	IAC/EBRT/Enucleation
SRS recurrence			IAC/ EBRT/Enucleation	
#lookfor retinal source of vitreous seed and treat the same, *tumor recurrence over scar does not respond well to TTT due to lack of underlying pigment in the scar, hence ICG enhanced TTT or cryo is better than TTT				

When to use Brachytherapy?

Ideal: Radioactive plaque brachytherapy is generally used as secondary/ adjuvant treatment for single

retinal tumors that are partially regressed with chemotherapy or recurrent, and are not responding to or not amenable to treatment with TTT.

Tumors eligible for brachytherapy are typically less than 15 mm in base diameter and less than or equal to 10 mm in thickness (81–83) with no vitreous seeding or seeding within 2 mm of the tumor surface.125I is used for thicker tumors and 106Ru plaques for thinner tumors i.e less than 6mm. Rb is typically treated with a dose of 40-50 Gy to the tumor apex.

When to use IAC?

IAC is a minimally invasive procedure where super-selective canulation of ophthalmic artery is done and chemotherapeutic agents are infused into the ophthalmic arterial territory. IAC has evolved as one of the important modalities for treatment of Retinoblastoma as primary as well as secondary line of treatment.(84,85) However its use in India like in other LMIC is limited by high cost of treatment.(86)

IAC requires an interventional radiology facility. Also, there is a learning curve. Since it is a targeted treatment, it does not take care of any systemic micrometastasis. It can be used in management of unilateral group B-D retinoblastoma, in affording patients where facility is available and for recurrent disease non responsive to other forms of conservative treatments. There is only very limited literature, case series (15 cases) reported from single center, on treatment outcome on IAC from India that show globe salvage rates of 100% in group B and 67% in group C and group D, with overall globe salvage of 67%.(86)

How to enucleate an eye with retinoblastoma?

Enucleation in a case of retinoblastoma must be performed taking care of the following

1)Not to perforate the globe during surgery

2) Harvest a long length of optic nerve(at least 15 mm)

<u>Surgical Technique</u>

The two most commonly used surgical techniques for enucleation are

a) The imbrication technique

b) The myo-conjunctival technique

In imbrication technique the extraocular muscles are sutured to each other, while in myoconjunctival technique the muscles are sutures to the conjunctival fornices in order to augment the forniceal mobility and translate into an improved prosthetic movement. Currently the myoconjunctival technique is performed by a significant proportion of surgeons. In a randomized controlled trial, Shome et al. compared traditional muscle imbrication technique using polymethyl methacrylate (PMMA) or porous polyethylene and myoconjunctival technique using PMMA implants. The study demonstrated statistically and clinically significant better implant and prosthesis movement with the PMMA myoconjunctival technique. Another study involving 30 patients also reported the superiority of the myoconjunctival technique. (87,88)

What can be the complications of enucleation?

Main post-operative complications of enucleation include:

Socket Infection

Implant Exposure

Extrusion

Socket contraction

Secondary surgery is usually required to manage the complications of enucleated socket. Re-surgeries are more likely to have less favorable cosmetic outcomes. Other complications include cyst formation, pyogenic granuloma, a smelly socket and limited prosthetic motility.(89–91) Further retinoblastoma patients are at risk of increased complication due to adjuvant radio- or chemotherapy. Enucleation at young age may lead to potential volume deficiency and need for implant replacement later in life patients

Which orbital implant to be used?

Orbital implants may be autologous or alloplastic; integrated, semi integrated or non-integrated.(92)

Non-integrated implants are widely available, cheap and affordable; and easy to place, making them the most commonly used implants worldwide. These are solid, spherical implants made of PMMA (Mules) or silicone that may be placed as it is or with wrapping materials like sclera, vicryl mesh or teflon mesh to allow suturing of the extraocular muscles. The most common complication with these implants is implant migration followed by implant extrusion. However appropriate sizing the implant and following appropriate surgical protocol may reduce the incidence of these complications.

Semi integrated implants bear tunnels or holes that allow for suturing of the muscles to each other through these spaces, example Universal and Iowa implant. However, they have higher risk of implant related exposure due to the non-spherical shape.

Integrated implants are porous implants that allow growth of fibrovascular tissue into the implant. These include the hydroxyappetite, polyethylene implants like Biopore and Medpore and bioceramic implants. These implants are significantly more expensive as compared to non-integrated implants and are limited by availability. These are the most commonly recommended implants in North America and Europe as they are virtually free of complications like implant migration and extrusion and allow for pegging of the prosthetic eye allowing a greater prosthetic motility. Although the porous nature of the implant reduces the risk of implant migration and extrusion due to tissue integration, the inherent rough surface significantly increases the risk of conjunctival erosion and implant exposure in these cases. *Also, it is difficult to carry out an implant exchange surgery if required*. *Hence these implants must be avoided in children less than 6 months of age*. However, no randomized controlled trials comparing different implant types and wrapping materials are available in literature. There are studies in literature showing that the motility of artificial eyes with unpegged porous is comparable with that of non-porous implants.(93,94) Apart from implants, dermis fat graft may be used for orbital volume replacement. However, its popularity is limited by the technical difficulty, long surgical time and associated donor site related morbidity.

Pathological Assessment of the Enucleated Eye

What are the high-risk histopathology features after enucleation?

Histopathologic risk factors help in predicting the occurrence of metastasis in children with RB. The most important histopathologic prognostic indicators for development of metastasis include post-laminar optic nerve involvement at the site of surgical transection of the nerve and extrascleral extension of tumor into the orbit. As children in developing countries have delay in diagnosis, 54% of them present with such high-risk features compared to 20% of children in developed countries.(95) Other high-risk histo-pathologic features include massive choroidal invasion of ≥3 mm, post-laminar optic nerve involvement (PLONI) without cut end positivity.(95) Certain histological features like anterior chamber seeding, iris/ ciliary body infiltration, neovascular glaucoma and buphthalmos have also been described as high risk but are debatable.(96)

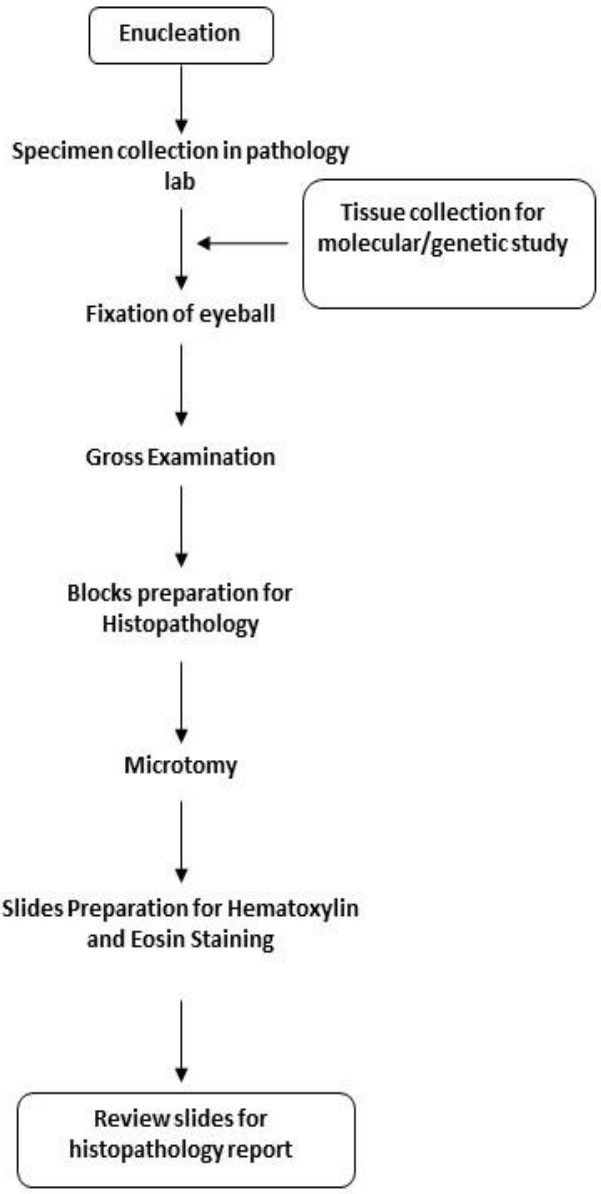
Escalation of treatment with adjuvant chemotherapy in the presence of these high-risk histopathologic features has shown to reduce the incidence of metastasis to 4%, compared to 24% who did not receive adjuvant therapy.(97) Also, a recent prospective study on high-risk histopathologic features in unilateral RB by Children's Oncology Group (COG) found 3 mm or greater choroidal invasion in the peripapillary posterior choroid (around the head of the optic nerve) in combination with PLONI (≥1.5 mm) confer a poorer prognosis and lumbar puncture is recommended in such patients.(98) It is hence critical that accurate histopathology assessment of the enucleated specimen is done for further management.

Necessary steps that need to be taken for processing an enucleated eye for histopathology examination:

Figure 5: Stepwise Normal Pathological Examination of an Eyeball

1. **Receiving of Eyeball**

Once the retinoblastoma enucleation is performed in the operation theatre, the patient details and clinical details are filled in the histopathology requisition form and sent to the pathology with the specimen. The specimen is received in saline for harvesting/processing the tumor tissue for molecular studies.



2. **Storage of tumor tissue for molecular studies**

Before being fixed, the tumor tissue is taken for molecular investigations. For DNA/protein preservation, the tumor is placed in a cryovial without any medium and kept at -20°C. Tumor tissue is kept at 4°C for penetration of RNA later solution, and -80°C for later RNA extraction processing.

3. **Tissue processing and slides preparation**

The enucleated globe should be fixed in 10% buffered formaldehyde (fixative solution) for at least 24-48 hours after being transferred to pathology and prior to processing. Fixation via injection of fixative into the globe is not recommended since it disrupts the histology. After the globe has been fixed, paraffin blocks are prepared and mounted onto a microtome for obtaining 4 µm sections. Sectioning of tissue must be done on albumin coated slides and stain with hematoxylin and eosin for light microscopic examination.

4. **Microscopic Examination for histopathological Parameters**

On microscopic examination, tumour differentiations are categorized into (a) fleurettes exhibiting advanced photoreceptor differentiation, (b) the classic Flexner-Wintersteiner rosettes

representing early retinal differentiation, (c) Homer Wright rosettes with primitive neuroblastic differentiation, or (d) poorly differentiated. Prognostic factors like massive choroidal invasion, optic nerve invasion (prelaminar, laminar and retrolaminar) and involvement of resected end of optic nerve, iris and ciliary body involvement, anterior chamber involvement, scleral/extrascleral involvement by tumour cells are associated with a greater risk of orbital recurrence and predictive of metastasis . (20) Optic nerve invasion is graded as prelaminar, post laminar and invasion of the resected margin. A tumour focus of less than 3 mm in any diameter (thickness or breadth) is classified as focal invasion, whereas massive invasion is defined as an invasive focus of tumour measuring 3 mm or more in any diameter. The importance of the anterior chamber as a high-risk factor for retinoblastoma should also be evaluated. Anterior chamber seeds do not constitute an independent risk factor for retinoblastoma metastasis, but it is important to screen frequently.(99)

Does histology after enucleation affect prognosis?

Microscopic evidence of invasion of orbital soft tissues, trans-scleral invasion, and residual tumor at the surgical margin of the ON are uniformly accepted as high-risk factors. (100) Recently published data from EURbG has reported that invasion of the resection margin or transscleral invasion is the most important prognostic factor resulting in 5 years OS of 80%. (101) Optic nerve invasion is considered as a major risk factor for developing CNS metastasis. In contrast, extra-scleral extension is the most important factor for distant metastasis since it violates the lympho-vascular channels outside the eye. (102)

Table 23: Actions to be taken in response to various histopathological high-risk parameters:

	Histopathological high-risk Parameters	**Action to be taken**
1.	Massive choroidal Invasion>3 mm	Adjuvant Chemotherapy
2.	Extrascleral invasion	Adjuvant Chemotherapy
3.	Anterior chamber, iris and ciliary body Invasion	Adjuvant Chemotherapy (debatable)

4.	Optic nerve invasion (prelaminar)	No Chemotherapy
5.	Post-laminar and cut end of resected margin	Adjuvant Chemotherapy
6.	Orbital invasion	Neoadjuvant and adjuvant chemotherapy
7.	Intraretinal extension	No Chemotherapy

5. **Pathology Report**

   The pathology report must routinely include the eye, right/left enucleation, tumor size, tumor differentiation (poorly/moderately/well), grading of calcification and necrosis, choroidal invasion (massive (>3mm) or focal (<3mm)), scleral invasion, anterior chamber invasion, iris and ciliary body invasion, optic nerve invasion (prelaminar or post laminar) and invasion of cut end of optic nerve. Additionally, if the eyeball is chemoreduced, the report should include whether eye is phthisical or not, presence of foamy macrophages, retinal gliosis, fibrosis, cholesterol clefts and extrascleral invasion. Pathological staging should be done according to the AJCC pTNM staging and it is optional to include in the report.

When to do exenteration in retinoblastoma?

In the current treatment scenario, the need for exenteration has significantly reduced. Exenteration involves removal of all the contents of the bony orbit along with the periorbita. It is a highly disfiguring surgery. It is used **when cases with overt extraocular extension (IRSS Stage III) or orbital recurrence post-enucleation fail to respond/ progress despite neoadjuvant chemotherapy.**

What is the role of radiotherapy in RB?

RBs are radiosensitive tumors, thus in earlier days, RT was the primary treatment for these tumors and long-term eye preservation rates range from 50 to 100% in multiple large series. (82,103)With increased risk of radiation induced secondary neoplasms and advent of other effective modalities for eye salvage,

the use of RT reduced substantially. Though latest RT techniques have the potential to reduce late side effects, in the present era, the role of RT is restricted to advanced or recurrent intraocular RB, EORB and metastatic RB.

What are the indications of RT in Group E RB?

Patients with group E RB are managed with enucleation. Adjuvant chemotherapy and/or radiotherapy depends on post-operative HPR. (101) Honavar et al have shown that post-enucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in RB patients manifesting high-risk histopathologic characteristics. (87)

For those undergoing enucleation, post-operative RT is not indicated for completely resected group E RB (stage 1). However it is uniformly indicated for high risk features such as presence of tumor at optic nerve cut end, scleral disease or microscopic orbital disease (stage 2). (104–106)Patients with these risk factors are considered to have extraocular disease and should be treated on the same lines of macroscopic residual disease. (level of evidence 3)

Use of EBRT for globe salvage has considerably reduced in the current era as compared to the 1970s.(107) EBRT can be used in advanced IORB for globe salvage in unilateral RB with vision potential, not responding to other treatment modalities.

In bilateral retinoblastoma or RB with germline mutations, use of EBRT increases the risk of second cancers, however it is still used as globe salvage treatment for salvage of the only remaining eye with useful vision not responding to other treatments.(108)

Side effects of EBRT include dry eye, cataract and radiation retinopathy. Radiation also affects the growth of the soft tissue and bone around the eye resulting in orbital hypoplasia. In the current era of chemoreduction, EBRT may have higher complication rate as it is used as a last resort in eyes already treated with multi-agent systemic and intravitreal chemotherapy and multiple sessions of focal treatment.(109,110) Newer techniques of Intensity modulated radiation therapy (IMRT) and proton Beam

therapy (PBT) have lesser complication rate as compared to conventional EBRT but are limited by availability and cost.

Management of Bilateral Retinoblastoma

Treatment of bilateral retinoblastoma is more challenging than unilateral retinoblastoma due to several reasons:

1) It indicates presence of a germline mutation and hence such patients are at an increased risk of trilateral retinoblastoma and secondary malignancies.

2) Radiotherapy increases risk of second malignancies and therefore must be avoided in such patients.

3) Bilateral enucleation is often required which may lead to treatment abandonment.

In a study from south India, Kaliki et al, reported that nearly half the patients (61/134, 45.5%) with bilateral advanced disease either did not take treatment or failed to complete treatment.(14)

Children with bilateral disease usually **present earlier** than unilateral disease. Depending on tumor grading in each eye, the child may have bilateral advanced disease, unilateral advanced disease with other eye group B-C retinoblastoma, or bilateral group B or C retinoblastoma. The most common modality of treatment used in bilateral cases of retinoblastoma is systemic chemotherapy. The reasons being that most parents do not accept bilateral upfront enucleation in cases with bilateral advanced disease, it also takes care of risk of trilateral retinoblastoma in bilateral cases with lesser grades of tumor and treats both eyes simultaneously causing chemoreduction of bilateral tumors.

The risk of abandonment in bilateral advanced cases is high despite starting on chemotherapy and therefore parent counseling forms a very important part of treatment in this group of patients.

The other treatment protocols described in literature include bilateral EBRT, bilateral enucleation, systemic chemotherapy, combination of systemic chemotherapy and EBRT, enucleation of the more severely affected eye and EBRT for the less affected eye, systemic chemotherapy with bilateral focal treatment, simultaneous intraarterial chemotherapy (IAC) with or without intravitreal chemotherapy. (110–123)The overall globe salvage rates reported range from 0 to 91%.(110–123)

Recently, studies have reported simultaneous IAC in both eyes with high rates of globe salvage and minimal systemic complications.

Intravenous chemotherapy may offer systemic protective effects against development of systemic metastasis and pinealoblastoma. (124) Thus IAC should be used with caution in cases with bilateral RB. Eyes with advanced intraocular RB have a higher chance of harboring high-risk histopathology features and thus the risk–benefit ratio of enucleation versus globe salvage treatment should be carefully weighed in such eyes especially in the setting of bilateral disease.

Table 24: Management guideline for Bilateral RB	
Should be treated at tertiary care centers with facility for EUA and enucleation	essential
Systemic chemotherapy	essential
Avoid treatment with Radiation	preferable
Lifelong followup for second cancers	essential
Genetic counseling and testing	optional

Figure 6: Flowchart For Treatment Of Bilateral Retinoblastoma

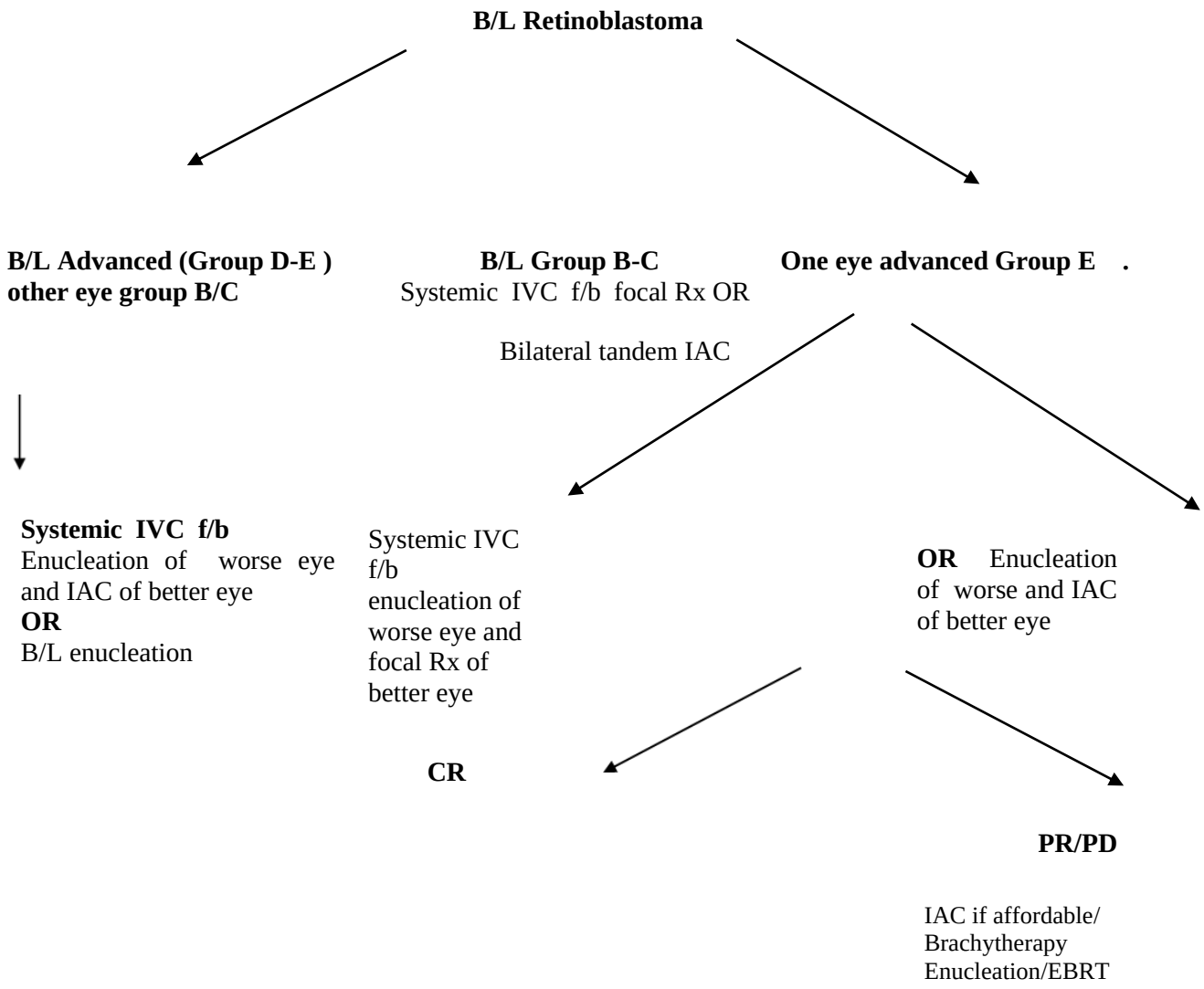


Table 25: Retinoblastoma Management at Primary Care Level

Primary care level:

Awareness about leukocoria

Screening for and Early Referral for cases of leukocoria

Who to screen?

Children less than 5 years of age

Where to screen?

Immunization centers and preschool

How to screen?

Ideal: Distant direct ophthalmoscope by trained nurses/ Anganwadi workers

Essential: Distant direct ophthalmoscopy forLeukocoria detection

Optional: Leukocoria detecting softwares

Where to refer?

Unilateral cases: secondary care facility

Bilateral cases/ those with family history: tertiary care facility

Research Questions

1. Studies are required to **evaluate the knowledge of the normal population and healthcare workers** about retinoblastoma with respect toclinical presentation, risk factors and diagnosis.

2. Validate smartphone-based leukocoria detection for early detection of Retinoblastoma (RB) in young children without pupil dilatation by non-ophthalmologists in community.

3. Studies to compare topotecan versus melphalan with respect to ocular toxicity when used for intravitreal injections.

4. Studies to assess Feasibility of use of IAC as primary and salvage treatment in India and outcomes of treatment.

5. Evaluate the need for adjuvant chemotherapy for isolated Histopathological high risk of AC involvement.

6. Long term follow up of cases treated with IAC for systemic metastasis.

Management Of Extraocular Retinoblastoma

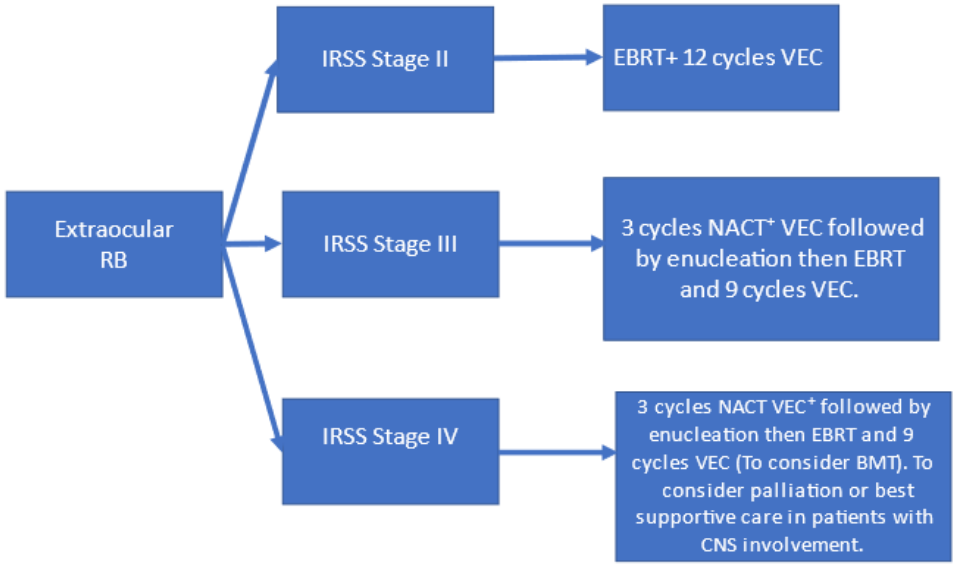
Definition and Staging

Extraocular retinoblastoma (EORB) or orbital RB is a heterogeneous disease and defined as an extension of the tumor beyond the globe either microscopically or macroscopically, with or without regional or metastatic spread. Extraocular dissemination occurs via ocular coats (choroid and sclera), emissary vessels, optic nerve, or anterior segment. According to International Retinoblastoma Staging System (IRSS), stages II-IV are considered extraocular retinoblastoma (Table 1). Extra-orbital disease is defined as lymph node metastasis, intra-cranial spread, leptomeningeal dissemination, or hematogenous spread, typically to bone and bone marrow and, occasionally to the liver.

Management

The management of extraocular retinoblastoma is multi-modality involving chemotherapy, radiotherapy, and surgery. (125) It is recommended that patients with extraocular retinoblastoma are managed in centers of excellence. A brief overview of the management of extraocular retinoblastoma is shown in Figure 6.

Figure 6: Management of extraocular retinoblastoma



Abbreviations. RB: Retinoblastoma; IRSS: International Retinoblastoma Staging System; EBRT: External Beam Radiotherapy; NACT: Neoadjuvant Chemotherapy (chemotherapy given before surgery); VEC: Vincristine, Etoposide, Carboplatin; BMT: Bone Marrow Transplant. CNS: Central Nervous System.
+ Can give up to 6 cycles of NACT if enucleation is not possible and patient is responding clinically and radiologically. Orbital exenteration to be performed if enucleation is not possible after 6 cycles neoadjuvant VEC or there is progression on NACT. Total chemotherapy cycles should be 12 (NACT+adjuvant).

Management of IRSS Stage II

Patients with IRSS stage II disease have evidence of microscopic extraocular extension (either scleral involvement or cut-end of optic nerve involvement) in the enucleated specimen. These patients are managed similar to patients with overt extra-ocular disease. Patients with rupture of eye during surgery are to be considered as stage II.

Chemotherapy in IRSS Stage II

Vincristine, etoposide, and carboplatin (VEC) is the standard chemotherapy regimen used. The dose and schedule for VEC is provided in Appendix. Patients are given 12 cycles of VEC chemotherapy.

Management of IRSS Stage III

Patients with IRSS stage III disease have overt extraocular extension clinically or radiologically. The management of these patients remains a challenge as orbital involvement is associated with a 10–27 times higher risk of metastasis when compared with cases without orbital extension. (102) Historically these patients were treated with orbital exenteration, followed by chemotherapy and radiotherapy. Orbital exenteration, unlike enucleation, is a cosmetically disfiguring procedure as it involves the removal of all orbital structures, including the eyelids. Studies have shown that 2-3 cycles of neoadjuvant chemotherapy cause adequate shrinkage of the tumor mass, making it suitable for enucleation. (125) In a series of 30 patients with IRSS stage III disease who received neoadjuvant chemotherapy, enucleation was possible in all the patients. (125) Therefore, orbital exenteration is no longer preferred in IRSS stage III disease. All patients should receive 2-3 cycles of neoadjuvant chemotherapy followed by enucleation of the affected eye, external beam radiotherapy and adjuvant VEC chemotherapy (total 12 cycles including neoadjuvant chemotherapy).

Patients with IRSS stage III or IV disease in whom enucleation cannot be performed after three cycles of neoadjuvant chemotherapy should be given additional cycles of neoadjuvant chemotherapy up to 6 cycles, provided there is a clinical or radiological response in the tumor. This regimen of systemic chemotherapy followed by surgery and radiotherapy provides cure in 60-80% of localised orbital RB, however, CNS remains the predominant site of recurrence.

Orbital exenteration should be performed in patients in whom enucleation is not possible after six cycles of VEC chemotherapy or if there is a disease progression on chemotherapy.

Chemotherapy regimens used in extraocular retinoblastoma.

Vincristine, etoposide and carboplatin (VEC) is the standard and preferred chemotherapy regimen in extraocular RB. (126) Chantada et al from Argentina have reported on the use of two different chemotherapy protocols for managing extraocular RB in 41 patients. The first protocol was used between 1987-1993 (protocol 87) and the second between 1994-2000 (protocol 94). Chemotherapy included cyclophosphamide, vincristine, etoposide, doxorubicin (in protocol 87), idarubicin (in protocol 94), cisplatin (in protocol 87), and carboplatin (in protocol 94). The 5-year event-free survival in the study was 84%.

A study from Brazil reported on the use of cisplatin, teniposide, vincristine, doxorubicin, and cyclophosphamide between 1987 and 1991, cisplatin and teniposide alternating with ifosfamide and etoposide between 1992-2000 for treating extraocular RB in 83 patients. (127) However; the addition of ifosfamide and etoposide did not significantly improve survival in patients with EORB (5 years survival 55.1% vs 59.4%, p=0.69).

The addition of ifosfamide/etoposide to chemotherapy with cisplatin/teniposide has been found to be effective in extraocular RB**. (127)**

There have been no randomized trials in extraocular RB comparing VEC with other chemotherapy regimens.

Is there any role of high dose carboplatin in VEC?

The dose of carboplatin in VEC has traditionally been 18.6 mg/kg. Radhakrishnan evaluated the role of a higher dose of carboplatin (25 mg/kg) in VEC in a prospective study of 28 IRSS stage III patients. (125) A higher dose of carboplatin was well tolerated in this study. The overall survival was 40.4% at a follow-up of 14.75 months. None of the patients in this study required orbital exenteration post neoadjuvant chemotherapy. A pilot randomized controlled trial in intraocular retinoblastoma (group C and D) compared standard-dose VEC (carboplatin 560 mg/m^2) versus high dose VEC (carboplatin 750 mg/m^2) for global salvage rates. The study included 38 patients of group C and D RB (21 patients in the standard dose VEC arm and 17 in the high dose VEC arm). Patients received at least six cycles of VEC chemotherapy up to a maximum of 12 cycles. Higher dose VEC did not improve globe salvage rate than standard dose VEC. (128) There is no randomized trial comparing standard versus higher dose carboplatin in EORB; therefore, the choice of dose of carboplatin is at the discretion of the treating oncologist.

Management of IRSS Stage IV:

Algorithmic guidelines of metastatic disease have been shown in Figure 7.

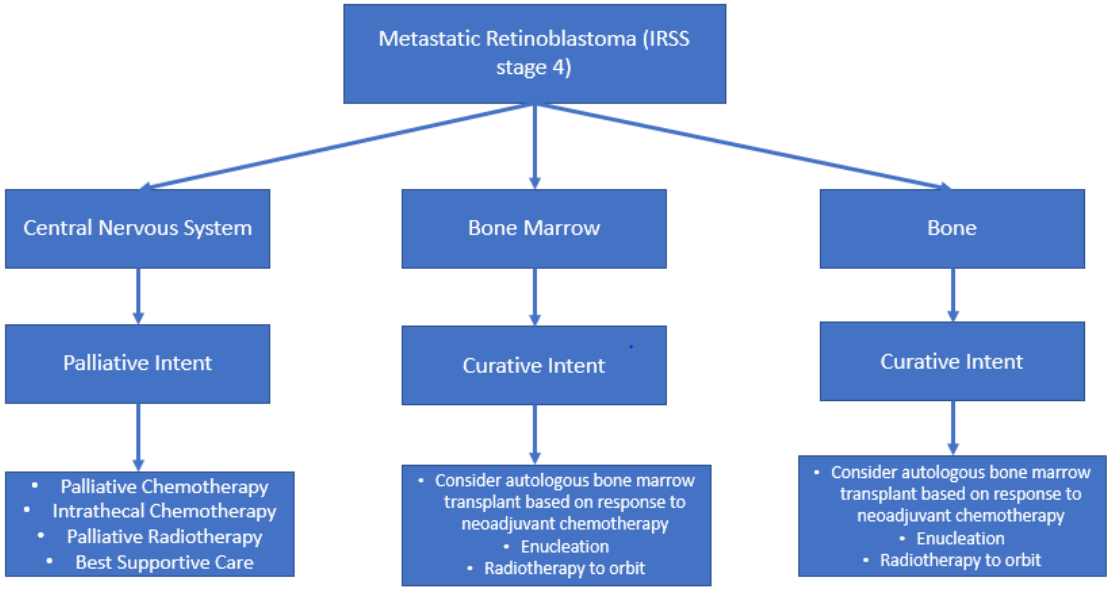


Figure 7: Management of IRSS 4 retinoblastoma

Is there any role of high-dose chemotherapy and autologous stem cell transplant?

High-dose chemotherapy and autologous stem cell transplant (HDCT with ASCT) can be curative in a few patients with metastatic RB. HDCT with ASCT has shown to be effective only in patients with bone metastases or bone marrow involvement. (129–131) It has not helped manage patients with central nervous system metastasis. Data on the role of HDCT with ASCT in RB is limited. Survival in a few case series has ranged from 63%-100%. (129,130) The HDCT conditioning regimens have included carboplatin, etoposide with either thiotepa, cyclophosphamide, or melphalan. Patients with CNS involvement have better survival outcomes with thiotepa-based conditioning regimens. (132,133)

Is there any role of Intrathecal chemotherapy in extraocular retinoblastoma?

The role of intrathecal chemotherapy in extraocular retinoblastoma for prophylaxis and treatment is not clear. Central nervous involvement in retinoblastoma is predominantly parenchymal as most disease extension occurs via the optic nerve to the optic chiasma. Cerebrospinal fluid or meningeal involvement is less common. Intrathecal chemotherapy with drugs like methotrexate and ARA-C is more effective with CSF positive disease than parenchymal disease. There have been reports of the use of intrathecal

topotecan based on its activity in retinoblastoma. (134) However, intrathecal topotecan is not available in India. Combined intraarterial and intrathecal chemotherapy have been tried to achieve higher drug concentration in a patient with retinoblastoma with CNS involvement. Craniospinal irradiation with intrathecal methotrexate has been used to control the disease in retinoblastoma patients with CNS involvement.

The dose, duration, and choice of drugs for intrathecal therapy in retinoblastoma are unknown. A common schedule is to use intrathecal preservative methotrexate at 15 mg twice a week till clearance of malignant cells from the CSF, followed by once a week for four weeks and then monthly. Other schedules include intrathecal methotrexate 12 mg, hydrocortisone acetate 30 mg, and cytarabine 25 mg.

What are the indication of RT in extraocular RB: Benefit of radiotherapy in EORB has been reported by several studies. Argentine and New York groups also reported the results of 12 patients with optic nerve margin positivity treated with the chemotherapy regimens above and orbital radiation therapy (40 to 45 Gy). All 12 were event-free survivors. In another study addition of orbital RT to a dose of 40-50 Gy was successful in 63% patients with orbital disease and 76% patients with optic nerve margin positivity. (127) The available data suggest that patients with extra-ocular retinoblastoma can be cured with intensive treatment that includes systemic chemotherapy and external beam radiation therapy. Therefore all patients with orbital disease should receive RT. (level of evidence 3)

Target volume post enucleation: Entire orbit should be irradiated. Gross tumor volume (GTV) includes all gross disease. Clinical target volume (CTV) includes the entire orbit. Planning target volume (PTV) margin according to institute protocols is usually 3-5mm. Though there is no strong evidence, it has been recommended that if cut end of optic nerve is positive, entire orbit along with the optic nerve and proximal chiasma should be irradiated as there is potential for subclinical spread that is not visible on a MRI. (though no strong evidence, extension of CTV till optic chiasma is considered by few centres. (105,135) Organs at risk (OAR) include lens, retina, bony orbit, lacrimal glands, temporal lobes, whole brain, and pituitary gland. The tolerance of each of these structures should be respected to reduce the side effects.

Radiotherapy dose:

Is there any difference in RT doses in optic nerve cut margin and scleral invasion: Patients with macroscopic disease in orbit and those with scleral disease should receive post-operative RT to entire

orbit to a dose of 40-45 Gy in 1.8 to 2 Gy per fraction. (126) In patients with positive optic nerve cut end, should receive whole orbit RT to a dose of 36 Gy followed by a boost of 9-10 Gy to the remainder of optic nerve and chiasma. (136) There is a lack of dose response relationship beyond 45 Gy, though larger tumors (>10DD) may require additional dose. (137)

Node positive RB: Pre-auricular and cervical lymph nodes should be imaged carefully because 20% of patients with orbital extension have lymphatic metastases. (138) Lymphatic dissemination may not carry a worse prognosis, provided that the involved lymph nodes are also irradiated. There is very little data on irradiation of lymph nodes. However, given that the outcome in this group of patients can still be favourable, it has been recommended that a RT dose of 40- 45Gy should be delivered to the proven/involved pre-auricular/cervical lymph nodes/entire LN chain (evidence is not strong on target volume but it is recommended). (126,139) Previous protocols have included entire lymph node chain or groups with margin rather than an involved node approach. Recent ongoing COG ARET 0321 trial has also incorporated RT as a part of the multimodality treatment to initially involved sites in stage 2 and 3 RB after induction chemotherapy. (Level of evidence 4)

Consensus guidelines: Though there is no strong evidence, it was recommended to give RT to initially involved nodal region.

Role of RT if radiological evidence of post-laminar optic nerve and trans-scleral extension is there but HPR does not show high risk features: EBRT should be given irrespective of response to chemotherapy and HPR findings. (level of evidence 4)

RT in children less than 1 year of age: Despite the fact that retinoblastoma is highly sensitive to radiation and radiotherapy provides a definitive treatment for many tumors refractory to focal and systemic therapy, the late effects of radiation, especially the high incidence of secondary malignancies, continue to be the subject of controversy. Risk of RISM depends on patients age, especially when RT is given to children less than 12 months of age. Abramson and colleagues reported significant decrease in tumor free survival and increased risk of infield second malignancies in the patients who were treated with RT before 12 months of age. (140,141) Also, the effect of radiation is most prevalent on orbital bone till the child attains 12 months of age. Thus, if radiotherapy is necessary, it should be delayed till the child attains 12 months of age to decrease the risk of SMNs and orbital growth abnormality.

Consensus guidelines: Whenever indicated, RT should be delayed till the child attains 12 months of age, unless palliative

Timing of RT: Ideally within 4-6 weeks of surgery.(13) (level of evidence 3)

Radiotherapy in metastatic disease: Metastatic disease seen rarely at diagnosis is associated with poor prognosis. A higher incidence is seen in LMICs due to delayed diagnosis. Patients may have metastatic disease at presentation or can develop metastasis during or after the course of treatment. Sites of distant metastatic disease includes CNS (or leptomeningeal spread) or haematogenous dissemination to bones, bone marrow, or occasionally liver. Role of RT in metastatic RB who receive high dose chemo with SCT is unclear, resulting in wide variation in patterns of practice. However; most of the times, the intent of RT remains palliative and can be used in extensive local and loco-regional disease, control of fungation/ulceration, bleeding, painful bony metastasis, multiple CNS or leptomeningeal spread. Though few recent series have shown 3 to 5 years of event free survival of 60-80% with the use of intensive multimodality treatment with multi-agent chemotherapy and radiotherapy to bulky sites.(130,132,142) **The panel recommends only palliative RT in these patients insufficient data and poor prognosis**.

Palliative RT in bone metastasis: Bone is the most common site of non CNS metastatic disease. Ribs and vertebrae are the most commonly involved bones in children which are the most active in the hematopoietic system. (143) There are many variations in dose fractionation schedules. Single fractionation schedules (8Gy in one fraction) can be used in children with shorter life expectancy or multiple metastasis. (Level of evidence from pediatric studies- 4). Dose fractionation schedule varies from more prolonged fractionation regimens to a short, hypo-fractionated regimen. (144) Few studies have reported a long term survival after a radiation dose of 20-60 Gy to bony metastatic sites. (126,134) Despite good initial response to treatment, most of these patients eventually die of CNS metastasis, thus the intent remains palliative in majority of these patients.

Palliative RT in liver metastasis: Due to rarity, there are only few reports on management of hepatic metastasis in paediatric patients. Role of metastatectomy and RT is unclear due to higher chemo-sensitivity. As an extrapolation from adults, resection or radio-ablation can be used in limited metastasis. However, majority of the children with liver mets will have diffuse parenchymal lesions or other sites of

metastasis and thus receive palliative RT to relieve pain or mass effect. (130,145) Different dose fractions that have been used (19.5 Gy or 20 Gy in 5 fractions to partial liver or 8 Gy in 1 fraction to partial or whole liver). (129,144) (Level of evidence - 5)

Palliative RT in CNS metastasis: CNS metastasis occurs due to direct invasion of the optic chiasma, optic nerve, supra-sellar cistern or meninges. The prognosis remains poor despite aggressive multimodality therapy. (127) Intent of radiotherapy is purely palliative. Whole brain radiotherapy (WBRT) or cranio-spinal irradiation (CSI) can be given to those with intracranial metastasis and positive CSF cytology or spinal metastasis respectively.(104,144,146) (Level of evidence - 4)

There is no consensus regarding the most suitable dose of fractionation for these children and a WBRT dose of 20 Gy in five fractions or 30 Gy in 10 fractions can be used, depending on the general condition of the child. (147)A CSI dose of 23.4 Gy (3-5 years) and 36 Gy (>5 years) can be used in symptomatic patients.

Ongoing trial COG ARET 0321: This trial will test HDCT in Stage 4 (a and b and trilateral). RT will be avoided in complete responders. Incomplete responders will receive radiation therapy, treatment at approximately day +42 post-autologous stem cell infusion. (131)

Is there any role of RT for primary in metastatic setting: Role of RT is this setting is not clear. However, it can be considered (40-45 Gy) after initial chemotherapy and enucleation if the number of metastasis are limited and there is at-least partial response at metastatic sites (with or without RT to metastatic sites). (148)

Radiotherapy technique: Majority of the patients require general anaesthesia/sedation. CT based RT planning is preferred. Though latest RT techniques including intensity modulated radiotherapy (IMRT) and volumetric modulated arch therapy (VMAT) can significantly improve conformity and spare surrounding organs at risks, these techniques should be used carefully in these children due to increased risk of second malignancies because of increased low dose bath. Unique property in reducing exit dose in proton beam therapy has the potential to reduce side effects, however cost and limited availability remains a significant issue.

RT dose in salvage setting: A radiotherapy dose of 36-45 Gy has been recommended in these situations. Some recommend a lower RT dose when radiotherapy is used as a consolidation treatment followed by other treatment modalities to avoid complications (level of evidence 4).

Epi-scleral plaque brachytherapy: Plaque brachytherapy can be effective in early stage of the disease when other forms of local therapies have failed to control the tumor. The American Brachytherapy Society Ophthalmic Oncology Task Force recommends primary brachytherapy for unilateral anterior lesions that are <15 mm in base and up to 10 mm in thickness, without vitreous seeding and at-least 3mm away from disc. (149,150) A variety of radionuclides have been used with comparable efficacy. Target volume in this case should be residual disease +1-2mm margin and prescribe the depth to either the apex of the lesion or to 5mm, when the lesion is fairly flat. A dose of 40-45 Gy is delivered at a dose rate of 40-50 cGy/hr, using I-125 or Ru-106 seeds. (151) In case of non-availability of brachytherapy, EBRT can be planned using adequate PTV margin (usually 3-5 mm).

RT dose and target volume in various circumstances has been summerised in table 3.

RT machine: What is ideal, essential and optional?

Ideal: Linear accelarator

Essential: Cobalt-60 with treatment planning system

Optional: Proton/ Carbon ions

Management of orbital recurrence:

Orbital recurrence can occur after enucleation of the primary tumor. Orbital recurrence can be suggested by displacement or extrusion of an orbital implant or a vascular conjunctival or subconjunctival nodule. Most orbital recurrences occur within 12 months from initial enucleation. (152) All patients with orbital recurrence need to undergo staging investigations to rule out metastatic disease. The investigations are the same as described for newly diagnosed extraocular retinoblastoma cases. The outlook for patients with orbital recurrence is dismal, with most cases developing metastatic disease. (152)

Management of orbital recurrence should be managed on a case-to-case basis. Surgical excision of the orbital mass should be considered after 3-6 cycles of chemotherapy. (153) Patients who have not received

radiotherapy upfront should be considered for external beam radiotherapy to the orbit. There is no standard recommended chemotherapy regimen for patients with recurrent disease. VEC chemotherapy can be tried if the patient had a good tumor response at initial diagnosis and recurrence has occurred one year after the last VEC chemotherapy. Other chemotherapy regimens used in the author's institutions for recurrent orbital retinoblastoma include ifosfamide, vincristine, doxorubicin or vincristine, carboplatin, and topotecan. (Table 2) (154)

Trilateral RB: Trilateral RB (TRB) consists of an intracranial tumor associated with retinoblastoma that is histologically similar but anatomically distinct. It is diagnosed in 3–4% of patients, occurring more frequently in patients with bilateral disease with/without a family history of retinoblastoma, who are younger than 1 year of age. Classically TRB was defined as bilateral retinoblastoma along with a tumor in the pineal region, though in some cases, the intracranial tumors can be in suprasellar or parasellar location. (155) A screening for a pineal tumour is suggested in patients with bilateral RB during the initial 3-4 years of diagnosis. Trilateral RB does not represent CNS metastasis. Prognosis remains poor and most of the children die within 9 months with neuraxial dissemination, however slight improvement in survival has been seen the recent years. In a meta-analysis of 174 patients in 90 studies, 5-year OS in pineal TRB patients improved from 6% (95% CI 2–15%) to 44 % (95% CI 26–61%) in patients diagnosed recently as compared to those diagnosed prior to 1995. Similarly, 5-year OS in non-pineal TRB improved from 0 to 57% (95% CI 30–77%). The improvement in survival resulted from early detection and improved chemotherapy regimens. (22) However, since 1995, there has been decreased use of RT with increasing use of chemotherapy, HD chemo and SCT, an approach similar to that in infants with brain tumors. (22)

LATE EFFECTS OF TREATMENT

Patients with retinoblastoma are prone to late effects of treatment due to surgery, radiotherapy, and chemotherapy. These late effects can be physical, psychological, and social.

Subsequent neoplasms (SN): SNs are the most common cause of death in RB, contributing to about half of the deaths in bilateral and hereditary RBs. Both radiotherapy and chemotherapy increase the risk of

SN. Hereditary RB (germline RB1 mutation) patients are at increased risk of SN due to faulty genes, and treatment with radiotherapy or chemotherapy increases the risk. In these patients, the incidence of SN is 0.5-1%/year with a cumulative incidence of 18-35% at 40 years as compared to only 2% in non – hereditary cohort. (156,157) In one study of 1854 patients treated between 1914 and 1996, cumulative mortality from SN at 50 years post diagnosis was 25.5% for hereditary RB survivors as compared to 1% for nonhereditary cohort. (158) In a German series, while radiotherapy was specifically associated with second cancers arising within the periorbital region in the previously irradiated field, chemotherapy with or without RT was the only significant risk factor for SNs outside periorbital region. (53) In a Dutch series, standardized mortality rate (SMR) in hereditary RB survivors was 60.9 vs 18.1 vs 7.95 for those treated with chemo-radiotherapy, radiotherapy, or surgery alone, respectively. (156) Sarcoma and melanoma are the most common SNs in hereditary RB, while carcinomas(lung, bladder, pancreas, intestine, kidney, and other epithelial) are the most common malignancies in non-hereditary RB. (156,159). Many of the estimates of radiation-induced tumors are based on the outcomes of patients treated in a different era of radiation. With modern radiotherapy techniques and modalities, incidence of side effects including RISM can be significantly reduced . (156,160) In one study proton therapy significantly reduced the 10 years cumulative incidence of RISM as compared to photon (0% vs 14%). Screening surveillance whole body MRI has not been found useful for detection of second malignancies in retinoblastoma survivors with germline mutation of the retinoblastoma gene.

Bony abnormality: These children are at increased risk of functional and cosmetic bony abnormalities that becomes evident in adolescence when orbital growth is complete. Both enucleation and RT adversely affect the bony growth. (161) Proton therapy limits the normal tissue exposure to radiation thus can reduce the risk of second malignancies and severe growth abnormalities. (162) However, cost and availability remains an issue in LMIC.

Vision, quality of life, and others: Batra et al. assessed the visual outcomes of 45 eyes of 43 patients with retinoblastoma above five years and completed two years of follow-up. (163) Half of the study patients had good visual outcomes. Patients with disease located at the macula or Group C and D disease or who received radiotherapy had poor visual outcomes.

Batra et al. studied the parent's perception of health-related quality of life (HRQOL) in 122 retinoblastoma survivors. (163) They compared it with parent-reported HRQOL of 50 siblings who acted as the control. The overall parent-reported HRQOL (74.4 ± 8.5 vs. 85.1 ± 4.6, $P < 0.001$) and all health domains were significantly worse in survivors than controls. Baseline and treatment associated factors did not predict the HRQOL.

Batra et al.analyzed the QOL in 122 retinoblastoma survivors above five years. (164) They completed more than one year of follow-up. The QOL was compared with 50 siblings. Overall, RB survivors had poor QOL with considerable effect on the emotional health domain. Retinoblastoma survivors had difficulties in sustaining relationships and higher school absenteeism. The physical health domain including exercise and self-care was similar between survivors and controls. Patient diagnosed at a younger age (<18 months) had better QOL.

Batra et al. also reported that 36% of retinoblastoma survivors were short-statured compared to their peers. (165) Carboplatin is used for treating retinoblastoma; it can cause hearing loss, although to a lesser extent than cisplatin. Studies have reported ototoxicity in retinoblastoma; however, there is a wide range, with studies reporting 0% toxicity to 79% toxicity. Batra et al. performed a cross-sectional study to detect carboplatin-induced ototoxicity in 116 retinoblastoma survivors more than five years of age and who were 12 months post-treatment. (166) They assessed hearing using pure tone audiometry. Only 1 out of the 116 patients had hearing loss. This study suggests that ototoxicity in retinoblastoma survivors in India is rare. However, more long-term prospective studies are required to assess the impact of carboplatin on hearing loss in retinoblastoma.

A study from Seth et al. from New Delhi on 213 retinoblastoma survivors observed that orbital growth was affected in about one-third of patients. (167) Most had received radiation. A diminished vision was observed in one-sixth, and hearing impairment was observed in 2.7%. Global intelligence delay was observed in one-sixth and second cancers in 0.01% of patients.

Table 26: Survivorship concerns

	Comments
Subsequent neoplasm	Incidence: 25-40% in hereditary and 1-2 % in non hereditary Sarcoma is MC in hereditary and carcinoma is MC in non hereditory
Bone abnormality	Both surgery and RT can lead to bony abnormality
Vision impairment	Tumors located at macula, RT and enucleation
Impaired QoL	RB surviors have impaired Qol as compared to siblings and controls Decreased global QoL Decreased school performance Short stature
Hearing loss	Rare

Research Questions:

1. Is there a role of prophylactic intrathecal therapy with radiotherapy or intrathecal chemotherapy in patients with IRSS stage II, III, or IV (without CNS involvement) disease?
2. Is there a role for a higher dose of carboplatin (750 mg/m^2) in patients with extraocular RB?
3. Can PET-CT be used for a staging and response assessment in extraocular RB?
4. Can the number of cycles of chemotherapy in extra-ocular RB be reduced from 12 to 9 or 6?

Levels of Evidence (based on the Oxford CEBM Levels of Evidence):

1. High dose carboplatin in extraocular RB: Level 4
2. Autologous bone marrow transplant in extra-ocular RB: Level 4
3. PET /CT scan for staging and response assessment in retinoblastoma. Level 4
4. RT for stage 2 (high risk) and stage 3- Level 3
5. RT for cervical/preauricular nodes: Level 4
6. RT for CNS/bone metastasis: Level 4
7. RT for hepatic metastasis: Level 5

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