Indian Journal of Pediatrics (November 2024) 91(11):1166–1176
https://doi.org/10.1007/s12098-024-05095-0

REVIEW ARTICLE

Management of Intraocular Retinoblastoma: ICMR Consensus Guidelines

Rachna Meel[1] · Suyash Kulkarni[2] · Lata Singh[3] · Girish Chinnaswamy[4] · Venkatraman Radhakrishnan[5] · Renu Madan[6] · Archana Sasi[7] · Tanvir Kaur[8] · R. S. Dhaliwal[8] · Sameer Bakhshi[7]

Received: 22 January 2024 / Accepted: 1 March 2024 / Published online: 13 April 2024

Abstract
Retinoblastoma (RB) is the most common childhood intraocular malignancy. Delayed presentation due to a lack of awareness and advanced intraocular tumors are a common scenario in low-middle income countries (LMICs). Remarkable treatment advances have been made in the past few decades allowing globe salvage in advanced intraocular RB (IORB) including systemic chemotherapy with focal consolidation and targeted treatments like intraarterial chemotherapy and intravitreal chemotherapy. However, a lack of availability and affordability limits the use of such advances in LMICs. External beam radiotherapy, despite risk of second cancers in RB with germline mutations, still remains useful for recalcitrant RB not responding to any other treatment. When choosing conservative treatment for advanced IORB, the cost and long duration of treatment, morbidity from multiple evaluation under anesthesias (EUAs), side effects of treatment and risk of treatment failure need to be taken into account and discussed with the parents. In this article, the authors discuss the ICMR consensus guidelines on the management of IORB.

Keywords Intraocular retinoblastoma · Consensus · Guideline · Classification · Intra-arterial chemotherapy · Intra-vitreal chemotherapy · Intravenous chemotherapy

Introduction

The management of intraocular retinoblastoma (IORB) has evolved tremendously over past few decades. With the advent of targeted therapies, ocular salvage in retinoblastoma (RB) has achieved unprecedented heights. However, in resource constrained countries, use of newer treatment modalities is limited by availability and affordability. Late presentation and high abandonment rates are typical to low-middle income countries (LMIC) and present unique challenges in management. Herein, the authors describe the management of IORB based on resource availability and level of evidence that may be best fit for treatment of IORB in LMICs.

Material and Methods

The current manuscript is written with the aim of developing a national consensus guideline for practitioners involved in the management of IORB. The guidelines were drafted after an exhaustive review of literature including national and international data and three rounds of meetings amongst the experts in the field of RB nominated by ICMR. A consensus was drawn on controversial issues and

✉ Rachna Meel
dr.rachnameel@gmail.com

1 Department of Oculoplasty and Ocular Oncology Services, Dr. Rajendra Prasad Centre of Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi 110 029, India

2 Department of Interventional Radiology, Tata Memorial Hospital, Parel, Mumbai, India

3 Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

4 Department of Pediatric Oncology, Tata Memorial Hospital, Parel, Mumbai, India

5 Department of Medical Oncology and Pediatric Oncology, Cancer Institute (W.I.A), Adyar, Chennai, India

6 Department of Radiotherapy and Oncology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

7 Department of Medical Oncology, Dr. B.R.A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

8 Division of Non-communicable Diseases (NCD Division), Indian Council of Medical Research (ICMR), New Delhi, India

the final guidelines were circulated on the website for a period of 30 d as per ICMR rules for any external comments from other experts [1].

Management of IORB

Treatment of IORB primarily depends on: the intraocular tumor classification, presence of germline mutations, disease laterality, multifocality in unilateral disease, psychosocial situation of the family, treatment compliance and existing institutional resources [2, 3].

Classification of IORB

IORB can be classified using International Classification of Retinoblastoma (ICRB) Philadelphia version or International Intraocular Retinoblastoma Classification (IIRC), the Children's Hospital Los Angeles version / TNM AJCC 8th edition/ Children Oncology Group classification version [3]. The 2 most commonly used classification schemes are IIRC and ICRB (Table 1). Both classifications are based on the extent of tumor involvement of ocular structures and guide local disease management i.e., conservative treatment vs. enucleation. ICRB is the most commonly used classification in Indian studies [4].

ICRB and IIRC mainly differ in class allocation of group D and E eyes. A study evaluating the same found that group assignment of 5.2% of the eyes (25% of group E eyes) was different in the two classification systems [5]. Also retinal detachment (RD) is not used as a criterion for classifying groups C and D tumors in ICRB. However, eyes with diffuse RD may harbour subretinal seeds (SRS) and thus have poorer treatment outcomes.

Consensus: For tumors with RD, IIRC criteria of classification may be used: tumors with RD≤1 quadrant may be classified as group C and those with >1 quadrant RD as group D.

Germline Mutations

Nearly 40% of RB patients carry germline mutations (GLM) in *RB1* gene. GLMs affect all cells of the body and predispose the patient to secondary non-ocular cancers.

GLM can be presumed from presence of bilateral disease/ family history or multifocality in unilateral disease. Early presentation (in first 6 mo of life) may also point towards GLM. Although genetic testing is definitive for identifying the mutation, its use is limited by cost in LMICs.

RB patients with GLM can develop midline neuroectodermal tumors, alternatively known as pinealoblastoma, most of which develop under the age of five years. The estimated

Table 1 Comparison of the two IORB classification systems

	International Intraocular Retinoblastoma Classification (IIRC)	Intraocular Classification of Retinoblastoma (ICRB)
Group A (very low risk)	All tumors ≤3 mm confined to the retina and ≥ 3 mm from the foveola and ≥1.5 mm from the optic nerve. No seeds	Retinoblastoma ≤3 mm (in basal dimension/ thickness)
Group B (low risk)	Eyes with no vitreous seeds and discrete retinal tumor of any size or location. Small cuff of subretinal fluid not extending ≥5 mm from the base of the tumor	Retinoblastoma >3 mm (in basal dimension or thickness/ Macular in location (≤3 mm to foveolar/ Juxtapapillary location (≤1.5 mm to disc)/ Additional subretinal fluid (≤3 mm from margin)
Group C (moderate risk)	Eyes with focal vitreous and subretinal seeds and discrete retinal tumors of any size and location. Up to one quadrant of subretinal fluid/ RD	Retinoblastoma with: Subretinal seeds ≤3 mm from tumor/ Vitreous seeds ≤3 mm from tumor/ Both subretinal and vitreous seeds ≤3 mm from tumor
Group D (high risk)	Eyes with diffuse vitreous and/or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease; Eyes with more extensive seeding than Group C; Massive and/or diffuse intraocular disseminated disease including exophytic disease and >1 quadrant of retinal detachment	Retinoblastoma with: Subretinal seeds >3 mm from tumor/ Vitreous seeds >3 mm from tumor/ Both subretinal and vitreous seeds >3 mm from retinoblastoma
Group E (very high risk)	Eyes that have been destroyed anatomically or functionally with one of the following: Irreversible neovascular glaucoma, massive intraocular hemorrhage, aseptic orbital cellulitis, tumor anterior to anterior vitreous face, tumor touching the lens, diffuse infiltrating retinoblastoma and phthisis or pre-phthisis	Extensive retinoblastoma occupying >50% globe/ with Neovascular glaucoma/ Opaque media from hemorrhage in anterior chamber, vitreous or subretinal space/ Invasion of postlaminar optic nerve/ choroid (>2 mm), sclera, orbit, anterior chamber on baseline imaging (CE-MRI)

CE-MRI Contrast-enhanced magnetic resonance imaging, *IORB* Intraocular retinoblastoma, *RD* Retinal detachment

chance of developing pinealoblastoma is less than 0.5% among unilateral, 5%-13% among sporadic bilateral and 5%-15% among familial bilateral retinoblastoma [6]. The downward trend in incidence of pinealoblastoma noted during the chemoreduction era, points towards a possible chemoprotective effect. Other authors believe that this may be related to the lack of use of external beam radiotherapy (EBRT) [7].

Studies show that EBRT significantly increases the cumulative risk of second cancers in patients with GLM (35.1% compared to 5.8%) [8].

Consensus: IORB with GLM may be screened with baseline magnetic resonance imaging (MRI) brain for pinealoblastoma. In view of low incidence and poor treatment outcome of pinealoblastomas, routine follow-up screening for same is not recommended.

IORB with GLMs may preferably be treated with systemic intravenous chemotherapy (IVC)

Management of Unilateral Retinoblastoma (Fig. 1a)

Retinoblastoma manifests unilaterally in all non-hereditary retinoblastomas and around 15% of hereditary RBs. It thus accounts for nearly 60% of all RB cases. Management of unilateral IORB is summarised in Tables 2 and 3.

Conservative Treatment

Group A-C Retinoblastoma

While group A RB can be treated with focal treatment (FT) methods, groups B and C are most commonly treated with chemoreduction followed by FT. The reported success rates of treatment with chemoreduction (VEC protocol: vincristine, etoposide, and carboplatin) and FT is 100% for group A, 93% for group B and 90% for group C [4]. Studies from India also report similar globe salvage rates: 100% for group A, 94–100% for group B and 83–100% for group C [9, 10]. Alternatively, they can be treated with intra-arterial chemotherapy (IAC). Globe salvage rates of 100% in groups B and C have been reported with primary IAC [11].

Chemoreduction

When systemic chemotherapy is used to reduce shrink retinal tumors in order to make them amenable for FT, it is called chemoreduction (Table 4). It is used in groups B-D tumors. Chemoreduction is known to reduce tumor height by 49% and base-diameter by 35% after 2–3 cycles with some regression of vitreous seeds (VS) and resolution of RD in about 50% cases. Therefore, FT is started at this time. Six cycles of treatment have shown to reduce tumor relapse/ recurrence when compared to only 2 cycles. The high-risk clinical features for failure after chemoreduction include older age at presentation (>12 mo), greater tumor thickness (base-diameter >15 mm, and height >5 mm), presence of VS and/or SRS, and retinal tumor recurrence [3, 12]. In children <6 mo of age, systemic chemotherapy may have long term side-effects.

Consensus: In children <6 mo of age, 2 drug chemotherapy with vincristine and carboplatin may be preferred to reduce long term side-effects.

Consensus: In view of low toxicity, easy availability and high globe salvage rates in groups B and C, IVC remains the ideal treatment.

Focal Treatment Methods for Retinoblastoma

The focal consolidation methods for treatment of RB are effective in tumors ≤2 mm in height and include laser photocoagulation, transpupillary thermotherapy (TTT), and cryotherapy. Laser photocoagulation, unlike TTT, produces significant scarring and hence is avoided for macular tumors. TTT can be used in larger tumors, also in combination with intra-venous carboplatin, administered within 24 h, this is termed as chemothermotherapy. Cryotherapy can be used for tumors anterior to equator, and to augment penetration of systemic chemotherapy for treatment of VS.

Response Evaluation of Tumor

This is based on ultrasound examination and direct visualisation of retinal tumor on serial evaluation under anesthesia (EUAs). A single target tumor is identified and measured at baseline EUA. After chemoreduction, tumor achieves a minimum height which is important to assess any subsequent increases in tumor size and hence tumor progression. A consensus on the response criteria for retinal tumors, vitreous and subretinal seeds was published recently (Table 5) [13].

Group D Retinoblastoma

The definition of group D varies in ICRB and IIRC classifications, resulting in an inability to compare different studies. Conservative treatment in unilateral Group D RB is long, expensive, has side-effects and often fails, requiring secondary enucleation [14]. Declining trends of enucleation and improving globe salvage rates have been reported by several studies and make the decision for primary enucleation vs. conservative treatment tougher for clinicians and patients.

In a survey evaluating treatment of group D RB worldwide, authors reported enucleation in mean 29% cases across all centres. Chemoreduction was the most common primary modality used with a mean of 57% per centre [15]. Studies report a globe salvage rate of 47% in group D eyes with complete

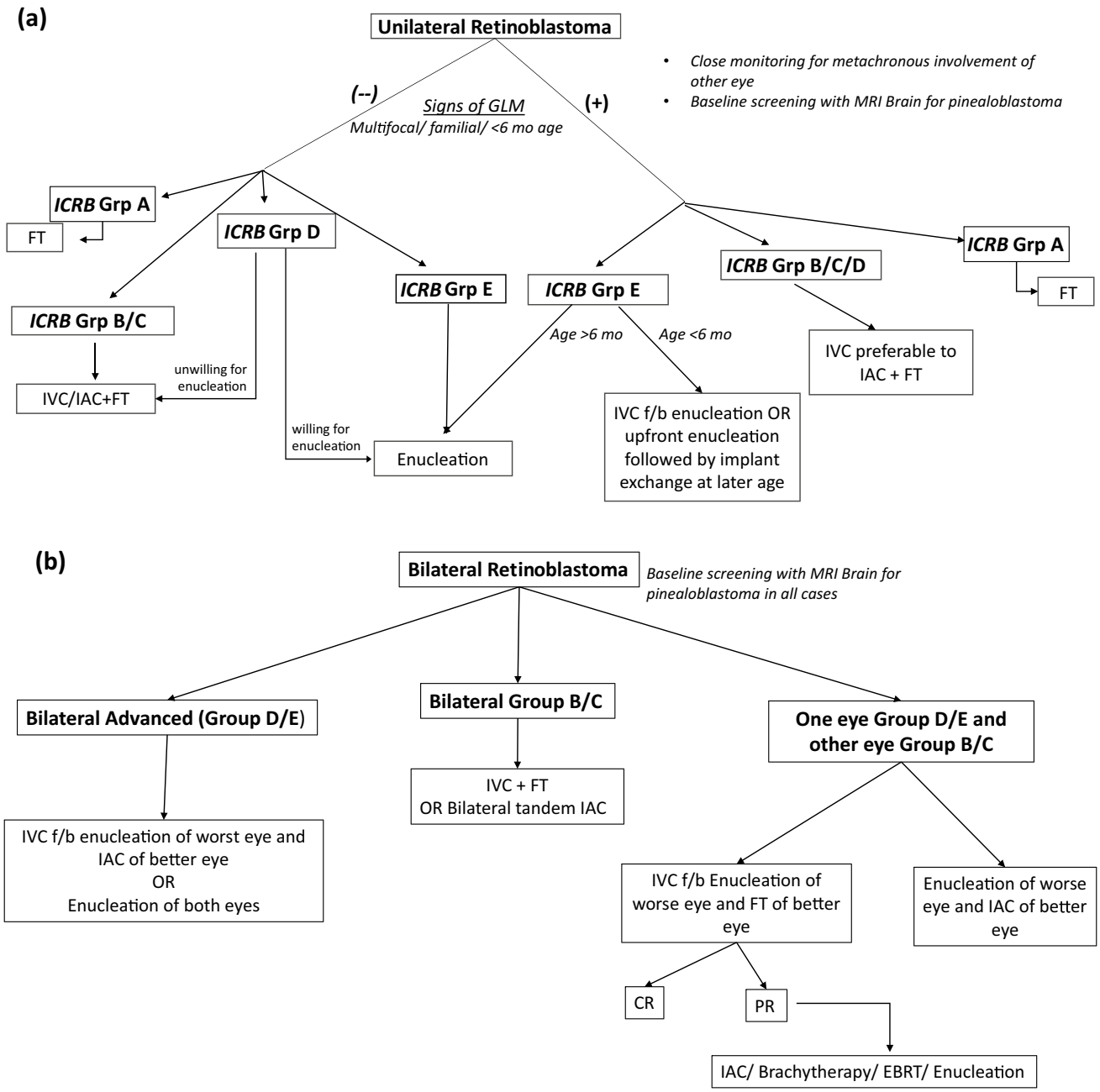

Fig. 1 Treatment algorithm for IORB (**a**) Unilateral retinoblastoma (**b**) Bilateral retinoblastoma. *CR* Complete regression, *EBRT* External beam radiotherapy, *f/b* Followed by, *FT* Focal treatment, *GLM* Germline mutations, *Grp* Group, *IAC* Intra arterial chemotherapy, *ICRB* International classification of retinoblastoma, *IORB* Intraocular retinoblastoma, *IVC* Intravenous chemotherapy, *MRI* Magnetic resonance imaging, *PR* Partial regression

response (CR) and FT of around 71–94% with IAC or intravitreal chemotherapy (IvC) after chemoreduction [4, 11]. Kiratli et al. reported ocular salvage in 76.7% of eyes in group D patients with primary IAC compared to 43.2% with IVC. However, IAC is costlier and scarcely available to patients in LMICs [16]. The risk of metastasis, as reported by Abramson et al. is 6% [17]. Berry et al. evaluated treatment outcomes of Group D RB using chemoreduction along with intravitreal melphalan for seeding and reported overall salvage rate of 75% [18].

Consensus: Both IAC and intravenous chemotherapy may be used for group D RB, depending on availability, if parents of the child refuse enucleation.

Group E Retinoblastoma

In a study from North America, globe salvage was evaluated in group E eyes using IVC alone or in combination with low dose EBRT (23 Gy) with a reported globe salvage of 20/42

Table 2 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. 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 mo 3 monthly follow up for 1 y 4 monthly follow up for 1 y Annual follow up till 7 y of age	There is no guidance in literature regarding frequency of follow up for metachronous presentation, the following follow up was agreed upon given that the *minimum latency reported was 30 d and maximum 2.5 y.*
Treatment Group E retinoblastoma (RB)	
Upfront enucleation Must be done for Group E RB with **high risk clinical or radiological features**	There is level 3 evidence that presence of certain clinical features (older age at presentation, longer lag time, history of orbital cellulitis, presence of hyphema, pseudohypopyon, staphyloma and massive bupthalmia predicts hHRF. Radiological features predicting higher risk of systemic metastasis include massive choroidal invasion, invasion of anterior chamber, sclera and PLONI.
Secondary enucleation May be done **in case of group E eyes with no high risk clinical or radiological features and age <6 mo of age,** to delay enucleation beyond 6 mo of age. In such cases chemotherapy is administered prior to enucleation.	There is level 4 evidence that chemotherapy provides prophylaxis against midline PNETs. 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 mo.*
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	

Table 2 (continued)

Recommendation	Evidence and Consensus
Chemoreduction group 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.

CE-MRI Contrast-enhanced magnetic resonance imaging, *GLM* Germline mutations, *hHRF* Histological high-risk features, *IAC* Intra-arterial chemotherapy, *IORB* Intraocular retinoblastoma, *PLONI* Postlaminar optic nerve invasion, *PNETs* Primitive neuroectodermal tumors, *UL* Unilateral

(48%) vs. 4/5 (80%) respectively and no metastasis at 5 y follow-up [19]. A study from the Indian subcontinent in group E eyes with neovascular glaucoma without buphthalmos reported globe salvage in 16/37 (43%) eyes at a follow-up of 20 mo [20].

Although several studies report use of IAC in primary or secondary settings for salvage of group E eyes with variable outcomes [19–36%], it's use in group E eyes remains controversial, as it does not treat systemic micro-metastases [11, 21].

Consensus: All unilateral group E IORB must be treated with upfront enucleation. Group E eyes with severe buphthalmia and a risk of globe rupture during upfront enucleation may be treated with chemotherapy prior to enucleation.

Risk of Metachronous Involvement

In a study evaluating 480 children with unilateral RB, authors found that 3.1% children later developed metachronous bilateral i.e., contralateral eye retinoblastoma [22]. The latency period varied from 30 d to 2.3 y after initial diagnosis. *The risk of developing metachronous disease was higher for children diagnosed at age ≤0.5 y compared with those diagnosed after 0.5 y (19.6% vs. 1.2%), and for multifocal compared with unifocal unilateral RB (17.1% vs. 2.2%).* Genetic analysis in unilateral RB thus can help to recognize children at high risk of developing metachronous bilateral disease, thus allowing a risk-adjusted follow-up and early treatment [23].

Consensus: Unilateral IORB presenting at <6 mo of age/ multifocal disease/ familial disease must be closely followed up for metachronous involvement of other eye.

Advanced Presentation and Enucleation

There are relatively fewer studies specifically evaluating unilateral RB in literature. Survival outcomes are clearly superior to bilateral disease [24]. Most unilateral RBs present with a delayed presentation, older age and advanced IORB i.e., group D/E as compared to bilateral disease [2, 25, 26]. A study from North America looking at unilateral RBs showed that 40% eyes with unilateral RBs were advanced Reese Ellsworth stage V, with a mean age of presentation of 16 mo [27]. A similar study from Egypt reported 75% patients presenting with group D/E retinoblastoma (41.9% group D and 33.5% group E) [28]. Another study from Latin America reported advanced IORB in 71% patients with a mean duration of symptoms of 22 mo [29].

Enucleation is the preferred treatment for advanced unilateral IORB. It is economical in terms of cost and duration of treatment and spares patient morbidity from multiple EUA, chemotherapy and/or EBRT. The vision outcomes

Table 3 Management guide for unilateral retinoblastoma without GLM

	Upfront enucleation	Chemotherapy (Intravenous chemotherapy/ IAC)	Focal treatment
Ideal	• All group E* • Diffuse infiltrating retinoblastoma • Group D retinoblastoma, willing for enucleation	• ICRB groups B and C • Group D unwilling for enucleation	Retinal tumors with fish flesh or mixed pattern regression following 2 cycles of chemoreduction
	Consensus: In view of poor globe salvage rate and vision salvage, long duration of treatment and high incidence of secondary enucleation, it was agreed that ***ideal treatment for unilateral group D treated must be enucleation.***	*Consensus: In view of low toxicity and easy availability and salvage rates as high as 100% in groups B and C, intravenous chemotherapy (IVC) 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*	
Essential	• Group E with radiological or clinical high risk features • Diffuse infiltrating retinoblastoma • Group D RB willing for enucleation	• 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 RB

GLM Germline mutations, *IAC* Intra-arterial chemotherapy, *ICRB* International Classification of Retinoblastoma, *RB* Retinoblastoma

*Group E eyes with severe Buphthalmia and a risk of globe rupture during upfront enucleation may be treated with chemotherapy prior to enucleation

remain poor in significant proportion of eyes salvaged for group D RB. Group E RB is associated with risk of systemic metastasis and therefore, most centres treat these eyes with upfront enucleation [27–31]. The risk for metastasis greatly increases with presence of histopathologic high-risk features (hHRF). High-risk IORB is more common in Asian Indians compared with Americans (35% vs. 23%) [32]. Studies from India show that 22.7% to 38.9% eyes harbour hHRF following upfront enucleation while 8.6–11.5% have microscopic residual disease [33, 34].

Table 4 Chemotherapy regimens used in intraocular retinoblastoma

Chemotherapy regimen	Drugs and Doses	Frequency
Intravenous		
VEC (standard dose carboplatin)	• Vincristine 0.05 mg/kg (≥3 y: 1.5 mg/m^2), intravenous over 15 min on day 1 • Carboplatin 18.6 mg/kg (≥3 y: 560 mg/m^2), intravenous over 60 min on day 1 • Etoposide 5 mg/kg (≥3 y: 150 mg/m^2), intravenous over 60 min on days 1 and 2	Every 3 wk
Vincristine in less than 12-mo-old: 0.05 mg/kg slow intravenous push on day 1		
Intra-arterial		
Melphalan	Slow pulsatile infusion over 30 min • 0–2-y-old 3 mg/30 cc • 2–5-y-old 5 mg/30 cc • 4–5-y-old 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-y-old 0.5 mg/30 cc • ≥2-y-old 1.0 mg/30 cc	
Intravitreal		
Melphalan	8–30 µg/0.1 cc	Deliver monthly
Topotecan	20–30 µg/0.05–0.1 cc	Deliver monthly
Inject intravitreally through pars plana or clear corneal approach, cryotherapy to injection site, jiggle eye to mix chemotherapy		
Sub-tenon		
Carboplatin	20 mg/2 cc	
Injected into subtenon's space directly over sclera in the area of tumor		

Table 5 Response criteria for retinal tumors, vitreous and sub-retinal seeds

Response criteria for retinal tumors	
Complete response (CR):	**Types 0 (no tumor remnant), I (chorioretinal scar), or IV (calcified) regression;** OR **Types II (fish-flesh) or III (mixed pattern) regression** that have demonstrated **clinical stability on fundus photography *and* ultrasound imaging for ≥6 mo** after cessation of first- and/or second-line plus local consolidation therapy
Partial response (PR):	**Decrease in apical tumor height by ≥30%** from baseline and/or Types II or III regression that have demonstrated **clinical stability on fundus photography for <6 mo**
Stable disease (SD):	**Decrease/ increase in apical tumor height by <30%** from baseline with lack of/minimal regression also seen on fundus photography (*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 lesion** ***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*
Response criteria for vitreous seeds	
Complete response (CR):	**Types 0 (no visible seeds)/ I regression** OR **Types II/ III regression that have demonstrated clinical stability on fundus photography for ≥6 mo** *Type I (refringent and/or calcified residues), Type II (amorphous, often non-spherical inactive residues with or without pigment), and Type III (combination of I and II)*
Partial response (PR):	Unequivocal improvement in seeding based on decreased number or density of seeds and/or Types II or III regression that have demonstrated **clinical stability on fundus photography for <6 mo**
Stable disease (SD):	Neither unequivocal improvement nor progression of seeding
Progressive disease (PD):	**Unequivocal progression of seeding** based on increased number or density of seeds, conversion from dust to spheres, or the presence of new preretinal tumors
Response criteria for sub-retinal seeds	
Complete response (CR):	**Disappearance** of all sub-retinal fluid and visible sub-retinal seeds, or **calcification** of all sub-retinal seeds for ≥6 mo
Partial response (PR):	Unequivocal improvement in sub-retinal seeding based on decreased number or density of sub-retinal seeds without complete calcification, and decreased sub-retinal fluid
Stable disease (SD):	Neither unequivocal improvement nor progression of sub-retinal seeding
Progressive disease (PD):	Unequivocal progression of sub-retinal seeding based on increased number or density of seeds, and/or increased sub-retinal fluid

Consensus: Enucleation for unilateral RB may be performed at a centre with adequate radiology, pathology and chemotherapy support.

Bilateral RB must be referred to higher centres capable of performing atleast focal treatment under EUA and preferably also brachytherapy and IAC.

In view of poor globe salvage and vision salvage rates, long duration of treatment and high incidence of secondary enucleation, it was agreed that ideal treatment for unilateral group D must be enucleation in absence of proven/ presumed GLM.

Histopathological High-Risk Factors and Prophylactic Chemotherapy

A consensus on pathology protocol for examination of enucleated eyes and definitions of hHRF has been published by the International Retinoblastoma Staging Working Group [35, 36]. High risk histopathological features include post laminar optic nerve invasion, massive choroidal invasion, anterior chamber invasion and scleral invasion. The use of post-enucleation prophylactic chemotherapy in patients with hHRF significantly reduces the risk of systemic metastasis.

Studies evaluating adjuvant chemotherapy for high-risk RB have reported several protocols, with agents such as, doxorubicin hydrochloride, etoposide, vincristine, cyclophosphamide, cisplatin, carboplatin, and cyclosporine [37]. A study from North America, found that untreated patients with hHRF developed metastases in 24% of cases [38]. In a subsequent study on 51 patients with hHRF by the same group, authors reported that post-enucleation chemotherapy using vincristine, etoposide, and carboplatin (VEC) was effective in preventing metastasis in 100% cases at a mean follow-up of 5 y [39]. This protocol appears to be most efficient in preventing post-enucleation metastasis (Table 4). A recent study from China reported that 5-y disease-free survival rate and overall survival rate were similar between three vs. six-cycle chemotherapy groups using VEC protocol [40].

Consensus: All enucleated eyes must be screened for hHRF as per standard protocol.

All eyes with hHRF must be given six cycles of adjuvant prophylactic chemotherapy.

Targeted Treatment in Retinoblastoma

This includes brachytherapy for retinal tumor, intravitreal chemotherapy for VS/SRS and IAC for both retinal tumors and seeds.

Radioactive plaque brachytherapy is used as a secondary/ adjuvant treatment for single retinal tumors that have partially regressed with chemoreduction and FT or are recurrent and not responding/ amenable to FT. I^{125} is used for thicker tumors and Ru^{106} plaques for thinner tumors i.e., <6 mm. RB is typically treated with a dose of 40–50 Gy to the tumor apex.

IAC is a 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 RB both as primary and secondary treatment. However, its use in India like in other LMICs is limited by high cost and non-availability. 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 RB, in affording patients where facility is available and for recurrent disease non-responsive to other forms of conservative treatments. The globe salvage rates reported with primary IAC (B and C - 100%, D - 94%, E - 36%) are higher as compared with secondary IAC (50–72%) [11]. There is very limited literature from India that shows globe salvage rates of 100% in group B, 67% in group C and D with overall globe salvage of 67% [41].

Intravitreal chemotherapy was first introduced by Kaneko and Suzuki in 2003 in an attempt to salvage eyes with advanced IORB. Subsequently, the technique was modified with a post-injection triple freeze-thaw cryotherapy to the site and proven to be safe. The risk of extraocular extension is reported between 0–0.08% [42]. It is the most effective method of treating refractory/ recurrent VS following chemoreduction/ IAC. It does not treat the retinal tumor [43]. The most frequently used drugs are melphalan and topotecan, either alone or in combination. Recommended dosage is 20–30 µg in 0.05–0.1 ml. Response is directly related to VS morphology; vitreous clouds require higher dose as compared with VS dust or spheres. This may be repeated every 1–4 wk.

External Beam Radiotherapy

The use of EBRT for globe salvage has considerably reduced in the current era as compared to the 1970s. EBRT can be used in unilateral advanced IORB with vision potential and not responding to other treatment modalities. Although use of EBRT in bilateral RB/ RB with GLMs increases risk of second cancers, it is still used for globe salvage of the only remaining eye with useful vision [44].

Consensus: EBRT is preferably avoided in bilateral RB, but it can still be used as last resort for globe salvage in the only remaining eyes of bilateral RB patients.

Management of Recurrent Tumor

Intraocular Tumor Recurrence

Recurrence may occur from retinal tumor or seeds. Retinal tumor recurrence may be treated with focal treatment methods, brachytherapy for unifocal recurrence or chemoreduction and FT for large/ multifocal recurrences. Tumor recurrence within a scar can be treated with Indocyanine green (ICG) enhanced TTT as TTT may not work alone in these cases due to lack of pigment.

Vitreous seed and SRS recurrence can be treated with IvC or IAC. The source of seeding must be looked for and treated. IAC or EBRT may be used if the recurrence involves both retina and vitreous/ sub retinal space and is multifocal. Enucleation may be required for recurrent tumor presenting with features of group E tumor after excluding extraocular disease with imaging.

Orbital Recurrence

Orbital recurrence can occur after enucleation and may be suggested by displacement or extrusion of an orbital implant. Majority occur within 12 mo of enucleation. All patients with orbital recurrence need to undergo staging investigations and management similar to extraocular retinoblastoma cases.

Management of Bilateral RB (Fig. 1b)

All bilateral RB harbour GLM and therefore share all treatment related concerns as discussed previously. Also, in this group of patients, treatment abandonment is high and vision salvage may be poor. In a study from south India, authors reported treatment abandonment in 45.5% cases with bilateral advanced disease [44].

The most common modality of treatment used is systemic chemotherapy. Other treatment protocols described in literature include bilateral EBRT, bilateral enucleation, combination of systemic chemotherapy and EBRT, enucleation of the more severely affected eye and EBRT for the less affected eye, and simultaneous IAC with/ without IvC. The reported overall globe salvage rates range from 0 to 91% [45].

Conclusions

In LMICs majority of RB cases still present with unilateral advanced intraocular disease which is best treated with enucleation. In order to improve globe salvage rates in IORB, we thus need to direct future efforts to improve early detection of IORB by (a) improving awareness in the medical and general community and, (b) develop a feasible and sustainable screening strategy for population at risk.

For ICRB groups B and C retinoblastomas, IVC remains a good choice of treatment with high globe salvage rates. Intravitreal chemotherapy has been adopted successfully in treatment of vitreous seeds; however, role of IAC remains limited and less defined due to poor availability and affordability. Efforts need to be made to improve accessibility of IAC, to cases of bilateral retinoblastoma with recalcitrant disease by means of financial assistance through non-government organizations (NGOs) and government health programs.

Acknowledgements This article is prepared as an outcome of Indian Council of Medical Research (ICMR) Sub-Committee on Retinoblastoma coordinated by the Division of Non-Communicable Diseases, ICMR.

Authors' Contributions RMeel prepared the draft; SK performed literature review and contributed to the draft; SB, GC, VR, LS and RMadan reviewed the manuscript; AS helped in editing; TK, RSD and SB coordinated the formation of the ICMR guidelines. All the authors finally approved the manuscript version to be published. RMeel will be the guarantor for this manuscript.

Funding Indian Council of Medical Research (ICMR) funded the proceedings of the meeting and publication of the guidelines.

Declarations

Conflict of Interest None.

Permission to publish this consensus guideline as an article in IJP was obtained from ICMR.

References

1. Indian Council of Medical Research. Consensus Document for Management of Retinoblastoma. 2023. Available at: https://main.icmr.nic.in/sites/default/files/whats_new/Draft_Consensus_Document_for_Management_of_Retinoblastoma.pdf. Accessed on 22 Jan 2024.
2. Meel R, Radhakrishnan V, Bakhshi S. Current therapy and recent advances in the management of retinoblastoma. Indian J Med Paediatr Oncol. 2012;33:80–8.
3. Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: a 2020 review. Indian J Ophthalmol. 2020;68:2356–65.
4. Shields CL, Mashayekhi A, Au AK, et al. The international classification of retinoblastoma predicts chemoreduction success. Ophthalmology. 2006;113:2276–80.
5. Novetsky DE, Abramson DH, Kim JW, Dunkel IJ. Published international classification of retinoblastoma (ICRB) definitions contain inconsistencies—an analysis of impact. Ophthalmic Genet. 2009;30:40–4.
6. Kivelä T. Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. J Clin Oncol. 1999;17:1829–37.
7. Shields CL, Meadows AT, Shields JA, Carvalho C, Smith AF. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). Arch Ophthalmol. 2001;119:1269–72.
8. Roarty JD, McLean IW, Zimmerman LE. Incidence of second neoplasms in patients with bilateral retinoblastoma. Ophthalmology. 1988;95:1583–7.
9. Singh U, Katoch D, Kaur S, Dogra MR, Bansal D, Kapoor R. Retinoblastoma: a sixteen-year review of the presentation, treatment, and outcome from a tertiary care institute in northern India. Ocul Oncol Pathol. 2017;4:23–32.
10. Kaliki S, Patel A, Iram S, Ramappa G, Mohamed A, Palkonda VAR. Retinoblastoma in India: clinical presentation and outcome in 1,457 patients (2,074 eyes). Retina. 2019;39:379–91.
11. Shields CL, Manjandavida FP, Lally SE, et al. Intra-arterial chemotherapy for retinoblastoma in 70 eyes: outcomes based on the international classification of retinoblastoma. Ophthalmology. 2014;121:1453–60.
12. Meel R, Bakhshi S, Pushker N, Vishnubhatla S. Randomized, controlled trial in groups C and D retinoblastoma. Ophthalmology. 2015;122:433–5.
13. Berry JL, Munier FL, Gallie BL, et al. Response criteria for intraocular retinoblastoma: RB-RECIST. Pediatr Blood Cancer. 2021;68:e28964.
14. Fabian ID, Stacey AW, Johnson KC, et al. Primary enucleation for group D retinoblastoma in the era of systemic and targeted chemotherapy: the price of retaining an eye. Br J Ophthalmol. 2018;102:265–71.
15. Scelfo C, Francis JH, Khetan V, et al. An international survey of classification and treatment choices for group D retinoblastoma. Int J Ophthalmol. 2017;10:961–7.
16. Kiratli H, Koç İ, Inam O, Varan A, Akyüz C. Retrospective analysis of primarily treated group D retinoblastoma. Graefes Arch Clin Exp Ophthalmol. 2018;256:2225–31.
17. Abramson DH, Dunkel IJ, Brodie SE, Kim JW, Gobin YP. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology. 2008;115:1398–404.
18. Berry JL, Shah S, Bechtold M, Zolfaghari E, Jubran R, Kim JW. Long-term outcomes of Group D retinoblastoma eyes during the intravitreal melphalan era. Pediatr Blood Cancer. 2017. https://doi.org/10.1002/pbc.26696.
19. Shields CL, Ramasubramanian A, Thangappan A, et al. Chemoreduction for group E retinoblastoma: comparison of chemoreduction alone versus chemoreduction plus low-dose external radiotherapyin 76 eyes. Ophthalmology. 2009;116:544–51.
20. Rao R, Honavar SG, Reddy VP. Preservation of retinoblastoma group E eyes with neovascular glaucoma using intravenous chemotherapy: risk factors and outcomes. Br J Ophthalmol. 2019;103:1856–61.
21. Weng PY, Chen SH, Kao LY, et al. Clinical spectrum and treatment outcome of retinoblastoma with Group D and E diseases: a single institution retrospective review. Medicine. 2020;99:e22201.
22. Temming P, Viehmann A, Biewald E, Lohmann DR. Sporadic unilateral retinoblastoma or first sign of bilateral disease? Br J Ophthalmol. 2013;97:475–80.
23. Abramson DH, Servodidio CA. Retinoblastoma in the first year of life. Ophthalmic Paediatr Genet. 1992;13:191–203.

24. Hussain Z. Impact of laterality on cumulative survival in patients diagnosed with retinoblastoma: a retrospective cohort analysis of 1925 cases in the surveillance, epidemiology, and end results (SEER) program. Clin Ophthalmol. 2021;15:991–1001.
25. Meel R, Kashyap S, Bakhshi S, Bajaj MS, Wadhwani M. Retinoblastoma in children older than 6 years of age. Ocul Oncol Pathol. 2020;6:395–404.
26. Kashyap S, Meel R, Pushker N, et al. Phthisis bulbi in retinoblastoma. Clin Exp Ophthalmol. 2011;39:105–10.
27. Mallipatna AC, Sutherland JE, Gallie BL, Chan H, Héon E. Management and outcome of unilateral retinoblastoma. J AAPOS. 2009;13:546–50.
28. El Zomor H, Nour R, Saad A, et al. Unilateral retinoblastoma; natural history and an age-based protocol in 248 patients. Eye (Lond). 2021;35:2564–72.
29. Pérez V, Sampor C, Rey G, et al. Treatment of nonmetastatic unilateral retinoblastoma in children. JAMA Ophthalmol. 2018;136:747–52.
30. Fabian ID, Shah V, Kapelushnik N, et al. Examinations under anaesthesia as a measure of disease burden in unilateral retinoblastoma: the London experience. Br J Ophthalmol. 2020;104:17–22.
31. Chantada G, Luna-Fineman S, Sitorus RS, et al; SIOP-PODC Graduated-Intensity Retinoblastoma Guidelines Writing Committee. SIOP-PODC recommendations for graduated-intensity treatment of retinoblastoma in developing countries. Pediatr Blood Cancer. 2013;60:719–27.
32. Kaliki S, Shields CL, Eagle RC Jr, Iram S, Shields JA. High-risk intraocular retinoblastoma: comparison between Asian Indians and Americans from two major referral centers. Retina. 2018;38:2023–9.
33. Kashyap S, Meel R, Pushker N, et al. Clinical predictors of high risk histopathology in retinoblastoma. Pediatr Blood Cancer. 2012;58:356–61.
34. Kashyap S, Sethi S, Meel R, et al. A histopathologic analysis of eyes primarily enucleated for advanced intraocular retinoblastoma from a developing country. Arch Pathol Lab Med. 2012;136:190–3.
35. Sastre X, Chantada GL, Doz F, et al; International Retinoblastoma Staging Working Group. Proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. Arch Pathol Lab Med. 2009;133:1199–202.
36. Kashyap S, Singh L, Kumar N, et al. Combined association of massive choroidal and optic nerve invasion as a prognostic relevance in primary retinoblastoma: a 10-year study. Asia Pac J Clin Oncol. 2021;17:e100–8.
37. Messmer EP, Heinrich T, Höpping W, de Sutter E, Havers W, Sauerwein W. Risk factors for metastasis in patients with retinoblastoma. Ophthalmology. 1991;98:136–41.
38. Honavar SG, Singh AD, Shields CL, et al. Postenucleation adjuvant therapy in high-risk retinoblastoma. Arch Ophthalmol. 2002;120:923–31.
39. Kaliki S, Shields CL, Shah SU, et al. Postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin for the treatment of high-risk retinoblastoma. Arch Ophthalmol. 2011;129:1422–7.
40. Ye H, Du Y, Chen R, et al. The potential benefit of three vs. six cycles of carboplatin, etoposide, and vincristine in post enucleation high-risk patients with IRSS stage I retinoblastoma. Curr Eye Res. 2016;41:1507–12.
41. Rishi P, Agarwal A, Chatterjee P, et al. Intra-arterial chemotherapy for retinoblastoma: four-year results from tertiary center in India. Ocul Oncol Pathol. 2020;6:66–73.
42. Francis JH, Abramson DH, Ji X, et al. Risk of extraocular extension in eyes with retinoblastoma receiving intravitreous chemotherapy. JAMA Ophthalmol. 2017;135:1426–9.
43. Mohanan A, Meel R, Venkatesh P, Kashyap S. Retinal tumour outcome with IVC in retinoblastoma. Eye. 2021;35:2046–7.
44. Kaliki S, Mittal P, Mohan S, et al. Bilateral advanced (group D or E) intraocular retinoblastoma: outcomes in 72 Asian Indian patients. Eye (Lond). 2019;33:1297–304.
45. Abramson DH, Marr BP, Francis JH, et al. Simultaneous bilateral ophthalmic artery chemosurgery for bilateral retinoblastoma (Tandem therapy). PLoS One. 2016;11:e0156806.