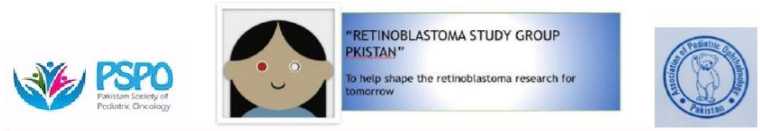
GUIDELINES

GUIDELINES FOR NATIONAL TREATMENT FOR NEWLY DIAGNOSED RETINOBLASTOMA (RB)

ASSOCIATION OF PEDIATRIC OPHTHALMOLGY PAKISTAN

PUBLISHED BY:
OPHTHALMOLOGICAL SOCIETY OF PAKISTAN



National Treatment Guidelines for Newly Diagnosed Retinoblastoma (RB)

Origination Date: 1.11.19
Next Revision Due: 1.11.22

FOREWORD

It gives me great pleasure to write a foreword for the guidelines developed by Retinoblastoma study group.

Scientific knowledge is expanding with every spent moment and we are living in an era of globalization through information technology and social media.

Guidelines are available from almost all international forums and associations and are just one click away from all of us. Why then there is a need of developing guidelines indigenously? The reasons are local pattern of disease, variable management protocols based on different ethnicities, culture and traditions.

I would like to acknowledge the efforts of the whole team of Retinoblastoma study group – and especially Prof. Seema Qayyum and Dr. Shanuil Ashraf. I would also like to appreciate the support of OSP Task Force for Education, Chaired by Prof Hamid Mahmood Butt and OSP Task Force for Publication chaired by Prof Muhammad Moin in this endeavor.

I hope these guidelines will serve as a land mark in better management of patients.

Prof. Nadeem Hafeez Butt
President
Ophthalmological Society of Pakistan
November 2019

Introduction

The first meeting of "Retinoblastoma Study Group" was held on 1st November 2018 in Lahore. Following extensive discussion and review of literature an overview of national guidelines for Retinoblastoma treatment in Pakistan was agreed on. This is a consensus document of the treatment guidelines discussed at that meeting. The object of this effort is to standardize treatment of Retinoblastoma across Pakistan. We would also like to collect data on outcomes for patients in our region utilizing a uniform approach. We hope to increase awareness and promote early detection of retinoblastoma.

These guidelines we then discussed and updated at the following forums to ensure participation and contributions by oncologist and ophthalmologist across Pakistan:

PSPOCON 2019, Karachi, March 2019

Lahore OSP Conference, Bhurban, April 2019

OSP Conference, Karachi, August 2019

We would like to thank all the participants at the above forums for their contribution and participation in the formulation of these guidelines.

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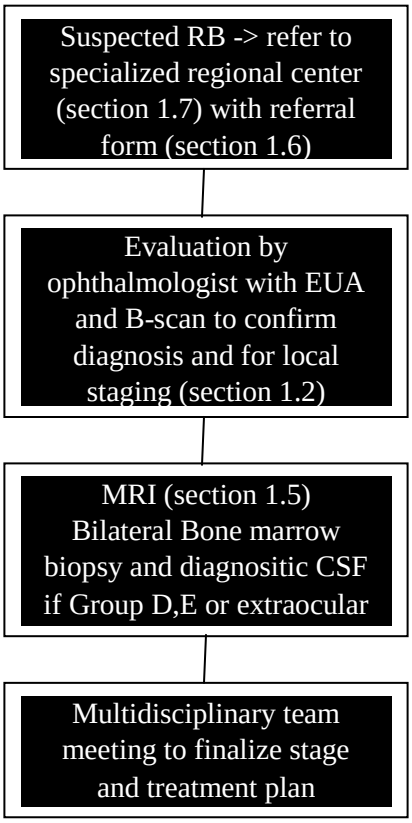
Section 1:

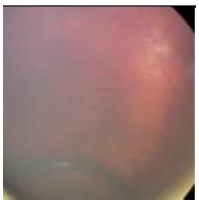
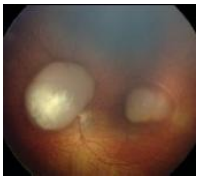
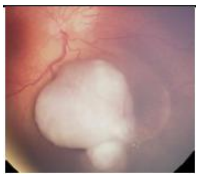
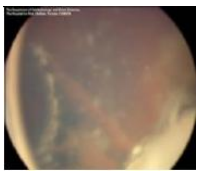
INITIAL ASSESSMENT AND SCREENING

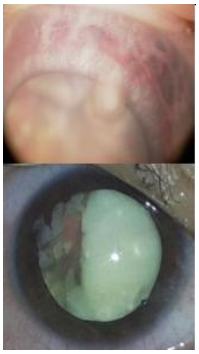
Section 1.1: Initial Assessment



Section 1.2

STAGING GUIDELINES

International Intraocular Rb Classification (IIRC)	
Group A: Very low risk	
Small discrete tumours not threatening vision (T1a)	
All tumours are 3mm or smaller confined to the retina	
Located atleast 3mm from the foveola and 1.5mm from the optic nerve	
No vitreous or subretinal seeding	
Group B: Low risk	
No vitreous or subretinal seeding (T1b)	
Tumours any size or location not in group A	
No vitreous or subretinal seeding	
Subretinal fluid no more than 5mm from tumour base	
Group C: Moderate risk (T2)	
Focal vitreous or subretinal seeding and discrete retinal tumours of any size and location	
Local, fine and limited seeding (T3)	
Discrete intraretinal tumours of any size and location (T2b)	
Up to one quadrant of subretinal fluid (T2a)	
Group D: High risk	
Diffuse vitreous or subretinal seeding (T3b)	
Diffuse intraocular disseminated disease	
Extensive or “greasy” vitreous seeding	

Subretinal seeding may be plaque like	
More than one quadrant retinal detachment	
Group E: Very high risk (T4a)	
Very high risk with one or more of the following:	
Irreversible neovascular glaucoma	
Massive intraocular hemorrhage	
Aseptic orbital cellulitis	
Tumour anterior to anterior vitreous base	
Tumour touching the lens	
Diffuse infiltrating RB	
Phthisis or pre-phthisis	

Murphee A. intraocular retinoblastoma: the case of a new group classification in. singh A, ed. Ophthalmic oncology, ophthalmology clinics of North America. Vol. 18. Philadelphia: Elsevier Saunders; 2005: 41-53.

Box 3
IRSS

Stage 0: Patients treated conservatively.

Stage 1: Eye enucleated, completely resected histologically.

Stage II: Eye enucleated, microscopic residual tumor.

Stage III: Regional extension.

a. Overt orbital disease.

b. Preauricular or cervical lymph node extension.

Stage IV: Metastatic disease.

a. Hematogenous metastasis disease (without central nervous system [CNS] involvement).

   1. Single lesion.
   2. Multiple lesions.

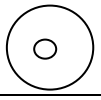
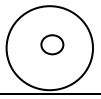
b. CNS extension (with or without any other site of regional or metastatic disease).

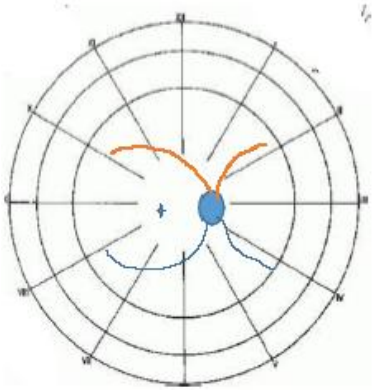
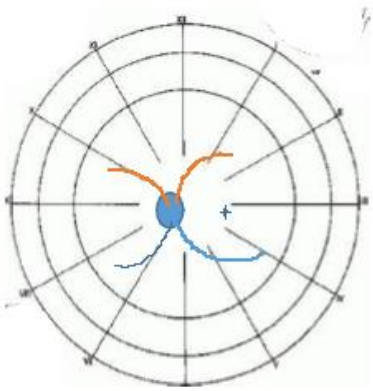
   1. Prechiasmatic lesion.
   2. CNS mass.
   3. Leptomeningeal and CSF disease.

From Chantada G, Doz F, Antonelli CB, et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer, 2006; 47: 801-5; with permission.

Section 1.3

EUA Reporting form

EUA Reporting Form		Date:
Name		
Hospital no		
Gender	□ Male	□ Female
Pre EUA assessment		
Visual Acuity	RE	LE
RAPD		
EUA	RE	LE
Orbital disease/Conjunctiva		
Anterior Segment		
Horizontal Corneal Diameter		
IOP		
Anterior Chamber Mets/Shallow/Hyphema/Hypopyon		
Iris- NVIs/Ectropion uvea		
Pupil- Irregular		
Lens- Cataract/Touch		
Vitreous- Endophytic/Exophytic		
Fundus		

 		
1. No of tumours 2. Site of tumours 3. Size of tumours 4. Fovea spare 5. Intravitreal seeds 6. Subretinal seeds 7. Retinal fluid 8. Retinal detachment 9. Others		
International Intra-Ocular Classification (IIRC)	RE	LE
Comments/Plan:		

Section 1.4

RADIOLOGY GUIDELINES

B-scan Ultrasonography

Reporting should include:

Calcifications, number of lesions, tumour height, diameter, retinal detachment, vitreous seeds, distance of the tumour from the optic nerve head.

MRI Recommendations for Retinoblastoma (Table 1.5)

MRI with contrast orbit and brain protocol under general anaesthesia or sedation.

Reporting should include:

Laterality, localization, size, signal intensity, growth pattern, tumour extension, optic nerve and meningeal extension, globe involvement, anterior segment involvement, brain involvement, and involvement of pineal region.

CT Scan

Not recommended for the diagnosis of retinoblastoma and to be avoided.

Section 1.5

MRI reporting guidelines

Table 1: *MRI Protocol in Retinoblastoma.*

Requirements
Scanner and coils
Field strength above 1 T
1.5-T system combined with one or two small surface coils (diameter < 5 cm)
3.0-T system combined with multichannel head coil
Sequences (minimum requirements)
Orbits
Transaxial T2-W (slice thickness ≤ 2 mm)
Optional, Transaxial CISS (Siement/FIESTA (GE/DRIVE (Philips)
Eye(s) and optic nerve(s)
In-plane pixel size < 0.5 × 0.5 mm; slice thickness ≤ 2 mm
Unilateral disease (0r bilateral disease with only one eye strongly affected)
Precontrast T1-W; at least one plane: transaxial or sagittal oblique
T2-W; at least one plane: transaxial or saggital oblique
Postcontrast T1-W, (transaxial)
T2-W (transaxial)
Postcontrast T1-W, no FS; sagittal oblique of both eyes and transaxial Brain
Transaxial T2-W (slice thickness ≤ 4 mm)
Postcontrast T1-W (2D SE with slice thickness ≤ 3 mm or 3D GRE ≤ 1 mm)

Table 2: *Retinoblastoma: Checklist for MRI Radiology Reports.*

Requirements
Scanner and coils
S1 relative to the vitreous body; moderately high on T1-W and low on T2-W
Laterality
Growth pattern
Tumor size and location; in contact with optic nerve
Buphthalmia
Tumor extension
Optic nerve and meningeal sheath invasion
Ocular wall invasion (choroid and sclera)
Extraocular extension
Anterior eye segment
Anterior chamber depth
Enhancement
Tumor invasion; ciliary body
Brain
Trilateral retinoblastoma; pineal gland and supra- or parasellar region
Leptomeningeal metastases
Malformations

SI signal intensity

Springer

De Graaf P et al. Guidelines for imaging retinoblastoma. Ped Rad 2012

Section 1.6

RETINOBLASTOMA REFERRAL FORM

Name		Surname	
DOB		Hospital No	
Address			
Mobile		Patient's NID	
Gender	□ Male	□ Female	
Date First Seen		Date First Seen	
Presenting Complaint		HOPI:	
□ Lecocoria/white reflex			
□ Strabismus / squint			
□ Orbital / prominent globe		Pedigree / Family tree	
□ Other			
Socioeconomic History & Ethnicity			
Family H/O RB		Family H/O Cancer	
Past history			
Enucleation Right □		Left □	
Exenteration Right □		Left □	
Investigations			
B-Scan	RE	LE	
Calcifications	□ Yes □ No	□ Yes □ No	
MRI/CT Scan done	□ Yes	□ No	
Referred To	Hospital		
	City	Contact No	
Department Refer To	Ophthalmology	Oncology	
Reference Letter given	□ Yes	□ No	
Contact to Rb team done	Yes	No	
Referring Doctor		Referred from	
Contact of referred Physician (for correspondence)			
Email:			

Section 1.7

LIST OF REGIONAL CENTRES

City	Hospital
Karachi	1. Aga Khan University Hospital 2. Patel Hospital 3 LRBT 4. Jinnah Post Medical Centre 5. Civil Hospital, Karachi 6. NICH (oncology) 7. Indus Hospital (Oncology)
Lahore	1. Children's Hospital 2. Lahore general hospital 3. Shaukat Khanum Hospital 4. Mayo Hospital 5. Jinnah Hospital
Rawalpindi/Islamabad	1. PIMS 2. Shifa eye Hospital 3. CMH
Multan	1. Children's Hospital Multan
Peshawar	1. Khyber Teaching Hospital 2. Lady Reading Hospital
Hyderabad	1. SIUVS
Quetta	

Section 1.8

SCREENING GUIDELINES
(IN THE ABSENCE OF RB1 GENE TESTING)

(Tables below have been taken from American Association of Ophthalmic Oncologists and Pathologists (AAOOP) guidelines for screening of children with family history of retinoblastoma*)

By Paediatrician

- irst 2 years of life on every visit of every child by the Red Reflex-method.

Referral to ophthalmologist of:

- Any child with strabismus
- Any child with history of leukocoria
- Any child with abnormal red reflex
- Any child with family history of Retinoblastoma

By the Ophthalmologist

Categorize the patient (see flow chart below for details):

High Risk

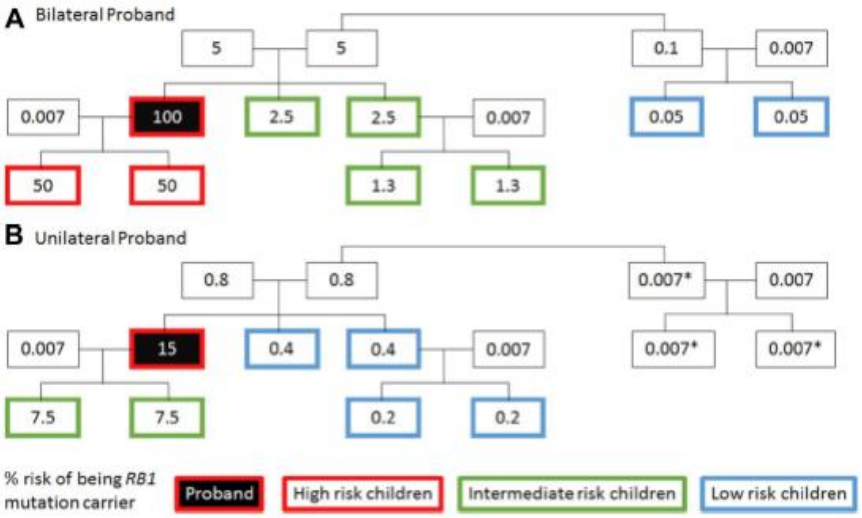
- Parent with bilateral disease.

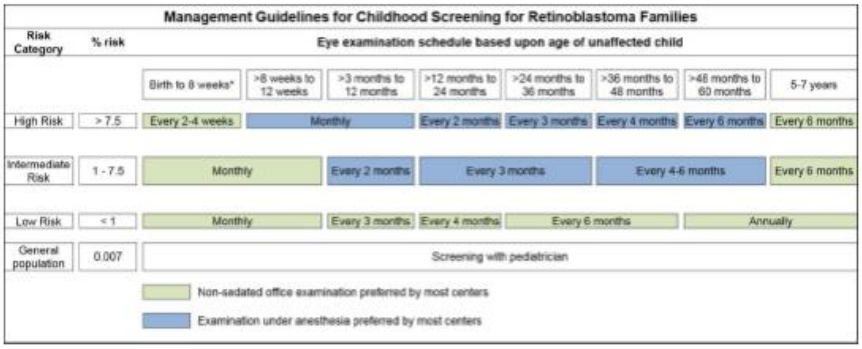
Intermediate Risk

- Parent with unilateral disease.
- Siblings with bilateral disease.
- Fellow eye of Child with multifocal unilateral.
- Parent with sibling with bilateral disease.

Low Risk

- Sibling with unilateral disease.
- Parent with sibling with unilateral disease.





*****Screening Children at Risk for Retinoblastoma. Skalet, Alison H. et al. Ophthalmology, Volume 125, Issue 3, 453 – 458.

Section 1.9

Counselling

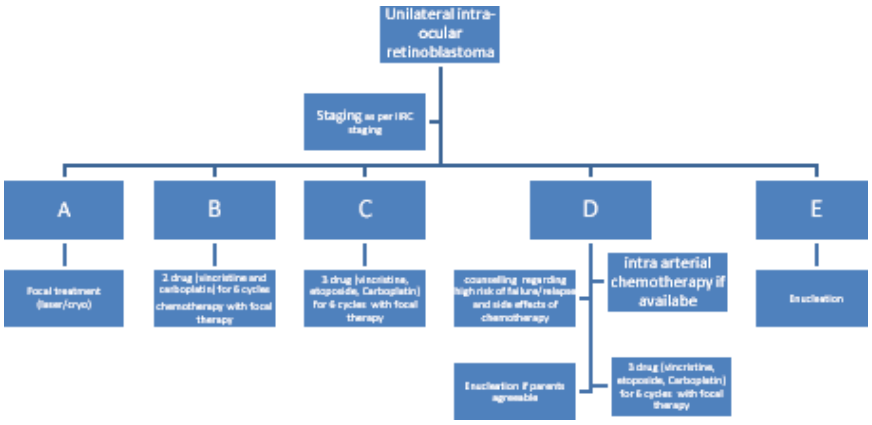
- To be done by Ophthalmologists and Oncologists.
- First listen to their queries- be empathetic.
- Try to do group counseling.
- Counsel about the importance of saving life, then globe and then vision.
- Show them pictorials of late presentation and patients with prosthesis in place.
- Counsel about rehabilitation.
- Counsel regarding sibling screening according to risk stratification.
- Counsel regarding screening of future offspring according to risk stratification.
- Include retinoblastoma specialist.
- Initiate support groups.

Section 2

INTRA-OCULAR RETINOBLASTOMA

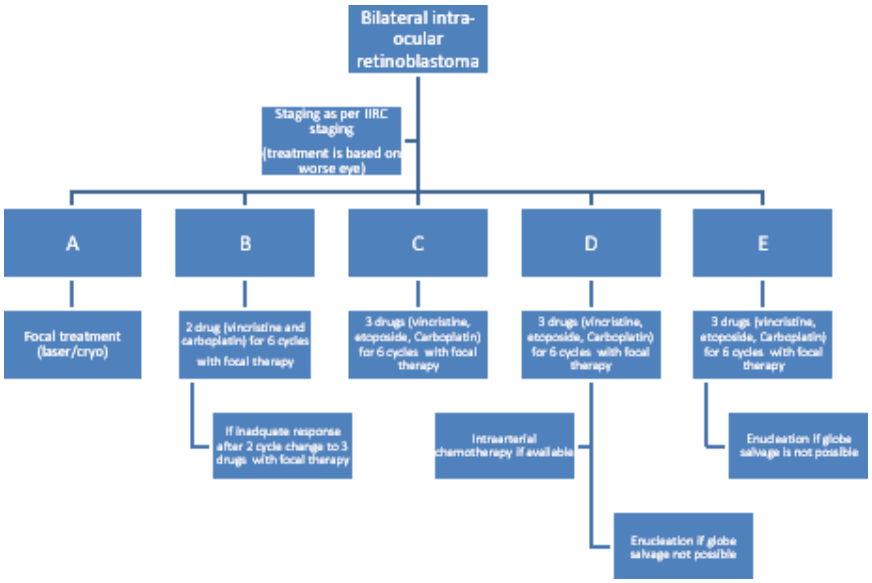
Section 2.1

UNILATERAL INTRAOCULAR RETINOBLASTOMA SUMMARY



Section 2.2

BILATERAL INTRAOCULAR RETINOBLASTOMA SUMMARY



Section 2.3

INTRAOCULAR RETINOBLASTOMA MANAGEMENT DETAILS

IIRC Stage	MANAGEMENT RECOMENADATIONS
A	Focal treatment only with laser/cryotherapy
	Send to a site with focal treatment (Laser or cryotherapy)
B	**Unilateral:**
	Systemic chemotherapy with 2 drugs Vincristine and

	Carboplatin 6 cycles + Focal Treatment
	Intra-arterial chemotherapy can be an option (if available) if unilateral B fails to respond to chemo/local
	Bilateral: Systemic Chemotherapy with 2 drugs Vincristine and Carboplatin 6 cycles if both group B with Focal (Laser/Cryotherapy)
	Intra-arterial chemotherapy can be an option (if available) if unilateral B fails to respond to chemo/local therapy **or** or is recurrent with other eye enucleated if chances of vision are present
C	**Unilateral:**
	Systemic Chemotherapy with 3 drugs Vincristine/carbo/ etoposide 6 cycles + Focal Treatment
	+ intravitreal chemotherapy for seeding Intra-arterial chemotherapy can be an option (if available) Unilateral C failed to respond to chemo/local or is recurrent with one eye enucleated. (Only if chances of vision are present) Needs close follow-up and enucleation if all above fail.
D	**Unilateral:**
	Upfront enucleation if parents agreeable Systemic Chemotherapy 3 drugs Vincristine/carboplatin/ etoposide, 6 cycles + Focal Treatment (Laser/Cryotherapy) +intravitreal chemotherapy if vitreous seeds Needs close follow-up and enucleation advised if progressive/residual disease on above treatment Parents need to be counseled that there is less than 50% chance of globe salvage in group D eyes with high probability of relapse later. Side effects of chemotherapy should also be discussed and joint decision made with family regarding upfront enucleation or systemic chemotherapy
	Intra- arterial chemotherapy if available 3-4 cycles (only if

	vision salvageable)
	Bilateral: Systemic Chemotherapy with 3 drugs vincristine/carbo/etoposide 6 cycles +Focal Treatment (Laser/Cryotherapy) + Intravitreal chemotherapy Intra-arterial to the more advanced eye and not responding to the above therapy.
E	**Unilateral/Bilateral:** Enucleation. (may require chemotherapy for second eye based on stage)

INTRAVITREAL CHEMOTHERAPY

Can be given every 2-4 week for 4-6 cycles.

Indications

- Persistent vitreous seeds after systemic intravenous chemotherapy and/or intra-arterial chemotherapy.
- Recurrent vitreous seeds after completion of treatment.
- Chemo resistant new vitreous seeds.

Contraindications

- Seeds dispersed diffusely in the entire vitreous cavity.
- Anterior segment and/or ciliary body invasion.
- Secondary glaucoma.
- High bullous retinal detachment.
- Vitreous hemorrhage obscuring the fundus view.

Preparation of Chemotherapeutic Drugs

Melphalan hydrochloride is available as 50 mg lyophilized powder that is reconstituted with preservative-free 0.9% sodium chloride solution in a sterile chamber. Initially 10 ml of 0.9% preservative-free normal saline is added to achieve a concentration of 5 mg/1 ml and vigorously shaken until a clear solution is obtained.

Further, 1 ml of melphalan is injected into an evacuated sterile vial to which 24 ml 0.9% sodium chloride is added to yield a solution of 0.2

mg/ml (200 ìg/ml). The reconstituted drug (0.3 ml) is then transferred to a 1 ml luer lock syringe through a 5 µ filter. Dosage is adjusted accordingly (20 µg/0.1 ml; 25 µg/0.125 ml; 30 µg/0.15 ml). The major limitation in using melphalan is its short half-life and should be administered within 1 hour of reconstitution.

Surgical Technique and Safety Measures

Although the technique of intravitreal injection appears simple, it carries a risk of extraocular tumor dissemination in tumor-filled eyes. However, modified injection techniques can avoid major complications. Prior to the injection, quadrant and site of injection decided according to the distribution of vitreous seeds. Clinical evaluation of 360° pars plana is essential to detect remote tumor foci for safety. Ultrasound biomicroscopy may be used for confirmation. Under aseptic precautions, eye is confirmed, and drug delivered intravitreally via pars plana approach. The needle track size should be kept as small as possible; ideally 32-gauge needle is preferred. Following injection, triple freeze-thaw cryotherapy should be performed at the injection site simultaneously, on withdrawal of the needle. The eyeball is gently jiggled with some forceps for the even distribution of the drug injected and reducing local toxicity. Fundus is examined post-injection for acute complications such as retinal detachment, vitreous and/or retinal hemorrhage. Topical balanced salt solution is used to rinse extraocular chemotherapy from the globe surface to minimize toxicity. Topical steroid/antibiotic is applied, and there is no patch or further eye drops prescribed. Family is instructed to not touch the eye for 1-week.

Complications

Vitreous hemorrhage, cataract, salt-and-pepper retinopathy, and pupil posterior synechia.

Reference

1. Manjandavida FP, Shields CL. The role of intravitreal chemotherapy for retinoblastoma. Indian J Ophthalmol. 2015; 63: 141-5
2. Ji X, Hua P, Li J, Li J, Zhao J, Zhao P. Intravitreal Melphalan for Vitreous Seeds: Initial Experience in China. *J Ophthalmol*. 2016; 2016: 4387286. Doi:10.1155/2016/4387286. Epub 2016 Feb 8. PMID: 26977313; PMCID: PMC4761678.

Section 3

POST PRIMARY ENUCLEATION GUIDELINES

Primary Enucleation

It is the preferred treatment in eyes with advanced intraocular unilateral retinoblastoma (where globe salvage is not possible) corresponding to group E in the IIRC system.

The enucleated eye is studied via histopathology to confirm the diagnosis of Retinoblastoma and to study other features of tumor. Management of the child is critically dependent on rigorous assessment of the tumor optic nerve and tumor choroid–sclera relationships. Tumor extension past the lamina cribrosa of the optic nerve head indicates increased risk that the tumor has spread into the meningeal space and CSF. Tumor extension into the choroid, anterior chamber, iris or ciliary body indicates risk for tumor metastasis, particularly to bone marrow.

Section 3.1

HISTOPATHOLOGY GUIDELINES

Enucleation specimens should have the following measurements taken:

- Antero-posterior globe diameter (normal 22–23 mm).
- Horizontal globe diameter (normal 22–23 mm).
- Vertical globe diameter (normal 22–23 mm).
- Four blocks should be taken:
- Optic nerve margin.
- Main tumor block with pupil and optic nerve.
- Two blocks containing the calottes (remainder of ocular tissue after obtaining the optic nerve block).

MACROSCOPIC DATA

- Number of tumor foci.
- Choroidal invasion.

- Extraocular spread.

MICROSCOPIC DATA

- Number of tumor foci.
- The degree of optic nerve invasion**.** The following grading applies to degree of optic nerve invasion:
  - Prelaminar.
  - Laminar.
  - Retrolaminar.
  - Tumor at optic nerve surgical margin.
  - Choroidal invasion Massive or significant choroidal invasion is defined as a maximum diameter (thickness or width) of an invasive focus of tumor measuring 3 mm or more. The criterion for focal choroidal invasion has been defined as a tumor focus of less than 3 mm in any diameter (thickness or width) and not reaching the sclera.
  - Intrascleral infiltration.

RISK STRATIFICATIONS BASED ON RISK FEATURES GIVEN BELOW:

Low Risk Features

- Prelaminar invasion/optic nerve head.
- Focal choroidal invasion (provided choroidal invasion depth is mentioned. If not, take it as intermediate risk).
- Ciliary body involvement.

Intermediate Risk Features

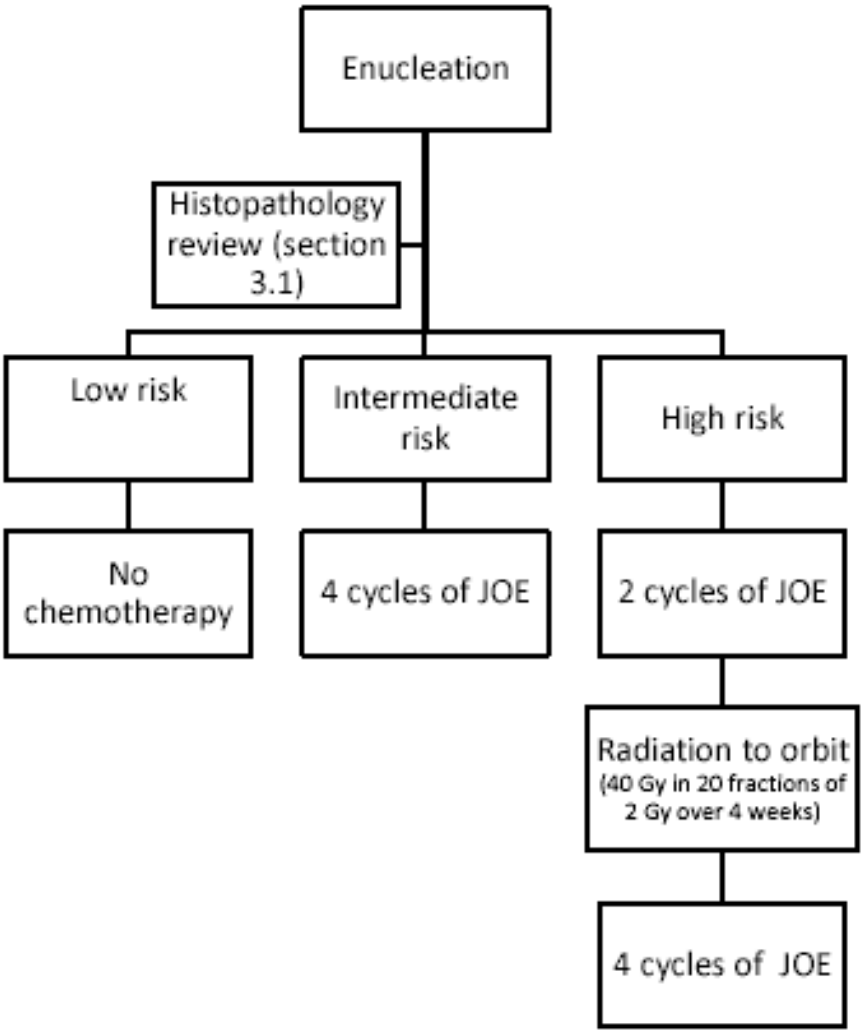
- Massive choroidal > 3mm full thickness.
- Retrolaminar optic nerve invasion.
- Disease in the anterior chamber.
- Intrascleral invasion.

High Risk Features

- Cut end of optic nerve invasion.
- Transcleral invasion (Will be treated as per extra-ocular protocol).

Section 3.2

RISK GROUP BASED CHEMOTHERAPY GUIDELINES



Section 3.3

INVESTIGATIONS PRIOR TO CHEMOTHERAPY

- Full blood count and differential.
- Blood group.
- Urea, creatinine and electrolytes.
- Liver function tests.
- Serum magnesium.
- Lumbar puncture + CSF cytology (Group D and E).
- Bone marrow aspirate and trephine (Group D and E) bilateral.
- MRI brain and orbit with contrast.
- Audiogram.
- Creatinine clearance.

Section 3.4

DETAILS OF CHEMOTHERAPY (3 DRUGS)

Each course at 21 -28 days' interval, ANC: >1 x109/L and Platelets: > 100 x 109/L

- Drug: **Vincristine** day 1.
  Dosage: 1.5 mg/m2.
  Administration: Intravenous bolus (max total dose 2 mg).
- Drug: **Carboplatin** day 1.
  Dosage: 600 mg/m2.
  Administration: Dilute to not less than 500 micrograms/ml according to the child's fluid requirements and infuse in 5% dextrose over 1 hour.
  Hydration: The etoposide infusion may act as post-carboplatin hydration ensuring an infusion rate of at least 2.5l/m2/day for a minimum of 4 hours.
- Drug: **Etoposide** day 1.
  Dosage: 300mg/m2 for children > 10 kg.

Administration: Dilute in 0.9% saline to a maximum concentration of 0.4 mg/ml and infuse over 4 hours.

DRUG MODIFICATIONS

Recommendations for Children < 10 kg in Weight

- Less than 6 months of age: 50% of calculated dose by body surface area.
- 6 months to 1 year of age: 75% of calculated dose by body surface area.
- Over 1 year of age: 100% of calculated dose by body surface area.

SUPPORTIVE CARE GUIDELINES

- Central line placement.
- Use of anti-emetics.
- Avoid using steroids during chemo.
- Management of FN as per institutional guideline.
- GCSF is not routinely required.

Details of chemotherapy (2 drugs) for only GROUP B
6 cycles to be repeated every 28days

Drug	Route	Dose	Day
Carboplatin (CARB)	IV over 60 min in 125cc/m^2 D5.4NS	Pts < 36 months: 18.6mg/kg Pts ≥ 36 months: 560 mg/m^2	1
Cincristine (VCR)	IV Push	Pts < 36 months: 0.05 mg/kg Pts ≥ 36 months: 1.5 mg/m^2 Maximum Dose 2 Mg	1

Section 3.5

FOLLOW-UP RECOMMENDATIONS

Follow Up for Enucleated Socket:
Management starts at enucleation and continues with subsequent EUA and clinic visit,

Examination for any infection, implant exposure and fit of the prosthetic eye.

Follow-Up Monitoring for Children Following Chemotherapy:

1. Clinical Examination for Relapse/Recurrence, Metastatic Disease-EUA

- 4 -8 weeks for first 6 months,
- 3 monthly for next 12 months,
- 4 monthly for next 12 months,
- 6 monthly until the age of 10 years.

2. Renal toxicity monitoring

There is a risk of renal tubular acidosis or glomerular damage by carboplatin. Baseline renal functions should be done after completion of chemo therapy and then annually. Blood pressure monitored annually.

3. Ototoxicity Monitoring

Perform pure tone audiogram at the end of treatment, as carboplatin carries risk of high tone hearing loss or can be done as child is old enough to co-operate.

Question hearing acuity, speech and language development and school and social functioning annually.

4. Patients receiving orbital radiotherapy should be followed up in a joint oncology endocrine clinic in order to monitor for potential anterior pituitary dysfunction.

5. Secondary tumors.

6. Etoposide poses risk of secondary myelodysplasia/myeloid leukemia.

7. Vincristine causes peripheral neuropathy, resolves with time. Survivors should be monitored by history and exam for persistence of neuropathies

8. Bilateral retinoblastoma should have MRI brain and orbit for every 6 months till 5 years.

SUMMARY OF FOLLOW-UP RECOMMENDATIONS

Disease Monitoring	**Toxicity Monitoring**
Clinical examination for relapse/ recurrent, metastatic disease. • 2-3 monthly for 6 months • 3 monthly for 12 months • 4 monthly for 12 months • 6 monthly until age 10 MRI brain and orbit (with contrast) for bilateral RB/ individual cases of high risk RB	End-of-treatment: • Creatinine, Calcium, Electrolytes and Magnesium • GFR (optional) recommended if Creatinine elevated • Pure tone audiogram Repeat 5 yearly Joint oncology/endocrine follow up for patients receiving orbital radiotherapy

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Section 4

TREATMENT OF EXTRA-OCULAR RETINOBLASTOMA

Section 4.1

TREATMENT OF STAGE III (LOCALLY ADVANCED ORBITAL RETINOBLASTOMA)

Inclusion Criteria

All patients with stage III disease as per the international retinoblastoma Staging system[1] can be treated on these guidelines.

These include the following:

Stage III	Regional Extension	a. Overt orbital disease
		b. Pre-auricular or cervical lymph node extension

Background:

Orbital retinoblastoma is associated with high risk of metastatic disease and relapse. According to the SIOPPODC guidelines, neoadjuvant chemotherapy followed by enucleation and then adjuvant chemotherapy and radiation should be considered for this group[2]. However, a single best chemotherapy regimen is not recommended. For the purpose of these guidelines we recommend twelve cycles of vincristine, etoposide and carboplatin as reported by Chawla et al[3]. The reasons for choosing this regimen are 1. Reported 63% survival at 4 years, 2. Outpatient administration, 3. Less toxicity and myelosuppression compared to anthracycline based regimens. The concern with this regimen will be use of higher doses of etoposide that may increase risk of secondary malignancies.

Treatment Plan (Table 4.1)

1. Baseline investigations as per guideline recommendations. Bilateral bone marrow and diagnostic lumbar puncture must be done to rule out metastatic disease.
2. Upfront enucleation should not be attempted due to high risk of residual disease.
3. Two cycles of carboplatin, etoposide and vincristine will be given at 21-day interval.
   Please note that the doses are different from JOE chemotherapy that is used for ocular retinoblastoma (Table 4.2).
4. Reevaluation with MRI and EUA after 2 cycles and plan enucleation if possible.
5. Further two cycle may be given if enucleation is not possible after first 2 cycle however surgery should be done within first 4-5 cycles of chemotherapy.
6. Postoperative chemotherapy should be continued to complete total of 10-12 cycles of treatment as tolerated by patient.
7. Radiation to orbit and lymph nodes (if involved), should be administered within 4 to 6 weeks of surgery. Dose of radiation will be 40Gy in 20 fractions as a 2 Gy fraction daily for 5 days per week.

Table 4.1: *Treatment plan for extra-orbital retinoblastoma.*

Cycle Number	**Date Administered**	**Investigations**	**Radiation**
1		CBC, LFT, Renal Panel, audiogram	
2			
MRI orbit, EUA and surgery if possible*	Surgery date:		
3		CBC, LFT, Renal Panel, audiogram, EUA	4 Gy in 20 fractions to begin within 4-6 weeks of surgery
4		CBC, LFT, Renal Panel	

5		CBC, LFT, Renal Panel, audiogram, EUA	
6		CBC, LFT, Renal Panel	
7		CBC, LFT, Renal Panel, audiogram, EUA	
MRI orbit and EUA			
8		CBC, LFT, Renal Panel	
9		CBC, LFT, Renal Panel, audiogram, EUA	
10		CBC, LFT, Renal Panel	
11		CBC, LFT, Renal Panel, audiogram, EUA	
12		CBC, LFT, Renal Panel, MRI and EUA	
*Surgery may be delayed up to cycle 6 if enucleation is not possible. EUA: exam under anesthesia, CBC: complete blood pictures, LFT: liver function test			

Table 4.2: *Chemotherapy for extra-ocular retinoblastoma.*

Requirements to begin each cycle: neutrophils >1x 109/l and platelets > 100 x 109/l, total bilirubin and creatinine in normal range. Audiogram and renal functions (DTPA or creatinine clearance if any rise in creatinine) to be monitored before alternate cycles			
Medication	**Dose (Per Day)**	**Days**	**Cycle Interval**
1. Vincristine	0.025 mg/kg	1	21 Days
2. Etoposide	12 mg/kg	1, 2	21 Days
3. Carboplatin	28 mg/kg	1	21 Days

Section 4.2

TREATMENT OF STAGE IV (METASTATIC RETINOBLASTOMA)

Inclusion Criteria

All patients with stage IV disease as per the international retinoblastoma Staging system[1] can be treated on these guidelines.

These include the following:

Stage IV	Metastatic	a. Hematogenous spread without CNS involvement
		b. CNS spread (CNS lesion, leptomeningeal disease or CSF positive)

Background

Patients with metastatic disease have very poor outcomes with less than 20% survival. SIOP-PODC guidelines recommend palliation only in this group unless ability to provide high dose chemotherapy with stem cell rescue is available[2]. In this case patients with stage IVa may be offered treatment.[4-6]

Treatment Plan

Stage IVb:

1. Counseling regarding poor expected outcome and futility of treatment with curative intent. Involve psychologist in care.
2. Palliative care with good pain control and symptom management.
3. Radiation and/or palliative chemotherapy (carboplatin, etoposide and vincristine) may be offered if it can improve quality of life.

Stage IVa:

1. If ability to provide high dose chemotherapy with stem cell rescue is not available, then treat with palliative intent as for stage Iva.
2. If facility to provide high dose chemotherapy with stem cell rescue is available, then it can be done as per institutional protocol.

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Section 5:

GUIDELINES FOR USE OF INTRA-ARTERIAL MELPHALAN IN RETINOBLASTOMA

Background

Retinoblastoma (RB) is the most common ocular malignancy in children. High cure rates of close to 100% have been reported in developed countries. However, two thirds of all case are diagnosed in developing countries where survival rate range from 40 to 60% due to advanced stage at presentation[1].

Currently, there is increasing evidence that systemic chemotherapy can be replaced by intra-arterial chemotherapy (IAC). This limits

systemic side effects and allows improved eye salvage. Abramson et al, in a review of current treatment of RB recommend IAC for all unilateral group C and D eyes. They report 94% ocular salvage in this population[2]. Similarly, Sheilds et al have reported success of 100% in group C and D eyes and 33% in group E eyes[1].

Gobin et al used IAC in 96 eyes and report a 70% ocular event free survival for all eyes and 81% when used as primary treatment[3]. Importantly, overall survival has not been compromised by use of IAC.

Complication of IAC include hematoma formation at groin entry site, carotid vascular spasm, stroke and local ocular side effects like cranial nerve palsy, orbit/eye lid edema, retinal detachment, vitreous hemorrhage and retinal pigment epithelial change. However, side effects decrease with increased experience. While earlier studies quote ocular side effect in up to 40% of cases ; centers with experience have less than 5% serious complications.[4,5].

Limitation of IAC include lower efficacy in cases of vitreal involvement. This can be overcome by use of intravitreal Melphalan along with IAC[6].

Based on the reported success of IAC with minimal side effects we propose using this technique for patient with unilateral group C and D eyes. Bilateral cases can be discussed on individual basis after trial of intravenous chemotherapy. Eyes with vitreous seeding in addition to retinal tumors will receive intravitreal Melphalan.

Patient Population

1. New patient with unilateral group C or D eyes (staging will be as per the COG version of the international classification of RB- appendix 1.
2. Eye with vitreous seeding will receive intravitreal Melphalan as per institutional protocol.
3. Metastatic disease will be excluded on MRI brain, CSF and bilateral bone marrow involvement.
4. There will be no intracranial or optic nerve extension on MRI.
5. Group E eyes will be excluded as they should have upfront enucleation.
6. Bilateral and relapsed cases will be discussed on individual basis and considered after MDT meeting discussion.

Methods

1. All patients will be evaluated by pediatric oncologist and ophthalmologist. Local stage with be done by evaluation under anesthesia (EUA) and documented on Retcam images. MRI brain, bilateral bone marrow aspirate and biopsy (BMAB) and CSF evaluation will be done for staging. Patients will be selected after discussion in multidisciplinary team meeting.
2. Baseline evaluation of all patients will include:
   a. CBC, LFT, Renal panel, blood group.
   b. Anti-HCV, HBsAg.
   c. PT, INR, APTT.
   d. CXR.
   e. Echo.
   f. EUA.
   g. CSF for cytology and BMAB.
   h. MRI orbit and brain.
3. Dosage of Melphalan[3]:
   (See appendix 2 for drug information)

Age Dose

3-6 months	2.5 mg in 30 ml sodium chloride 0.9%
6-12 months	3 mg in 30 ml sodium chloride 0.9%
1year -3 years	4 mg in 30 ml sodium chloride 0.9%
3 years and older	5 mg in 30 ml sodium chloride 0.9%

If Melphalan is not available carboplatin (30 mg) can be used instead in children above 6 months of age[3].

4. **Frequency:**
   Melphalan will be administered every 3- 4 weeks for a maximum of 4 doses. EUA with Retcam images will be performed at 3-4 weeks after each dose to assess response and therapy will only be continued if response is documented.
5. Procedure details: (as per IR/interventional neurology- copied below from NHS guidelines).

(Administration of Melphalan

1. Oxymetazoline 0.05% (two sprays) is sprayed in the nostril on the treatment side, to reduce the blush from the nasal mucosa and risk of epistaxis.
2. The child will be anti-coagulated with Heparin (70 units/kg) by the Anesthetist at the start of the procedure. The Anesthetist will also be asked to administer a dose of IV Ondansetron prior to the administration of Melphalan and a dose of Dexamethasone 200 mcg/kg at the end of the administration of Melphalan.
3. The Interventional Neuroradiologist will catheterize the femoral artery. He will then catheterize the appropriate ophthalmic artery under fluoroscopic control and carry out an angiogram to check the anatomy of the vascular supply to the brain and orbit. If there is evidence of arterial spasm, the Interventional Neuroradiologist will consider giving a dose of Glyceryl trinitrate (dose ~5 micrograms/ kg) via the femoral artery catheter.
4. In view of the short expiry time of one hour for the Melphalan once reconstituted, Pharmacy will be contacted once the child has been anaesthetized and asked to prepare the Melphalan which will take about 20 minutes. Usually the pharmacist will bring the drug to IR as soon as it has been reconstituted or otherwise pharmacy will call IR for it to be collected.
5. The consultant Pediatric Oncologist, or named deputy, will check the Melphalan (made up in 30ml of sodium chloride 0.9%) with an Oncology trained Nurse then administer it as a hand controlled infusion over 30 minutes at a rate of 1 ml/minute followed by a flush of 6 ml of sodium chloride 0.9%. Any waste generated during the procedure will be disposed of as cytotoxic waste in an appropriate purple lidded sharps bin.

Post Procedure

1. Following completion of the infusion of Melphalan a further angiogram may be undertaken to screen for any evidence of vascular thrombosis. The femoral catheter will then be removed in IR by the Neuroradiologist and the child returned to the ward when fully recovered from the GA for close monitoring of the circulation to the leg, together with neuro observations for 6 hours.

2. If the procedure is undertaken during the morning and there are no immediate complications, the child may be discharged home in the early evening otherwise all children on the afternoon list will remain in hospital under observation for the night following the procedure and longer if unstable. Providing they are well, the child will be discharged home the next day. An appointment for a reassessment EUA to be made for3-4 weeks after the IA Melphalan.

Medication during Period of Hospitalization and on Discharge

1. Dexamethasone 100 mcg/kg 8 hourly for 5 days to reduce inflammatory response + to try to reduce the orbital apex syndrome.
2. Ibuprofen 10 mg/kg 8 hourly for 3 days also to reduce inflammatory response.
3. Ondansetron 5 mg/m2 8 hourly as needed for 3 days as required for emesis.
4. Paracetamol 15 mg/kg 6 hourly as required.
5. Dexamethasone 0.1% eye drops (Minims) one drop in the affected eye three times a day for 4 weeks.

Dose Modifications for Toxicities

1. Dose of Melphalan can be increased by 0.5 mg in case of large extra orbital branches of the ophthalmic artery (meningeal, ethmoid arteries) for the second and third cycle
2. The standard dose should be decreased by 0.5 mg if there are signs of poor tolerance of previous intraarterial treatment.

This includes any Grade 4 inflammation of the eyelids and conjunctiva (see grading scale below.)

Grading scale for inflammation of the eyelids and conjunctiva:

Grade 1: Mild erythema of eyelids, orbit or forehead.
Grade 2: Erythema and swelling over eyelids, orbit or forehead.
Grade 3: Pain in the eye or orbit with erythema and/or swelling.
Grade 4: Swelling and/or pain lasting more than 7 days.

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APPENDIX I: CLASSIFICATION SYSTEM FOR INTRAOCULAR RETINOBLASTOMA

(As per ARET 12P21, pg. 51)

INTERNATIONAL CLASSIFICATION SYSTEMS FOR INTRAOCULAR RETINOBLASTOMA

Group A

Small intraretinal tumors away from foveola and disc

- All tumors are 3 mm or smaller in greatest dimension, confined to the retina *and*
- All tumors are located further than 3 mm from the foveola **and** 1.5 mm from the optic disc.

Group B

All remaining discrete tumors confined to the retina

- All other tumors confined to the retina not in Group A.

- Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding.

Group C

Discrete Local disease with minimal subretinal or vitreous seeding

- Tumor(s) are discrete.
- Subretinal fluid, present or past, without seeding involving up to 1/4 retina.
- Local fine vitreous seeding may be present close to discrete tumor.
- Local subretinal seeding less than 3 mm (2 DD) from the tumor.

Group D

Diffuse disease with significant vitreous or subretinal seeding

- Tumor(s) may be massive or diffuse.
- Subretinal fluid present or past without seeding, involving up to total retinal detachment.
- Diffuse or massive vitreous disease may include “greasy” seeds or a vascular tumor masses.
- Diffuse subretinal seeding may include subretinal plaques or tumor nodules

Group E

Presence of any one or more of these poor prognosis features

- Tumor touching the lens.
- Tumor anterior to anterior vitreous face involving ciliary body or anterior segment.
- Diffuse infiltrating retinoblastoma.
- Neovascular glaucoma.
- Opaque media from hemorrhage.
- Tumor necrosis with aseptic orbital cellulites.
- Phthisis bulbi.

APPENDIX 2: Drug Information
(As per ARET 12P1 pg. 25)

Melphalan, a phenylalanine derivative of nitrogen mustard, is a bifunctional alkylating agent. Melphalan forms covalent cross-links with DNA or DNA protein complexes thereby resulting in cytotoxic, mutagenic, and carcinogenic effects. The end result of the alkylation process results in the misreading of the DNA code and the inhibition of DNA, RNA, and protein synthesis in rapidly proliferating tumor cells. It is cell cycle non-specific. After IV administration, Melphalan plasma concentrations decline rapidly in a bi-exponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Plasma Melphalan levels are highly variable after oral dosing, both with respect to the time of the first appearance of Melphalan in plasma (range approximately 0 to 6 hours) and to the peak plasma concentration achieved. These results may be due to incomplete intestinal absorption, a variable "first pass" hepatic metabolism, or to rapid hydrolysis. The oral dose averages 61% ± 26% of that following IV administration. The terminal elimination plasma half-life of oral Melphalan is 1.5 ± 0.83 hours. The steady-state volume of distribution of Melphalan is 0.5 L/kg. The extent of Melphalan binding to plasma proteins ranges from 60-90%. Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. The 24-hour urinary excretion of parent drug is approximately 10% suggesting that renal clearance is not a major route of elimination of parent drug. Penetration into CSF is low. Despite the fact that the contribution of renal elimination to Melphalan clearance appears to be low, one pharmacokinetic study suggests dosage may need to be reduced in patients with renal impairment.

Toxicity

Only limited data exist on the toxicity of intra-arterial Melphalan. The anticipated toxicities for intra-arterial Melphalan are listed in the first table.

The table below lists the anticipated toxicity profile of	**Toxicities**

Melphalan (intra-arterial for retinoblastoma):	
Incidence	
Common (>20% of patients)	Retinal vascular disorder, retinopathy, eye disorders – other: loss of vision, blurred vision, cataract, eye disorders – other: thinning or loss of eyelashes, eye disorders – other: periocular edema
Occasional (5-20% of patients)	Neutrophil count decreased, fever, bronchospasm
Rare (< 5% of patients)	Injection site reaction, reproductive system and breast disorders – other: amenorrhea, azoospermia, reproductive system and breast disorders – other: sterility or male infertility, anaphylaxis, allergic reaction, pneumonitis, pulmonary fibrosis, treatment related secondary malignancy, febrile neutropenia

Formulation and Stability

Melphalan for Injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains Melphalan hydrochloride equivalent to 50 mg Melphalan and 20 mg povidone. Melphalan for Injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and SWFI to a total of 10 ml. Store at controlled room temperature 15°-30°C (59°-86°F) and protect from light.

Intra-arterial Preparation

- Using appropriate aseptic technique, reconstitute to a concentration of 5 mg/mL by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder using a sterile needle (20-gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution.

- Immediately dilute the dose to be administered in up to 20 mL of NS; the final volume of the product should be 20 mL. The concentration of the final drug product should be ¡Ü 0.45 mg/mL.
- The final drug product should be filtered (e.g., with a 0.22 micron filter) prior to being dispensed.
- A precipitate forms if the reconstituted solution is stored at 5°C. Do not refrigerate the reconstituted product.
  (*The time between reconstitution/dilution and administration of Melphalan should be kept to a minimum because reconstituted and diluted solutions of Melphalan are unstable. Over as short a time as 30 minutes, a citrate derivative of Melphalan has been detected in reconstituted material from the reaction of Melphalan with the sterile diluent for Melphalan. Upon further dilution with saline, nearly 1% label strength of Melphalan hydrolyzes every 10 minutes.)*
  The drug is then injected manually by repeated small bolus –pulsatile injection- at a rate of **1 mL/minute**. **The injection must be completed within 60 minutes of product reconstitution.**

Section 6

FOCAL THERAPY GUIDELINES

Examination under anesthesia to be scheduled 3weeks after chemotherapy, and focal therapy applied.

1. LASER

Indications:

- Indicated for posteriorly located small (< 3mm) tumors accessible with laser indirect ophthalmoscopy.
- Large size tumors (>3mm) after chemoreduction.
- Laser in normal peripheral retina posterior tumor can form a protective barrier to retinal detachment prior to cryotherapy and plaque radiotherapy.
- It can be used to ablate ischemic retina isolated by extensive scar and protects against neovascularization and vitreous hemorrhage.
- Recurrent and residual tumors.

Contraindications

Tumours underlying exudative retinal detachment

Method:

Group A Tumor: Laser is applied directly on the tumor till a grey white burn covers the entire lesion.

Group B and C Tumour:

1) In a ring like manner around the tumor to coagulate feeding blood vessels leading to ischemic necrosis of tumor.
2) Aggressively on the surface (avoiding hemorrhages) to slowly cook the tumor.
3) In the next 2-3 sessions laser is applied consecutively at 4 weeks' intervals.

Types:

- Frequency doubled ND; YAG.
- Semiconductors diode.

	Frequency Doubled Nd-YAG	**Semiconductor Diode**
Type of laser	Green	Infrared
Wave length	532nm	810nm
Delivery	Trans-pupillary	Trans-pupillary/Trans-scleral
Mechanism	Photocoagulation	Photocoagulation/thermotherapy
Penetration	Superficial (~2 mm in non-pigmented tumors) limited by resultant coagulation and shorter wavelength	Deep (4.2 and 5.1 mm, respectively)
Parameters	Power: 0.3 – 0.8 W Duration: 0.5–0.7 s	Power: 0.3 – 1.5 W Duration: 0.5–2.5 s

Clinical end point	Increase power by 0.1W increments until tumor/ retinal whitening / swelling visible with or without minute surface hemorrhages	Increase power until tumor/ retinal whitening / swelling visible with or without minute surface hemorrhages without causing vascular spasm

Laser Approaches

- Photocoagulation.
- Thermotherapy.

Complications

- Vitreous seedings.
- Vascular occlusion.
- Preretinal fibrosis.
- Vitreous hemorrhage.

2. Cryotherapy

- It is used for anterior and small tumors.
- It involves application of below freezing temperature (below -90.) directly to the tumor mass.
- Triple freeze thaw technique is used through the conjunctiva in two sessions with three week interval.
- Pre-chemotherapy cryotherapy 24–72 hours before chemotherapy maybe used to increase drug penetration into the eye, particularly for vitreous seeding, but not in the presence of retinal detachment
- Cryotherapy through a conjunctival incision may be used for posterior Rb refractory to laser focal therapy.

3. Intravitreal Chemotherapy

Indications

1. It can be used when progression or relapse is mostly intravitreal, its retinal source(s) being accessible to focal treatment.
2. Persistent vitreous seeds after systemic intra venous chemotherapy (4cycles) and/or intra-arterial chemotherapy.
2. Recurrent vitreous seeds after completion of treatment.
3. Chemo resistant new vitreous seeds.

Contra Indications

1. Anterior segment and/or ciliary body invasion.
2. Secondary glaucoma.
3. High bullous retinal detachment.
4. Vitreous hemorrhage obscuring the fundus view.
5. Diffuse vitreous seeding in all four quadrants.

Drugs used are:

1. Melphalan (25 μg/0.125 ml; 30 μg/0.15 ml).
2. Topotecan hydrochloride (20 μg/0.1 ml with 0.9% normal saline).

Dispensing

Drug	Volume in Vial	Dose	Dispensing
Intravitreal Melphalan	50 mg	0.008-0.03 mg/ 0.1 ml	50 mg +2 ml =25 mg/ml 25 mg/ml + 7 ml = 25 mg/8 ml = 3.1 mg/ml 3.1mg/ml+9ml=3.1 mg/ 10ml = 0.3 mg/ml Take 0.1 ml = 0.03 mg/0.1 ml

Number of Injections

- Six injections are delivered on weekly or biweekly schedule if only one injection is being used.
- Only one or two injections are used if combination of Melphalan and Topotecan is used.

Classification of Seeding

1. Dust
2. Spheres
3. Cloud

1. Dust

Dust results from a displacement of tumor cells into the vitreous, appears as small granules of vitreous opacities, and can be seen as a vitreous haze overlying tumor.

2. Spheres

Spheres result from translocation of tumor cells into the vitreous, which then undergo clonal expansion into spheres. They are spherically shaped opacities within the vitreous, and dust may be present around them. They can be homogeneously opaque and have a translucent outer shell with a relatively transparent or whitish center.

3. Cloud

Clouds result from massive transference of tumor cells into the vitreous and are typically visualized as a dense collection of punctate vitreous opacities. They can appear as a sheet or globule of seed granules and often with wispy edges, and dust and spheres are sometimes also visible.

Regression Patterns

1. Type 0: not visible.
2. Type I: calcific.
3. Type II: amorphous.
4. Type III: calcific and amorphous configuration.
5. Type IV: Atrophic chorio-retinal flat scar.

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Section 7

ENUCLEATION GUIDELINES FOR RETINOBLASTOMA

In our country, despite the availability of skills and technology, enucleation remains the commonly used treatment option for advanced retinoblastoma to save the lives of affected children. This is due the late presentation of our patients with advanced intraocular disease. New treatment options offer the possibility of eye salvage. Recently, in the west,Intra-arterial chemotherapy has reduced the rate of enucleation. Intraarterial chemotherapy has also been started in a few centers in Pakistan. Since it is not commonly performed at many centers in Pakistan, enucleation still remains the common treatment modality for advanced retinoblastoma.

Enucleation for Retinoblastoma

1. Indications of Primary and secondary enucleation.
2. Pre-operative Counseling with family.
3. Pre-operative Preparation.
4. Surgical Procedure.
5. Post-operative care.
6. Indications for post enucleation adjuvant chemotherapy and radiotherapy based on histopathology report of the enucleated eye.

1. Indications of Primary Enucleation

- Unilateral retinoblastoma Group D of International Classification for eyes not salvageable and no visual potential
- Unilateral retinoblastoma Group E of International Classification In Bilateral disease in eye with advanced tumor not salvageable and no visual potential.

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Secondary Enucleation

- Non responding advanced intraocular tumor with no visual potential despite maximum systemic and focal treatment.
- Phthisical eye after systemic Chemotherapy.

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   Doi:10.1111/j.1442-9071.2010.02426.x. Epub 2011 Feb 22.

2. Pre-operative Counseling with Family

Counseling with the family is an important part of retinoblastoma management.

Following points must be discussed with the family:

- Why are we doing enucleation? The answer is to save the life which is the primary goal of treatment. If required, pictures of advanced disease can be shown to the family to make them understand that what will happen if enucleation is not performed on time.
- Details regarding the anesthesia, nature of surgery, time required for general anesthesia and surgery and post operative care and rehabilitation.
- Make it clear that orbital implant, conformer and prosthetic eye will have *no visual potential*.
- Prosthetic eye will only be used for cosmesis.
- Prosthetic eye will be fitted by oculist 6 weeks after surgery.
- Further treatment and follow up plan will be decided on the basis of histopathology report.
- Informed consent should be obtained from the parent. It is preferred to have the consent form printed in Urdu.

3. PRE OPERATIVE WORK UP

- Treating Ophthalmologist should confirm the diagnosis and laterality of retinoblastoma.
- Two consultant ophthalmologists should give opinion for enucleation since it involves an organ removal.
- Ophthalmologist should make sure that the grouping of the disease is documented. Take pre-operative pictures if possible.
- Preoperative metastatic work up should be completed by pediatric oncologist.
- Pediatrician, pediatric oncologist and anesthesiologist should examine and investigate the child and write a fitness report after systemic and hematological work up.
- Proper communication of nurse with the family regarding the preoperative orders.
- Arrange adequately sized orbital implant and conformer/prosthetic eye.

The orbital implant is used to replace orbital volume, to aid bone growth, motility of ocular prosthesis and for cosmetic purpose. There are two main types. They are made up of nonporous inert material (silicone, methyl methacrylate) and porous bio-integrated material (hydroxyapatite and porous polyethylene).

The inert implants are not expensive but they are associated with decreased motility. On the other hand, bio-integrated implant provides excellent motility, but they are expensive.

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Day of Surgery

- Surgeon should confirm that the consent form is signed by one of the parents.
- Perform indirect ophthalmoscopy and confirm the eye to be enucleated. Give clear instructions to the assisting staff.

4. Surgical Procedure:

- *Aims are:*
  - The procedure should be less manipulative
  - Avoid perforation of the globe
  - Try to cut long stump of the optic nerve (ideally ¡Ý15mm)
  - Gross examination of the eyeball and nerve to look for extraocular extension of the disease. Measure the length of the optic nerve stump
  - Send the specimen for histopathology examination with details of the specimen mentioned and required information requested on the request form.

- *Procedure:*
  - After induction of general, the marked eye is prepped and draped under strict aseptic conditions.
  - Lid speculum is applied.

- Silk suture is applied to stabilize the globe.
- Peritomy is performed.
- Horizontal and vertical extraocular muscles are isolated and held with 6/0 vicryl sutures and then.
- disinserted from globe. Leave 3mm of lateral or medial rectus stump (depending upon the choice of surgeon) to hold the globe while cutting the nerve.
- Obliques are disinserted from the globe.
- Confirm that all the tenon and muscular attachments are separated from the globe.
- Apply artery forceps to the remaining stump of medial or lateral rectus muscle (surgeon's choice) and proptose the globe.
- Use sharp and less curved scissors to cut the long stump of optic nerve ((ideally¡Ý15mm).
- Use gauze to apply pressure for hemostasis.
- Orbital implan t (wrapped or unwrapped) is deeply inserted in the orbital cavity.
- Muscles are reinserted with 6/0 vicryl.
- Tenon and conjunctiva are sutured in layers.
- Antibiotic and steroid ointment and Conformer is applied.
- Pressure bandage is applied for 48 hours.
- Specimen should be sent for detailed histopathology report mentioning presence or absence of high risk histopathological factors.

5. Post-operative Care

- General monitoring of child.
- Oral antibiotic and NSAID are given.
- Patient can be discharged next day.
- Topical antibiotic and steroid are prescribed after removal of dressing.
- Patient should be kept under close follow.
- Protective eye wear in case of unilateral retinoblastoma.
- Prosthetic eye will be fitted by ocularist 6 weeks after surgery.

6. Indications for Post Enucleation Adjuvant Chemotherapy Based on Histopathology Report showing any of the Following Histopathological High Risk Factors Predictive of Metastasis:

- Anterior chamber seeding.
- Iris infiltration.
- Ciliary body infiltration.
- Massive choroidal infiltration (≥ 3 mm).
- Invasion of optic nerve lamina cribrosa.
- Retro-laminar optic nerve invasion.
- Invasion at site of optic nerve transaction.
- Scleral infiltration.
- Extra scleral infiltration.

In the presence of high risk histopathological features, child should be referred to pediatric oncologist for systemic chemotherapy (See references below).

Indications for Post Enucleation Adjuvant Radiotherapy Based on Histopathology Report Showing any of the Following Histopathological High Risk Factors Predictive of Metastasis:

- Invasion at site of optic nerve transaction.
- Scleral infiltration.
- Extra scleral infiltration.

In the presence of any of the above mentioned high risk histopathological features, child should be referred to pediatric radiation oncologist for radiotherapy. (See references below).

Post Enucleation Adjuvant Chemotherapy References

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Post Enucleation Adjuvant Radiotherapy References

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Genetic Testing Recommended

Genetic testing is recommended for all unilateral and bilateral cases if available, to rule out familial disease.