A RESOURCE MANUAL

FOR THE

MANAGEMENT

OF

RETINOBLASTOMA

IN

LOW & MIDDLE RESOURCE SETTINGS

UPDATED SEPTEMBER 2017

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INTRODUCTION

1. Retinoblastoma (Rb) is a cancer of children which if treated early is curable.

2. Rb affects young children mostly under the age of 5 years.

3. The incidence of retinoblastoma is 1:15,000-20,000 live births and with birth rates varying between 10,000 – 45,000 / million population in different countries that equates with approximately <1-3 cases / million total population.

4 . There is no known gender or racial predilection.

5 . Retinoblastoma is curable if detected and treated early.

6 . The aim of treatment is:
   - Survival of the child
   - Salvage of the eye
   - Salvage of useful vision
   - Improve quality of life for child and caregiver.

7 . Treatment of Rb is best delivered in Rb centres staffed with multi-disciplinary teams.

SERVICE LEVEL for Rb MANAGEMENT

Primary
Able to screen for red reflex and make a preliminary diagnosis of retinoblastoma.

Secondary
Able to make a clinical diagnosis of Rb.
Able to treat by enucleation & send the eye for pathological examination to a tertiary Rb centre.

Tertiary
Provides a multi-disciplinary management team for Rb including Counselling, Ophthalmology, Oncology and Pathology (COOP). Radiotherapy services may also be required in some cases.

SCREENING

Early diagnosis and referral of Retinoblastoma is critical.

Mothers and other family members may notice a white pupil (leukocoria) or an abnormal red reflex or a squint.

Health workers can be trained to screen infants and small children by checking for **a retinal red reflex** particularly if the family members have a concern.

The following groups should be targeted for screening:

- All children with siblings or parents with a history of retinoblastoma or enucleation.
- All neonates 24hrs after delivery before discharge.
- All children attending Reproductive and Child Health (RCH) clinics.
- All children less than 5 years attending immunization campaigns.

All infants should also be checked for strabismus and any child with strabismus must have their fundi examined after dilating the pupils.

EARLY DIAGNOSIS & MANAGEMENT

1. Any child with no retinal red reflex, a white pupil or strabismus should be referred to an ophthalmologist as soon as possible.

2. Any child with no red reflex, a white pupil or strabismus should receive from an ophthalmologist a full retinal examination after dilating the pupils of both eyes.

3. The common differential diagnoses of a white pupil includes:
   - Retinoblastoma
   - Congenital cataract
   - Coats' disease
   - Intraocular inflammation e.g. toxocariasis
   - persistent hyperplastic primary vitreous
   - Retinopathy of prematurity.

4. The following cases of Rb should be referred to a tertiary centre for management of Rb as soon as possible; any child:
   - having a small tumour with potential to save the eye
   - with bilateral or multifocal tumours
   - after enucleation for further management
   - with extra-ocular disease.

RADIOLOGY & IMAGING

1. All suspected cases of retinoblastoma should have an ocular ultrasound if available.

2. All cases of Rb with probable extra-ocular extension should have a MRI if available to evaluate the extent of the disease. If MRI is not available CT scan can be considered. This should be done as soon as possible, preferably within a week of diagnosis.

3. The standard CT and MRI scan protocol should be used which includes less or equal to 2mm slice thickness. In cases of CT, reconstructed coronal and axial planes should be provided.

4. The radiologist should report on the following in CT scan/MRI:
   - Presence of mass
   - Presence of calcification
   - Extra-ocular extension
   - Status of optic nerve, orbit and adnexa.

STAGING AND CLASSIFICATION

Establishment of the correct diagnosis and staging of the disease is important before embarking on any specific treatment for Rb.

The International Retinoblastoma Staging system (IRSS) incorporates intraocular and extraocular disease and is used to stage the patient in order to plan appropriate treatment.

International Retinoblastoma Staging System

Stage	Definition
0	Eye can be salvaged with focal treatment or systemic chemotherapy
I	Enucleation with no tumour residue (low risk features on pathology)
II	Enucleation with tumour residue (high risk features on pathology: (tumour at optic nerve cut end or scleral or extra-scleral extension)
III	Regional extension
IIIA	Overt orbital disease with optic nerve extension or extraocular extension
IIIB	Regional lymph node extension
IV	Metastatic disease
IVA	Haematogenous metastases
IVB	CNS extension

In cases of Rb confined to the globe the **International Intraocular Retinoblastoma Classification (IIRC**) is used to classify the intraocular tumour. Both eyes are classified on the day of presentation (i.e. an eye is **not** reclassified to a higher grade if it progresses)

International Intraocular Retinoblastoma Classification (IIRC)

Group A
Small tumours (<3 mm) that are only in the retina and are not near the optic disc or the fovea.

Group B
All other tumours (>3 mm or close to the optic disc or fovea) that are still only in the retina.

Group C
Well-defined tumours with small amounts of sub-retinal seeding or vitreous seeding.

Group D
Large or poorly defined tumours with widespread vitreous or sub-retinal seeding+/- retinal detachment of greater than a quarter.

Group E
The tumour is very large, extends near the front of the eye, is bleeding or causing glaucoma or has other features that mean there is almost no chance the eye can be saved.

TREATMENT MODALITIES

Focal treatment

Cryotherapy for small peripheral Rb.
Diode laser therapy for small posterior Rb.

Enucleation

The ophthalmologist should try and obtain at least 17mm of optic nerve length, and comment on the length and pliability of the optic nerve.
See surgical technique:
https://www.youtube.com/watch?v=FgGtw6oyHl8&t=53s
A primary orbital implant should be inserted if available. It is important to fit a good prosthesis as soon as possible.

Chemotherapy

This may be given systemically as first line treatment (see protocols later) or by intravitreal injection (usually Melphalan) if vitreous seeds are present after systemic chemotherapy.
In very specialised centres it is occasionally given via the ophthalmic artery.

Radiotherapy

Occasionally a radiotherapy plaque is placed on the sclera over the tumour.
External beam radiotherapy may be used to salvage the only remaining eye or in patients with extra ocular disease or for palliation in metastatic disease.

Extra ocular disease

Decide if treatment is to cure or to palliate.
Cure may be possible without evidence of systemic metastasis or involvement of the brain.

TREATMENT PROTOCOLS

Children with Rb should be managed by a multidisciplinary team (MDT) consisting of a Counsellor, Ophthalmologist, Oncologist, Pathologist (COOP) and if available radio-oncologist in specialised centres.

Intraocular Retinoblastoma

International Classification of Intraocular Retinoblastoma		
	Definition	**Treatment**
A	Small tumours <3 mm outside macula	Focal treatment. If no focal treatment available either: • Send to a site with focal treatment • If no focal treatment is available in country please seek expert guidance
B	Bigger tumours >3 mm or Tumours in the macula or Tumours with sub-retinal fluid	Focal treatment +/- systemic chemotherapy up to 6 cycles
C	Localized (within 3 mm from the tumour) vitreous or sub-retinal seeds	**Unilateral**: Enucleate **Bilateral:** Attempt 'Second Eye' Salvage: Systemic chemotherapy 6

		cycles +/- focal treatment
D	Diffuse (> 3 mm away from the tumour) vitreous or sub-retinal seeds **If Enucleated** look for: **High Risk Histopathological Features**: • Retrolaminar optic nerve involvement • Choroidal Invasion >3mm	**Unilateral:** Enucleate **Bilateral:** Attempt 'Second Eye' Salvage: Systemic chemotherapy +/- focal treatment. IF EYE SALVAGE FAILS: enucleation. **Post Enucleation**: If low risk histopathological features present – no further treatment If high risk histopathological features present: 6 cycles of chemotherapy
E	Any of the following: Tumour touching the lens; neovascular glaucoma; tumour in the anterior chamber; opaque media due to vitreous hemorrhage; aseptic orbital cellulitis; phthisis bulbi	Enucleation. If low risk – no further treatment. If high risk histopathological features present (as for Group D): 6 cycles of chemotherapy

Standard dose systemic chemotherapy given every 3 week for Intraocular RB

Drug	**Dose: Mg/m^2**	**Rate of infusion**	**Diluent**
Vincristine	1.5 mg/m^2 body surface area (BSA D1) *(to a max. of 2mg/ dose)*	Slow Bolus	Not less than 10mls of 0.9% NaCL. **Note: RISK of EXTRAVASATION**
Etoposide	300 mg/m^2 BSA D1	4-hour infusion	0.4mg/ml in 0.9% NaCl
		Note: Rapid infusion will lead to hypotensive crisis	
Carboplatin	600 mg/m2 BSA D1	1-hour infusion	0.5mg/ml in D5% or DNS
Requirements before each cycle			
ANC > 1; Platelets > 100; Check Hb, Renal profile, LFT's and Magnesium level are adequate.			
Age	**Dose Modifications**		
< 6 mth	Give 50% of the dose for each drug		
6-12 mths	Give 75% of the dose for each drug		
12+ mths	No modification		

Retinoblastoma with Extraocular Extension

International Retinoblastoma Staging System		
Stage	**Definition**	**Standard of care**
0	Eyes salvaged with focal treatment or systemic chemotherapy	See Intraocular Protocol
I	Enucleation with no tumour residue	See Intraocular Protocol
II	Enucleation with microscopic tumour residue: • Scleral • Extrascleral extension • Tumour at optic nerve cut end	Enucleation done so histopathology informs treatment. Confirm CSF/MRI (or CT) Brain/ BMA are all normal (i.e. no brain involvement or metastases). Chemotherapy: 12 cycles for tumour at optic nerve cut end or extraocular extension; 6-12 cycles for scleral involvement. (Clinical review & CSF analysis following every 3 cycles). Then EBRT if available.

<table>
<tr><td>III</td><td>Regional extension</td><td rowspan="4">If child has ophthalmitis give 3 days of steroids.
If child responds and globe appears normal consider second EUA and decide if to downstage.
Confirm CSF/MRI (or CT) Brain/ BMA are all normal (i.e. no brain involvement or metastases).
6 cycles of chemotherapy
then
Enucleation (or exenteration)
then
EBRT (45 Gy)
then
6 more cycles of chemotherapy
(Total of 12 cycles).
Do clinical review & CSF analysis following every 3 cycles.</td></tr>
<tr><td>III A</td><td>Overt orbital disease with optic nerve extension or extraocular extension</td></tr>
<tr><td>IIIB</td><td>With regional lymph node extension</td></tr>
<tr><td></td><td></td></tr>
<tr><td>IV</td><td>Metastatic disease</td><td rowspan="3">Palliative care
May include: Oral Etoposide, limited courses of IV chemotherapy, or other treatments depending on resources at each site.</td></tr>
<tr><td>IVA</td><td>Haematogenous metastases</td></tr>
<tr><td>IVB</td><td>CNS extension</td></tr>
</table>

Systemic chemotherapy given 3 weekly for Orbital RB

Drug	**Dose: Mg/m^2**	**Rate of infusion**	**Diluent**
Vincristine	1.5 mg/m^2 body surface area BSA D1 *(to a max. 2mg/dose)*	Slow Bolus	Not less than 10mls of 0.9% NaCL **Note: RISK of EXTRAVASATION**
Etoposide	300 mg/m^2 BSA D1	4-hour infusion	0.4mg/ml in 0.9% NaCl
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Carboplatin	600 mg/m2 BSA D1	1-hour infusion	0.5mg/ml in D5% or DNS
Requirements before each cycle			
ANC > 1; Platelets > 100; Also check Hb, Renal profile, LFT's and Magnesium level are adequate.			
Age	**Dose Modifications**		
< 6 months	Give 50% of the dose for each drug		
6-12 months	Give 75% of the dose for each drug		
12+ months	No modification		

Remaining questions regarding chemotherapy

1. Can high dose chemotherapy be given safely?
2. Should intra thecal chemotherapy be used, if so when?
3. Should the number of cycles for microscopic invasion be 6 or 12?
4. Should neoadjuvant chemotherapy be given to E children?

PATHOLOGY REPORTING

After an enucleation the histopathology contributes to the staging of the Rb that determines further treatment.
The main high-risk factor (HRF) is extension of the tumour in the optic nerve to the margin of the surgical resection.
Other risk factors include:

- post laminar optic nerve invasion;
- involvement of anterior segment;
- massive invasion of choroid $\geq$ 3mm;
- invasion of sclera;
- extra scleral tumor extension.

FOLLOW-UP

Children with unilateral Rb need to be seen every 3 months up to the age of 3 years and every 6 months up to the age of 5 years and thereafter annually for life.
For children at high risk of developing new Rb tumours (*Rb1* germ line mutation, family history of disease or bilateral Rb) continue with EUAs as often as every month depending on the child's age.
Rb survivors treated with chemotherapy or EBR, require oncology clinic follow-up at 6-monthly intervals for 5 yrs. Survivors of Rb should receive individualised lifelong follow-up with counselling and treatment for late effects of disease.

GENETIC COUNSELLING

1. Retinoblastoma can be hereditary or sporadic.

2. Hereditary forms are often bilateral and multifocal.

3. Hereditary Rb has up to a 50% chance of being passed on to offspring. Siblings and first cousins are also at an increased risk.

4. Children with hereditary Rb should be frequently examined under general anesthetic in the first 3 years of life.

5. Relatives of children affected by Rb (siblings, cousins, and offspring) should be screened for Rb as soon as possible after birth.

6. Parents and other relatives of children with Rb should be given counselling from someone well trained in Rb counselling.

7. Children with Rb should be offered genetic counselling as they grow up.

8. If *Rb1* gene mutation identification is available then test the first affected person in each Rb family, and if the *Rb1* gene mutation is found offer genetic testing for all at-risk relatives.

9. If *Rb1* gene mutation identification is NOT available then the following guidelines may be used:

Bilateral case with no Family History

- Siblings have 5% risk; screen all siblings to age 18 months
- Offspring have a 50% risk; screen all offspring to age 3 years

Unilateral case with no Family History

- Siblings have 1% risk; screen all siblings to age 12 months
- Offspring have a 5-10% risk; screen all offspring to age 18 months

PSYCHOSOCIAL SUPPORT

Ongoing psychosocial support from a trained social worker or clinical psychologist with expertise in Rb counselling is important for all Rb children and their families.

RETINOBLASTOMA NETWORK, ICEH

This Resource manual is a product of the work of the Retinoblastoma Network, part of the Commonwealth Eye Health Consortium at the International Centre for Eye Health, LSHTM, London.

The Retinoblastoma Network currently consists of a partnership of many individuals and institutions from a number of African, Asian and European countries involved in improving the management of Retinoblastoma with an emphasis on low and middle income countries.