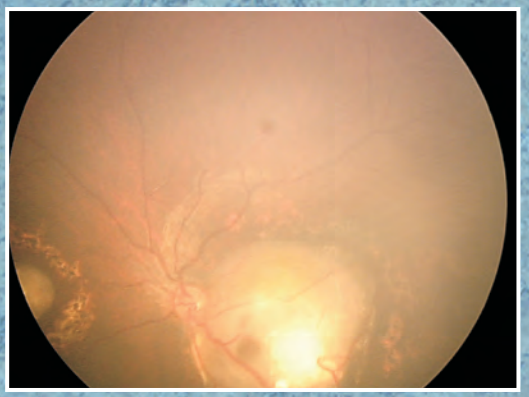
National Guidelines in the Management of Retinoblastoma



Indian Council of Medical Research
2010

National Guidelines in the Management of Retinoblastoma

ICMR sponsored along with Pediatric Hematology Oncology (PHOCON 2008 pre congress) consultative meeting on guidelines and standard operating procedures (sop) for the management of retinoblastoma on NOV. 6th 2008

INDIAN COUNCIL OF MEDICAL RESEARCH
NEW DELHI
2010

Published by:
Director-General
Indian Council of Medical Research
New Delhi 110 029

Production Controller:
J.N. Mathur, Press Manager, ICMR, New Delhi

Printed at: Aravali Printers & Publishers Pvt. Ltd., W-30, Okhla Industrial Area, Phase-II, New Delhi - 110 020

Foreword

Retinoblastoma is a malignant tumor of the eye arising from fetal retinal cells. It affects children under 5 years of age . When retinoblastoma is diagnosed early, we can often save the eyes and therefore the vision and the life of the child. It is estimated that India has the highest number of affected children with retinoblastoma in the world, about 1200 new cases each year.

The survival of children with retinoblastoma has improved in the last decade due to the increasing awareness about cancer and improved technologies and improved chemotherapy protocols in the management of retinoblastoma.

It is hoped that the Guidelines will help the practising ophthalmologist, pediatrician, and general practitioners to diagnose early cases of retinoblastoma and refer for treatment to a tertiary hospital at the earliest. Such uniform guidelines will also help to conduct clinical trials to develop better protocols in the management of retinoblastoma. Such guidelines are a valuable effort to save the lives of children and their vision from retinoblastoma

Dr. Vishwa Mohan Katoch
MD, FNASc, FNAMS, FASc, FNA
Secretary to the Govt. of India
Department of Health Research
Ministry of Health & Family Welfare &
Director General
Indian Council of Medical Research
Post Box No. 4911, Ansari Nagar
New Delhi - 110029, India

Foreword

I am very pleased to announce the release of the ICMR National guidelines for management of retinoblastoma.

There are divergent views at various institutes in the appropriate management of Retinoblastoma. All such national experts and specialists who treat children with Retinoblastoma were brought under one roof in 2008 to brainstorm and produce consensus guidelines for a unified approach to the diagnosis and management of Retinoblastoma in our country. This was an unique effort and the first of its kind, spearheaded by Dr.Vasantha Thavaraj under the auspices of ICMR and the Pediatric Hematology & Oncology Chapter of Indian Academy of Pediatrics. The mechanism of evolving such consensus guidelines is quite elaborate and time consuming. But the results of this labour will help us in standardisation of our practices for appropriate treatment of Retinoblastoma at the national level.

I applaud the important work of ICMR / PHO Chapter of IAP in conceptualising and promoting the Retinoblastoma guidelines that are crucial for improving the outcome in our children treated for Retinoblastoma. I am sure that the publication of these guidelines will prove to be one of the important steps in improving childhood cancer survival in India.

Dr. Bharat Agarwal
Hon. Secretary General
International Society of Pediatric Oncology
Head, Department of Pediatric Hematology & Oncology,
B.J. Wadia Hospital for Children
Parel, Mumbai – 400 012

Foreword

It is indeed a well offer to be associated with the Indian Retinoblastoma Interest Group. We are extremely happy to have brought out these guidelines under the able leadership of Dr Vasantha Thavaraj. Retinoblastoma is an important childhood cancer and with the research innovations in chemotherapy protocols, we are able to salvage a lot of eyes. These guidelines should educate the ophthalmologist at large as well as those who concentrate on treatment of retinoblastoma. Once again, we wish to thank Dr Vasantha who took the pain to put the team together and also would like to thank each one of the team members who contributed to the guidelines.

Dr Lingam Gopal
Founding member of Indian Retinoblastoma Group
Consultant, Shri Bhagwan Mahavir Vitreoretinal
Services Consultant
Neuro-Ophthalmology
Director-Research
Vision Research Foundation
Sankara Nethralaya
18 College Road
Chennai - 600 006

Preface

Retinoblastoma is a rare cancer of childhood, if diagnosed early we can save the eye and the life of the child. The Indian retinoblastoma Group was formed in 2005. All the Pediatric oncologists treating retinoblastoma, Ocular oncologist and radiotherapist came under this group. It was necessary that a standard operating procedures (sop) for the management of retinoblastoma is published. During the Pediatric Hematogy –oncology annual meeting which was held in New Delhi in 2008, it was decided to hold a meeting on guidelines in the management of Retinoblastoma. I am indeed grateful to Dr. L. Gopal who readily agreed to be the chairperson of the meeting. He prepared the agenda and conducted the meeting. I also thank him for the hard work put in to correct the manuscript of the Guidelines. The council is appreciatively acknowledges the valuable contribution of all the expert group members who took part in the guidelines meeting. I am also grateful to K. Sathyanarayanan Head of the Division of Reproductive health and nutrition for all the encouragement and support given to me in bringing out this publication. I am also grateful to Prof David Abramson Chief, Ophthalmic Oncology , Memorial Sloan-Kettering Cancer Center, Prof. G.L. Chantada Pediatric Oncology, Argentina and Prof. Anna T. Meadows, The Children's Hospital of Philadelphia, who graciously accepted to comment on the manuscript . We are grateful to Dr. Meadows for having taken out some precious time from her busy schedule to correct the manuscript. We acknowledge her contribution .

Dr Vasantha Thavaraj
MD, FIAP,DNCI
Deputy Director General (SG)
Chair Child Health
Division Of RHN
Indian council of Medical Research,
New Delhi 110-029

Indian Council of Medical Research
Guidelines in the Management of Retinoblastoma
Peer reviewers

Bharat Agarwal

Rashmi Dalvi

Gupta VP

Mohanti BK

Seth T

Brenda L Gallie (Canada)

Lalit Kumar

Grover AK

Katoch VM

Advani SH

Guillermo L Chantada (Argentina)

Ram Marwah

Raghunadharao D

R. Carlos (USA)

S.C. Howard (USA)

Arya LS

Murali Chintagumpala (USA)

Doris Hadjistilianou(ITALY)

Ama Rohatiner(UK)

Sidnei Epelman(Brazil)

Melissa Adde(INCTR, Belgium)

Anupam Sachdeva

David Abramson (USA)

Purna Kurkure

Brijesh Arora

Purvish Parikh

Sathyanarayanan K

Supriyo Ghose

Anita Sethi

D'Souza,P

P.Kusuma kumari

Anupama Borker

Y Ravindranath (USA)

Bansal R

Sima Das

Aziza Shad (USA)

Amita Mahajan

Anna T Meadows(USA)

Paul Ribero(USA)

Carol L Sheild (USA)

Nurdan Tacyilidiz(Turkey)

Gauri Kapoor

Ian Magrath (INCTR, Belgium)

Contents

Section 1

Introduction

Retinoblastoma is the most common intraocular tumour of childhood. When retinoblastoma remains confined to the eye, it has one of the best survival rates of all the childhood cancers, but once the spread occurs outside the globe, the treatment needs to be more aggressive and many children do not survive. Management of the child with metastatic disease remains a considerable challenge to all concerned. Early diagnosis is, therefore, of paramount importance in the survival of the child.

1.1 Aims and scope

These Guidelines are intended to provide knowledge to the treating ophthalmologists, pediatricians, ocular oncologists, pediatric oncologists, and general physicians to arrive at an early diagnosis of retinoblastoma in the settings of district hospital, in private clinics and hospitals. The guidelines will enable the contact health personnel to refer at the right time to the tertiary care hospital for management of retinoblastoma .

1.2 Historical Background

The first clinical report of recognizable retinoblastoma is from the mid-18th century. The first accurate description of retinoblastoma was in the early 19th century by Wardrop, who recognized that the tumor arose from the retina and advocated early enucleation. Virchow thought that the tumor was of glial origin. Hence, until recently, the term retinal glioma persisted in some reports from Europe. The true natural history and histology of retinoblastoma were finally established by Flexner and Wintersteiner, both recognizing that the tumor arose from neuroepithelial cells of the retina. Verhoeff coined the term retinoblastoma, which was generally agreed up on in the 1920s. Tso and colleagues established that the tumor arises from photoreceptor precursors.

The initial treatment, about which there was a great controversy in the 19th century, was enucleation. Most of the patients subjected to enucleation then did not survive probably because the tumor was too advanced at the time of the treatment. Radiation therapy was advocated beginning in the early part of this century but the first long-term survivor after radiation therapy was a patient treated by Verhoeff in 1921 at the Massachusetts Eye and Ear Infirmary. The modern era of radiation therapy was introduced by Reese and colleagues in the 1930s and 1940s. Since the mid 1990s, institutions have successfully introduced chemotherapy for the treatment of intraocular disease. The drugs that penetrate the retina have been used together with

focal therapy to eradicate tumors that would have necessitated enucleation, and many eyes have been saved.

1.3 Statistics in Retinoblastoma

The National Cancer Registry Project (NCRP) (ICMR) 1999-2000 (a population based project at Delhi) has registered retinoblastoma under "Eye tumors". The probable **incidence of retinoblastoma** in Delhi is 28 cases per million population of children < 5 years of age.

Study period	1999-2000
Total population of children less than 5 years	1,416,193
Total ocular tumors identified	32
Total eyes with probable retinoblastoma	28 (90% of all ocular tumors)

In the United States the reported incidence is 11 new cases per million of children less than 4 yrs of age .

1.4 Risk factors :

1.4.1 Age:

Most children diagnosed with retinoblastoma are younger than 3 years old. Most congenital or hereditary retinoblastomas are found during the first year of life, while non-inherited retinoblastomas tend to be diagnosed in 1- and 2-year-olds. Retinoblastomas are extremely rare in older children and in adults.

1.4.2 Heredity

About 1 out of 3 cases of retinoblastoma are caused by a mutation (change) in the Rb (RB1) gene that is present in all the cells of the body, and therefore can be passed on to the next generation. However, of these cases, only about 1 in 4 are inherited from one of the child's parents. In the rest, the gene mutation has not been inherited, but has occurred during early development in the womb. About 85% of congenital or hereditary retinoblastomas affect both eyes.

The remaining 2/3rd cases occur as a result of a random Rb gene mutation that occurs only in one cell of one eye; these tumors are obviously not inherited and occur only in one eye.

1.4.3 Histopathological Risk factors

- Retrolaminar optic nerve involvement, even with free resection line, and massive choroidal invasion significantly increase the risk for orbital and/or metastatic disease.

Section 2

Guidelines for initial examination in clinic, planning of EUA, investigations and initial documentation before treatment in Retinoblastoma

2.1 Patient Identification Data:

1. Name
2. Age (in years and months) and date of birth
3. Age of parents
4. Sex of the child
5. Religion
6. Patient identification (registration) number
7. Address and contact details including phone number and e mail if any
8. Socio economic status

2.2 History

2.2.1 Presenting history (complaint and when noted):

1. Leukocoria or unusual pupillary appearance
2. Squint
3. Nystagmus
4. Change in visual status or loss of vision
5. Pain and swelling of the lids
6. Protrusion of the eye

2.2.2 Perinatal history:

1. Weight and gestational age at birth of the child and need for oxygen administration (Keeping ROP in mind)
2. History of rubella (Keeping congenital cataract in mind)

2.2.3 Family history (If history positive, the relationship to the affected child noted):

1. History of intra ocular tumor (including retinoblastoma) in any of the family members
2. History of death due to ocular cause.
3. History of any other cancers like osteosarcoma, Breast cancer, leukemia, Brain tumors in the family.
4. History of Blindness at birth
5. Family tree should be charted for three generations depicting the ages.

2.2.4 Treatment history:

Full details of previous treatment received such as enucleation, radiation, cryopexy, laser, chemotherapy (including the details of the drugs administered and their dosage) etc.

2.3 Clinical examination in office

2.3.1 Ocular examination:

1. Visual acuity- recording according to the age group involved
2. Anterior segment evaluation (either slit lamp or using the magnification of the +20 D lens with indirect ophthalmoscope)- look for
    a. Hyphema
    b. Rubeosis iridis and ectropion uvea
    c. Nodules on the iris
    d. Corneal edema
    e. Cataract (not usually seen in RB)
    f. Retrolental mass
    g. Retrolental fibroplasia (seen in mimicking disease like ROP or PHPV or Retinal dysplasia)
3. Posterior segment examination (gross examination possible by restraining the child)
    a. Mass lesion and its description – endophytic/ exophytic/ mixed
    b. Secondary retinal detachment
    c. Visible ciliary processes and retrolental fibroplasia (ROP and PHPV)
    d. Visible vascular abnormalities and no mass with secondary RD (Coat's disease)
4. Ultrasonography (possible under mild sedation or by restraining)- Refer section on imaging

In most cases, the diagnosis can be made with reasonable certainty at this stage. MRI orbits and brain is ordered to look for extra ocular extension- especially optic nerve invasion, and trilateral retinoblastoma. In many cases, a decision regarding enucleation can also be taken at this stage. Anesthesia examination and if need be, enucleation can be planned.

2.3.2 Examination under anesthesia:

2.3.2.1 *Purpose:*

- Total retinal evaluation up to ora serrata in both eyes

- Retinal drawing
- Retcam imaging

2.3.2.2 *Instrumentation needed:*

- Operating microscope with attachment for trans pupillary thermo therapy
- Hand held slitlamp
- Indirect ophthalmoscope with +20 diopter lens
- Eye speculum
- Perkins hand held tonometer or tonopen
- Calipers
- Cryo machine with probe
- Laser machine with indirect ophthalmoscope delivery

2.3.2.3 *Procedure of examination:*

- Measurement of corneal diameter
- Intra ocular pressure recording
- Confirmation of Anterior segment findings
- Fundus examination with Binocular Indirect Ophthalmoscopy and 360º scleral depression
- Drawings of retina of the involved eye
    - Tumor –faithful depiction as to number, size in DD, site (anterior/posterior to equator and distance in DD from disc and macula), elevation and growth pattern –(Endophytic, Exophytic, Diffuse Infiltrating)
    - Retinal detachment
    - Subretinal seeds
    - Vitreous seeding
- Retcam Photography (if available)
- Ultrasound, if not done previously

2.3.3 Examination of siblings and parents:

At the earliest opportunity, the siblings and parents are examined and blood samples are collected if DNA studies are contemplated

2.4. Discussion with parents and finalizing the treatment plan:

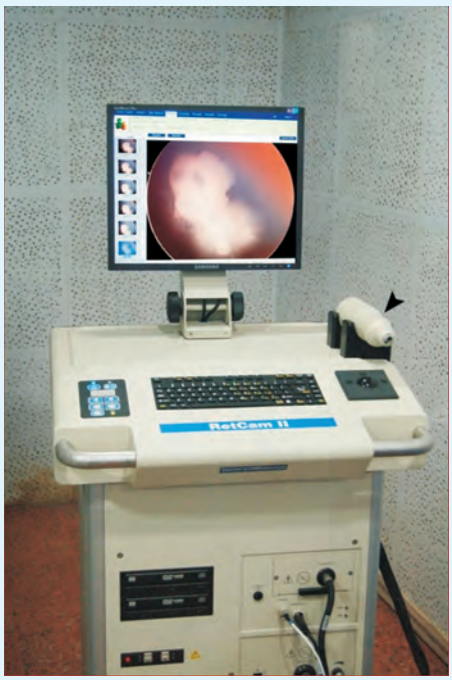
It is assumed that some amount of discussion has taken place in the office after the clinical office examination and investigations such as ultra sound and MRI.

After the detailed examination under general anesthesia, further discussion and counseling should take place. This should cover

- The diagnosis- should cover discussion on what is cancer

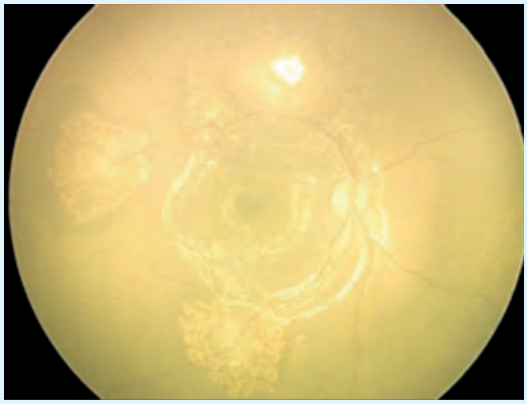
- Its implications- should cover the risk to life, the eye and the vision in that order.
- Prioritisation- should cover the need to place life first and then only, preservation of eye and vision.
- The treatment plan- A detailed discussion on the treatment plan for each eye should be discussed. The parents should be told about change of plan depending on the response or otherwise.
- Explaining about enucleation and its implications-
  - That it involves total removal of the eye ball
  - That there is never a possibility of replacing with seeing eye
  - That an artificial eye shell can be placed for cosmetic purposes
- Need for long term follow up-
  - Need for serial anesthesia examinations should be discussed.
  - Stress on the periodicity and the need to keep up the visits

Certain procedures like cryo pexy, laser photocoagulation can be carried out under the same anesthetic sitting after consent is taken from the parents. Enucleation can also be carried out at the same sitting if prior discussion has already primed the parents regarding its possible need and consent has been obtained.

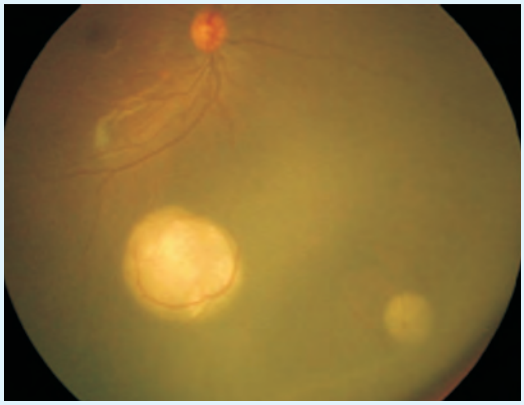


RETCAM IMAGES

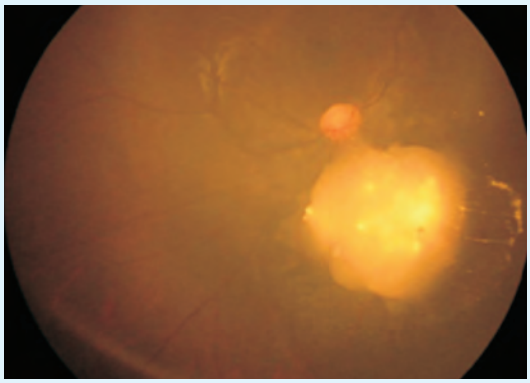
Stage A



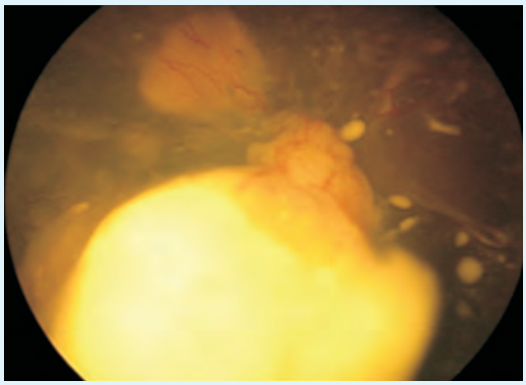
Stage B



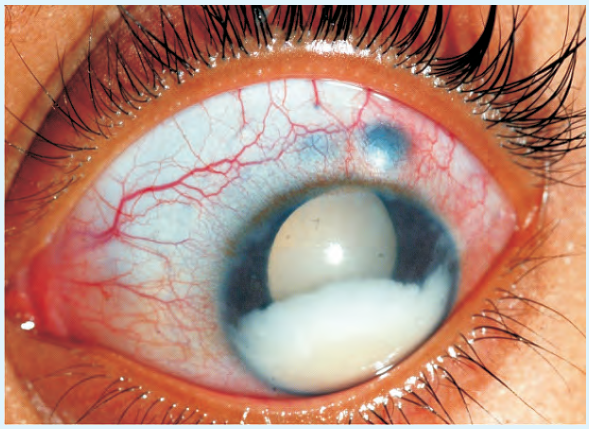
Stage C



Stage D



Stage E



To Summarize,

- Documentation of patient data
- History
- Presenting history, Perinatal history, Family history, Treatment history
- Clinical examination
- Ocular examination
- Visual acuity, anterior segment evaluation, Posterior segment, Ultrasonography
- Examination under anesthesia
- Examination of siblings and parents
- Discussion with parents and finalizing the treatment plan

Section 3

Enucleation for retinoblastoma: Indications and procedure

3.1 Purpose:

To describe the indications and surgical technique of enucleation for eyes with retinoblastoma

3.2 Outline:

- Definition
- Indications for primary and secondary enucleation
- Preoperative work up and counseling
- Surgical procedure
- Post operative care

3.2.1 Definition:

Enucleation involves the removal of the entire globe with preservation of the eye muscles.

3.2.2 Indications:

3.2.2.1 *Primary enucleation:*

- Unilateral retinoblastoma with Reese-Ellsworth stage V disease
- Non-salvagable eye or with no visual potential in a unilateral tumor
- Group D of International Classification for eyes not salvageable and no visual potential
- Group E of International Classification

3.2.2.2 *Secondary enucleation:*

- Non responding tumor with no visual potential despite maximum treatment
- Phthisical globe after neoadjuvant Chemotherapy
- Regressed orbital and/ or extrascleral retinoblastoma following chemotherapy, with no evidence of residual tumor in the orbit/systemic foci on imaging and/ or systemic investigations

3.2.3 Preoperative work up:

- Complete ophthalmological examination with unequivocal diagnosis of retinoblastoma based on clinical and radiological examination.
- Routine pre-anaesthetic workup .
- A minimum of 9-10 gms% of hemoglobin is mandatory. If the hemoglobin is lower (especially possible in cases that have undergone chemotherapy), the same is built up with packed cell transfusions before surgery.
- Preoperative planning for placement of orbital implant (size of implant is selected based on intraoperative assessment by appropriate sizers).

3.2.3.1 *Pre operative counseling:*

The parents of the child should be thoroughly counseled. The nature of surgery should be explained. Counseling should include detailed explanation that

- The eyeball cannot be replaced with a seeing eye.
- The implants and prosthesis will be given to achieve cosmetic correction.
- The enucleated eyeball requires histopathological examination and this will suggest further treatment plan and future follow up.
- Informed special consent should be obtained from the parents for enucleation.

3.2.4 Surgical Procedure

3.2.4.1 *Who should perform the enucleation?*

- Ophthalmologists specialized in the treatment of such patients.
- Novice ophthalmologist should not perform enucleation independently.

3.2.4.2 *Issues regards to surgery:*

- First and foremost, the eye to be enucleated should be confirmed. One should use patient's records and intra-operative examination with indirect ophthalmoscopy of both eyes, before proceeding with the surgery.
- A minimum of 10mm of optic nerve stump is aimed at.
- Clamps and snares are to be avoided since they produce crush artifacts.
- Post-enucleation, eye ball and optic nerve are examined to look for evidence of extraocular tumor.
- The specimen should be submitted for histopathology reporting making sure that the form contains patient treatment details.

3.2.4.3 Steps of surgery:

- Eye is prepared and draped.
- Lid speculum is placed.
- 360 degrees conjunctival peritomy is done
- Tenon's adhesions to sclera are cleared in all four quadrants with tenotomy scissors
- Pediatric muscle hook is used to hook the recti, one at a time.
- Each rectus muscle is tagged with double-armed 6-0 vicryl sutures passed 3-4 mm beyond the insertion. The suture ends are secured with small bulldog clamps. The rectus muscle is cut at the insertion leaving behind a small 1-2 mm stump attached to the sclera.
- The inferior and superior oblique muscles are isolated and cut.
- The hook is swept next to the globe and all other adhesions are lysed.
- The speculum is next removed and the globe is prolapsed by pushing the lid margins backwards.
- The optic nerve can be cut either from the temporal side or nasal side.
    - Temporal approach- The enucleation guide is passed from the temporal side and the optic nerve engaged in its wedge. Scissors with minimal curve is slid behind the optic nerve guide, optic nerve is felt and cut with a slight tilt of the scissors forwards so that the tip goes as far posteriorly as possible
    - Nasal approach- The medial rectus stump is held by a curved hemostat and used to turn the eye ball firmly temporally. The enucleation scissors with minimal curve is introduced; the optic nerve is palpated with the closed blades and then cut.
    - The eye is removed after teasing away any surrounding tissues
    - The orbit is packed with wet gauze and firm pressure is applied to secure hemostasis.
    - The implant is placed in the orbit (soak in antibiotic solution before placing the same). The preplaced 6-0 vicryl sutures attached to the recti will help anchor them. The type of anchorage and the tissue to which they are sutured depends on the technique adopted (wrapped Vs non wrapped implant etc.)
    - Conjunctiva and tenon's capsule are closed in layers with 6-0 vicryl.
    - Antibiotic ointment is instilled and a conformer is placed.
    - Pressure pad and bandage is applied.

3.2.5 Post operative Care:

- Post operative dressing is done
- Topical antibiotic ointment is prescribed
- Oral antibiotics are preferably given at the discretion of surgeon
- Ocular prosthesis is given 4-6 weeks following surgery.
- Patient should be kept under close follow up till the histopathological report is available

Steps of enucleation

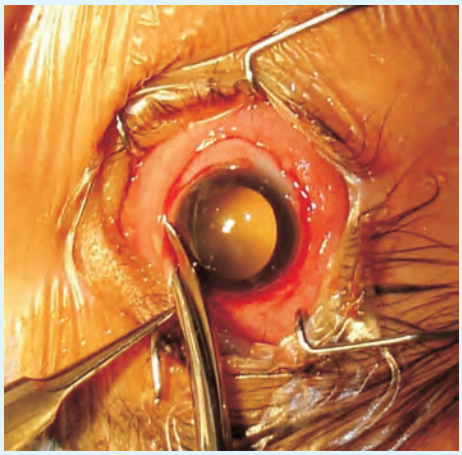


Figure 1: 360 degree conjunctival peritomy being done

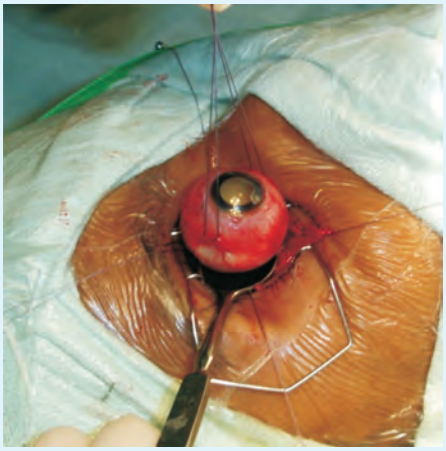


Figure 2: Globe is prolapsed upwards and enucleation guide is passed underneath while engaging the optic nerve after the extraocular muscles are cut from the globe

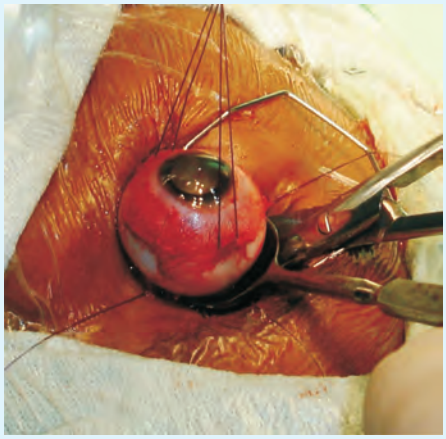
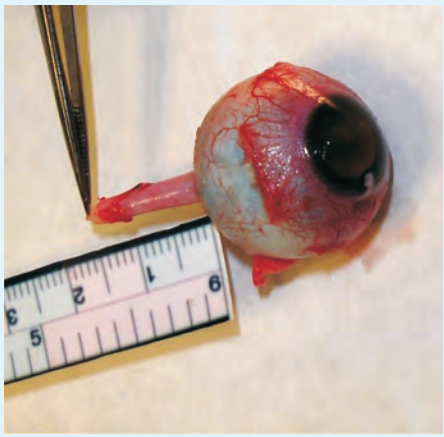


Figure 3: Enucleation scissor is passed below the enucleation guide and optic nerve is cut as posteriorly as possible to get a long stump

Figure 4: Globe is examined for extra scleral extension and adhesions. Optic nerve length and thickness at base is measured.



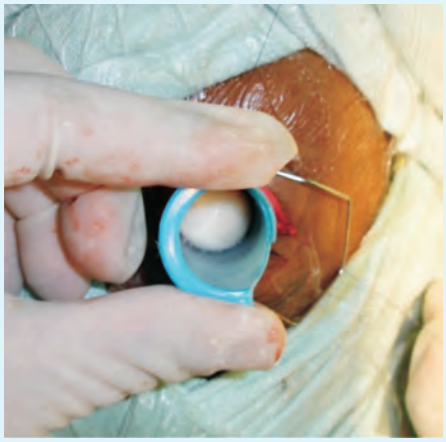


Figure 5: Implant is placed deep into the socket

To summarize,

- Enucleation is performed for eyes with advanced retinoblastoma with non salvagable globe having no potential for vision
- Appropriate preoperative systemic and haematological workup is essential prior to taking the patient for surgery.
- Special informed consent is mandatory.
- While enucleating, care has to be taken not to cause injury to the globe and muscle while applying traction.
- Long optic nerve should be obtained.
- Further postoperative treatment decision is taken after the histopathology report is available

Section 4
Focal therapy for retinoblastoma

4.1 Purpose

To describe the modalities of focal therapies available for treating retinoblastoma, their indications, limitations and complications.

4.2 Ouline:

- What is focal therapy
- Indications
- Laser photocoagulation
- Cryo therapy
- Brachy therapy
- Thermo therapy
- Local chemotherapy

4.2.1 What is focal therapy?

Focal therapy is treatment applied locally to the tumor mass, either trans sclerally or trans pupillary. These treatment modalities have no systemic complications and barring brachy therapy, can be repeated if necessary.

- Laser photocoagulation
- Cryotherapy
- Thermochemotherapy
- Plaque brachytherapy
- Sub tenon's chemo therapy

4.2.2 Indications for focal therapy (focal consolidation)

1. Group A – primary focal therapy
2. Group B – Six cycles of chemotherapy, especially if only two drugs are used followed by focal consolidation
3. Group C – six cycles of chemotherapy plus focal consolidation

4.2.3 Laser Photocoagulation

4.2.3.1 *Commonly used lasers:*

- 532 nm argon green
- 810 nm diode infrared

4.2.3.2 *Indications for laser therapy*

- Group A :primary laser photocoagulation
- Group B –D: primary chemotherapy followed by laser photocoagulation

4.2.3.3 *Timing of treatment*: start concurrently with the beginning of the 2nd or 3rd cycle of systemic chemotherapy

4.2.3.4 ***Goal of therapy***: To completely cover each lesion with 30% overlap during at least three different sessions

Power settings:

- 532 argon –> 250 -300 mW (not > 500-600 mW) with a duration of 300-500 ms (not > 700 ms)
- 810 diode –> 400-600 mW (not > 700-800 mW) with a duration of 500 ms

4.3.3.5 *Technique of laser therapy*

The first burns are placed at the edge of the lesion with the spot half on and off the tumor. The power and/or duration can be adjusted to achieve gentle whitening of the tumor. Once the lesion is outlined, then the entire lesion including any type I regression-associated calcium is covered with overlapping rows of burns. The burns over the thicker areas of the tumor may be virtually invisible compared to those placed at the edge of the lesion. The power or duration should not be increased to compensate for the decreased “take” over the thicker parts of the lesion. Repeat the laser coverage at 2-4 week intervals during and/or after the administration of systemic chemotherapy until the entire lesion has been covered on at least 3 different occasions.

Infrared 810 nm diode laser has longer wavelength than the argon laser, it penetrates further and is absorbed mainly by the RPE. It is useful primarily if RPE is intact under the lesion to be treated. One major advantage of the infrared laser is its larger spot size allowing more rapid coverage of the lesion and offering less opportunity to deliver excessive concentrated energy that might cause bleeding or tumor disruption.

4.3.3.6 *Complications of focal laser consolidation*

- Iris burns at pupillary margin

- Focal lens opacities
- Subhyaloid and vitreous hemorrhage
- Decreased vision from RPE scar migration or "creep"
- Rarely, tumor disruption and vitreous seedings

4.2.4 Cryotherapy

Cryotherapy produces ice crystals which directly destroy tumor cells by rupturing the cellular membranes. It is useful in controlling local group A disease anterior to the equator when the tumor is confined to the sensory retina. It is useful in tumors up to 3.5 mm in diameter and 2.0 mm in thickness.

4.2.4.1 *Technique of Cryotherapy*

Tumor is localized and it is elevated on the tip of the cryoprobe. Once the probe is directly beneath the tumor, freezing is performed so that the ice ball covers the entire tumor mass. The ice ball is allowed to thaw, and this freeze-thaw cycle is repeated for a total of two or three applications.

4.2.4.2 *Complications of cryotherapy*

- Vitreous hemorrhage
- Subretinal fluid
- Retinal holes and rhegmatogenous retinal detachment

4.2.5 Brachytherapy

Plaque brachytherapy may be the treatment of choice in isolated group B intraocular retinoblastoma located at or anterior to the equator.

Radioactive isotopes used

- Iodine^{125} isotope
- Ruthenium^{106} isotope – a beta emitter, longer t1/2

Isotopes iodine^{125} seeds are secured in a gold carrier which prevents radiation from penetrating the substance of the plaque and shields normal bone and tissue from most of the radiation. Dosimetry planning is carried out with the help of sophisticated software. The calculated dose to the apex of the tumor is generally in the range of 40 Gy.

The advantage of ruthenium is that the half-life is much longer than iodine so that a single plaque may be reused for up to one year. There are two major disadvantages. Because ruthenium is a beta emitter, a retinoblastoma lesion higher than 5 mm cannot be treated easily. Secondly, in ruthenium plaques, the plaque itself contains the radiation sources. Therefore the possibility of differentially loading radiation seeds

in the plaque to conform to the shape of the tumor is not possible, thus ideally, one may have to stock several sizes of ruthenium plaques.

4.2.5.1 *Indications*

1. Primary therapy for unilateral tumours less than 10-15mm in diameter and less than 6-8 mm in height
2. Primary therapy for solitary tumours at ora serrata with overlying focal vitreous seedling
3. Secondary therapy for recurrent tumours of similar dimensions not amenable to other modes of therapy
4. Primary therapy for bilateral tumours in a child more than 1 year old, when the ocular tumours can be adequately treated with either cryotherapy, phototherapy and the main tumour in an eye is 8 to 15 mm in diameter and 3 to 7 mm thick
5. Residual tumors after shrinkage of the tumor with chemo therapy etc.

4.2.5.2 *Contraindications (relative)*

1. Larger tumours
2. Eyes with total vitreous seeding
3. Tumours that involve the fovea or optic disc

4.2.5.3 *Plaque selection*

NUCLIDE	T ½	HVL@ (cm)	TVL*(cm)
Gamma ray/ **X ray emitters**			
Cobalt-60	5.3yrs	10.8	4.6
Iodine 125	60.2 days	3	0.01
Pallidium 103	17 days	2	0.003
Beta emitters			
Strontium 90	28 years	1.5	0.04
Ruthenium 106	368 days	2.4	0.07

@HVL (half value layer) in water is the extent to which radiation is absorbed in water; the value indirectly determines tissue penetrance.
*TVL (tenth value layer) of lead is the index of shielding required for protection

Thus, iodine plaques have good penetrance and require thinner shields, hence, are better for implantation.

Another advantage of Iodine Plaques is that they are customisable and the seed placement can be made according to the dimensions of the tumour.

4.2.5.4 *Dosimetry*

Inverse square law governs the radiation penetrance in the tissue. The dose rate falls more rapidly near the source of radiation than away from it. Thus the scleral dose to the apex of the tumour can be reduced by introducing space between the eye ball and the plaque. Normally, 35-40 Gy of radiation is to be delivered to the apex of tumour.

4.2.5.5 *Technique*

The technique of localizing the tumour is different in retinoblastoma compared to melanoma. This is due to the fact that in retinoblastoma, there is absence of pigmentation, hence a 'cold' plaque is first sutured on sclera and location verified. Once the correct position is verified, then the 'hot' plaque containing radioactive seeds is placed.

Dosage of 3500-4000 cGy is delivered to the tumour apex. The implant is kept in situ for 3-4 days. Maximal response to the radiation is obtained by 3 weeks. The regression pattern noted is similar to one seen with EBRT. The characteristic appearance is one of cottage cheese. There may be pigmentary changes and scar tissue around the regressed tumour.

The radiotherapy is administered by means of a saucer-shaped plaque, which has an inner, concave radioactive surface and an outer, convex protective shield. The plaques are made of gold, which helps to limit the radiation damage to surrounding tissues. I-125 seeds are made as titanium cylinders and these are stuck to the concave side of the plaque according to the plan decided by using the soft ware meant to calculate the dosage. Eye plaques are custom made to the dimensions of the tumor, usually ranging in size from about 12 to 22 mm. in diameter (about the size of a quarter). Careful calculations determine how long the plaque must remain in place to give the tumor the proper amount of radiation. Special plaques are available to treat tumors adjacent to the optic disc. These have a notch that permits the plaque to be placed next to the optic nerve.

Surgical placement of the plaque can be performed either under local or general anesthesia. The conjunctiva is opened at the limbus and the required extra ocular muscles are tagged. The location of the tumor is marked on the sclera using indirect ophthalmoscopy similar to the localization of a retinal break. Sutures are passed through the eye lets of the plaque and the sclera. The location of the plaque (cold) is confirmed in relation to the tumor. Then the cold plaque is replaced with the hot plaque. The conjunctiva is then sewn back over the plaque. All the radiation safety measures are taken as per the AERB (Atomic Energy Research Board) protocol. A lead shield is placed over the operated eye. Using the appropriate counter, the amount of radiation at 1 meter from the eye is measured. After the appropriate duration, the plaque is

removed. During this period, usually the patient stays admitted in a designated room to limit exposure of radiation to other people.

An exception to the general rule that the base of the tumour with 2mm tumour free perimetery has to be covered is made in juxtapapillary tumors. In that case a specially designed plaque with a 'notch' going around the optic nerve is placed. However problems like posterior tilting of plaque, uncertain dose distribution in these cases has resulted in higher recurrence rates.

The effects of radiation on the tumor typically are first evident three months after treatment. After radioactive plaque treatment, many patients note some dryness and irritation of the eye. In some instances, eyelashes may be permanently lost.

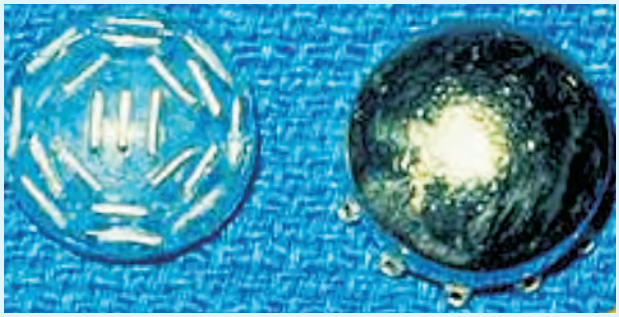


Figure1: Showing the front and back of a plaque

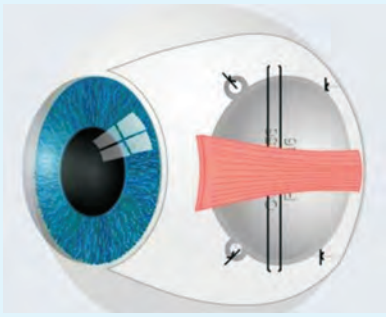


Figure 2: Showing a diagrammatic representation the eye

4.2.5.6 *Complications*

1. Cataract
2. Scleral necrosis
3. Radiation retinopathy
4. Optic neuropathy
5. Strabismus
6. Radiation Papillopathy

4.2.6 Thermotherapy

Thermotherapy involves focal heat generation using infrared diode laser to a sub-photocoagulation level to induce tumor necrosis. Thermotherapy via infrared radiation can be delivered through an operating microscope, indirect ophthalmoscope, or transscleral probe. Hyperthermia is achieved by either the more classic low temperature (40-46^0 C) long time-period (5-30 min), or by intense short bursts of heat. The delivery

is time-intensive and tedious; it involves a continuous period of tumor monitoring by the ocular oncologist as the temperature in the tumor is elevated and maintained. Often, a gray-white discoloration in the tumor is seen, indicating a successful take. Retinal vessels generally maintain their caliber during treatment, but retinal hemorrhage can occur. Thermotherapy may be used alone for very small tumors, or along with chemotherapy for larger tumors, where the combination may have a more potent effect (thermo-chemotherapy).

Complications of thermotherapy for retinoblastoma

- focal iris atrophy
- peripheral focal lens opacity
- retinal traction
- retinal vascular obstruction
- transient serous retinal detachment

4.2.7 Local chemo therapy:

Sub conjunctival chemotherapy is possible with administration of subtenon's injection of carboplatin. The dosage is 1.4 to 2.0 ml of 10mg/ml. Potential complications of the injection include fibrosis of the orbital tissue leading to more difficult enucleation, if such a procedure is required subsequently. Sub conjunctival carboplatin could be a useful addendum to the oncologist's armamentarium. Slow release of the drug is being attempted using admixture of fibrin sealant. Another drug being tried for local injection is 'Topotecan'.

To summarize

- **Retinoblastoma therapy is tailored to each individual case based on overall situation of ocular and/or systemic involvement.**
- **Focal therapy to individual tumor is to be delivered in order to preserve vision and possibly to avoid enucleation and external beam radiotherapy.**
- **Different types of focal therapies are Laser photocoagulation, Cryotherapy, Thermochemotherapy, Plaque brachytherapy ,Sub tenon's chemo therapy.**
- **Focal therapy can be given either trans sclerally or transpupillary.**
- **It can be given either as a primary treatment or concurrently with beginning of systemic chemotherapy and /or after 6 cycles of chemotherapy for focal consolidation.**

Section 5
Histopathology of retinoblastoma

5.1 Purpose:

To describe the processing of the enucleated eye in a case of retinoblastoma as well as the procedure for harvesting tumor tissue for molecular biological studies

5.2 Outline:

- External examination
- Harvesting the tumor tissue for molecular studies
- Grossing of the eye ball
- Sectioning
- Tissue processing
- Microscopic examination
- Histopathological high risk factors

5.2.1 External examination:

The patient details are confirmed from the requisition form and tallied with the details on the specimen. The enucleated eye is inspected externally for obvious evidence of any extra ocular tumor nodules, scleral discoloration, thickened optic nerve etc. The length of the optic nerve is measured by stretching the nerve.

5.2.2 Harvesting the tumor tissue for molecular biological studies:

- Fresh tumour tissue for molecular genetic studies should be harvested from unfixed globes immediately after enucleation. This can be done by ophthalmic surgeon or ocular pathologist.
- Optic nerve should be measured for length and cut margin should be obtained separately before opening the eye.
- First technique is opening of a window in the sclera by a trephine or using a sharp blade under stereoscopic or surgical microscope visualization. The site chosen is overlying the location of maximum tumour mass. Preferably, fresh tumour should be retrieved from areas without necrosis. Second technique is the aspiration of tumour by introduction of a 22-gauge needle under sterile conditions through the sclera posterior to the lens taking a slight oblique course under visual control. Once the needle is within the tumour, tumour material is

aspirated by connecting a syringe to the needle. In case of nonfriable tumour, a few milliliters of culture medium can be introduced, allowing dilution of the tumour material and facilitating aspiration. When the material is collected, an aliquot may be analyzed to evaluate the tumor cellularity of the aspirate.

- After tumour harvesting by any one of the methods, the eye is placed in sufficient 10% formalin to cover the globe and fixed.

5.2.3 Grossing of the enucleated eye ball:

- Proper fixation of eyeball is a crucial step in tissue processing. Ophthalmic surgeon must ensure that the tissue is put in 10% neutral buffered formalin. Volume of the fixative is about 10 to 15 times that of the volume of the biopsy specimen.
- At least 48 hours immersion in a fixative is required .
- Measurements taken include the corneal diameter, antero- posterior, horizontal and vertical globe diameters, and length of optic nerve (although the optic nerve length is already taken before fixation)
- Other features noted are the clarity of cornea, pupil and iris details

5.2.4 Transillumination:

- Performed with a bright point source of light in a dark room
- The tumor is silhouetted from outside and the same is marked with a tissue pencil
- The location is noted in relation to the limbus, optic nerve and in terms of number of clock hours.

5.2.5 Sectioning:

- The globe is placed in a wax filled tray
- Cross section of optic nerve: obtain a section from either the surgical margin of the optic nerve (the transected edge) or cut surface of optic nerve as it inserts the eye
- The eyeball is opened by a sharp blade taking pupil optic nerve axis .
    - The pathologist should hold the eyeball by left hand with cornea placed down against cutting block.
    - The blade is held between the thumb and middle finger of right hand. With sawing motion, eye is opened from the back 2-4 mm away from the optic nerve and moving to the front.

- The globe is opened in such a way that the pupil and optic nerve are in the same section.
- The section of the globe (called calotte) is then examined from anterior to posterior limits.
- Lateral calottes are also taken to see the choroidal involvement in histopathology. (Consult COG ARET 0332 Guidelines for tissue handling March 2008)
- Gross photographs are taken in dissecting microscope with camera/digital camera.

5.2.6 Internal Description:

- Number, size and location of the lesion are noted
- The mass is described with calcification if present
- Pattern of growth- exophytic, endophytic or both is noted.
- Seeding in the vitreous cavity and associated retinal detachment are also noted.
- High risk factors to be noted such as
  - Anterior chamber seeding
  - Iris and ciliary body infiltration
  - Choroidal infiltration
  - Invasion of optic nerve
  - Scleral and extrascleral extension

Most of these risk factors are better evaluated under the microscope although gross examination also gives some idea

5.2.7 Tissue Processing:

- The calottes are then put into cassettes and processing is done in automated tissue processor (ATP).
- In ATP, tissue undergoes series of dehydration and clearing and the entire process takes around 17 hours.
- Tissues are then embedded in paraffin in desired direction so that histological sections (using the automated microtome) can be obtained through a plane that contains all tissue layers including the area of pathology.
- Care should be taken to orient the block properly to prevent tears, folds and cellular distortion.
- Sections should be of adequate thickness (4-7 micron, average 5 micron). Ribbons of serial sections are taken and placed in clean and coated (Chrome alum) slides and then the slides are deparaffinised.

- Two or three sections should be mounted and placed for staining on each slide. Routinely, haematoxylin-eosin stain is done.
- At least eight slides for each specimen should be done which includes few pupil optic nerve sections, lateral calottes and separate transected optic nerve section.

5.2.8 Microscopic examination:

- Low power:
  - Basophilic mass (tumour zone) with eosinophilic areas (necrosis).
  - Multiple densely basophilic foci of calcification (can be stained with Alizarin Red or Von Kossa)
- High power-
  - Tumours show two different types of cellular characteristics-poorly differentiated and well–differentiated.
  - Poorly differentiated tumors are characterized by round cells with hyperchromatic nuclei and scanty cytoplasm with mitosis (Fig. 1).
  - Well-differentiated tumours are either rosettes or fleurettes . Rosettes can be Flexner-Wintersteiner or Homer-Wright rosettes (Figs. 2 & 3).
- Histopathological slides are documented by digital or manual photography.

5.2.9 Histopathological high risk factors predictive of metastasis:

- Anterior chamber seeding
- Iris infiltration
- Ciliary body infiltration
- Massive choroidal infiltration (Fig. 4)
- Invasion of optic nerve lamina cribrosa (Fig. 5)
- Retro-laminar optic nerve invasion (Fig. 6)
- Invasion at site of optic nerve transection
- Scleral infiltration
- Extra scleral infiltration

5.2.10 Some important issues:

- If the cut section of the optic nerve adjacent to the eye is negative for tumor, then it may be concluded that there is no involvement of the nerve posterior to the eye (the tumor extends through the nerve without skip lesions).
- Frequently, the surgical margin of the optic nerve (the cut edge of the nerve) is crushed by enucleation scissors. Pathologists should be aware of this crush artifact.

- If retinoblastoma is detected in a phthisical eyeball, pathologist should comment on the presence/absence of viable tumour cells and guide the oncologist accordingly.

5.2.11 Grading of choroidal Invasion: (Ref: COG ARET 0332 histopathologic guidelines of tissue handling):

I: Posterior uveal invasion absent
II: Posterior uveal invasion present
IIA: Largest dimension of intrachoroidal tumour on slide less than 1mm
IIB: Largest dimension between 1-3 mm
IIC: Largest dimension greater than 3mm (Massive)
IID: Posterior uveal tumour noted grossly (Massive)

It is termed 'massive or significant choroidal invasion', when the maximum diameter (thickness or width) of invasive focus of tumour measures 3mm or more in any diameter and, additionally, when most of the tumours reach at least the inner fibres of scleral tissue.

It is termed 'focal choroidal invasion' when the area of choroidal invasion is less than 3mm in any diameter (thickness or width) and not reaching the sclera.

5.2.12 *Typed reports should contain*

- The details of gross findings
- The details of microcopic findings
- Presence or absence of high risk factors
- Overall impression keeping in mind the TNM classification also.

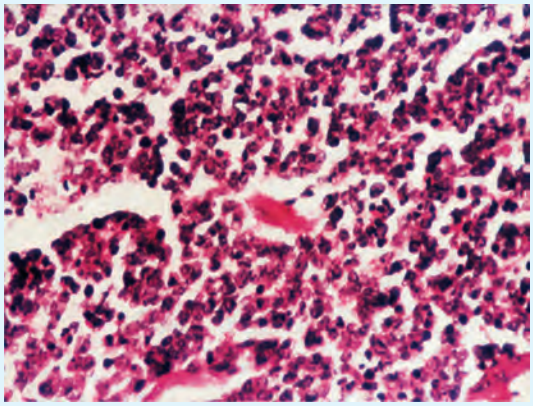


Figure 1: Poorly differentiated Retinoblastoma

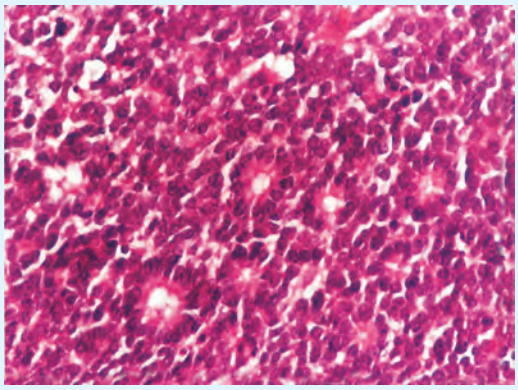
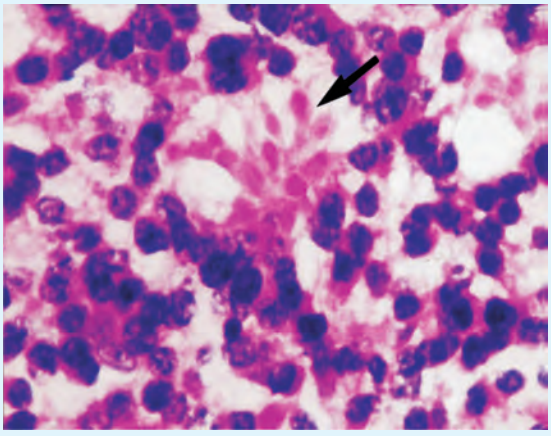


Figure 2: Well differentiated retinoblastoma, Flexener wintersteiner Rosettes

Figure 3: Fleurettes in Well differentiated Retinoblastoma



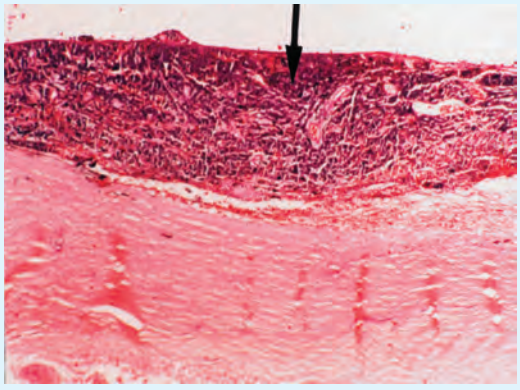


Figure 4: Massive Choroidal invasion

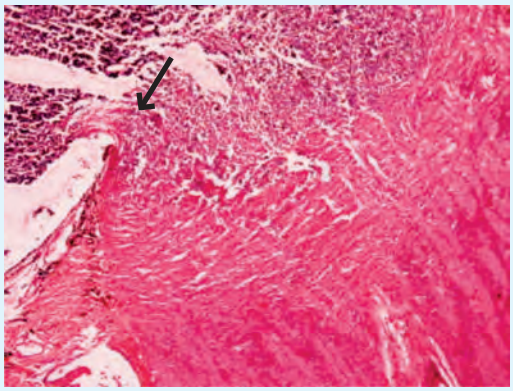
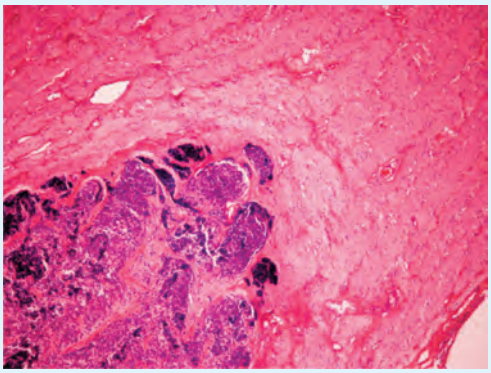


Figure 5: Pre-laminar invasion of optic nerve (arrow points to lamina cribrosa)

Figure 6: Invasion of optic nerve (Post lamina cribrosa)



To summarize

- Enucleated eyeball of retinoblastoma patient should have optimum optic nerve and there should be minimum manipulation during surgery and handling.
- Harvesting tumour tissue for molecular biology studies should be done prior to processing for histopathological studies.
- High risk factors should be seen both during the grossing and microscopic studies.
- Histopathological report should contain grossing, microscopic description, presence or absence of high risk factors including points for TNM classification to enable ophthalmologist and oncologist to guide future treatment.

Section 6
RB Imaging

6.1 Purpose: To provide guidance on the role of imaging (ultrasound, CT scan and MRI) in overall management of retinoblastoma.

6.2 Outline: This chapter will be covered under the following heads

- Preamble
- Ultra sound
- Computerised tomography
- Magnetic resonance imaging
- When and how frequently to image

6.2.1 Preamble: Diagnosis of retinoblastoma is mainly clinical- based on indirect ophthalmoscopy. Imaging in children is required to confirm the diagnosis and stage the disease. Until recently, Computed Tomography was considered the imaging of choice due to its sensitivity to detect calcification that is seen in 80 % of the cases. With increasing awareness of sensitivity of children to radiation especially familial retinoblastoma, the policy is to do a contrast enhanced Magnetic Resonance Imaging. Both these modalities have their advantages and disadvantages and at times can compliment each other.

6.2.2 Ultrasound:

Ophthalmic ultrasound is used to measure the parts of the eye, document pathology such as tumors, and examine inside the eye. The sound frequency emitted from the probe determines the resolution and depth of penetration. For evaluation of intra ocular tumors, a 10 MHZ probe is usually used.

Evaluation is commonly done using A-Scans and B-Scans.

6.2.2.1 *A- Scan*

A-Scan is a one-dimensional display of echos. The tissue characteristics dictate the acoustic impedance and depending on the tissue interfaces, the intensity of the echo varies and is represented by the height of the A-scan. In relation to retinoblastoma, presence of calcification is often inferred from the very high spikes generated by the calcium.

6.2.2.2 *B- Scan*

B- Scan gives two dimensional display with brightness of each pixel indicating the reflectivity at that point. Tumour and calcification can be identified. Tumor dimensions can be recorded which are important for assessing the response to treatment.

6.3 Computed tomography

- Can be done as the initial diagnostic tool in patients with moderate sized tumors.
- Not useful in non-calcified or diffuse retinoblastoma
- Not very useful in scleral invasion/ optic nerve infiltration or intracranial disease.
- Sedation if required, with pedichloryl 50 - 75 mg/ kg body weight (maximum 2g), should be given. Contraindicated in renal and hepatic impairment and severe cardiac disease.

6.3.1 Protocol for CT- Spiral CT

- KV – 100 -110 Kv
- mA – 90 – 100
- Time – 0.8 – 1.0 sec rotation time
- Slice thickness – 2 mm
- Pitch 1.5 : 1
- Reconstruction interval – 0.5 – 1.0 mm (for good reformations)
- Scanning plane - - 5 to -10 degree to the orbito-meatal line or no tilt
- Scan coverage – hard palate to above roof of the orbit
- Coronal and Sagittal reformations – no need for direct coronal
- Curved reformations for comparing both optic nerves
- Contrast indicated in optic nerve invasion, intracranial disease and extraocular extension.
- Post contrast same protocol as above.
- Non –ionic contrast at 1 ml/ kg body weight (concentration 300 mg iodine / ml)
- Contrast contraindicated in renal disease and previous sensitivity to contrast.

6.3.2 Features on computed tomography:

- Hyperdense intraocular lesion with calcification.
- Calcification can be – single, multiple, fine speckled or clump like

- Optic nerve invasion – thickened optic nerve or asymmetry of the optic nerves
- Intracranial (trilateral retinoblastoma) – suprasellar and pineal region masses
- Subarachnoid spread suspected if there is effacement of cisterns or sulcal space with abnormal contrast enhancement.

6.4 Magnetic resonance imaging:

MRI is the primary mode of imaging recommended for retinoblastoma. It facilitates the identification of optic nerve invasion and extra ocular extension. Although MRI is done as a routine at presentation and diagnosis, it is especially indicated in cases with large tumors, tumors close to or invading the optic disc. It is also important for children with bilateral disease since they are at risk for pineoblastoma (trilateral RB) and should be screened once every 6 months until 5 years of age, since an early diagnosis may be more treatable.

6.4.1 Protocol:

Dedicated surface coil with post gadolinium imaging is recommended if the child co-operates.

6.4.2 Brain imaging – Head coil

- Axial FLAIR – sensitive to subarachnoid disease
- Post contrast – Axial T1 spin echo

6.4.3 Both orbits- using head coil

- axial T1 spin echo and axial T2 fast spin echo – 3 mm slice thickness 0.5 sp , FOV – 22 x 22 cm,
- Coronal T1 spin echo and T2 Fast spin echo 2- 3 mm slice thickness
- Oblique sagittal T2 fast spin echo - parallel to optic nerve

6.4.4 Eye imaging – dedicated 3 inch surface coil

Head tilted 45 degrees

- Axial 3D T1 FSPGR 1.5 - 2 mm slice thickness
- Axial 3D T2 FRFSE 1.5 -2 mm slice thickness
- Coronal T1 FSPGR 1.5 - 2 mm slice thickness
- Coronal 3D T2 FRFSE 1.5 -2 mm slice thickness
- Sagittal 3D T2 FRFSE 1.5 -2 mm slice thickness
- Post contrast axial, coronal and Sagittal 3D FSPGR fat sat

FOV – 16 - 18 cm

Spine post contrast if subarachnoid disease seen in brain imaging

Contrast: Gadolinium - DTPA 0.1mmol/kg is the recommended dose

6.4.5 Magnetic Resonance imaging features:

- Lesion is intermediate or hyperintense in T1 weighted images and has hypointense signal in T2 weighted images with respect to vitreous.
- Moderate enhancement post contrast.
- Tumors less than 2 mm cannot be identified.
- Choroidal invasion – suspected when normal uniform enhancement of the choroid is replaced by inhomogenous enhancement.
- Scleral invasion suspected –when normal low signal intensity of the sclera is replaced with altered signal.
- Optic nerve invasion- Seen as enhancement or irregularity of the optic nerve. But cannot identify pre laminar invasion.

6.5 When and how frequently the imaging should be done:

- At the first visit.
- In cases with optic nerve invasion on HPE- prior to 4th cycle of chemotherapy and once every 6 months for 2 years from diagnosis.
- In cases of orbital recurrence, every 6 months for 3 years
- In bilateral cases, MRI should be performed every 6 months until the child is 5 years of age

6.6 PET SCAN: If available, PET Scan may be helpful in extra ocular retinoblastoma to detect metastasis:

Key points:

1) MRI is preferred modality of imaging now, however it is not cost effective in many developing countries.
2) CT scan is used only for planning of EBRT .

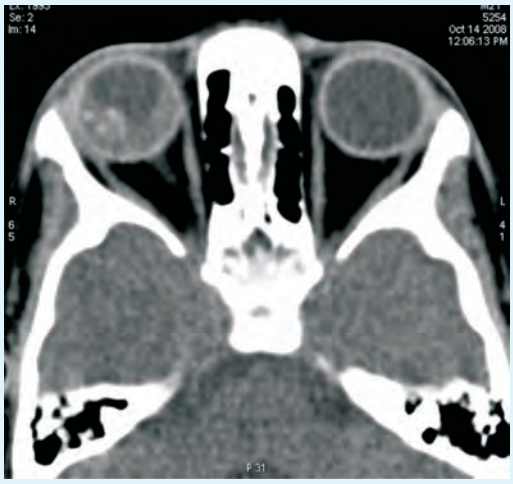


Figure 1: Axial CT scan of the orbit showing hyperdense mass in the right eye with multifocal calcifications in the temporal quadrant.

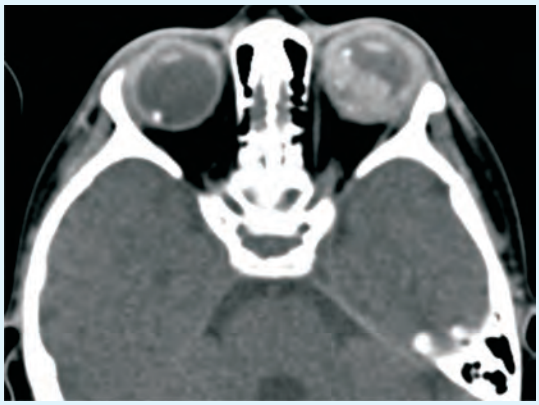


Figure 5: Axial CT scan of the orbit showing bilateral retinoblastoma with multifocal calcification in the left eye.

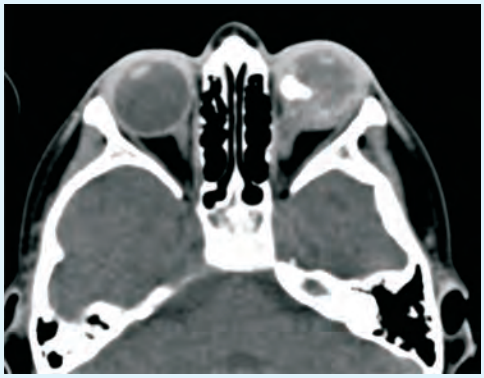


Figure 5: Axial CT scan of the orbit showing retinoblastoma in the left eye with clump of calcification and optic nerve invasion.

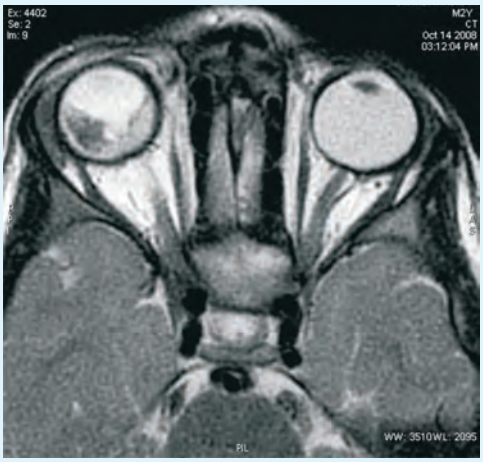


Figure 4: Axial T2 weighted image of the orbit showing an irregular T2 hypointense right intraocular mass lesion with associated retinal detachment.

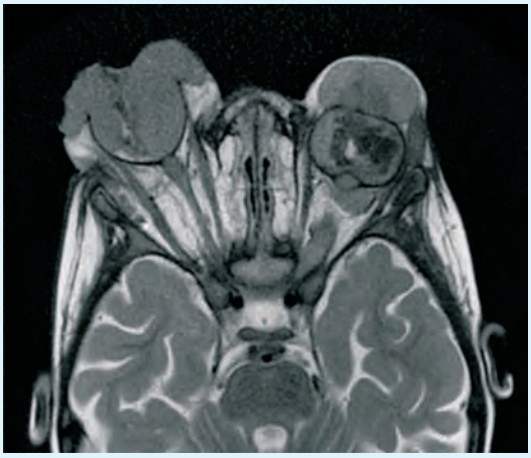


Figure 5: Axial T2 weighted image of the orbit showing bilateral retinoblastoma with extraocular extension and optic nerve invasion

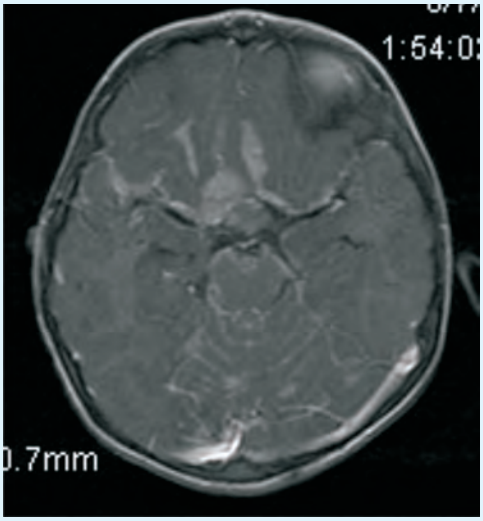


Figure 5: Axial T1 post contrast image of the brain showing extensive subarachnoid deposits enhancing with contrast (arrow)

Section 7

External Beam Radiotherapy (EBRT) for retinoblastoma

7.1 Purpose:

To describe the indications, planning and administration of EBRT in retinoblastoma.

7.2 Outline:

- Indications
- Planning
- IMRT, stereotactic radiation and Proton beam radiation
- Sequelae of EBRT

7.2.1 Indications:

1. Adjuvant after enucleation with optic nerve involvement, scleral involvement and orbital extension.
2. Spontaneous or accidental ocular perforation and if there has been a breach of the vitreous
3. Failed focal therapy
4. Residual tumor following chemoreduction- failure of chemotherapy
5. Large tumors with vitreous seeding.
6. Recurrent disease
7. Palliative radiotherapy

7.2.2 Planning of radiotherapy:

The aim is to deliver a homogeneous tumoricidal dose to the entire retina and vitreous while sparing the surrounding normal tissue. The reasons for this target volume are:

1. In RB, all cells have neoplastic potential
2. Vitreous seeding can occur
3. Multiple lesions could be present
4. Sub retinal spread of tumor can occur

Planning is done using CT scan with immobilization device.

Treatment is done under general anesthesia

Anterior and lateral oblique portals are used for treatment of one eye, while parallel oppose portals are used for treatment of both eyes.

7.2.2.1 *Total dose:*

1. A total of 40Gy/20 fractions/5 weeks. Children who have had chemotherapy may only require 26-30 Gy, since anything more will damage the retina and impair vision.
2. Dose per fraction should be 2Gy
3. Requires special expertise in Pediatric Radiation therapy

Brachy therapy is covered in the section on Focal therapy.

7.3. IMRT, 3D conformal radiation therapy, Stereotactic radiation therapy and Proton beam radiation therapy:

These innovations in the delivery of radiation permit safer treatment of retinoblastoma while trying to reduce the exposure of radiation to normal structures and bone.

Intensity modulated radio therapy (IMRT) perhaps permits greatest reduction in the dosage of the radiation to the orbit and the lacrimal gland while permitting therapeutic dosage to the retina up to the ora serrata and the vitreous.

7.4 Sequelae of EBRT

1. Skin and Adnexa : Loss of hair, eyelash.
2. Corneal injury
3. Cataract
4. Vascular damage in retina and choroid
5. Risk of second malignancy (sarcomas),
6. Stunted orbital growth

To summarize

- Not used as primary modality because of side effects and complications.
- Only used as an adjunct therapy
- The dose of radiation needed is less when used in conjunction with chemotherapy.

Section 8

Systemic chemotherapy in the management of Retinoblastoma

8.1 Purpose: To describe the indications of chemotherapy in retinoblastoma, the drugs of choice, modes of administration and the toxicity.

8.2 Outline:

- Definition
- Aims of chemotherapy in retinoblastoma
- Indications for chemotherapy
- Common chemotherapeutic drugs used
- Drug delivery protocols
- Newer approaches
- Drug administration
- Drug toxicity
- Dose modification

8.2.1 What is systemic chemotherapy?

Chemotherapy uses anticancer drugs that are administered intravenously, intra muscularly or orally. Systemically administered chemotherapy attains good concentration in the eye and hence are of use in treating retinoblastoma. In some cases, chemotherapy is given by intrathecal injection (into the spinal fluid) to treat extended Retinoblastoma

8.2.2 What are the aims of chemotherapy in retinoblastoma?

- Increase eye salvage and avoid enucleation.
- Avoid external beam radiation therapy and thus reduce the risk of second malignancies due to radiation.
- The priority is firstly, to preserve the life of the child; secondly, to preserve vision, and thirdly, to minimize any complications or side effects of treatment.
- The considerations while selecting treatment options for a child with retinoblastoma are as follows:
    - Is the disease unilateral or bilateral?

- Does the affected eye have potential for useful vision
- Is the tumor confined to the globe or does it extend to the optic nerve?
- Is there orbital/ lymph-nodal/ bony/ central nervous system or, hematogenous spread?

8.2.2.1 *What does the term "chemo reduction" mean?*

Intravenous chemotherapy is used to shrink the volume of the tumor, thus facilitating focal treatment with less invasive procedures such as cryo therapy, laser photocoagulation, or plaque radiotherapy. This has been shown using three drug chemotherapy with vincristine, carboplatin and etoposide.

8.2.2.2 *When to give chemotherapy?*

- Adjuvant therapy: Administration of chemotherapeutic agents systemically after removal of primary tumor with no evidence of residual disease only in patients who have evidence of high risk features such as massive choroidal invasion or retrolaminar tumor with any choroidal disease.
- Neo-adjuvant therapy or anterior chemotherapy is what chemoreduction implies. Chemotherapy is given to localize a disseminated disease. Neo adjuvant therapy can be given prior to enucleation in eyes with evidence of optic nerve spread. The histopathological evaluation however is affected due to the chemo therapy.

8.2.3 Chemotherapy may be useful in the following clinical settings:

- Intra-ocular retinoblastoma
- Extra ocular Retinoblastoma
- Recurrent Retinoblastoma
- Trilateral Retinoblastoma
- Palliative care of Retinoblastoma

8.2.4 What are the common chemotherapeutic drugs used?

While chemotherapeutic agents vary according to the preference of the pediatric oncologist, most of the current studies have relied on vincristine, etoposide and Carboplatin. To circumvent the multidrug resistance, cyclosporine has been added to chemotherapy at some centers.

Drugs used in chemotherapy of RB

Drug	Vincristine	Platinum cisplatin / carboplatin	Epipodophyl-lotoxins Etoposide/ Teniposide	Taxanes	Topote-can	Cyclo-phos ph-amide
Source	Periwinkle plant	First introduced in 1961	extracts of May apple (1946-1960)	Bar of pacific yew extract (1971)	Synthetic derivative of camp-tothecin	World war II
Mode of Action	Microtubu-lar inhibition	Platinum complexes can react with DNA forming both intra- and inter strand cross links.	DNA Topoi-somerase II inhibitor	Microtubu-lar inhibi-tion	DNA Topoi-somerase I inhibitor	

8.2.5 Protocols for chemotherapy administration:

8.2.5.1. *Two drug chemotherapy protocol for intraocular unilateral Retinoblastoma*

This involves use of Vincristine and carboplatin

Early intraocular Retinoblastoma –especially unilateral, of Reese- Elseworth group I, II, III and International classification Groups A, B can be given 6-8 cycles of chemotherapy with two drugs - Vincristine and carboplatin. In all chemotherapy protocols, local consolidation is a must since chemotherapy rarely ever totally eradicates the tumor except for very small tumors.

8.2.5.2. *Three drug CEV protocol:*

Indication: Intra ocular Retinoblastoma Reese Ellsworth II and III and International Classification Group C.

Protocol: Treatment schema for adjuvant chemotherapy includes 6 cycles of standard CEV given every 28 days.

Day 1 Inj. Vincristine 0.05mg/kg IV - PUSH

Inj. Carboplatin 18.6mg/kg IV infusion

Inj. Etoposide 5mg/kg IV infusion

Day 2 Inj. Etoposide 5mg/kg/IV infusion

8.2.5.3. *High dose three drug CEV cycle along with local administration of carboplatin:*

Indications: for Groups C, D

Protocol: High dose CEV given every 28 days for 6 cycles. (Radiotherapy may be indicated if there is only some response; In that case, a lower dose, 26-30Gy is recommended for adjuvant therapy.) This protocol requires the administration of growth factor (GCSF) for 7-10 days following chemotherapy beginning on Day 2.

Day 1	Vincristine 0.05mg/kg IV PUSH
Day 1 and 2	Carboplatin 14 mg/kg IV infusion
	Etoposide 6mg/kg IV infusion
	Sub-tenon Carboplatin Day 0 to 1
	20mg/dose in courses 2-4

8.2.5.4. Dose calculation for infants: For all infants less than 10 kg, the drug doses will be calculated according to the formula: (m^2/30) x weight in kg.

8.2.5.5 *Chemotherapy of bilateral retinoblastoma:*

Standard 3-drug or high dose CEV protocol (depending on the intraocular stages). The total number of cycles will depend upon the regression of the tumor as assessed periodically under anesthesia, but at least 6 cycles is recommended. The eye that responds less well may need to be enucleated if there is no chance for useful vision, or lower dose radiotherapy 26-30Gy may be added as an adjuvant.

8.2.5.6 *Extra ocular retinoblastoma treatment:*

A. Bone marrow metastasis
B. Brain metastasis
C. Local orbital and lymph node metastasis

8.2.5.7. *Treatment of Metastatic retinoblastoma -overview*

Metastatic retinoblastoma has been treated with Intensive chemotherapy, consolidation with mega therapy and autologous stem cell rescue.

Chemotherapy included courses of carboplatin and Etoposide alternating with Carboplatin/Cisplatin, Etoposide, Cyclophosphamide. Radiation therapy to areas of bone metastasis may be given. Conditioning regimen may include thiotepa (900mg/m) or Etoposide(40mg/kg),and Carboplatin (1.5g/m2), orBCNU(300mg/m), Cyclophosphamide(6.8g/m) and/or etoposide (1.6g/m)

The survival in Metastatic Retinoblastoma is poor. Some long term survivors have been reported. Patients with metastatic disease without CNS disease survived better,

8.2.5.7 *A. Bone marrow metastasis*

Induction (4 cycles)

- Day 0: Cisplatin 3.5 mg/kg, vincristine 0.05 mg/kg
- Day 1,2: Cytoxan 65 mg/kg, Etoposide 4 mg/kg IV

Consolidation Carbo/VP/Thiotepa

Radiotherapy- Involved field radio therapy to bulky sites

Autologous stem cell rescue

8.2.5.7 *B. Brain metastasis*

Induction (4 cycles)

- Day 0: Cisplatin 3.5 mg/kg, vincristine 0.05 mg/kg
- Day 1,2: Cytoxan 65 mg/kg, Etoposide 4 mg/kg IV

Consolidation - Carbo/VP/Thiotepa

Radiotherapy- Involved field radio therapy to bulky sites

Autologous stem cell rescue

8.2.5.7 *C. Local orbital and lymphnode metastasis*

Induction (4 cycles)

- Day 0: Cisplatin 3.5 mg/kg, vincristine 0.05 mg/kg
- Day 1,2: Cytoxan 65 mg/kg, Etoposide 4 mg/kg IV

Consolidation- Carbo/VP/Thiotepa

Radiotherapy- Involved field radio therapy to bulky sites

No Autologus stem cell Transplantation

8.2.5.8 Cisplatin and Teniposide based protocol

Induction chemotherapy: 3 cycles of with Cisplatin and teniposide, followed by maintenance with same drugs alternating with Cyclophosphamide, vincristine, and doxorubicin every 21 days for 60 weeks.

Surgery:- Exenteration with eye lid preservation Exenteration is recommended only if there is no other way to control extraocular disease. This is a highly morbid procedure.

Radiotherapy : Orbital Radiotherapy 45 cGy is given

Intrathecal Triple Therapy:- Intrathecal therapy with Triple drugs Methotrexate, Cytarabine, and dexamethasone was given .

8.2.5.9 *Ifosphamide and etoposide based protocol:*

Induction chemotherapy- 3 cycles of ifosfamide and Etoposide followed by maintenance with same drugs, alternating with Cisplatin and teniposide every 21 days for 36 weeks

Surgery: Exenteration with eye lid preservation. Rarely is exenteration needed; RT is preferred to control extraocular disease.
Radiotherapy:-Orbital Radiotherapy 45 cGY was given

8.2.5.9.1 Intrathecal Triple Therapy: Intrathecal therapy with triple drugs namely methotrexate, Cytarabine, and dexamethasone is given

The addition of Ifosphamide/Etoposide to chemotherapy with Cisplatin /teniposide improves the survival

8.2.5.10 *Thermo chemo therapy:*

This was first introduced by Murphree et al. The therapy involves administration of platinum group of drugs (carboplatin) intravenously followed 15- 30 minutes later by administration of diode laser in continuous exposure format to the tumor raising the temperature by 9 degrees centigrade. The levels of carboplatin were seen to have doubled with this treatment. The treatment is preferred in RE groups I to IV. Larger tumors respond less and may need prior chemo reduction with CEV protocol.

8.2.5.11 *Chemotherapy for macular tumors:*

Direct focal treatment of macular tumors is associated with significant visual morbidity. Chemo reduction facilitates saving as much of functional retina as possible before local treatment with thermo therapy is administered. Reports of up to 83% tumor control have been reported over a follow up of 4 yrs. Like tumors elsewhere in the retina it is realized that only chemoreduction cannot cure most of the cases and serial local aggressive therapy is needed to achieve long term control.

8.2.5.12 *Chemotherapy for trilateral retinoblastoma:*

Trilateral retinoblastoma is usually fatal despite chemotherapy. Dunkel et al, 2000 have shown a cure in 5 of 13 patients with intensive high dose chemo therapy and autologuous hematopoietic stem cell rescue. Induction was with vincristine, etoposide, carboplatin and cyclophosophamide and high dose protocol was based on thiotepa, melphalan or cyclophosphamide.

8.2.6 Newer approaches:

8.2.6.1 *Topotecan*:

Topotecan is a semisynthetic derivative of camptothecin and is an inhibitor of DNA topoisomerasel. Periocular delivery of this has been tried for retinoblastoma. Topotecan loaded ocular delivery system using polymer implants can deliver 50% of the drug load in 48 hours (Chantada et al). Experimental studies in albino rats have

shown high levels of drug in the vitreous both when administered peri ocularly and intra venously (Caracabaso et al). Tsui et al have administered the drug in fibrin sealant and found the release of the drug to occur over 3 weeks and having affect on contra lateral eye as well indicating hematogenous dissemination rather than trans scleral. Laurie et al have shown the efficacy of combination of topotecan with carboplatin in rodent models

8.2.6.2 *Melphalan:*

Melphalan has been tried as intra vitreal injections (10 micrograms) in eyes with vitreous seeds by Kaneko et al with reported success. However the administration intra ocularly is considered controversial at this point of time. Melphalan has also been administered by selective ophthalmic artery catheterization (40mgs) coupled with hyperthermia by Abramson et al.. 2 to 6 infusions were given in the same eye with minimal ocular and systemic toxicity. The dose administered is 10% of the usual systemic dose. 2 of the 9 eyes so treated had recurrence and needed enucleation.

Note: There is no evidence that this therapy has resulted in preservation of vision. Therefore, this should not be advocated outside of a highly investigational setting. If vision cannot be salvaged, then enucleation is the preferred therapy.

8.2.7 Administration of chemotherapy

Treatment protocols have different schedules, but usually the cycles are repeated once in 3-4 weeks. The chemotherapy is usually administered on ambulatory basis but in some cases over 24 to 48 hours in hospital.

8.2.7.1 *Pre chemo therapy evaluation:*

General examination specifically to rule out any infection. The following tests may be preformed;

1. Complete hemogram including absolute neutrophil and platelet count
2. Urine analysis
3. Baseline hepatitis and HIV status (before the first cycle)
4. Liver and kidney function tests (during the course of therapy)

8.2.7.2 *Evaluation during chemotherapy*

The leucocyte count is lowest in the second and third weeks after a cycle of chemo therapy. The counts should be tested before every cycle and one should look for any signs of infection. Children who develop fever and have low neutrophil counts should be cultured and treated with intravenous antibiotics until the culture is negative. G-CSF may be required in cases where there is unusual delay in recovery of counts.

8.2.8 Drug toxicity

8.2.8 I. *Vascular toxicity:*

1. Direct endothelial damage

a. Vesicant drugs- Vinca alkaloids, Anthracyclines (doxorubicin)
b. Hepatic veno occlusive- cyclophosphamide

2. Vasospasm

a. Cerebral ischemia - cisplatin
b. Raynaud's phenomenon- Bleomycin, Vinca alkaloids, Cisplatin

3. Fibrinolytic factor deficiency

a. Protein C and S deficiency –Cyclophosphamide

4. Platelet aggregation and von willibrand factor

a. Increased von Willibrand factor vWf antigen- Cisplatin
b. Qualitative changes in vWF- Vincristine

8.2.8 II. Ocular toxicity:

1. Alkylating Agent

Cyclophosphamide (Blurred vision, Blepharo conjunctivitis)

2. Antibiotics

Doxorubicin (Conjunctivitis, Increased lacrimation)

3. Plant Alkaloids

Vinblastine, Vincristine (Cranial nerve palsies, Optic neuropathy, Transient cortical blindness)

8.2.8 III. Hyper sensitivity reactions to chemo therapy (Gell and Coombs classification):

Allergic reactions can occur after taking almost any drug (including chemotherapy). They can occur immediately or can be delayed. If severe, the drug will need to be discontinued. If mild, anti allergy treatments can be instituted and one can proceed with chemotherapy. Patient is to be informed that If they notice skin rashes, weakness while standing or sitting, progressive swelling or any unusual changes, they should contact their physician immediately.

Drugs	Type of Reaction	Frequency	Probable Reaction
1. Anthracylines antibiotics (Doxorubicin)	I	Varies <1%	Unknown
2. Etoposide	I	Case reports	Non-specific
3.Cyclophosphamide	I	Case report	IgE
4. Ifosfamide	I	Case report	Unknown
5. Vincalkaloids(VCR)	I	Case report	Unknown

8.2.8 IV. Extravasation injury:

Can occur with Doxorubicin, Vinblastin, VP16, Cisplatin

8.2.8 V. Neurotoxicity:

Agent	Neurotoxicity
1. Alkylating agents -Cyclophosphamide - Ifosamide	SIADH (rare) Encephalopathy, confusion, lethargy, coma, psychosis, seizures (commonly with high dose and reversible), ataxia, cranial neuropathies, peripheral neuropathy (uncommon)
2. Plant alkaloids - Etoposide (VP 16)	Peripheral neuropathy (uncommon at usual doses) of exacerbate neuropathy of vincristine, Cisplatin encephalopathy, confusion, somnalescence, seizures at high does.
- Vincristine	Peripheral neuropathy, areflexia, distal sensory loss, motor weakness, foot drop, ileus, constipation, impotence, urinary retention, postural hypotension, muscle pain, cranial neuropathy, optic atrophy, diplopia, VI nerve palsy, VII nerve palsy, encephalopathy, seizure is dose related and reversible.
3. Antibiotics Doxorubicin IV usual dose Intra thecal	None Severe fatal myelopathy, Encephalopathy, cerebral damage, ant. Horn cell loss after experimental injection into peripheral nerve.

8.2.8 VI. Bone marrow depression

Bone marrow depression (suppression) is a side effect caused by certain chemotherapy drugs. It includes anemia, leucopenia and thrombocytopenia . Typically it happens 7-10 days after the chemotherapy is started and usually recovers after 3 weeks. G-CSF and Pegalated G-CSF can speed bone marrow recovery. Due to low white cells there can be infections due to bacteria, fungi and other organisms. They may develop febrile neutropenia which will require broad spectrum antibiotics and anti fungals. The infections due to Pneumocystis carinii have to be kept in mind and a prophylaxis containing co-trimoxazole could be started along with chemotherapy. Platelets may be required for transfusion if critically low and 'Packed cells' could be transfused if the hemoglobin level is severely low.

8.2.8.VII. Mucositis:

Chemotherapy can cause mucositis of the mouth and throat. One should watch for redness of the mouth and development of white patches due to candidiasis. Mouth Care should be done after every meal and at bedtime.

- Regular, gentle cleaning of the teeth
- Mouth should be rinsed with a mixture of 1/2 teaspoon of salt in 8 ounces of water or 1/2 teaspoon of sodium bicarbonate (baking soda) in 8 ounces of water.
- Avoid alcohol containing mouthwash
- Avoid acidic or spicy foods
- Avoid drinking alcohol and smoking

8.2.8.VIII. Prophylaxis

- Oral Sulfamethoxazole and trimethoprim; *cotrimoxazole* (Bactrim, Septra), is given thrice a week to prevent **Pneumocystis pneumonia** (**PCP**) but being a source of opportunistic infection, it can cause a lung infection in people who are immunosupressed.
- Hepatitis B vaccination and Chicken pox vaccination to be given before the start of therapy when the child is undergoing initial investigations.

8.1.8. IX. Nausea and Vomiting:

The causes of nausea and vomiting in a child who is undergoing chemotherapy are due to chemotherapy itself, stress, radiation of the brain, and anesthetics (associated with surgery).

The primary treatment for nausea is anti-nausea drugs. Anti emetic should be taken 1 hour before chemotherapy, and continue the anti emetics for 2-3 more days.

Large meal and carbonated beverages are avoided. Food with a lot of residue, salads, high fiber cereals or fatty and fried foods are also avoided. Light meals are recommended on the day of chemotherapy.

Other methods to manage nausea and vomiting include: acupressure wrist bands (which are available at most drug stores), fasting for a couple of hours before treatment. Keeping the eyes open, and slow deep-breathing through nose also helps. If nausea and vomiting persist, the patients may need to receive intravenous (IV) fluids and electrolytes.

8.2.8 X. Long term toxicity

Second malignancies- Although radiation is mostly associated with risk of second malignancies, chemotherapy can also be associated with this risk. However, there is no evidence that chemotherapy increases the risk for second malignancies in hereditary retinoblastoma, although there is much evidence that RT increases the risk of second malignancies three-fold over that which occurs secondary to the genetic mutation. Secondary leukemia has been reported with etoposide to the extent of 2 to 3% (Pederson and Jergaard et al (1991), Smith et al (1999); this risk occurs when the drug is given once or twice weekly, but not as prescribed in the protocols recommended for RB. Platinum compounds also have been associated with this risk although to a less extent (Travis et al 1999)

8.2.9 Dose modification

8.2.9.1 *Renal failure and dose modification:*

Based on the Glomerular filtration rate (GFR), the dose of the following drugs is modified:

Drug	>60ml/min	30-60 ml/min	10-30 ml/min	<10ml/min
Cisplatin	No change	50	Omit	Omit
Cyclophosphamide	No change	No change	No change	50
Nitrosoureas	No change	Omit	Omit	Omit

Most other drugs including Doxurubicin, Etoposide, Carboplatin, Vinblastine, Vincristine, and Melphalan do not need any dose modification.

8.2.9.2 *Hepatic dysfunction and dose modification:*

Bilirubin (mg/dl)	SGOT (IU/L)	Doxorubicin	Vinblastine, vincristine VP-16	Cyclophosphamide
<1.5	<60	100%	100%	100%
1.5-3.0	60-180	50%	50%	100%
3.1-5.0	>180	25%	Omit	75%
>5.0		Omit	Omit	Omit

8.2.9.3 *Haematological findings and dose modification:*

Leucocytes (per mm^3)	Platelets (per mm^3)	Dose (%)
Over 3,000	Over 150.000	100
2,500-3,000	100,000-150,000	75
2,000-2,500	75,000-100,000	50
Below 2,000	Below 75,000	Stop

To Summarize,

- Systemically administered chemotherapy attains good concentrations in the eye
- Systemic chemotherapy may be administered upfront to reduce the size retinoblastoma and make the tumor amenable to local consolidation
- Six cycles of standard CEV cycles are given to enucleated eyes with low risk histopathology
- Six high dose CEV cycles may be given to Group D and enucleated eyes with high risk histopathology . The number of cycles will depend on the regression patterns shown in the examination under anaesthesia .
- Extra ocular and recurrent retinoblastoma need intensive chemotherapy and remissions can be achieved in some cases. Radiotherapy is also indicated
- Metastatic retinoblastoma and trilateral retinoblastoma have a poor prognosis
- The common toxicity like nausea and vomiting can be taken care of with anti emetics given for 2-3 days post chemotherapy
- High dose chemotherapy and intensive protocols may give rise to febrile neutropenia which will need admission of the patients to the hospital and IV broad spectrum antibiotics are given till the bacterial and fungal cultures are sterile.

Section 9
Metastatic survey- when and how

9.1 Purpose:

To describe the metastatic work up of a patient with retinoblastoma in terms of the extent of investigations to be performed and their timing and frequency.

9.2 Outline:

- Routes of spread of retinoblastoma
- Common sites of metastasis
- Work up at presentation
- Work up after enucleation
- Work up during follow up.

9.2.1 Routes of spread of retinoblastoma:

1. Direct infiltration of the optic nerve and then into the brain
2. Dispersion into the subarachnoid space and the CSF.
3. Haematogenous metastasis secondary to involvement of the Choroid
4. Local extension to the sclera and then the orbit and bones.
5. Lymphatic spread secondary to invasion of the conjunctiva and eyelid

9.2.2 Sites of distant metastases:

- Central nervous system
- Lymph nodes (pre auricular and cervical nodes)
- Bone marrow (Skeletal System)
- Lung

9.2.3 Metastatic work up at presentation:

Metastatic work up at presentation is required only under special conditions as in frank orbital retinoblastoma and cases where optic nerve head is not visible. The work up includes:

1) Clinical history relevant to metastatic disease such as visible lumps any where in the body.

2) General physical examination
   a. Look for lymphadenopathy- especially involving pre auricular and cervical nodes.
   b. Look for hepatosplenomegaly
   c. Look for any bony swelling
3) Blood counts
4) Chest X- ray
5) Ultra sonography of the abdomen (optional)
6) CT / MRI of the orbit and brain (MRI preferable)
   a. In addition to primarily identifying the tumor, calcification etc, these imaging studies help in identifying extra scleral extension as well as trilateral retinoblastoma (pineal gland tumor).
7) A more detailed physical examination is possible under general anesthesia
   a. Enables detailed evaluation of the ocular condition keeping in mind the risk factors for metastasis such as anterior chamber involvement, lesions close to and involving the optic disc etc.
8) CSF and bone marrow evaluation are performed based on the individual perception of risk of metastasis in a given case .

9.2.4 Metastatic work up following enucleation:

The enucleated eye is evaluated for histopathological risk factors for metastatic disease. It is understood that all attempts have been made to achieve more than 10 mm of length of optic nerve.

HPE factors evaluated:

1. Disease at the cut end of the optic nerve.
2. Anterior chamber disease
3. Choroid involvement
4. Tumour beyond Lamina cribrosa
5. Intra ocular Haemorrhage
6. Scleral excrescenses or extra scleral excrescenses
7. Histology of the tumour – if it is poorly differentiated

9.2.5 Metastatic work up on follow up:

The periodicity of follow-up is 3 monthly examinations for the first year, 4 monthly examinations in the second year, 6-monthly in the third year and yearly there after.

Each follow up visit should include

- Examination of the fellow eye
- Examination of the an ophthalmic socket
  - Palpation should be done after the artificial shell is removed. Since most sockets will have orbital implant of various types, one should palpate around the implant and also evaluate the mobility of the implant.
- A thorough physical examination for any metastatic disease

To summarize,

- **Systemic metastasis is the main cause of mortality in patients with retinoblastoma**
- **Retinoblastoma patients may have locally advanced disease or metastatic disease at presentation**
- **Direct infiltration of optic nerve is the commonest mode of spread.**
- **Metastatic work-up should be done at presentation and during follow-up.**
- **Histopathological high risk factors predictive of metastasis will guide the work-up.**
- **Metastatic work-up is a multidisciplinary approach which includes ophthalmologists, oncologist, pathologists, radiologists etc.**

Further reading

FURTHER READING

General Reading

1. Rodriguez-Galindo C, Meadows AT: Retinoblastoma, *in* Cancer in Children: The Clinical Biology of Childhood Cancer, William L. Carroll and Jonathan L. Finlay, eds. Jones and Bartlett Publishers, Sudbury, MA, 2010, pp 437-457.

Incidence

1. Reis LAG, Smith MA et al (eds) Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER Program. NIH Pub. No.99-4649. Bethesda, MD, 1999.
2. National Cancer Registry Programme Two-year report of the Population based Cancer registries 1999-2000. Incidence and distribution of cancer Indian Council of Medical Research, New Delhi.

Imaging :

1. A pushkin, MA, Shapiro MJ, Mafee MF. Retinoblastoma and simulating lesions-Role of Imaging. Neuroimaging clinics of North America 2005; 15: 49-67
2. Graaf PD, Barkhof F, Moll AC, Imhof SM, Knol DL, Van der valk P, Castelijns JA. Retinoblastoma: MR imaging parameters in Detection of tumor extent. Radiology 2005; 235: 197-207.
3. Kaufman LM, Mafee MF, Song CD. Retinobaslstoma and simulating lesions: Role of CT, MR and use of Gd-DTPA contrast enhancement. Radiology Clinics of North America 1998; 36:1101 -1117.

Histopathology:

1. Folberg R, Salomao D, Grossniklaus HE, Proia AD, Rao NA, Cameron JD; Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of tissues removed as part of the surgical treatment of common malignancies of the eye and its adnexa. Am J Surg Pathol. 2003 Jul;27:999-1004
2. Chantada GL, Doz F, Orjuela M, Qaddoumi I, Sitorus RS, Kepak T, Furmanchuk A,Castellanos M, Sharma T, Chevez-Barrios P, Rodriguez-Galindo C; International

Retinoblastoma Staging Working GroupWorld disparities in risk definition and management of retinoblastoma: a report from the International Retinoblastoma Staging Working Group. Pediatr Blood Cancer. 2008;50:692-4.

3. Schilling H, Yang H, Havers W, Bornfeld N, Schuler A. Changes in the retinal pigment epithelium and choroidal invasion in 297 enculeated eyes with retinoblastoma: histologic staging and metastatic rate. Presented at the Xth International Congress of Ocular Oncology; June 17-21, 2001; Amsterdam, The Netherlands,
4. Biswas J, Das D, Krishnakumar S, Shanmugam MP. Histopathologic analysis of 232 eyes with retinoblastoma conducted in an Indian tertiary-care ophthalmic center. J Pediatr Ophthalmol Strabismus. 2003;40(5):265-7
5. Duke-Elder S. Dobree jH: System of Ophthalmology, vol X, Diseases of the Retina St. Louis, CV Mosby, 1967, p 672.
6. Albert DM, Robinson N: Wardrop Lecture,. James Wardrop. A brief review of his life and contributions. Trans Ophthalomol Soc UK. 94:892-908
7. Zimmeman LE: Retinoblastoma and retinocytoma. In Spencer WH (ed): Ophthalmic Pathology Philadelphia, WB Saunders, 1985, p 1292.
8. Tso MOM Zimmerman L.E Fine BS: The nature of retinoblastoma. I Photoreceptor differentiation. A clinical and histologic study. Am J Ophthalmol 1970;69:339-350
9. Albert DM, McGhee CNJ Seddon JM, et al: Development of additional primary tumors after 62 years in the first patient with retinoblastoma cured by radiation therapy. Am J Ophthalmol 1984;97:189-196
10. Reese AB Merriam GR JZ Martin HE: Treatment of bilateral retinoblastoma by irradiation and surgery. Report on 15 year result. Am J ophthalmol 1949;32:175-195
11. Farks TG: Hereditary tumors. In Krill AE (ed): Krill's Hereditary Retinal and Choroidal Diseases. Hagerstown, MD, Harper & Row, 1977, p 1174.
12. Knudson AG. Retinoblastoma: a prototypic hereditary neoplasm. Seminars in Oncology, 1978;5:57-60.
13. Draper GJ, Sanders BM, Kingston JE) Second primary neoplasms in Patients with Retinoblastoma B J Cancer 1986;53:661-71

Risk factors

1. Khelfaoui F, Validire P, Auperin A, Quintana E, Michon J, Pacquement H, Desjardins L, Asselain B, Schlienger P, Vielh P, Dufier JL, Zucker, JM, Doz F Histopathologic risk factors in retinoblastoma: A retrospective study of 172 patients treated in a single institution. Cancer 1997;77: 1206-13.

International classification:

1. Murphree L: Staging and grouping of retinoblastoma. In: Singh A, Damato B: Clinical Ophthalmic Oncology. Philadelphia, Pa: Saunders Elsevier, 2007, pp 422-7.

Bilateral Introcular Retinoblastoma

1. Cohen VML, Kingston J, Hungerford JL The Success of primary chemotherapy Br J Ophthalmol. 2009; 93:887-90

Chemo thermotherapy

1. Lumbroso L, Doz F, Urbieta M, Levy C, Bours D, Asselain B, Vedrenne J, Zucker JM, Desjardins L. Chemothermotherapy in the management of retinoblastoma. Ophthalmology. 2002 Jun;109(6):1130-6.
2. Shields CL, Santos MC, Diniz W, Gündüz K, Mercado G, Cater JR, Shields JA. Thermotherapy for retinoblastoma. Arch Ophthalmol 1999 Jul;117(7):885-93.
3. A O Schueler, C Jurklies, H Heimann, R Wieland, W Havers, N Bornfeld Thermochemotherapy in hereditary retinoblastoma *Br J Ophthalmol* 2003;87:90-95.

Staging

1. Chantada. G Doz, F. Antonelli, C.B.G. Grundy, R. Stannard C, Dunkel, I J. Grabowski, EF Leal-Leal, C. Rodriguez-Galindo, C. Schvartzman, E. Beck Popovie M., Kremens, B Meadows, A.T., and Zucker, JM A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer 47, 2006;47:801-805

Chemotherapy for Trilateral Retinoblastoma

1. Nelson et al 1992 and Helveston EM et al Successful therapy for trilateral retinoblastoma *Am J Ophthalmol 1992*; *114: 23*–9.
2. Holladay DA, Holladay A, Montebello JF, Redmond KP. Clinical presentation , treatment and out of trilateral retinoblastoma cancer 1990;67: 710-715
3. M. Skulski, J. C. Egelhoff, S. S. Kollias, C. Mazewski and W. S. Ball Jr.Trilateral Retinoblastoma with suprasellar involvement Neuroradiology1997;39:41-43
4. Meadows AT Regarding chemoreduction for retinoblastoma and neoplasms Arch ophthal mol 2004: 122; 1570-1
5. Donoso LA et al Intracranial malignancy in patients with bilateral retinoblastoma retina 1981:1; 67-74

6. Kivela T Trilateral retinoblastoma: A meta Analysis of hereditaryretinoblastoma with primary ectopicintracrainial retinoblastomaJ clin oncol 1999;17:1829-1837
7. *Jubran RF*, Erdreich-Epstein A, Butturini A, *et al*. Approches to treatment for Extraocular retinoblastoma . Children's Hospital of Los Angeles experience J Pediatr Hematol Oncol 2004 : 26; 31-4

Novel modes of Drug Delivery

1. Refillable Episcleral drug delivery devices for controlled unidirectional trans scleral drug delivery Murphee et al Abstracted International congress of ocular oncology 2005

Subtenon /Sub conjuctival and Topotecan

1. Abramson DH, Frank CM, Dunkel IJ: A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. Ophthalmology 1999;106 (10): 1947-50
2. Villablanca JG, Jubran R, Murphree AL: Phase I study of subtenon carboplatin with systemic high dose carboplatin/etoposide/vincristine (CEV) for eyes with disseminated intraocular retinoblastoma (RB). [Abstract] Proceedings of the XIII Biannual Meeting of ISGED and the X International Symposium on Retinoblastoma, May 4, 2001, Fort Lauderdale, Fla. USA .
3. S Ghose, A Mahindrakar, V Thavaraj, Balasubramanium ST, V Sharma, Balasubramaya R, A Purohit, A Sethi, LS Arya, Subconjunctival caboplatin and its problems in Retinoblastoma (RB). A Preliminary Report. Indian J Pediatr 2002; 69: S3, 10
4. Sui JY, Dalgard C, Van Quill KR et al Subconjuctival topotecan in fibrin sealant in the treatment of transgenic murine Retinoblastoma. Investigative Ophthalmology and Visual Science 2008; 49:490-496

Intra vitreal Injection

1. Ueda M, TanabeJ, Inomata M, KanekoA, Kimra T Study on conservative treatment of Retinoblastoma –effect of Intravitreal injection of melphalan on the rabbit retina Nippn Ganka Zashi 1995; 99: 1230-5
2. Usha Singh et al. Intravitreal Melphalan in management of partially treated retinoblastoma. European Society of Ophthalmologists(SOE) 2009 Electronic Poster Notification - EP-ONC-440

Macular tumors

1. Dan S Gombos , Alison Kelly, Pietro G Coen, Judith E Kingston, John L Hungerford Retinoblastoma treated with primary chemotherapy alone: the significance of tumour size, location, and age Brit J Ophthalmol 2002; 86:80-83

2. Shields CL, Mashayekhi A, Cater J, et al.: Macular retinoblastoma managed with chemoreduction: analysis of tumor control with or without adjuvant thermotherapy in 68 tumors. Arch Ophthalmol . 2005;123 (6): 765-73.

Metastatic Retinoblastoma:

1. K. Gündüz, O. Müftüoglu, I. Günalp, E. Ünal, N. Taçyıldız Metastatic Retinoblastoma Clinical Features, Treatment, and Prognosis. Ophthalmology. 2006;113:1558-1566
2. Matsubara H, Makimoto A, Higa T, et al.: A multidisciplinary treatment strategy that includes high-dose chemotherapy for metastatic retinoblastoma without CNS involvement. Bone Marrow Transplant 2005;35 : 763-766
3. Dunkel IJ, Aledo A, Kernan NA, et al.: Successful treatment of metastatic retinoblastoma. Cancer 2000; 89 : 2117- 21,.
4. Kremens B, Wieland R, Reinhard H, et al.: High-dose chemotherapy with autologous stem cell rescue in children with retinoblastoma. Bone Marrow Transplant 2003;31 : 281-4
5. Rodriguez Galindo C, Wilson MW, Haik BG, Lipson MJ, Cain A, Merchant TE, Kaste S C, Pratt CB. Treatment of metastatic retinoblastoma. Ophthalmology. 2003;110:1237-40

Extraocular Retinoblastoma:

1. Guillermo Chantada, Adriana Fandiño, Sandra Casak, Julio Manzitti, Elsa Raslawski, Enrique Schvartzman. Treatment of overt extraocular retinoblastoma. Med Pediatr Oncol 2003;40:158-161
2. Antoneli CBG, Steinhorst E et al Extraocular retinoblastoma a 13 year experience Cancer 2003;98 : 1292-1298
3. Antoneli CBG, Ribeiro KC, Steinhorst F, Novaes PE, Chojniak MM, Malogolowkin M. Treatment of retinoblastoma patients with chemoreduction plus local therapy: experience of the AC Camargo Hospital, Brazil. J Pediatr Hematol Oncol. 2006;28:342–5.

Three Drug Chemotherapy

1. Shields et al Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral Retinoblastoma Arch ophthalmol 2003: 121 :1513
2. Demirci H, Shields CL, Meadows AT, Shields JA. Long-term visual outcome following chemoreduction for retinoblastoma. Arch Ophthalmol 2005;123:1525-1530

3. Friedman DL, Himelstein B, Shields CL, Shields JA, Needle M, Miller D, Bunin GR, Meadows AT. Chemoreduction and Local Ophthalmic Therapy for Intraocular Retinoblastoma. J Clin Oncol 2000;18:12-17.

Secondary Malignancies:

1. Shields CL, Meadows AT, Shields JA, et al.: Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). Arch Ophthalmol 2001; 119 : 1269-72.
2. Gallie BL, Dunn JM, Chan HS, et al.: The genetics of retinoblastoma. Relevance to the patient. Pediatr Clin North Am 1991;38 : 299-315
3. Wong FL, Boice JD Jr, Abramson DH, et al.: Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 1997; 278 : 1262-7.
4. Gombos DS, Hungerford J, Abramson DH, et al.: Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor? Ophthalmology 2007;114 : 1378-83
5. Kleinerman RA et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up J Clin Oncol 2005; 23:2272-2279.

Radiotherapy

1. Krasin MJ, Crawford BT, Zhu Y, et al.: Intensity-modulated radiation therapy for children with intraocular retinoblastoma: potential sparing of the bony orbit. Clin Oncol (R Coll Radiol) 2004;16: 215-22.
2. Reisner ML, Viégas CM, Grazziotin RZ, et al.: Retinoblastoma–comparative analysis of external radiotherapy techniques, including an IMRT technique. Int J Radiat Oncol Biol Phys 2007;67: 933-41.
3. Lee CT, Bilton SD, Famiglietti RM, et al.: Treatment planning with protons for pediatric retinoblastoma, medulloblastoma, and pelvic sarcoma: how do protons compare with other conformal techniques? Int J Radiat Oncol Biol Phys 2005;63: 362-72.
4. Sterzing F, Eva M Stoiber, Simeon Nill, Bauer H, Peter H ,Jurgen Debus . Intensity Modulated Radiotherapy (IMRT) in the treatment of children and adolescent –single institution experience and review of literature.Radiation Oncology 2009; 4:37
5. Reiser ML, Vieegas CMP, Grazziotin RZ, Batista DVS, Carneiro TM, Araujo AMM, et al Retinoblastoma –comparitive analysis of external radiotherapy techniques, including an IMRT technique Radiation Oncol Biol Physc 2007;67:933-941
6. Lee CT, Bilton SD, Famiglietti RM, Riley BA, Mahajan A, Chang El et al Treatment planning with protons for pediatric retinoblastoma, Medulloblastoma, and

pelvic sarcoma : how do protons compare with other conformal Techniques ?? Int J Radiat oncol Biol Phys. 2005; 63:362-37

Expert Group Members (in alphabetical order)

- Dr. Archana Kumar (Lucknow)
- Dr. Aruna Kumari (Bangalore)
- Prof Raj Vardhan Azad (New Delhi)
- Dr. Shripad Banavali (Mumbai)
- Dr. C Bhuyan (Guwahati)
- Dr. Bhavna Chawla (New Delhi)
- Dr. Dipankar Das (Guwahati)
- Prof. S. Ghoshe (New Delhi)
- Dr. L. Gopal (Chennai))
- Dr. Harsha Panchal (Ahemadabad)
- Dr. S. Honavar (Hyderabad)
- Dr. Krishna Kumar (Chennai)
- Dr. Kasturi Bhattacharjee (Guwahati)
- Dr G. Kumaramanickavel (Chennai)
- Dr. P. Kusuma Kumari (Trivandrum)
- Dr. Mridula Mehta (New Delhi)
- Dr. N. Pushker (New Delhi)
- Dr. Sameer Bakshl (New Delhi)
- Dr. Seema Sen (New Delhi)
- Dr. Seema Kashyap (New Delhi)
- Dr. Sushmita Pathy (New Delhi)
- Dr. Usha Kim (Madhurai)
- Dr. Usha Singh (Chandigarh)
- Dr. Vasantha Thavaraj (New Delhi)
- Dr. Vikas Khetan (Chennai)
- Dr. Veena Noronha (Chennai)
- Dr. L. Venkatesh (Bangalore)

ICMR Secretariat

Dr. K. Sathyanarayanan
Dr. Vasantha Thavaraj

Drafting Committee

- Dr. L. Venkatesh
- Dr. Vikas Khetan

- Dr. Kasturi Bhattacharjee
- Dr. L. Gopal
- Dr. Vasantha Thavaraj
- Dr. Dipankar Das
- Prof Raj Vardhan Azad

Pediatric Hematology Oncology Chapter Of IAP

Dr. Anupam Sachdev (Chairman 2008)
Dr. Anupama Borker (Secretary 2008)
Dr. ATK Rau (Chairman 2009)
Dr. R.Dalvi (Secretary2009)

SIOP Hon. Secretary General

Dr. Bharat Agarwal

Appendix I

Initial Examination in clinic

Retinoblastoma Clinic Number: _____ **Date**

Child's Identification Data

Child's name: _____
Mother's Name: _____
Father's Name: _____
Child's age: _____ years _____ months
Child's sex: ☐ Male ☐ Female
Address: local
Permanent

Telephone Landline: _____ **Mob:** _____**PCO (PP)** _____

Informer: ☐ Mother ☐ Father ☐ Guardian

Clinical history:

Presenting complaint with duration

1. Leucocoria
2. Squint
3. Pain
4. Red eye
5. Protruding eye/large eye
6. Change in vision/Loss of vision
8. Swelling of eye lids
9. Others (specify)
10. Progressive ☐ Yes ☐ No
11. Associated problems:
    - Appetite
    - Bone pain
    - Sleep
    - Others

Past history (medical /surgical)

Treatment history

Personal history

Family history

Status of parents	**Mother**	**Father**
Alive		
Age		

1. Any history of "losing eyes" or "shrunken eyes" in the family?
2. Other cancers in the family? (Osteosarcoma /Bone cancers, Breast Cancer, Leukemia, Cancer of cervix in child's mother, Brain tumors). If YES, indicate the relationship to the child and the approximate age at diagnosis.
3. Consanguinity in the family.

Family Tree (Three Generation with age)

Birth history

Prenatal history

Exposure to radiation
Exposure to X-rays
Exposure to drugs
Exposure to chemicals (farming)
Mother's nutritious diet
Infections in pregnancy
Natal history
Birth weight
Premature
Mode of delivery
Birth asphyxia
Kept in incubator
White reflex at birth

Socio-economic status

Examination

General physical examination

Height Weight
Low set ears, malar hypoplasia, other congenital abnormalities
Lymph nodes: (Preauricular, Submandibular, Cervical, Others)
Systemic examination

Ocular examination

Clinical findings (tick)	Right eye	Left eye
Vision (Snellens' / preferential looking)		
White pupillary reflects	_____	_____
Nystagmus	_____	_____
Hazy Conea	_____	_____
Pupil (fixed / reacting)	_____	_____
Redness	_____	_____
Hyphaema	_____	_____
Buphthalmos	_____	_____
Estropia/Exotropia	_____	_____
Heterochromia iridis	_____	_____
Scleral thickening / staphyloma	_____	_____
Microphthalmic/ phthisis bulbi	_____	_____
Orbital inflammation	_____	_____
Proptosis	_____	_____
Others (specify)	_____	_____

Examination under anaesthesia (EUA)

Size of eyeball (normal/increased/decreased)	Right eye	Left eye

Anterior segment evaluation

Congestion
- Cornea- clear/hazy/diameter

Anterior chamber-depth
- content
- hypopyon / hyphema

Iris- neovascularisation
- ectropion uveae
- seeds / nodules
- Lens- clear/cataract

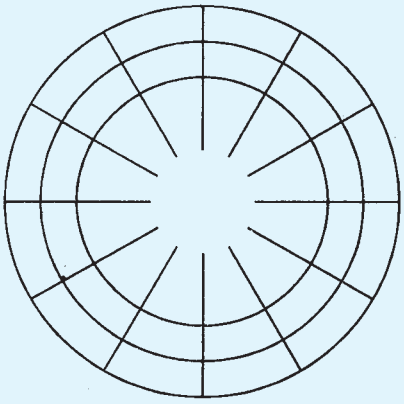
Intraocular pressure by Perkin's tonometer

Posterior segment

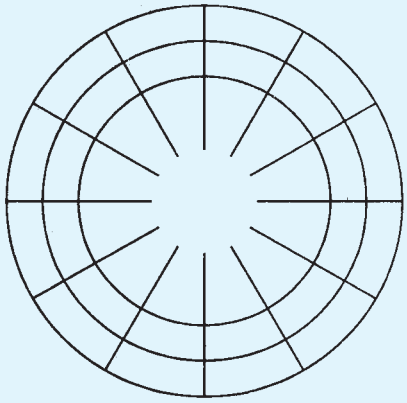
Indirect ophthalmoscopy along with diagrammatic representation: to study tumor characteristics

Size of tumor (DD)	Location of tumor
Appearance of tumor	Vascular pattern
New vessels	Vitreous /subretinal seeds
Retinal detachment	

Right eye



Left eye



Group : A /B / C/ D/ E

No. of tumours	Right eye :	☐ 0-2	☐ 2-4	☐ 4-6	☐ > 6
	Left eye :	☐ 0-2	☐ 2-4	☐ 4-6	☐ > 6

Parent's & Sibling Screening

Investigations:

Hemogram
LFT
KFT

Imaging

Ultrasonography (findings) (T=Tranverse: L=Longitudinal scan)

	Right eye		Left eye	
	T	L	T	L
Base (mm)	____	____	____	____
Height (mm)	____	____	____	____

Computed tomography

Magnetic resonance imaging

Metastatic work up

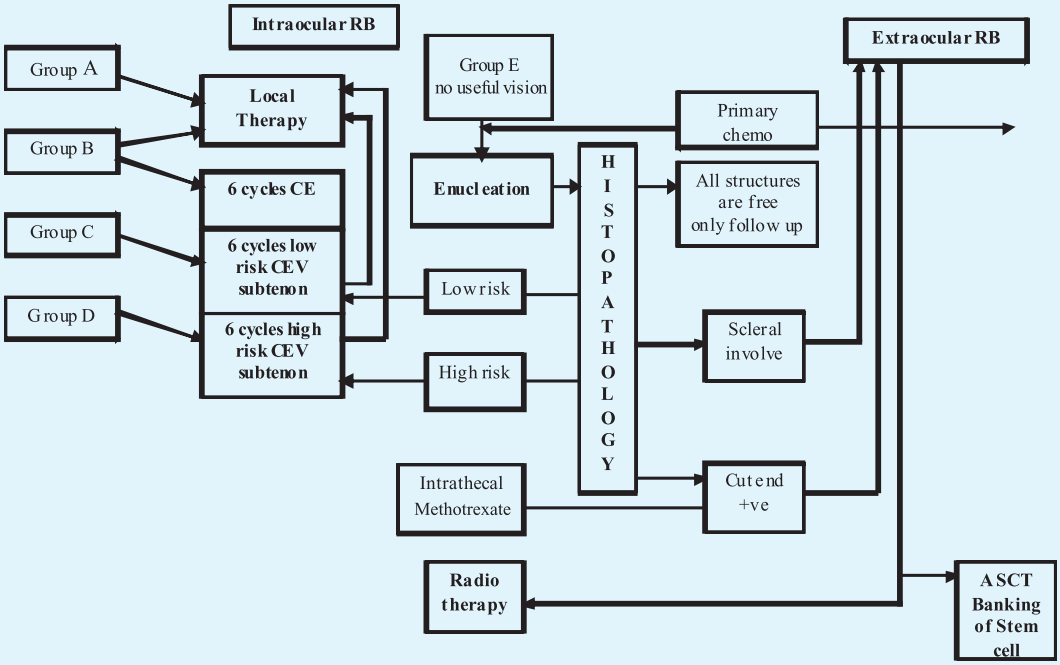
Bone marrow aspiration
CSF analysis
Others

Photographic documentation

Clinical photograph of the patient, imaging and Retcam photograph of the tumor

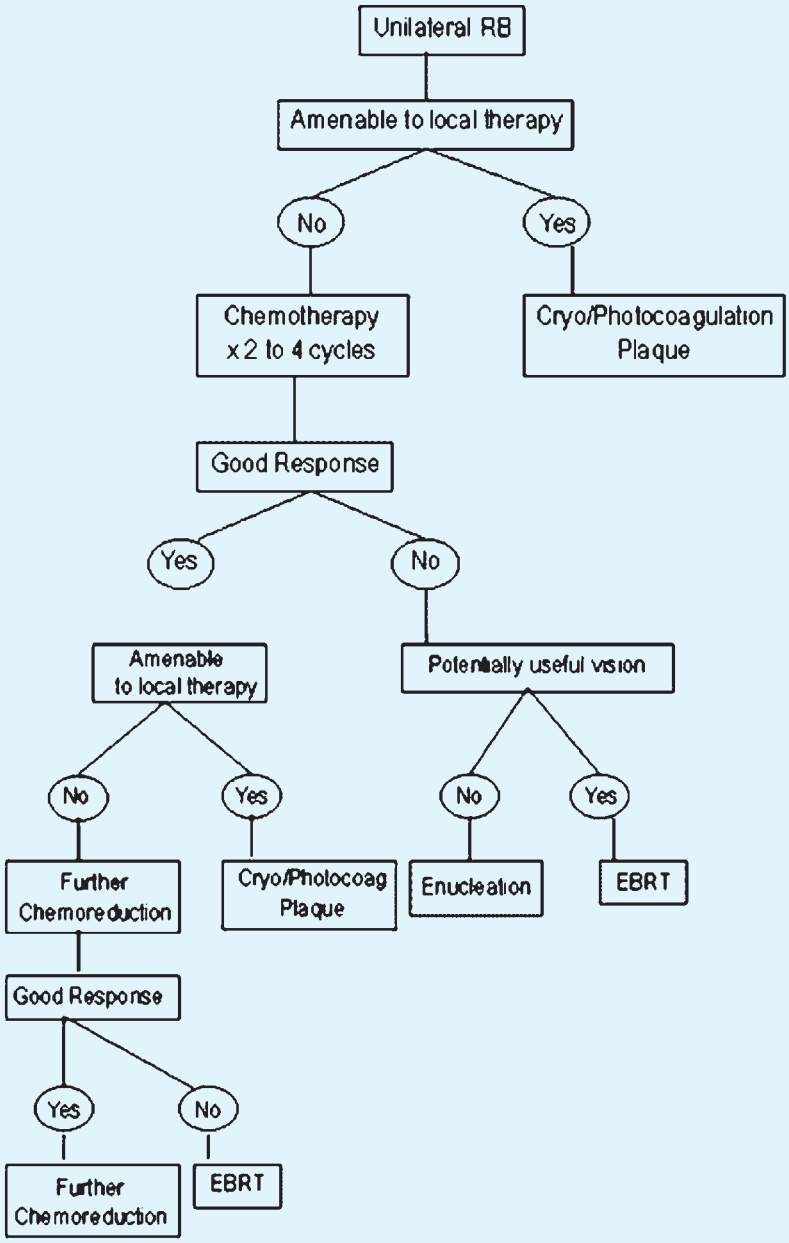
Appendix II

Flow Chat Chemotherapy of Retinoblastoma (RB)



Appendix III

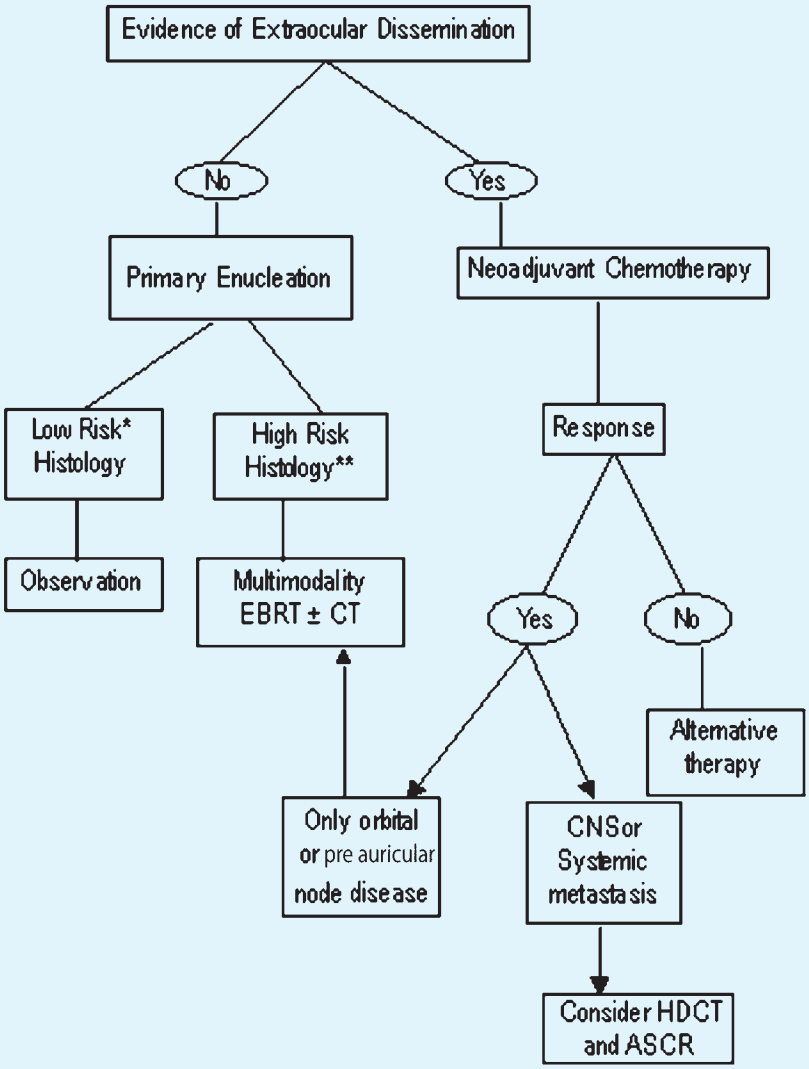
Guidelines for management of intraocular unilateral RB



EBRT External Beam Radiation therapy

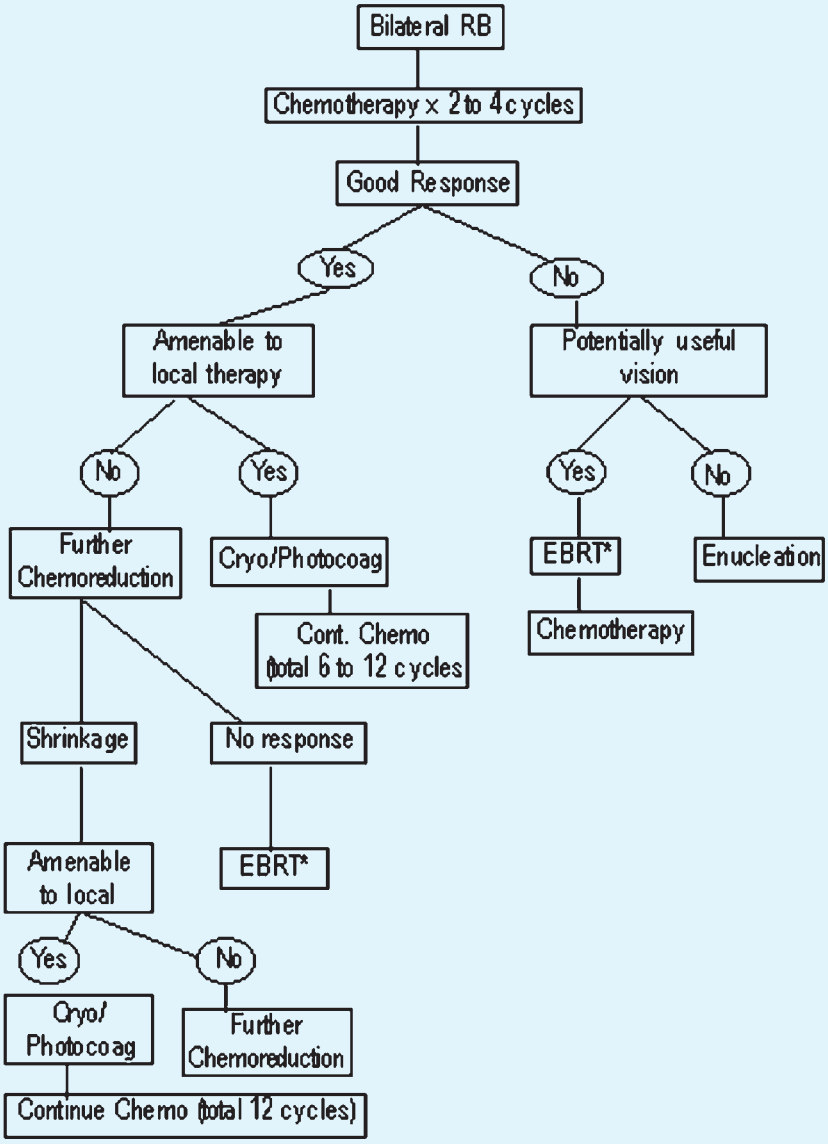
Appendix IV

Guidelines for management of advanced unilateral RB



Appendix V

Guidelines for management of Bilateral RB



Appendix VI

INTERNATIONAL CLASSIFICATION FOR INTRAOCULAR DISEASE

Group A – Very low risk

Small discrete intraretinal tumours away from the foveola and disc

- All tumours 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 15 mm from the optic disc

Group B – Low risk

All remaining discrete retinal tumors without seeding

- All tumors confined to the retina not in group A
- Any tumor size and location with no vitreous or subretinal seeding

Group C – Moderate risk

Discrete local disease with minimal focal subretinal or vitreous seeding

- Tumor(s) must be discrete
- Subretinal fluid, present or past without gross seeding, involving up to one quadrant of retina
- Local subretinal seeding, present or past, less than 5 mm from the tumor
- Focal vitreous seeding close to discrete tumor

Group D – High risk

Diffuse disease with significant vitreous and/or subretinal seeding

- Tumor(s) may be massive or diffuse
- Subretinal fluid, present or past, up to total retinal detachment
- Diffuse subretinal seeding, may include subretinal plaques or tumor nodules
- Diffuse or massive vitreous disease, may include “greasy” seeds or avascular tumor or masses

Group E – Very high risk

Presence of any one or more of these poor prognosis features

- Tumor touching the lens

- Neovascular glaucoma
- Tumor anterior to anterior vitreous face involving ciliary body or anterior segment
- Diffuse infiltrating retinoblastoma
- Opaque media from hemorrhage
- Aseptic orbital cellulitis
- Phthisis bulbi

Appendix VII

Staging of Retinoblastoma

STAGE 0. Patients treated conservatively

Stage I. Eye enucleated, completely resected histologically

Stage II. Eye enucleated, microscopic residual tumor

Stage III. Regional extension

III a. Overt orbital disease
III b. Preauricular or cervical lymph node extension

Stage IV Metastatic disease

IV a. Hematogenous metastasis (without CNS involvement)
1. Single lesion
2. Multiple lesions

IV 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

Acknowledgment

Retinoblastoma is a rare cancer in children, but most of these children can grow up and live healthy normal lives with good vision. About 2/3 of these children develop the tumor in one eye and there children and other relatives are not at risk for having it. But about 1/3 of them, develop the tumor as a consequence of a genetic error in a tumor suppressor gene. Only about 2 in 10 of the children with this form of retinoblastoma will have a parent with tumor, but all of them (including all with tumor in both eyes) will be able to pass this mutation on to their offspring. Counseling for these children is critically important.

It is also important to make an early diagnosis in the case of unilateral retinoblastoma so that enucleation can be performed and the child can live with good vision in the remaining eye. Bilateral disease is more of a problem, and all of these children should be treated in a tertiary care center where the pediatrician, pediatric oncologist, ocular oncologist and radiation oncologist are familiar with the disease. In this way, these children can also live healthy lives with a minimum of late complications of treatment. These Guidelines are important in assisting all professionals who care for children with retinoblastoma and their families.

Anna T. Meadows, MD
The Children's Hospital of Philadelphia
Philadelphia, PA, 19104, USA

Glossary

RB	Retinoblastoma
EUA	Examination under anesthesia
RT	Radiotherapy
CEV	Carboplatin, Etoposide and Vincristin
PHO	Pediatric Hematology Oncology
COG	Children Oncology Group
IMRT	Intensity Modulated Radiotherapy
EBRT	External Beam Radiotherapy
MRI	Magnetic Resonance Imaging
CT SCAN	Computerized Tomography Scan
G-CSF	Granulocyte - Colony Stimulating Factor
CSF	Cerebrospinal Fluid
CNS	Central Nervous System
U/S	Ultra sound
ASCT/R	Autogous stem Cell Transplantation/Rescue

Indian Council of Medical Research
Department of Health Research
(Ministry of Health & Family Welfare)
V. Ramalingaswami Bhawan
Post Box 4911, Ansari Nagar, New Delhi-110 029

Phone: 01-11-26588980, 26589794, 26588895
E-mail: icmrhqds@sansad.nic.in
Website: http://www.icmr.nic.in