EYES make World Beautiful
Retinoblastoma
Demographics, Clinical profile & Current Concepts of Management

Dr. Vijay Anand P. Reddy
Director
Apollo Cancer Institute, Hyderabad
Preamble

• Most common Intra Ocular Malignancies in Children
• Estimated incid: 3000-4000 cases / annum
• Asia accounts for 50% of RB in the World
• 1 in 15000 - 18000 live birth
• 1500-2000 new cases/yr in India
• No racial or gender predisposition
Preamble

• Average age of Diag – 18 months
• Bil. is more common in younger <12 mths
• Unilateral @ 24 mths.
• Bil. RB 25-35% , Unilateral 65-75%
Genetics

• Newly diagnosed cases
  
  6% are familiar  94% Sporadic

• Bil. RB involve germinal mutation in all cases

• Unil RB only 15% involve mutation, 85% are Sporadic
Genetic Counseling

• Positive F/H
  • 40% of the sublings may develop RB

• With no F/H RB - Unilateral RB
  • If the child has RB
    (a) 1% of sublings are at risk
    (b) 8% of the offspring may develop RB

• With no F/H RB - Bilateral RB
  (a) 6% of the siblings may have a chance of RB
  (b) 40% of the offspring have a chance of RB
Preamble

• Current management modalities are restricted to very few Tertiary care centers

• Only about 10-15% pts have access
Preamble

• Survival rate
  • West 95%
  • Underdeveloped Countries <50%

• Problems
  • Late referral
  • Misdiagnosis
  • Suboptimal treatment
Ocular Oncology Service
LV Prasad Eye Institute, in assoc Apollo Cancer Inst, Hyderabad

• Established in Jan 2004
• First integrated RB treatment center with state-of-the-art facilities for
  Diagnosis, pathology, genetics, management, documentation & rehab

• Supported by the
  Sight Savers International, Wills Eye Hospital, PA & Children’s Hospital of Philadelphia, PA
RB Referrals 2000 - 2006

Ocular Oncology Service

Increasing Referrals
Retinoblastoma in Hyderabad

Jan 1990 – Dec 2005

460 patients
648 eyes

1564 pts till date!
Demographic Data
Sporadic (96%) Vs Familial (4%)

N=460 patients

Only 19 of 460 (4%) pts manifested Familial Retinoblastoma
Demographic Data
Age at Diagnosis

N = 460 patients

About 2/3 diagnosed <3 years age
Demographic Data Laterality

N=460 patients

60% unilateral, 40% bilateral
# Common Presenting Features of RB

<table>
<thead>
<tr>
<th></th>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Leucocoria</td>
<td>56%</td>
</tr>
<tr>
<td>2.</td>
<td>Strabismus</td>
<td>20%</td>
</tr>
<tr>
<td>3.</td>
<td>Red painful eye</td>
<td>7%</td>
</tr>
<tr>
<td>4.</td>
<td>Poor vision</td>
<td>5%</td>
</tr>
<tr>
<td>5.</td>
<td>Asymptomatic</td>
<td>3%</td>
</tr>
<tr>
<td>6.</td>
<td>Orbital Cellulitis</td>
<td>3%</td>
</tr>
<tr>
<td>7.</td>
<td>Unilateral Mydriasis</td>
<td>2%</td>
</tr>
<tr>
<td>8.</td>
<td>Heterochromia Iridis</td>
<td>1%</td>
</tr>
<tr>
<td>9.</td>
<td>Hyphema</td>
<td>1%</td>
</tr>
</tbody>
</table>
Initial Clinical Presentation

- Leucocoria: 375
- Asymptomatic: 117
- Squint: 62
- Proptosis: 30
- Fungating Mass: 14
- Visual Loss: 9
- Pthisis Bulbi: 9
- Eyelid Edema: 9
- Pain: 8
- Enlarged Eyeball: 8
- Redness: 6

Total eyes: N = 648 eyes
Moderately Advanced Lesions

- **Endophytic**
  Tumor grows into the vitreous cavity

- **Exophytic**
  Tumor grows towards subretinal space

- **Diffuse Infiltrating tumor**
  Tumor diffusely involves the retina causing just a placid thickness of the retina and not a mass (older children)
Very advanced

- Proptosis due to ON or Orbital Extn.
- Spread through ON after breaching Lamina cribrosa
- Orbital Extension at the site of scleral emissalry veins
- Systemic – Brain, Skull, distant bones, LN
- Phthisis bulbi
- Orbital cellulities
Clinical Spectrum

.................................................Intra-ocular RB

..........................................Extra-ocular RB
**Diagnosis**

- Clinical evaluation – complete ophthalmic evaluation including dilated fundus exam under G.A.
- **Direct visualization of the tumor by an indirect ophthalmoscope** is diagnostic of RB in over 90%.
- Ret cam - wide angle fundus camera
  - Useful in accurately documenting RB and monitoring response to therapy.
- Ultrasound – B Scan
- CT Scan & MRI Scan
  - Where extra-ocular or Intra Cranial extn is suspected
Retinoblastoma

Diagnosis

Indirect Ophthalmoscopy

Ultrasonography B-scan

MRI / CT
Ret cam

Assessment of response, documentation
Retinoblastoma

Classification
NEW International Staging System

- **Stage 0**  No enucleation
  (one or both eyes may have intraocular disease)

- **Stage I**  Enucleation, tumor completely resected

- **Stage II**  Enucleation with microscopic residual tumor

- **Stage III**  Regional extension
  A. Overt orbital disease
  B. Preauricular or cervical lymph node extension

- **Stage IV**  Metastatic disease
  A. Hematogenous metastasis
    1. Single lesion
    2. Multiple lesions
  B. CNS Extension
    1. Prechiasmatic lesion
    2. CNS mass
    3. Leptomeningeal disease

**International Classification of Intraocular Retinoblastoma**

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>Small tumors (&lt;3 mm) outside macula</td>
</tr>
<tr>
<td>Group-B</td>
<td>Bigger tumors (&gt;3 mm) or any tumor in macula or any tumor with subretinal fluid</td>
</tr>
<tr>
<td>Group-C</td>
<td>Localized seeds (subretinal or vitreous)</td>
</tr>
<tr>
<td>Group-D</td>
<td>Diffuse seeds (subretinal or vitreous)</td>
</tr>
<tr>
<td>Group-E</td>
<td>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, Tumor necrosis with aseptic orbital cellulitis and Phthisis bulbi</td>
</tr>
</tbody>
</table>
International Grouping of Intraocular Retinoblastoma

Group A < 3 mm

Group B macula > 3 mm

Group B tumor + SRF

Group C focal SR seeds

Group D diffuse SR seeds

Group D diffuse vitreous seeds

Group C focal vitreous seeds

Group C focal vitreous seeds

Group E high risk
- NVG
- blood
- invasion

International Grouping of Intraocular Retinoblastoma
Retinoblastoma - Management

Goals of Treatment

- Save life
- Salvage the eye
- Provide optimal residual vision

Salvage Life
Salvage Organ
Salvage Function
Primary Treatment for Intraocular Tumors

N=451 eyes
Intraocular RB Treatment Options

- Cryotherapy
- Thermotherapy
- Laser photocoagulation
- Chemoreduction
- Plaque brachytherapy
- External beam radiotherapy
- Enucleation
- Adjuvant therapy
- Orbital exenteration
Cryotherapy

- Small equatorial & peripheral retinal tumors
- Up to 4 mm in basal diameter and 2 mm in thickness.
- Produces a scar much larger than the tumor.
- Cryo done 2-3 hours prior to chemo can increase the delivery of chemo agents across the blood retinal barrier and thus has synergistic effect.
Cryotherapy

Good local therapy. Leaves Big scars
Laser Photocoagulation

- For small posterior tumors 4 mm in basal diameter and 2 mm in thickness.
- The treatment is directed to coagulate the blood supply to the tumor.
- It is less often employed now with the advent of thermotherapy.
- It is contraindicated while the patient is on active chemotherapy.
Photocoagulation

Good local therapy.
Causes big scaring, loses vascularization
Transpupillary Thermotherapy

• Focused heat generated by infrared radiation is applied at subphotocoagulation levels to induce tumor necrosis.
• Complete tumor regression can be achieved in over 85% of tumors using 3-4 sessions
• The major application of thermotherapy is as an adjunct to chemoreduction.
• The application of heat amplifies the cytotoxic effect of platinum analogues.
• This synergistic combination with chemoreduction protocol is termed chemothermotherapy.
Thermotherapy

GOOD LOCAL THERAPY. MINIMAL SCARING
Plaque Brachytherapy

- Chemoreduction failure or recurrence
- Rarely as primary therapy
- Commonly uses Iodine$^{125}$, Ruthenium$^{106}$
- 4000-4500 cGy to tumor apex
- 90% success in tumor control
Radioactive Plaques

- Various sizes & shapes
- Round, Single notched, Double notched etc
- 10-25 mm in diameter
Ruthenium 106

Brachytherapy

Plaque therapy
Plaque Brachytherapy

Procedure

- The tumor thickness is measured by ultrasonography.
- The data is used for dosimetry on a three dimensional computerized tumor modeling system.
- The plaque design is chosen depending on the basal tumor dimensions, its location and configuration.
- The dose to the tumor apex ranges from 4000-5000 cGy.
- The plaque is sutured to the sclera after confirming tumor centration and is left in situ for the duration of exposure, generally ranging from 36 to 72 hours.
Tumor assessment

Clinical & Radiological assessment

• Location
• Basal diameter
• Height

Tumor thickness by ultrasound B-scan  CT-based tumor volumetry
Radiotherapy Planning

- Brachy software: BEBIG, Germany
- Tumor is drawn on the retinal diagram
- Select the plaque size and shape
- Required dose is prescribed to base/apex
- Dosimetry: Autotomated dosimetry
- Dose & Exposure time are calculated
- Team Work
  - Ophthalmologist, Radiotherapist, Radiation Physicist
Tumor and Plaque placement
Tumor and Plaque placement
Dosimetry
Dose distribution
Plaque placement

- Under GA / LA
- Conjunctival peritomy
- Tumor location marked on sclera
- Dummy plaque used to confirm location
- Rh Plaque placed & sutured to sclera
- Conjunctiva sutured
- Patient is kept in isolation
Plaque Brachytherapy
Ext Beam Radiotherapy in RB

Novalis Tx
Radiotherapy: Indications

1. Residual disease after Chemotherapy and local therapy
2. Diffuse vitreous seeds
3. Recurrence after chemotherapy
4. Post enucleation – High risk features
   a). Sclera involvement
   b). Extraocular extension
   c). Optic Nerve involvement

Dose of Radiation 3500 to 4600 cGy depending on age and dose per fraction.
Radiotherapy – Techniques

- EBRT is delivered by either Cobalt-60 (γ-rays) or Linear Accelerator (X-rays).
- It is preferable to use LA with multi-beam technique with open eyes.
- Newer methods of delivering EBRT are being used to increase dose conformity to the target, minimize toxicity.
  - Intensity Modulated Radiotherapy (IMRT), Image Guided Radiotherapy (IGRT), Steriotactic Radiotherapy (SRT) and Proton Beam therapy.
## Ext Beam Radiotherapy
### Eye Salvage Rates

<table>
<thead>
<tr>
<th>RE Group</th>
<th>Ellsworth 1977</th>
<th>Hungerford 1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>91%</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
<td>83%</td>
<td>84%</td>
</tr>
<tr>
<td>III</td>
<td>82%</td>
<td>82%</td>
</tr>
<tr>
<td>IV</td>
<td>62%</td>
<td>43%</td>
</tr>
<tr>
<td>V</td>
<td>29%</td>
<td>36%</td>
</tr>
</tbody>
</table>
EBRT Complications

- Corneal ulcers, scaring
- Cataract, retinopathy, papillopathy
- Phthisis bulbi
- Growth retardation, Orbital & facial
EBRT
Second Malignant Neoplasm

- Increased risk
- 35% Vs 6% in bil cases
- Dependant on pt age (age < 12 mo)
not an ideal situation..
change was necessary...
a change came about...
Chemoreduction!
Chemoreduction

- Reduces tumor volume
- Allows more focused, less damaging therapeutic measures

“going back in time – down staging”
Chemoreduction
Bilateral Retinoblatoma
Chemoreduction
Chemoreduction
Advantages

• Allows for salvage of the eye
• Maximizes potential for residual vision
• Possibly prevents systemic metastasis
• Delays onset of or prevents pinealoblastoma
## Chemo Regimen and Doses for RB

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Vincristine + Etoposide + Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>Etoposide</td>
</tr>
</tbody>
</table>

### Standard Dose (3 weekly, 6 cycles):
- Vincristine $1.5 \text{ mg/m}^2$ ($0.05 \text{ mg/kg for } <3\text{y} \& \text{ max dose } <2\text{mg}$).
- Etoposide $150 \text{ mg/m}^2$ ($5 \text{ mg/kg for children } <3\text{yrs of age}$).
- Carboplatin $560 \text{ mg/m}^2$ ($18.6 \text{ mg/kg for children } <3\text{y of age}$).

### High Dose (3 weekly, 6-12 cycles):
- Vincristine $0.025 \text{ mg/kg}$.
- Etoposide $12 \text{ mg/kg}$.
- Carboplatin $28 \text{ mg/kg}$.
Chemoreduction for retinoblastoma

Chemoreduction alone

Macular tumor: laser not done to optimize vision
Chemoreduction for retinoblastoma

Chemoreduction + TTT

Macular tumors

Two large tumors, scar sizes are much smaller than the tumor
Juxtapapillary, next to optic disc

Two large tumors, scar sizes are much smaller than the tumor.
Chemoreduction + TTT
Periocular Chemotherapy

- Deep posterior subtenon Carboplatin injection
- Currently under trial
- Encouraging results in Grp V B
- (70% eye salvage Vs 30%)
**EBRT Vs Chemoreduction**

**Eye Salvage Rates**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>EBRT</td>
<td>EBRT</td>
<td>CRD+SALT</td>
<td>CRD+SALT*</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>91%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
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<td>62%</td>
<td>43%</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>V</td>
<td>29%</td>
<td>66%</td>
<td>50%</td>
<td>75%</td>
</tr>
</tbody>
</table>

* HD Chemotherapy for group V, Periocular chemotherapy for VB
Enucleation
Changing Trends

• 1970 : 95%
• 1980 : 75%
• 1990 : 50%
• 2000 : 25%
Enucleation

- Advanced unilateral tumor
- Secondary glaucoma, pars plana invasion, anterior segment seeding
- Worse eye of an advanced bil case
Enucleation in Retinoblastoma

1. Minimal manipulation
2. Avoid perforation of the eye
3. Harvest long (>15mm) optic nerve stump
4. Inspect the enucleated eye for macroscopic extraocular extension and optic nerve involvement
5. Harvest fresh tissue for genetic studies
6. Avoid biointegrated implant if postoperative radiotherapy is necessary
Enucleation

- Minimal manipulation technique
- Long optic nerve stump
Enucleation is NOT the end of Rx

It is JUST the beginning!
Histopathologic risk factors

- Anterior chamber infiltration
- Trabecular meshwork infiltration
- Ciliary body infiltration
Histopathologic High risk Factors Predictive of Metastasis

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anterior chamber seeding</td>
</tr>
<tr>
<td>2</td>
<td>Iris infiltration</td>
</tr>
<tr>
<td>3</td>
<td>Ciliary body infiltration</td>
</tr>
<tr>
<td>4</td>
<td>Massive choroidal infiltration</td>
</tr>
<tr>
<td>5</td>
<td>Invasion of the optic nerve lamina cribrosa</td>
</tr>
<tr>
<td>6</td>
<td>Retrolaminar optic nerve invasion</td>
</tr>
<tr>
<td>7</td>
<td>Invasion of optic nerve transection</td>
</tr>
<tr>
<td>8</td>
<td>Scleral infiltration</td>
</tr>
<tr>
<td>9</td>
<td>Extrascleral extension</td>
</tr>
</tbody>
</table>
Histopathologic Risk Factors
152 of 277 (55%) N=277 eyes

Numbers do not total up to 152 because multiple HRF were present
Investigations in a patient with histopathologic high-risk factors

CSF +ve, Intracranial exten.

BM +ve,
Adjuvant Chemotherapy

- All pts with histopath risk factors
- 6 cycles of VCE
- 12 cycles of High Dose chemo for pts with EOE and ON-TR
Adjuvant Orbital EBRT

- Optic nerve invasion to the level of transection
- Scleral / extraocular extension
- Inadvertent ocular perforation or intraocular surgery in unsuspected retinoblastoma
Does adjuvant therapy help?
Incidence of metastasis

<table>
<thead>
<tr>
<th>No adjuvant therapy</th>
<th>Adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 76%</td>
<td>44 96%</td>
</tr>
<tr>
<td>24%</td>
<td>4%</td>
</tr>
</tbody>
</table>

p = 0.015

Number of Patients

- No Metastasis
- Metastasis
Orbital Retinoblastoma

- Primary
- Secondary
- Accidental
- Overt
- Microscopic
Orbital Retinoblastoma
Management Options

- Orbital exenteration
- External beam radiotherapy
- Systemic chemotherapy

70% MORTALITY!
Orbital Retinoblastoma Treatment Protocol

- High-dose chemotherapy
- Enucleation after minimum 3 cycles
- Orbital EBRT
- Continued high-dose chemotherapy for 12 cycles
Neo-adjuvant Chemotherapy
Neo-adjuvant Chemotherapy
Neo-adjuvant Chemotherapy
Retinoblastoma
Overall Outcome
Final Ocular Status
All Treatment Summary

Overall, 61% eyes needed enucleation

N = 451 eyes

<table>
<thead>
<tr>
<th>Loss of Eye</th>
<th>Eye Salvage</th>
<th>Vision Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>277</td>
<td>8</td>
<td>166</td>
</tr>
</tbody>
</table>
Final Systemic Status
All Treatment Summary

N=460 patients

434
(94%)

ALIVE AND WELL (94%)

ALIVE WITH METASTASIS (3%)

DEAD WITH METASTASIS (2%)

DEAD, OTHER CAUSES (1%)

12
(3%)

8
(2%)

6
(1%)
Summary

• In a tertiary care situation with integrated RB clinic in India, the OS was 94%, comparable to the West

• 61% of eyes needed enucleation

• 55% of eyes undergoing enucleation had HP risk factors and needed adj. therapy

• Chemoreduction had 92% eye salvage
Summary

• RB management is complex Individualized management

• Current trend is towards Chemoreduction and focal therapy with *improving life, eye and vision salvage*

• Team approach
Summary of Recent Advances

- Replacement of EBRT as primary modality
- Use of Chemoreduction to minimize the regression scar hence, increases the visual potential
- Identification of histo high-risk factors following enucleation
- Provision of Adjuvant therapy to reduce the local and distant recurrence
- Neo adjuvant chemotherapy in Orbital RB
**CURRENT SUGGESTED PROTOCOL**

<table>
<thead>
<tr>
<th>Intraocular tumor, International Classification – Group A to C, Unilateral or Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Focal therapy (cryotherapy or transpupillary thermotherapy) alone for smaller tumors (&lt;3mm in diameter and ht.) located in visually noncrucial areas</td>
</tr>
<tr>
<td>2. Standard 6 cycle chemoreduction and sequential aggressive focal therapy for larger tumors and those located in visually crucial areas</td>
</tr>
<tr>
<td>3. Defer focal therapy until 6 cycles for tumors located in the macular and juxtapapillary areas. Transpupillary thermotherapy or plaque brachytherapy for residual tumor in the macular and juxtapapillary areas after &gt;6 cycles</td>
</tr>
<tr>
<td>4. Focal therapy for small residual tumor, and plaque brachytherapy / external beam radiotherapy (&gt;12 months age) for large residual tumor if bilateral and enucleation if unilateral</td>
</tr>
</tbody>
</table>
**CURRENT SUGGESTED PROTOCOL**

### Intraocular tumor, International Classification – Group D, Unilateral or Bilateral

<table>
<thead>
<tr>
<th></th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>High dose chemotherapy and sequential aggressive focal therapy</td>
</tr>
<tr>
<td>2.</td>
<td>Periocular carboplatin for vitreous seeds</td>
</tr>
<tr>
<td>3.</td>
<td>Consider primary enucleation if unilateral, specially in eyes with no visual prognosis</td>
</tr>
</tbody>
</table>

### Intraocular tumor, International Classification – Group E, Unilateral or Bilateral

<table>
<thead>
<tr>
<th></th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Primary enucleation</td>
</tr>
<tr>
<td>2.</td>
<td>Evaluate histopathology for high risk factors</td>
</tr>
</tbody>
</table>
# CURRENT SUGGESTED PROTOCOL

## High risk factors on Histopathology, International Staging – Stage 2

1. Baseline systemic evaluation for metastasis
2. Standard 6 cycle adjuvant chemotherapy
3. High dose adjuvant chemotherapy and orbital external beam radiotherapy in patients with scleral infiltration, extraocular extension and optic nerve extension to transection

## Extraocular tumor, International Staging – Stage 3A

1. Baseline systemic evaluation for metastasis
2. High dose chemotherapy for 3-6 cycles, followed by enucleation or extended enucleation, external beam radiotherapy and continued chemotherapy for 12 cycles
CURRENT SUGGESTED PROTOCOL

<table>
<thead>
<tr>
<th>Regional Lymph Node Metastasis, International Staging – Stage 3B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Baseline evaluation for systemic metastasis</td>
</tr>
<tr>
<td>2. Neck dissection, high dose chemotherapy for 6 cycles, followed by external beam radiotherapy and continued chemotherapy for 12 cycles</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematogenous or Central Nervous System Metastasis, International Staging – Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intent-to-cure or Palliative therapy in discussion with the family</td>
</tr>
</tbody>
</table>
# Eye Salvage Rates

## EBRT Vs Chemoreduction

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<td>V</td>
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</tr>
</tbody>
</table>
EYES
make
World Beautiful

thank u

Dr Vijay Anand P Reddy