Retinoblastoma
Current Concepts of Management

Dr. P Vijay Anand Reddy
Introduction

• Global: 2-4% of childhood malignancies (Europe, N America, Australia)
• India: 5 - 7% of childhood malignancies

• Global incidence: 8-11 cases per million children <5 yrs
• India: 19.6 per million 0-4 yrs age grp Annual incidence
• Global incidence: 1 in 15,000 live births

• Singh AD, Damato, Jacob Pe’er, A. Linn Murphree, Julian D. Perry. Clinical ophthalmic oncology p414
Disease Burden: Global

- 2 - 4% of childhood malignancies (Europe, N America, Australia)
- Global incidence:
  - 8-11 cases per million children <5 yrs

Introduction

- India accounts for about 25% of RB in the World
- Incidence: 1200-1500 cases per yr
- 6% have orbital retinoblastoma at initial presentation
- Advanced tumor at initial presentation continues to be a barrier for eye salvage
Indian Picture

- 80-85% pts treated in primary or secondary health care set ups without any protocol based management - 50% mortality

- Visual outcome and survival:
  
depends on early detection and appropriate referral to dedicated centers

*http://www.icmr.nic.in/ncrp/cancer_regoverview.htm

#Ref: National Guidelines in the management of Retinoblastoma, ICMR 2010
Retinoblastoma Registry in India

- Indian Council of Medical Research
- Hospital Based Cancer Registry
- Commenced on 1\textsuperscript{st} April 2009
- 13 sites\(^{\text{^}}\)
- Registered approx. 600 cases / year
- Approx 1100* registered so far

*Unpublished data, Personal communication with Dr Vasantha Thavaraj Deputy Director General (SG), Chair Child Health, Division Of RHN-ICMR

\(^{\text{^}}\) Majenta -FINAL RB PROFORMA 2nd year.doc
Epidemiology

- No racial predilection
- No sex predilection
- No eye predilection
- Mostly unilateral
- Bilateral in 25 to 35% of cases
Genetics

- Hereditary nature identified late 1962,
- Stallard noted deletion of D group chromosome, chromosome 13
- Locus of deletion 14 band on the long arm (q) of 13th chromosome
- Intact gene protects against retinoblastoma
- Recessive tumour suppressor gene and for RB to occur both genes should be damaged
Rb gene

Phosphorylation

E2F-RB

Transcriptionally Inactive

G₁

M

G₂

S

RB-P

E2F

Transcription Stimulated

Cell-cycle progression through check point
Genetics...

- Of all newly diagnosed cases
  - 6% familial
  - 94% sporadic

- Unilateral
  - 15% are hereditary, 85% non hereditary
1971, Knudson, 2 hit hypothesis

**Hereditary retinoblastomas:**

- 1st hit germinal mutation, affects all cells,
- 2nd hit somatic retinal cells.
  - Hence predisposition to second non-ocular tumours like osteosarcoma

**Unilateral sporadic:**

- both hits somatic mutations, no risk of second non-ocular tumours
Pathogenesis

- Derived from glial cells, called Glioma by Virchow in 1864
- Flexner 1891 and Wintersteiner 1897, believed it to be a neuroepithelioma due to rosettes
- Later, retinoblasts
- RETINOBLASTOMA term accepted in 1926 by American Ophthalmological society
Pathology…

Microscopy…

Poorly differentiated tumours:
- small round cells with large hyperchromatic nuclei and scanty cytoplasm with mitotic figures

Well differentiated tumours: rosettes and fleurettes
1. Flexner-Wintersteiner: cells arranged around central lumen
2. Homer Wright: cells arranged around central neuromuscular tangle
3. Pseudorosette: cells arranged around blood vessels
4. Fleurettes: pear shaped eosinophilic structures
RB Classifications

- Reese Ellsworth
- St Jude’s
- Grabowosky
- Essen
- Chantada et al
- NEW International Staging System
Reese Ellsworth classification RB

1. **Group I - Very favorable**
   A. Solitary tumor, < 4 disk diameters, at or behind the equator
   B. Multiple tumors, none > 4 disk diameters, all at or behind the equator

2. **Group II - Favorable**
   A. Solitary tumor, 4-10 disk diameters in size, at or behind the equator
   B. Multiple tumors, none > 4-10 disk diameters, behind the equator

3. **Group III - Doubtful**
   A. Any lesion anterior to the equator
   B. Solitary tumors larger than 10 disk diameters behind the equator

4. **Group IV - Unfavorable**
   A. Multiple tumors, some larger than 10 disk diameters
   B. Any lesion extending anteriorly to the ora serrata

5. **Group V - Very unfavorable**
   A. Tumors involving more than half the retina
   B. Vitreous seeding
Group A < 3 mm

Group B macula > 3 mm

Group B tumor + SRF

Group C focal SR seeds

Group D diffuse vitreous seeds

Group C focal vitreous seeds

Group D diffuse SR seeds

Group E high risk
- NVG
- blood
- invasion

International Grouping of Intraocular Retinoblastoma
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

Retinoblastoma in Hyderabad
January 1988-December 2010

1543 eyes of 1067 patients

591 Unilateral
476 bilateral
RB Referrals 2000 - 2006

Increasing Referrals

Ocular Oncology Service
Socioeconomic Status

1067 patients

517 Nonpaying
48%

550 Paying
52%
N = 1067 patients

Age at Diagnosis

- 0 - 6 m: 153
- 6 - 12 m: 148
- 12 - 18 m: 129
- 18 - 24 m: 123
- 24 - 30 m: 106
- 30 - 36 m: 130
- > 36 m: 278
Age at diagnosis

- Average: 18 months
- Unilateral: 23 months
- Bilateral: 12 months

Clinical Spectrum

Intraocular RB

Extra ocular RB
Retinoblastoma Diagnosis

Indirect Ophthalmoscopy

Ultrasonography

MRI / CT
Tumor Location

N=1543 eyes
Initial Clinical Presentation

N = 1543 eyes

- Pain: 16
- Eyelid Edema: 17
- Redness: 30
- Squint: 34
- Asymptomatic: 80
- Enlarged Eyeball: 103
- Proptosis: 121
- Visual Loss: 512

VAR
Reese Ellsworth Group

N=1543 eyes

[Bar chart showing data distribution]
Intraocular Retinoblastoma
International Classification

N=1543 eyes
Decade back…..
Eye Salvage Rates…

<table>
<thead>
<tr>
<th>RE Group</th>
<th>Ellsworth 1977</th>
<th>Hungerford 1995</th>
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<tbody>
<tr>
<td>I</td>
<td>91%</td>
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<tr>
<td>IV</td>
<td>62%</td>
<td>43%</td>
</tr>
<tr>
<td>V</td>
<td>29%</td>
<td>36%</td>
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</table>
Retinoblastoma - Management

Goals of Treatment

- Save life
- Preserve the eye
- Provide optimal vision
Intraocular RB
Treatment Options

Early
Grp I, II
- Cryotherapy
- Thermotherapy
- Laser photocoagulation

Intermediate
Grp III, IV
- Chemoreduction + Local Therapy
- Plaque brachytherapy
- External beam radiotherapy

Late
Grp V
- Enucleation
- Adjuvant therapy – Chemo / EBRT
- Orbital exenteration
Cryotherapy

Good local therapy. Leaves Big scars
Photocoagulation

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

✓ Good local therapy. Minimal scaring
Primary Treatment for Intraocular Tumors

- Cryotherapy
- CRD + SALT
- Plaque Brachytherapy
- TTT
- Enucleation
- Chemotherapy
- Laser PHC
- EBRT

Chart showing treatment methods and their respective counts.
Chemoreduction
Group II, III, IV, V

- Reduces tumor volume
- Allows *more focused, less damaging* local measures – TTT, Cryo etc

Makes your job easy!
Chemoreduction VEC Protocol

- Inj. Vincristine 1.5 mg/m² day 1 (0.05 mg/kg BW <36 months age)
- Inj. Etoposide 150 mg/m² day 1&2 (5 mg/kg BW <36 months age)
- Inj. Carboplatin 560 mg/m² day 1 (18.6 mg/kg BW <36 months age)

3 - 4 weekly, 6 cycles, EUA before each cycle

- High dose chemo protocol
  - Vcn 1.5mg/m2; Etop 250mg/m2; Carb 750mg/m2
Chemoreduction: Shield’s Protocol

- **Inj. Carboplatin** 560 mg/m² day 1
  - (18.6 mg/kg BW <36 months age)
- **Inj. Etoposide** 150 mg/m² day 1 and day 2
  - (5 mg/kg BW <36 months age)
- **Inj. Vincristine** 1.5 mg/m² day 1
  - (0.05 mg/kg BW <36 months age)
- High dose protocol
  - Vcn 1.5mg/m2; Etop 250mg/m2; **Carb 750mg/m2**
- **3 - 4** weekly, 6 cycles
- EUA before each cycle
  - Chemocryotherapy and SALT
Retinoblastoma: Chemo Protocol

- **Neo adjuvant chemotherapy** - Chemo reduction (Grp IV, V)
- **Concurrent** - SALT - Sequential Aggressive Local Therapy
  - EUA before each cycle
  - Cryo / TTT → Chemotherapy
- **Adjuvant Chemo** after Enucleation or exenteration

**Chemo Intervals:** 3 - 4 weekly, 6 – 12 cycles
Bilateral Retinoblastoma Chemoreduction
Chemoreduction for retinoblastoma

Chemoreduction alone

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

SALT : Chemoreduction + TTT

Macular tumors

Two large tumors, scar sizes r much smaller than the tumor
Chemoreduction + Focal Rx Results

312 of 375 (83%) eyes regressed with CRD + Focal Rx

337 (90% had eye salvage)
Chemoreduction
Advantages

• Allows for salvage of the eye
• Maximizes potential for residual vision
• Possibly prevents systemic mets
• Delays or prevents pinealoblastoma
Periocular Chemotherapy

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

- 16 mm diameter, 8 mm thickness
- Chemoreduction failure or rec
- Rarely as primary therapy
- Commonly used Iodine$^{125}$, Ruthenium$^{106}$
- 4500-5000 cGy to tumor apex
- 90% success in tumor control
Ruthenium 106

Brachytherapy

Plaque therapy
Plaque Brachytherapy
BEBIG System

Plaque

Brachy therapy
3 yr OU RB, Left enucleated, Right recurrent RB Plaque in 2002

3 yr old from Bihar / Nepal border
now 15 yrs Age
RETINOBLASTOMA

Ext Radiotherapy

Indications

Intra Ocular RB
- Persistent RB
- Rec. Grp V

Extra ocular RB
- Post enucleation
  - Extra ocular extn
- Orbital RB

Minimal Role!
External Beam Radiotherapy

Under Anesthesia
External Radiotherapy

Styrofoam Cutter

Customized Lead block
External Radiotherapy

Customized Lead Block
External Beam Radiotherapy

Unilateral field with Half Beam Block

CENTERED AT ORA SERRATA

3 1/2cm x 7cm FIELD
BLOCKED TO 3 1/2cm x 3 1/2cm
80cm SSD

10

90

50

100
External Beam Radio Therapy

Bilateral fields with Half Beam Blocks
External Beam Radiotherapy

Lateral beam with customized block
External Radiotherapy

Pencil Beam Block for Lens Shielding
High definition Rapid Arc BiL RB
Bil Retinoblastoma - Volumetric ARC
Locally advanced disease
Enucleation

- 1970: 95%
- 1980: 75%
- 1990: 50%
- 2000: 25%
- 2010: <10%!

Changing Trends!
Enucleation

- Advanced unilateral tumor
  - Secondary glaucoma
  - pars plana invasion
  - anterior segment seeding
- Worse eye in advanced bilateral
Enucleation is NOT the end!
It is JUST the beginning!!
Post Enucleation
Histopath risk factors – for adjuvant Chemo / RT

- Anterior chamber infiltr
- Trabecular meshwork infiltr
- Ciliary body infiltration
- Choroid infiltration
- Optic nerve invasion
- Extra Scleral infiltration

Bone marrow & CSF involvement
Histopathologic Risk Factors
285 of 547 (52%)

Numbers do not total up because multiple HRF were present
Adjuvant Chemotherapy

- 6 cycles of VCE - histo risk factors
- 12 cycles of HD Chemo - EOE & ON-TR
Post Enucleation
Adjuvant Orbital EBRT

- Optic nerve invasion @ cut end
- Scleral / extraocular extension
- Inadvertent ocular perforation
- Intraocular surgery in unsuspected retinoblastoma
Does adjuvant therapy help?
Incidence of metastasis

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<tr>
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<th>No adjuvant therapy</th>
<th>Adjuvant therapy</th>
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<tr>
<td>No Metastasis</td>
<td>26 (76%)</td>
<td>44 (96%)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>8 (24%)</td>
<td>2 (4%)</td>
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p = 0.015
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 chemo for 12 cycles

70% Survival!
Neo-adjuvant Chemotherapy
Neo-adjuvant Chemotherapy
## Summary

### Chemoreduction Era

#### Eye Salvage Rates

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* HD Chemotherapy for group V, Periocular chemotherapy for VB
Outcome

N=1067 patients

- 1014 (95%) ALIVE AND WELL
- 23 (2%) ALIVE WITH METASTASIS
- 30 (3%) DEAD WITH METASTASIS

1200
1000
800
600
400
200
0
1014
(95%)
23
(2%)
30
(3%)
Retinoblastoma Overall Outcome

- Overall survival was 95%
- 36% of eyes needed enucleation
- 55% of eyes undergoing enucleation had HP risk factors and needed adjuvant therapy
- Chemoreduction had 90% eye salvage
Bil. Retinoblastoma - Post Chemo / Radiotherapy

Make the Difference!
EYES make World Beautiful
Thank You

Dr. Vijay Anand P. Reddy
Prof, Head, Dept of Oncology
Director, Apollo Cancer Institute, Hyderabad