Updates in the Treatment of Retinoblastoma
Multidisciplinary Management of Solid Tumors in Children
Bangkok, 29-30 June 2015

Retinoblastoma: Incidence and Age Distribution

- Annual Incidence
  - 3.7 cases per million children < 15 years
  - US: 300 new cases/year
- ~3% of all pediatric cancers
- 11% of cancers < 1 yr
- Age at presentation
  - 63% < 2 years
  - 95% < 5 years
- Laterality is age dependent
  - < 1 yr: 42% BL – 58% UL
  - 1-2 yr: 21% BL – 79% UL
  - > 3 yr: 9% BL – 91% UL

Retinoblastoma Biology
- Biallelic inactivation of RB1
  - First hit is germline in heritable form and somatic in sporadic non-heritable form
  - Additional events required for transformation
    - PS3 pathway: MDM2 and MDM4 amplification
    - Epigenetics
      - BCOR mutations
      - SYK upregulation
- Wild type RB1 with MYCN amplification (1.5%)

Retinoblastoma Clinical Presentation

The Retinoblastoma Problem
In US

Treatment of Intraocular RBL with VCR+CBP and Early Focal Treatments

Ocular Survival in 36 eyes
Wilson, Heli, Rodriguez-Galindo, Am J Ophthalmol 2005
### The Retinoblastoma Problem

**In US**
- New Mexico: 6.8
- Alaska: 7.4

**In Developing Countries**
- India: 5.2
- Brazil: 5.9
- Nigeria: 7.6

### Incidence of Retinoblastoma

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence (per million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>4</td>
</tr>
<tr>
<td>New Mexico</td>
<td>6.8</td>
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<tr>
<td>Alaska</td>
<td>7.4</td>
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<td>India</td>
<td>5.2</td>
</tr>
<tr>
<td>Brazil</td>
<td>5.9</td>
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<tr>
<td>Nigeria</td>
<td>7.6</td>
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</tbody>
</table>

### High Incidence of Retinoblastoma in South and Southeast Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Retinoblastoma ASR per million &quot;0-4 years&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam, Ho Chi Minh</td>
<td>14.8</td>
</tr>
<tr>
<td>Singapore, Chinese</td>
<td>18.8</td>
</tr>
<tr>
<td>Philippines</td>
<td>17.4</td>
</tr>
<tr>
<td>Vietnam, Hanoi</td>
<td>18.9</td>
</tr>
<tr>
<td>USA</td>
<td>12</td>
</tr>
</tbody>
</table>

### Incidence of Retinoblastoma

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</table>

**Ethnicity?**
**Environment?**
**Socioeconomic (human development)?**
Embryonal Tumors

- Known (suspected) international variations
- Geographic, ethnic, or socio-economic?
  - Brazil
    - Higher AAIR for retinoblastoma (> in Salvador and Bahia)
    - RB correlates with low SE status
    - NB correlates with high SE status
  - Mexico
    - Low incidence of NB
    - High incidence of RB in Chiapas

Socioeconomic Factors?

The Retinoblastoma Burden

The Burden Gap

Building a Retinoblastoma Program
Building a Retinoblastoma Program

CRADLE
Computer Assisted Detector of LEukocoria

Treatment of Retinoblastoma
The Context

Multidisciplinary Team
- Pediatric Oncologist
- Ophthalmologist
- Radiation Oncologist
- Infrastructure
- Supportive care

Priorities in Treatment
Cure
Eye Salvage
Vision Preservation

Nitin Shrivastava
Alex Power-Hays

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Alex Power-Hays
Incidence of Second Neoplasms in Patients with Bilateral Retinoblastoma is Radiation-Dependent

Cumulative incidence and 95% CIs of new cancers by time since diagnosis of hereditary retinoblastoma by radiotherapy.


Treatment of Retinoblastoma

The Context

Multidisciplinary Team
- Pediatric Oncologist
- Ophthalmologist
- Radiation Oncologist
- Infrastructure
- Supportive care

Priorities in Treatment
- Cure
- Eye Salvage
- Vision Preservation
- Prevention of Neoplasms

Treatment of Retinoblastoma

- Must be individualized
  - Stage, group
  - Laterality
- Major concepts
  - Ocular preservation vs. enucleation
    - Avoid or delay RT
  - Risk-adapted therapies
    - Intraocular vs. orbital vs. extraorbital
  - Two different scenarios: UL and BL
- Avoid or delay RT for ocular salvage
  - Important impact on orbital growth
  - Risk of second malignancies (heritable RB)

Management of Retinoblastoma: Two Scenarios

Intraocular Retinoblastoma
- Ocular Salvage
- Intra-arterial Chemotherapy
- Systemic Chemotherapy
- Focal Treatments
- (Radiation Therapy)

Extraocular Retinoblastoma
- Enucleation
- Ocular Salvage

International Classification System of Intraocular Retinoblastoma

Ocular Salvage vs. Enucleation

A B C D E

Enucleation
Concepts in Ocular Salvage

**Chemoreduction**
- **Systemic**
  - Standard: VCR + CBP + ETO
  - Early stage: VCR + CBP
- **Intra-arterial**
  - Single-agent melphalan
  - Combination CBP/TPT/MEL

**Focal Treatments**
- Cryotherapy (anterior)
- Thermotherapy (posterior)
- Photocoagulation (posterior)
- Brachytherapy (posterior)
- Cryotherapy (anterior)
- Thermotherapy (posterior)
- Photocoagulation (posterior)
- 4-10 DD

Ocular Salvage

**Chemoreduction**
- Systemic
- Early stage: VCR + CBP
- Intra-arterial
- Single-agent melphalan
- Combination CBP/TPT/MEL

**Focal Treatments**
- Cryotherapy (anterior)
- Thermotherapy (posterior)
- Photocoagulation (posterior)
- Brachytherapy (posterior)

**Tumor size**
- Vitreous seeding
- Retinal detachment and seeding

**Progression**
- Radiotherapy (45 Gy)
- Enucleation

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Super-selective Ophthalmic Artery Treatment of Intraocular Rb

The treatment of retinoblastoma by fractional intra-arterial TEM and x-ray therapy

Green arrow: left globe filled with tumor
ICA: solid red arrow
OA: dashed red arrow

Microcatheter with purchase in the OA (dashed red arrow):
no ICA runoff (solid red arrow)
Green arrow: microcatheter tip in the OA

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Super-selective Ophthalmic Artery Treatment of Intraocular Rb

The treatment of retinoblastoma by fractional intra-arterial TEM and x-ray therapy

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I-A Publications

Yamane et al. Int J Clin Oncol 2004
Abramson et al. Ophthalmology 2008
I-A Chemotherapy

95 eyes (78 patients)

RE classification
73 group Vb (= D)
10 group Va
4 group IV
8 groups I-III


Advanced Intraocular Retinoblastoma

What is the role and place of I-A chemotherapy in the treatment of RB?
• Ocular salvage in refractory disease?
• Ocular salvage in unilateral disease?
• Ocular salvage in bilateral disease?
• All of the above?
• How about retinal toxicity? Long term effects? Under-staging?

ARET12P1: A Multi-Institutional Feasibility Study of Intra-Arterial Chemotherapy Given in the Ophthalmic Artery of Children with Retinoblastoma

Study Chairs: M. Chintagumpala, D. Gombos

• Primary Aim
  • Feasibility of I-A MEL for patients with unilateral Group D retinoblastoma

• Secondary Aims
  • Ocular salvage rate
  • Vision outcomes
  • Toxicities

iViT MEL + Chemotherapy for Advanced Bilateral Retinoblastoma

• Long-term effects of I-A MEL on retinal vasculature and vision are not well defined
• Direct delivery of chemotherapy via ophthalmic artery is not possible in a large proportion of young infants with bilateral RB
• Recent data shows safety and efficacy of direct intra-vitreal administration for patients with advanced disease

iViT MEL + Systemic VCE for children with advanced bilateral retinoblastoma
R. Brennan and M. Wilson, Chairs

Therapeutic Targets in Retinoblastoma

* Brennan et al. Can Res 2011;71:4205
Zhang et al. nature 2012; 481:329
### Epigenetics Targeted Library Screening Results

High proportion of hits (active in retinoblastoma cell lines, inactive in BJ) are HDAC inhibitors.

### Pilot: SAHA + CBP + TPT (systemic)

- Days
- Probability EFS

<table>
<thead>
<tr>
<th>Days</th>
<th>Control</th>
<th>VCE</th>
<th>CBP TPT</th>
<th>N-A-P</th>
<th>SAHA</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*p < 0.001*

### Treatment of Intraocular Retinoblastoma

- Ocular Salvage vs. Enucleation
- A, B, C, D, E
- Enucleation
- Ocular Salvage
- Intra-arterial Chemotherapy
- Systemic Chemotherapy
- Focal Treatments (Radiation Therapy)

### Enucleation

- Upfront treatment of advanced disease
  - Always indicated in Group E eyes
  - Alternative to ocular salvage depending on laterality
  - Unilateral > Bilateral
- Treatment after failure of ocular salvage
- Surgery: Expert surgeon
  - Removal of long section of optic nerve (~ 10 mm)
  - Placement of orbital implant
- Histopathological exam

### No high-risk pathology (intra-retinal)

- Observation
  - Examination of orbital socket
  - Examination of contralateral eye
- Imaging not typically required

### High-risk pathology (extra-retinal)

- Adjuvant Chemotherapy
  - VCR/ETO/CBP x 6 (VCR/CYC/DOX)
Retinoblastoma

ARET0332
A Study of Unilateral Retinoblastoma With and Without Histopathologic High-Risk Features and the Role of Adjuvant Chemotherapy
Chair: M. Chintagumpala

Opened 12/05
Activated in 2 Indian Sites

N= 331 patients
30% High-risk pathology
US = India
13-24% discrepancy Institution - Central

Retinoblastoma

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A Study of Unilateral Retinoblastoma With and Without Histopathologic High-Risk Features and the Role of Adjuvant Chemotherapy
Chair: M. Chintagumpala

Opened 12/05 - closed 9/11
Activated in 2 Indian Sites

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Retinoblastoma

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Chair: M. Chintagumpala

Bilateral Retinoblastoma

- Multifocal disease
- Dynamic process
  - Tumors develop until 4-5 years of age
  - Treatment decisions must include (for each eye)
    - Tumor burden ("Group")
    - Potential for vision
    - Status of contralateral eye
- Risk factors for ocular salvage:
  - Tumor size
  - Vitreous seeding
  - Retinal detachment/seeds

Management of Bilateral Retinoblastoma

- Usually more conservative approach than for unilateral RB
- Intra-arterial or systemic chemotherapy + intensive focal treatments (+/- radiation therapy)
- Avoid or delay enucleation and radiation therapy when possible
  - BUT: Surgery is curative and radiation therapy is the single most effective conservative treatment in retinoblastoma
- Side effects of irradiation: bone growth delay and second malignancies
- Timing of enucleation and irradiation also depends on status of contralateral eye
- Ocular salvage rates: 65-75%
### Treatment of Bilateral Retinoblastoma

- **Group A (both eyes):**
  - Focal Treatments
  - Chemotherapy
  - Progression
  - Brachytherapy

- **Group B (worse eye):**
  - 2-drug chemotherapy or I-A chemotherapy
  - Progression
  - Brachytherapy

- **Group C (D worse eye):**
  - 3-drug chemotherapy or I-A chemotherapy
  - Progression
  - Brachytherapy

- **Group E (worse eye):**
  - Treatment based on pathology
  - Enucleation

*EBRT = External beam radiation therapy*

### Management of Retinoblastoma: Two Scenarios

- **Intraocular Retinoblastoma**
- **Extraocular Retinoblastoma**

### Extraocular Retinoblastoma

- **Orbital Retinoblastoma**
  - Trans-scleral involvement
  - + cut end optic nerve
  - + pre-aureicular LN

- **Extra-Orbital (metastatic)**
  - CNS
  - Extra-CNS

### Extraorbital (Metastatic) Retinoblastoma

- < 5% in US (more frequent in low-income countries)
- Metastatic sites
  - Bone
  - Bone marrow
  - Liver
  - CNS
- Extra-CNS disease curable with cisplatin-based chemotherapy + auto HSCT + RT (survival > 50%)
- CNS disease = dismal prognosis

### Extraocular Retinoblastoma

- **Regional**
  - Platinum-based chemotherapy
  - Surgery
  - Radiation therapy

- **Metastatic**
  - If available: HD-chemotherapy and ABMT + Surgery and response-based RT
  - Palliation

### Retinoblastoma

**AR10321**

A Trial of Intensive Multi-Modality Treatment for Extraocular Retinoblastoma

Chair: Ira Dunkel, MD

- VCR
- CDDP
- CYC
- ETO

- ENUC
- RT

- SP
- ETO

- HSCT
Management of Retinoblastoma in LMIC: More than Two Scenarios

Intraocular Retinoblastoma  Extraocular Retinoblastoma

Management of Retinoblastoma in LMIC: More than Two Scenarios

Intraocular Retinoblastoma  Extraocular Retinoblastoma

Management of Retinoblastoma in LMIC: More than Two Scenarios

“Risk in Transition”

Intraocular Retinoblastoma  Extraocular Retinoblastoma

Management of Retinoblastoma in LMIC: More than Two Scenarios

“Risk in Transition”

Intraocular Retinoblastoma  Extraocular Retinoblastoma

Ocular Salvage  Intensive Treatments  Palliation

“Management in Transition”

Retinoblastoma in South and SE Asia

High Incidence of Retinoblastoma in South and Southeast Asia

Retinoblastoma ASR per million "0-4 years"

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International Incidence of Childhood Cancer, IARC Vol 2
**Incidence of Second Neoplasms in Patients with Bilateral Retinoblastoma is Radiation-Dependent**

- Osteosarcoma
- Fibrous histiocytoma
- Leiomysarcoma
- Angiosarcoma
- Rhabdomyosarcoma
- PNTE
- Meningoma
- Glioma
- Schwannoma
- Myoepithelioma

**Incidence of Second Malignancies in Retinoblastoma Survivors**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Observed</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>260 (100%)</td>
<td>19 (16-21)</td>
</tr>
<tr>
<td>Bone</td>
<td>75 (28.9%)</td>
<td>160 (284-483)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>34 (13%)</td>
<td>122 (84-170)</td>
</tr>
<tr>
<td>Nodal arteries</td>
<td>32 (12.3%)</td>
<td>1,111 (760-1,569)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>29 (11.1%)</td>
<td>28 (18-49)</td>
</tr>
<tr>
<td>Eye and orbit</td>
<td>17 (6.5%)</td>
<td>266 (135-426)</td>
</tr>
<tr>
<td>Brain</td>
<td>10 (3.8%)</td>
<td>13.6 (6.5-25)</td>
</tr>
<tr>
<td>Breast</td>
<td>10 (3.8%)</td>
<td>3.96 (1.9-7.3)</td>
</tr>
<tr>
<td>Corpus sphenoid</td>
<td>7 (2.7%)</td>
<td>20 (6.8-43)</td>
</tr>
<tr>
<td>Buccal cavity</td>
<td>7 (2.7%)</td>
<td>20 (8.3-42)</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (1.9%)</td>
<td>5.94 (1.3-14)</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>5 (1.9%)</td>
<td>90.8 (29-212)</td>
</tr>
<tr>
<td>Colon</td>
<td>3 (1.1%)</td>
<td>6.26 (1.3-33)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>3 (1.1%)</td>
<td>3.4 (0.7-10)</td>
</tr>
<tr>
<td>Bladder</td>
<td>2 (0.7%)</td>
<td>6.15 (0.7-22)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2 (0.7%)</td>
<td>3.34 (0.6-12)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2 (0.7%)</td>
<td>2.29 (0.3-8.1)</td>
</tr>
</tbody>
</table>

*SIR: Standardized incidence ratio*

Second Malignancies in Retinoblastoma Survivors

- Most are radiation-induced
  - 60-70% head and neck area
  - Dose-effect
  - Age-effect (higher risk for < 1 yo)
- Malignancies:
  - Osteosarcoma (25-40%): Most common inside and outside irradiated field
  - Soft tissue sarcomas (10-15%): Inside > outside irradiated field (leiomyosarcoma > fibrosarcoma > MFH > STS NOS > RMS)
  - Melanoma and other skin cancers (15-20%)
  - Lung cancer and other common cancers of adulthood

Trilateral Retinoblastoma

- Bilateral RBL + asynchronous midline intracranial tumors
  - Pineoblastomas
    - 3-9% of bilateral RBL
    - Median interval B-RBL to T-RBL: 35 m.
    - Very poor prognosis
  - Lower vertebrae: Pineal gland is a photoreceptive organ
  - Role of screening (MRI every 6 months until 5 years of age): Unclear impact on outcome
  - Caution: > 5% of patients with bilateral RB develop pineal cysts
    - Forme fruste of trilateral retinoblastoma?

Counseling and Screening

Thank You!

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