Retinoblastoma Update 2008

A. Linn Murphree, M.D.
Director, The Retinoblastoma Program
The Vision Center and The Children’s Center for Cancer and Blood Disorders
Children’s Hospital Los Angeles
Professor of Ophthalmology and Pediatrics
Keck School of Medicine, USC

Symposium Lecture Outline

• Terminology/RB1 Testing
• New Stage and Group Classification
• Early Detection/Red Reflex Testing
• Management Issues, Protocols, Cost of Care
• Kaiser/CHLA Shared Management
• View to the Future
Terminology/RB1 Testing
(Pitfalls of “Cliff Note” Thinking)

- Unilateral
- Sporadic
- Bilateral
- Hereditary
- Heritable

RB1 Cancer Predisposition Syndrome

Common errors:
1. Confusing phenotype with genotype
2. Applying group statistics to an individual patient

Age at diagnosis in 178 unilateral and bilateral Rb patients referred for genetic counseling

Expected Findings in Age-at-Diagnosis Plots
(The Case for Routine RB1 Testing)

Age at diagnosis in 99 unilateral sporadic Rb patients with and without germline mutations (including cytogenetic deletions)

Age at Diagnosis is an Unreliable Predictor of RB1 Status
(The Case for Routine RB1 Testing)

Among 17 unilateral germ line (+)patients, 4 had gross deletions, 2 had deletions of the entire RB1 gene, and 11 had intragenic mutations
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New International Stage and Group Classification

Modifications to Staging (Outcome = Patient Survival) is Driven by Needs in Developing Countries

Staging the Disease in the Patient

- Stage 0: No enucleation
- Stage I: Enucleation, tumor completely resected
- Stage II: Enucleation, microscopic residual tumor in orbit
- 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

Grouping -- Retooling Reese-Ellsworth

- Reese-Ellsworth - 1960’s
- Survival of the eye following radiation
- Today Reese-Ellsworth no longer reflects clinical reality

Natural History of Intraocular Retinoblastoma

Key to a Logical Group Classification

1. Symmetrical clonal growth
2. Generate a blood supply
3. Initial "progression of malignancy" mutations
4. Tumors seed diffusely after acquiring anchorage independence
5. Tumors destroy the eye
Early tumors are round

Color: Changes from translucent to opaque yellow-white with acquisition of a blood supply

Independently arising tumors

Response to CEV depends on extent of the blood supply!

Group A and B Tumors
(Confined to retina)
Shape: Round

Group C Tumors
(Early focal intraocular dissemination)
Shape: Nodular

Loss of anchorage dependence

Local Vitreous or Subretinal Seeding

Transition to Groups C and D
Loss of Anchorage Dependence & Adjustment to Hypoxia

Intraocular dissemination begins from tumor “nipple”

Under expression of extracellular matrix adhesion molecules such as fibronectin and its integrin receptors?

Diffuse tumor “seeding”
Group D
Patterns of Presentation

- Fine vitreous haze
- Focal subretinal implantation
- Small to medium vitreous spherules
- Large vitreous spherules and intracocular masses

Group E

• Preoperative Diagnosis:
  - Probable bilateral retinoblastoma, RE > LE
  - Family history of retinoblastoma

• Post Operative Diagnosis:
  - Retinoblastoma, bilateral, familial, 190.5
  - International Stage 0: Group E, RE; Group B, LE

How to Apply both Staging and Grouping
In 1,890 eyes (Web based validation from 20 international centers):

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Early Detection
Teach Our Pediatric Colleagues Correct Red Reflex Testing Skills
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Management Issues

- Routine RB1 screening
- Resistance to chemotherapy
- Focal consolidation – key to success
- Low dose (26-36 Gy) IMRT consolidation of Group D eyes

Open COG Protocols/Cost of Care

- High Risk Pathology Protocol
- Metastatic Disease Protocol
- Group B Protocol
- Group C/D Protocol

- Costs of Treating a Child with Bilateral RB is $200K
- Costs of Treating Unilateral Group E with Ophthalmic Artery Delivery of Mitomycin – (4 injections) $200 K
- RB1 Testing Reduces Costs
Routine RB1 Testing is Cost Effective

- Blue Cross/Blue Shield
- HealthNet
- TriCare
- Blue Cross
- Interplan Corp.
- Pacificare
- Blue Shield
- Cigna

- State of California MediCal/CCS
- Nevada MediCaid
- Kaiser Permanente
- United Healthcare
- AFTRA

With or without tumor tissue (sent to Retinoblastoma Solutions, Inc. in Toronto)

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Thank you!