Early detection of Retinoblastoma in children

Max Mantik
Introduction

- The most common primary intraocular malignancy of childhood
- 10 to 15% of cancers that occur within the first year of life
- Typical as Leukocoria in a child < 2 years
- Untreated retinoblastoma is a deadly disease
- Metastatic spread is typically diagnosed within the first 12 months
- Survival in the contemporary era is >95%
- The prognosis for eye salvage is far lower and depends on the stage of disease at diagnosis
A SEER Program

- Melanoma, 3.0%
- Thyroid cancer, 3.2%
- Germ-cell tumor, 6.1%
- Non-rhabdomyosarcoma STS, 4.2%
- Rhabdomyosarcoma, 2.9%
- Ewing's sarcoma, 1.7%
- Osteosarcoma, 2.9%
- Hepatoblastoma, 0.9%
- Wilms' tumor, 3.9%
- Retinoblastoma, 2.1%
- Neuroblastoma, 5.0%
- ACT, 1.7%
- Other, 5.8%

B PCGP Cohort

- Melanoma, 0.4%
- Rhabdomyosarcoma, 3.8%
- Ewing's sarcoma, 4.1%
- Osteosarcoma, 3.5%
- Retinoblastoma, 1.3%
- Neuroblastoma, 8.9%
- CNS tumors, 21.9%
- Leukemia, 52.5%

EARLY DETECTION
Leukocoria

Window of the world
Prompt referral to an ocular oncologist and appropriate management by a multidisciplinary team are necessary to optimize visual outcome and survival. 
The multidisciplinary team

- Primary care practitioner
- Pediatric ophthalmologist
- Pediatric oncologist
- Radiation oncologist
- Clinical geneticist
- Retina specialist
- Ocular oncologist
- Neuroradiologist
- Craniofacial plastic specialist
- Nurse specialist
- Pharmacist
- Child life specialist
- Clinical social worker
- Low-vision specialist
- Nutritionist
• **Heritable retinoblastoma** – Heritable (hereditary, familial, or germline) retinoblastoma is associated with **germline mutations** (ie, mutations that occur in reproductive cells [sperm and eggs]) in the retinoblastoma (RB1) gene

• **Nonheritable retinoblastoma** – Nonheritable (nonhereditary, nonfamilial, sporadic, or somatic) retinoblastoma results from **somatic mutations** (ie, mutations that occur in nonreproductive cells) in the RB1 gene
Incidence

- 1 in 15,000 to 1 in 16,600 live births
- 13% of cancer in the **first year of life**
- The median age at diagnosis is 18 to 20 months;
- An average of:
  - 12 months for children with bilateral disease
  - 24 months for children with unilateral disease
- 95% < 5 years.
- Boys and girls are the same
Unilateral and bilateral retinoblastoma age-specific incidence rates, age <3, all races both sexes, SEER, 1976-84 and 1986-94

Genetic predisposition

- Retinoblastoma occurs in heritable and nonheritable forms
- **Germline mutations** in the retinoblastoma (RB1) gene ± 40% of cases, predominantly in **bilateral** disease
- **Nonheritable** retinoblastoma incur new **somatic mutations**
- <10% of retinoblastoma patients have a positive family history
PATHOGENESIS

- Mutational inactivation of both alleles of the retinoblastoma (RB1) gene
- Chromosome 13q and encodes a nuclear protein (Rb) that acts as a tumor suppressor
- The Rb protein restricts the cell's ability to progress from the G1 phase to the S phase of the cell cycle
PATHOGENESIS......

• A germline mutation at the RB1 locus (most common) or deletion of chromosome 13q (containing the RB1 gene locus) is present in all cells of the body

• A second "hit," occurring later in development (the second hit of the Knudson two-hit hypothesis), affects the remaining RB1 allele within retinal cells a typical for the heritable form

• A "two-hit" model has been proposed to explain the different clinical features of heritable and nonheritable cases of retinoblastoma
The genetics of retinoblastoma formation

Hereditary (familial) retinoblastoma

First somatic mutation

Second somatic mutation

Result: multifocal, bilateral tumors

Nonhereditary (sporadic) retinoblastoma

Result: unifocal, unilateral tumor

\( \times \) = inactivated RB1 gene
GENE PATTERN

• The Heritable retinoblastoma is associated with germline mutations in the retinoblastoma *RB1* gene.
  • Early age
  • Most cases are bilateral and/or multifocal
  • ± one-quarter have a positive family history
• The nonheritable form results from somatic *RB1* mutations in the tumor only
  • Unilateral and unifocal
  • Negative family history
  • later age
Morphologic features

- Solitary or multifocal, well-circumscribed, translucent intraretinal mass
- In advance → more pink in color, with dilated feeding blood vessels
- Growth pattern
  - **Exophytic** → lead to subretinal seeds
  - **Endophytic** → the anterior chamber and layer behind the cornea, causing a pseudo-hypopyon
  - **Diffuse infiltrating retinoblastoma** → relatively flat (very little vertical growth) and grows intraretinally, mimicking retinitis
The routes of metastatic spread

- **The most common** are the optic nerve to the central nervous system
- **The choroid** into the sclera and into the orbit
- **The subarachnoid space** to the contralateral optic nerve
- The cerebrospinal fluid to the CNS;
- **Hematogenous dissemination** to the lung, bone, liver, or brain; and lymphatic dissemination
Second malignancies

- Heritable retinoblastoma $\Rightarrow$ approximately 30% at 40 years after the original treatment
- In contrast, nonheritable retinoblastoma $\Rightarrow$ less common 2%
- PNET tumors
## Causes of leukocoria in children

<table>
<thead>
<tr>
<th>Lens abnormalities</th>
<th>Optic disc abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract (congenital or acquired)</td>
<td>Colobomata of choroid and optic disc</td>
</tr>
<tr>
<td>Posterior lenticous</td>
<td>Morning glory disc anomaly</td>
</tr>
<tr>
<td></td>
<td>Myelinated nerve fibers</td>
</tr>
<tr>
<td><strong>Vitreous hemorrhage</strong></td>
<td></td>
</tr>
<tr>
<td>Ocular trauma (especially</td>
<td></td>
</tr>
<tr>
<td>penetrating)</td>
<td></td>
</tr>
<tr>
<td><strong>Retinal detachment</strong></td>
<td></td>
</tr>
<tr>
<td>Ocular trauma</td>
<td></td>
</tr>
<tr>
<td>Nonaccidental trauma</td>
<td></td>
</tr>
<tr>
<td>(abusive head trauma)</td>
<td></td>
</tr>
<tr>
<td>Norrie disease</td>
<td></td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
<td></td>
</tr>
<tr>
<td>Cutis marmorata</td>
<td></td>
</tr>
<tr>
<td>telangiectatica</td>
<td></td>
</tr>
<tr>
<td>Turner syndrome</td>
<td></td>
</tr>
<tr>
<td>Walker-Warburg syndrome</td>
<td></td>
</tr>
<tr>
<td>Stickler syndrome</td>
<td></td>
</tr>
<tr>
<td>Familial exudative</td>
<td></td>
</tr>
<tr>
<td>vitreoretinopathy</td>
<td></td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td></td>
</tr>
<tr>
<td><strong>Other retinal abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Coats disease</td>
<td></td>
</tr>
<tr>
<td>Persistent hyperplastic</td>
<td></td>
</tr>
<tr>
<td>primary vitreous (persistent</td>
<td></td>
</tr>
<tr>
<td>fetal vasculature)</td>
<td></td>
</tr>
<tr>
<td>Congenital retinoschisis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intraocular inflammation/infection</strong></td>
<td></td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td></td>
</tr>
<tr>
<td>Ocular toxocariasis</td>
<td></td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td></td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td></td>
</tr>
<tr>
<td>Leukemia (with ocular involvement)</td>
<td></td>
</tr>
<tr>
<td>Choroidal melanoma</td>
<td></td>
</tr>
<tr>
<td>Metastatic tumors</td>
<td></td>
</tr>
<tr>
<td>Choroidal osteoma</td>
<td></td>
</tr>
<tr>
<td>Medulloepithelioma (&quot;diktyoma&quot;)</td>
<td></td>
</tr>
<tr>
<td>Combined hamartoma of the retina</td>
<td></td>
</tr>
<tr>
<td>and the retinal pigment epithelium</td>
<td></td>
</tr>
<tr>
<td>Choroidal hemangioma</td>
<td></td>
</tr>
<tr>
<td>Benign astrocytic hamartomas in</td>
<td></td>
</tr>
<tr>
<td>tuberous sclerosis</td>
<td></td>
</tr>
<tr>
<td>Glioma of the optic nerve head</td>
<td></td>
</tr>
</tbody>
</table>
CAUSES OF LEUKOCORIA

• Retinoblastoma (18 to 62 %)
• Cataract (60 %)
• Persistent fetal vasculature (31 % of those referred for retinoblastoma)
• Coats disease (29 % of those referred for retinoblastoma)
CAUSES OF LEUKOCORIA
less common

- Astrocytic hamartoma
- Coloboma (fissure or cleft) of choroid or optic disc
- Uveitis (pars planitis)
- Toxocariasis
- Retinopathy of prematurity (stage 4, 5)
- Vitreous hemorrhage
- Retinal dysplasia
<table>
<thead>
<tr>
<th>Causes of leukocoria in children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lens abnormalities</strong></td>
</tr>
<tr>
<td>Cataract (congenital or acquired)</td>
</tr>
<tr>
<td>Posterior lenticonus</td>
</tr>
<tr>
<td><strong>Vitreous hemorrhage</strong></td>
</tr>
<tr>
<td>Ocular trauma (especially penetrating)</td>
</tr>
<tr>
<td><strong>Retinal detachment</strong></td>
</tr>
<tr>
<td>Ocular trauma</td>
</tr>
<tr>
<td>Nonaccidental trauma (abusive head trauma)</td>
</tr>
<tr>
<td>Norrie disease</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
</tr>
<tr>
<td>Cutis marmorata telangiectatica</td>
</tr>
<tr>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Walker-Warburg syndrome</td>
</tr>
<tr>
<td>Stickler syndrome</td>
</tr>
<tr>
<td>Familial exudative vitreoretinopathy</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td><strong>Other retinal abnormalities</strong></td>
</tr>
<tr>
<td>Coats disease</td>
</tr>
<tr>
<td>Persistent hyperplastic primary vitreous (persistent fetal vasculature)</td>
</tr>
<tr>
<td>Congenital retinoschisis</td>
</tr>
<tr>
<td><strong>Optic disc abnormalities</strong></td>
</tr>
<tr>
<td>Colobomata of choroid and optic disc</td>
</tr>
<tr>
<td>Morning glory disc anomaly</td>
</tr>
<tr>
<td>Myelinated nerve fibers</td>
</tr>
<tr>
<td><strong>Intraocular inflammation/infection</strong></td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Ocular toxocariasis</td>
</tr>
<tr>
<td>Endophthalmitis</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
</tr>
<tr>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>Leukemia (with ocular involvement)</td>
</tr>
<tr>
<td>Choroidal melanoma</td>
</tr>
<tr>
<td>Metastatic tumors</td>
</tr>
<tr>
<td>Choroidal osteoma</td>
</tr>
<tr>
<td>Medulloepithelioma (“diktyoma”)</td>
</tr>
<tr>
<td>Combined hamartoma of the retina and the retinal pigment epithelium</td>
</tr>
<tr>
<td>Choroidal hemangioma</td>
</tr>
<tr>
<td>Benign astrocytic hamartomas in tuberous sclerosis</td>
</tr>
<tr>
<td>Glioma of the optic nerve head</td>
</tr>
</tbody>
</table>
## Assessment of the visual system in infants and children

<table>
<thead>
<tr>
<th>Age</th>
<th>Important aspects of history</th>
<th>Examination</th>
<th>Ophthalmology referral indications</th>
</tr>
</thead>
</table>
| Newborn to 6 months | Birth weight <3500 grams or gestational age <30 weeks Family history of:  - Congenital cataracts  - Retinoblastoma  - Metabolic or genetic disease | Vision assessment (fixate and follow response)  - External eye examination (lids, orbit, conjunctiva, cornea, irus)  - Pupillary response  - Simultaneous red reflex | - Positive history  
- Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of 21 mm, unilateral ptilisis, unable to fix and follow by age 3 months) |
| 6 to 12 months | Neurologic abnormality  
Systemic disease associated with eye abnormalities  
Does the infant recognize faces and objects?  
Does the infant fix and follow?  
Do the parents notice:  - Eye deviation?  - Tearing? | Vision assessment (fixate and follow response)  
- External eye examination (lids, orbit, conjunctiva, cornea, irus)  
- Pupillary response  
- Simultaneous red reflex | - Positive history  
- Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of 21 mm, unilateral ptilisis, unable to fix and follow) |
| 1 to 3 years | Neurologic abnormality  
Systemic disease associated with eye abnormalities  
Does the child recognize faces and objects?  
Does the child fix and follow?  
Do the parents notice:  - Eye deviation?  - Tearing? | Age-appropriate visual assessment:  - Infants and young toddlers: Fixate and follow response  
- Cooperative older toddlers: Monocular visual acuity with HRT® or LEA® eoptotypes  
- Instrument-based vision screening (eg, photoscreening, autorefrac) if available  
- External eye examination (lids, orbit, conjunctiva, cornea, irus)  
- Pupillary response  
- Simultaneous red reflex  
- Ophthalmoscopy if possible | - Positive history  
- Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of 21 mm, unilateral ptilisis)  
- Eye preference or unable to fix and follow  
- Ocular alignment abnormalities  
- Visual acuity worse than 20/50 in one or both eyes  
- Visual acuity difference of two or more lines between eyes  
- Failed instrument-based screening as indicated by the device |
| 4 to 5 years | Neurologic abnormality  
Systemic disease associated with eye abnormalities  
Does the child recognize faces and objects?  
Do the parents notice:  - Abnormal head posturing?  - Squinting or blepharospasm?  - Eye deviation?  - Tearing? | External eye examination (lids, orbit, conjunctiva, cornea, irus)  
- Pupillary response  
- Simultaneous red reflex  
- Corneal light reflex  
- Ocular alignment (cover-uncover test)  
- Monocular visual acuity:  - Sloan or Snellen letters or numbers  
- Surrounded HRT® or LEA® eoptotypes  
- Instrument-based vision screening (eg, photoscreening, autorefrac) if available  
- Ophthalmoscopy if possible | - Positive history  
- Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of 21 mm, unilateral ptilisis)  
- Eye preference  
- Ocular alignment abnormalities  
- Visual acuity worse than 20/40 for children 48 through 59 months or worse than 20/20 for children 46 months in one or both eyes  
- Visual acuity difference of two or more lines between eyes  
- Failed instrument-based screening as indicated by the device |
| >6 years | Neurologic abnormality  
Systemic disease associated with eye abnormalities  
Does the child recognize faces and objects?  
Do the parents notice:  - Abnormal head posturing?  - Squinting or blepharospasm?  - Eye deviation?  - Tearing? | External eye examination (lids, orbit, conjunctiva, cornea, irus)  
- Pupillary response  
- Simultaneous red reflex  
- Monocular visual acuity:  - Sloan or Snellen letters or numbers  
- Surrounded HRT®  
- LEA symbols®  
- Ophthalmoscopy if possible | - Positive history  
- Abnormal examination (eg, abnormal red reflex, pupillary asymmetry of 21 mm, unilateral ptilisis)  
- Eye preference  
- Ocular alignment abnormalities  
- Visual acuity worse than 20/30 in one or both eyes  
- Visual acuity difference of two or more lines between eyes |
SCREENING CHILDREN AT RISK

• A positive family history
• A personal of family history of 13q deletion or retinoblastoma [RB1] gene mosaicism
• Should be evaluated by an ophthalmologist shortly after birth
• Every 1 to 2 months during the first 2 years of life
Metastatic evaluation

- Rarely present at the time of diagnosis
- Formal staging studies (ie, bone marrow examination, lumbar puncture, and/or radionuclide bone scan) are not routinely performed due to their low yield
- If there is clear evidence of tumor outside the eye (ie, optic nerve invasion, or choroidal involvement that is extensive) a full metastatic evaluation may be pursued
  - Bone marrow aspiration and biopsy
  - Lumbar puncture
  - Radionuclide bone scan
Genetic testing and counseling

• Are important aspects in the management of patients with retinoblastoma in order to estimate the risk of disease in family members and future offspring

• Understand the genetic consequences of each form of retinoblastoma (relates to secondary cancers in children with heritable retinoblastoma)
### International classification of retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Specific features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Very low risk: Eyes with small discrete tumors away from critical structures</td>
<td>Tumor ≤3 mm in basal dimension or thickness</td>
</tr>
</tbody>
</table>
| B     | Low risk: Eyes with discrete retinal tumor of any size or location without vitreous or subretinal seeding | Tumor >3 mm in basal dimension or thickness, or any of the following:  
  - Macular location ≤3 mm to foveola  
  - Juxtapapillary location ≤1.5 mm to disc  
  - Clear subretinal fluid ≤3 mm from margin |
| C     | Moderate risk: Eyes discrete retinal tumors of any size or location with only focal vitreous or subretinal seeding | One of the following:  
  - Subretinal seeds ≤3 mm from tumor  
  - Vitreous seeds ≤3 mm from tumor  
  - Both subretinal and vitreous seeds ≤3 mm from tumor  
  - Less than one quadrant of subretinal fluid in the fundus |
| D     | High risk: Eyes with massive nondiscrete tumors and/or diffuse vitreous or subretinal seeding | One of the following:  
  - Subretinal seeds >3 mm from tumor  
  - Vitreous seeds >3 mm from tumor  
  - Both subretinal and vitreous seeds >3 mm from tumor  
  - Greater than one quadrant of subretinal fluid in the fundus |
| E     | Very high risk: Eyes that have been destroyed anatomically or functionally by the tumor | Extensive retinoblastoma, or one of the following:  
  - Neovascular glaucoma  
  - Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space  
  - Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber  
  - Tumor anterior to the anterior vitreous face, including the ciliary body or iris  
  - Diffuse infiltrating tumor  
  - Phthisis bulbi or orbital cellulitis |
Algorithmic overview of initial treatment options for children with newly diagnosed retinoblastoma based on disease classification

Child with newly diagnosed retinoblastoma

Is there metastatic disease?

Metastatic disease

Intensive multimodal therapy with/without stem cell rescue is commonly used; however, this approach remains experimental

Is the disease unilateral or bilateral?

Unilateral

What is the disease classification?

Unilateral group A tumors

Treatment options include:
- Laser photocoagulation
- Cryotherapy
- Plaque radiation therapy

Unilateral group B tumors

Treatment depends on size and location of tumor:
- Small peripheral tumors may be treated with local therapies (e.g., laser photocoagulation, cryotherapy)
- Larger, central tumors are treated with intra-arterial or systemic chemotherapy

Unilateral group C and D tumors

Treatment options include:
- Ophthalmic artery chemosurgery
- Systemic chemotherapy
- Intravitreal chemotherapy (used in conjunction with intra-arterial or systemic chemotherapy)

Unilateral group E tumors

Treatment involves:
- Enucleation
- Adjunct chemotherapy and radiosurgery for high-risk patients

Both eyes have greater than group A or B disease (or bilateral macular and/or papillary involvement)

Both eyes have group A or B disease with sparing of the macula and papilla

Treatment options for both eyes include:
- Laser photocoagulation
- Cryotherapy
- Plaque radiation therapy

Group A or B with sparing of the macula and papilla in one eye; greater involvement in the second eye

Treatment options for the least affected eye include:
- Ophthalmic artery chemosurgery
- Systemic chemotherapy
- Intravitreal chemotherapy (used in conjunction with intra-arterial or systemic chemotherapy)
- Enucleation (group E tumors)

Treatment options for the second eye include:
- Ophthalmic artery chemosurgery
- Systemic chemotherapy
- Intravitreal chemotherapy (used in conjunction with intra-arterial or systemic chemotherapy)
- Enucleation (group E tumors)

Bilateral

What is the disease classification in each eye?
Ultrasonography of retinoblastoma (right eye)
Retinoblastoma on magnetic resonance imaging
SUMMARY

• The most common primary intraocular malignancy of childhood and accounts for 10 to 15 percent of cancers within the first year of life
• Retinoblastoma occurs in heritable (approximately 40 % of cases) and nonheritable (approximately 60 % of cases) forms
• Should undergo clinical screening and/or genetic testing for retinoblastoma
• The evaluation by an ocular oncologist and includes Complete physical examination, Ophthalmologic examination, ultrasonography, MRI of the brain and orbits
• Metastatic disease is rarely present at the time of diagnosis, and formal staging studies are not routinely performed
• Molecular genetic testing is suggested for all affected patients
Thankyou
Family history

- Are presumed to have heritable retinoblastoma
- 50% risk of passing the mutation on to their offspring
- Patients with an RB1 germline mutation have a 90 percent chance of the mutation manifesting with retinoblastoma
## Summary of molecular genetic testing used in retinoblastoma

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Test method</th>
<th>Mutations detected</th>
<th>Mutation detection frequency by test method</th>
<th>Test availability</th>
</tr>
</thead>
</table>
| *RBB1*     | Gross deletion/duplication analysis*<sup>1</sup>  
Heterozygosity testing  
MLPA, quantitative multiplex PCR, other methods*<sup>2</sup>  
Mutation scanning  
Sequence analysis (genomic)  
Targeted mutation analysis  
Methylation analysis  
Sequence analysis of RNA from blood | Submicroscopic deletions and translocations  
Submicroscopic whole exon(s) deletions, insertions, and rearrangements  
Single-base substitutions, small length mutations  
Specific panel of recurrent point mutations  
Hypermethylation of the promoter region  
(Deep intronic) splice mutations, gross rearrangements | >8%  
8%  
16%  
70 to 75%  
25%  
10 to 12%<sup>3</sup>  
<5%<sup>4</sup> | For a list of available laboratories, please see [the Genetic Testing Registry](http://www.genetests.org) |

*<sup>1</sup>*<sup>1</sup> For a list of available laboratories, please see [the Genetic Testing Registry](http://www.genetests.org)
Approach to the child with leukocoria
Retinoblastoma gross pathology
Retinoblastoma pathology
Strabismus as presenting manifestation of retinoblastoma

Exotropia plus slightly enlarged corneal diameter and loss of red reflex in left eye.
Combined exophytic-endophytic retinoblastoma