Retinoblastoma

Retinoblastoma (RB) is the most common childhood intraocular tumor. However, it is rare, accounting for 1% to 3% of all childhood cancers. The tumor originates in one or both eyes, arising from embryonic retinal cells and growing into the vitreous humor and the sub-retinal space. The tumor has a variable growth rate and may have a single or multiple foci in one (unilateral) or both eyes (bilateral).

Twenty-five to forty percent of retinoblastomas are bilateral and hereditary (familial) (A – 1); and approximately 60-75 % are unilateral and occur as a (A – 2) non-hereditary, spontaneous (sporadic) form. The term “familial” or “hereditary” is commonly used for bilateral retinoblastoma. However, only 25% of children with bilateral disease have family history of retinoblastoma. The other 75% usually acquire the mutation of the RB1 gene in utero, in the absence of a family history of this cancer.

However, from then on, these survivors can transmit the mutation to their children. Bilateral RB is often diagnosed at an early age (< 1 year old), and is often hereditary, while unilateral RB is commonly diagnosed during the toddler years.

In rare cases, RB can present as trilateral disease involving the pineal gland. Trilateral retinoblastoma is a pineal tumor typically appearing approximately 3-5 years after diagnosis of bilateral RB. It is often associated with high mortality.

Risk Factors:

The retinoblastoma gene (RB1) is located on band 14 of chromosome 13. RB1 is a tumor suppressor gene (acts as a brake on the cell division cycle to prevent uncontrolled cell division). The loss of RB1 causes unregulated cell proliferation and tumor development. Abnormalities in the retinoblastoma gene not associated with RB are very common and occur in many types of malignancies.

Researchers have proposed a (A – 3) two-step model of oncogenesis (two-hit hypothesis) to explain the development of retinoblastoma. In hereditary RB, loss of regulation of cell proliferation results from both an initial germline mutation (inherited mutation affecting all cells) and a secondary somatic mutation (occurring after conception). The hereditary form is...
Retinoblastoma transmitted as an autosomal dominant trait (A – 4 90% penetrance). Children who inherit the RB1 mutation have a high incidence of non-ocular, second tumors, a significant part of which are osteosarcomas believed to be caused by the same mutation.

In sporadic/non-hereditary RB, the first and second mutations occur in the retinal cells and are generally associated with unilateral disease.

Congenital anomalies are not commonly associated with retinoblastoma. When instead of a mutation of the RB1 gene there is a deletion of the long arm of chromosome 13, patients may present with what is called “13q- syndrome,” which is characterized by bilateral retinoblastoma, mental retardation and a characteristic facies. This syndrome accounts for less than 5% of all cases of bilateral retinoblastoma.

Clinical signs and symptoms

Most RB diagnosis occurs during the first three years of life. Prospective screening of children with a positive family history can detect the disease before clinical symptoms are evident. Parents are often the first ones to note early signs and symptoms. The most common presentation is “leukocoria,” that is, a white reflex through the pupil. This reflex can often be seen in a flash photograph, when the child has a (A – 5) red eye in a picture instead of “white eyes.”

The second most common reason for consultation is the presence of strabismus, or lazy eye.

Finally, parents may report behaviors that suggest vision changes, such as bumping into things, missing part of the meal, and frequently ignoring toys on one side of the field of vision. Health care providers should take note of these comments and investigate the possibility of retinoblastoma.

Common clinical symptoms are:

- (A – 6) Leukocoria: “cat’s eye reflex,” “white eyes,” white pupil, the most common presentation
- (A - 7) Strabismus: esotropia (eye turning in) and extropia (eyes turning out)
- Decreased vision: especially if only in one eye (unilateral)
- Painful eyes
- Erythematous conjunctivae
  (Hardeman, B., 2004)

Diagnostic Workup:

- Complete history of illness including familial incidence of retinoblastoma, ocular loss of unknown etiology, decreased vision in one eye, changes in the appearance of eyes. The child may be bumping into things because he does not see them.
- Physical exam assesses visual acuity and tracking, strabismus, esotropia, exotropia, and leukocoria
- A – 8 Funduscopic exam (direct or indirect) is done under anesthesia by a retinal surgeon
Retinoblastoma

- Ultrasound and CT of the brain and orbits to confirm diagnosis and detect extent of the disease; and to identify areas of tumor calcification. Biopsy is not performed as a confirmatory procedure because of the danger of extraocular tumor spread.
- A – 9 MRI of orbits to localize the intraocular extent of the disease.
- Examination of bone marrow aspirate and CSF to determine tumor dissemination to extraocular sites, such as the CNS.

- Tumor Staging:
  - International Classification for Intraocular Retinoblastoma determines the extent of intraocular disease.
  - International Staging System evaluates extraocular and disease dissemination.

Treatment:

The treatment for RB depends on the size of the tumor and the extent of the disease. Treatment goals are aimed at curing the cancer while maximizing useful vision and decreasing the risk for late effects, especially a secondary malignancy.

The treatment of RB is individualized and takes into account the laterality of the tumor, its size, location, number of lesions, and extent of the disease. In cases of bilateral RB, the eyes are treated independently.

Treatment modalities for retinoblastoma include:

- **Surgical enucleation:** Complete removal of the eye is recommended when there is no chance for vision in the affected eye due to advanced disease.
- **Cryotherapy:** A freezing process that kills tumor cells is used mostly for tumors in the anterior retina.
- **Photocoagulation:** Using a laser to destroy the blood vessels supplying the tumor in order to starve the tumor and cause necrosis; used for posteriorly situated tumors.
- **Thermotherapy:** The use of heat from a laser to destroy the cancer cells; the heat can also improve the efficacy of chemotherapy or radiotherapy.
- **Radiation therapy (RT):** Considered for use when the eye has potential useful vision.
- **External Beam RT:** Used in multifocal advanced disease, usually after chemotherapy and focal treatments. Lateral or anterior fields are used.
- **Brachytherapy (Radioactive applicators - Plaques):** Used to treat individual tumors that are too large for treatment with cryotherapy, laser or thermotherapy, usually after chemotherapy. It requires a surgical implantation of the plaques in the outer surface of the eye, which remain for approximately 4 days to deliver the radiation locally, after which time they are removed surgically.
Chemotherapy: In patients with bilateral disease, chemotherapy is generally used prior to cryotherapy, photocoagulation, or plaque RT. The goal of chemotherapy in these cases is to reduce tumor burden, facilitate focal treatments, preserve vision, and to avoid or postpone radiation therapy.

In patients with unilateral disease, chemotherapy is used after enucleation if the pathological evaluation of the enucleated eye suggests that there is a risk of extraocular dissemination, or when there is evidence of metastatic disease at diagnosis. Common chemotherapy agents used include:

- Carboplatin
- Etoposide (VP 16)
- Vincristine (Oncovin)
- Cyclophosphamide
- Doxorubicin

Disseminated/Extraocular Retinoblastoma

Retinoblastoma grows rapidly and often disseminates through direct extension across the ocular coats (choroids, sclera, and episcleral vessels) and the optic nerve (beyond the lamina cribrosa). With appropriate and timely treatments (orbital irradiation and chemotherapy), the outcome for orbital disease is still favorable, with 60-70% cure rates. Poor outcomes are often associated with extraorbital extension.

RB usually metastasizes to the bones, bone marrow, liver, and CNS. CNS involvement in RB patients is an ominous sign, and often has a dismal prognosis. Patients with metastatic disease outside the brain may still be cured with intensive chemotherapy and consolidation with an autologous hematopoietic stem cell transplant.

Treatment Late Effects:

Radiation: erythema, epilation, conjunctivitis, scleral injection, dermatitis, keratitis, decreased corneal sensation leading to corneal ulcerations, myopia, iritis, retinal edema, decreased tear production, and retarded orbital bone growth.

External orbital irradiation: cataract, retinopathy, vitreous hemorrhage, orbital deformities, glaucoma, degenerative shrinkage of the eye, decreased corneal sensation/ulcerations, Chronic dry eye/ulcerations
Second cancers in the irradiated area (skin cancer and soft tissue and bone sarcomas)

Changes in peripheral vision that can cause reading problems that interfere with schoolwork and learning.
Visual field deficits
Scotoma (areas of visual loss)

A major concern is the occurrence of second malignancies in survivors of bilateral retinoblastoma. The most common cancers are osteosarcoma, fibrosarcoma and other spindle cell sarcomas. However, the risk of developing any type of cancer is increased in this population. Early after treatment, two-thirds of the cancers occur in the radiation field; however, as patients grow, cancers develop elsewhere. The incidence of second malignancies increases over time, implying the need for continued surveillance and monitoring.

Future Directions

Though much progress has been made in developing effective therapies, retinoblastoma, with 5 year survival rates up to 90%, clinical investigations seek to further improve treatment modalities while reducing treatment side effects.

Subtenon (subconjunctival) chemotherapy is generally used in conjunction with systemic and local therapies for RB with vitreous seeding. In subtenon chemotherapy, carboplatin is administered directly into the subconjunctival space by a trained ophthalmologist. Early data suggests this approach is somewhat effective, and the level of toxicity is acceptable.

Increased understanding of the molecular pathogenesis of RB will lead to better prevention and screening. Studies of RB-specific antigens and genetic markers will provide improved diagnostic, prophylactic, and treatment strategies. In patients with inherited RB, gene therapy, including direct transfer of the tumor suppressor gene, transfer of genes that encode a particular toxic product, and the use of a vector/suicide gene (HSV-TK) to introduce drug-sensitive genes into the RB cell, might hold promise for improved outcome.
Helpful Web Links:

**Retinoblastoma – MedNews - The National Cancer Institute**
This website contains professional information about retinoblastoma, its diagnosis and treatments.  
http://www.meb.uni-bonn.de/cancer.gov/CDR0000062846.html

**Children’s Cancer Web**
This site contains information on various resources available for retinoblastoma patients and their families.  
http://www.cancerindex.org/ccw/guide2r.htm

**American Cancer Society**
This web site contains detailed information about retinoblastoma. Good resource.  
http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=37

**Eye Cancer Network**
This website contains information on retinoblastoma, genetic abnormalities associated with RTB, and treatment modalities.  

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  Michael Dyer, Ph.D., Barrett Haik, MD, Carlos Rodriguez-Galindo, MD and Matthew Wilson, MD  
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Appendix

A – 1  Hereditary/Familial Retinoblastoma

In this family tree (genogram), the grandmother (I) has retinoblastoma disease. Out of the three children (II), a daughter and a son develop the disease. Two of the son’s children (III), a male and a female, also develop the retinoblastoma.

A – 2  Sporadic/Spontaneous/Non Hereditary Retinoblastoma

Out of 3 generations, only a daughter (II) develops the disease.
A – 3 Two-Step Model of Oncogenesis
Process of RB Development

A. Germline Predisposition

B. Sporadic Cases

Penetrance
The fraction of the individuals carrying the gene for a trait who manifest the condition; the probability that a person inheriting the mutation will have the disease. A trait (RB mutation) with 90% penetrance will not be manifested by 10% of the people possessing the gene.
A – 8  Retinoblastoma Tumor on Funduscopic Examination

Carlos Rodriguez-Galindo, MD, St. Jude Children's Research Hospital
Retinoblastoma

A – 5  Red Eye

A – 6  White Eye (Leukocoria)

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A - 7 Strabismus and leucocoria

Carlos Rodriguez-Galindo, MD St. Jude Children's Research Hospital

A – 9 MRI Retinoblastoma

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A - 10 International Classification for Intraocular Retinoblastoma

**Group A**

*Small tumors away from foveola and disc*

- Tumors ≤3 mm in greatest dimension confined to the retina, and
- Located at least 3 mm from the foveola and 1.5 mm from the optic disc

**Group B**

*All remaining tumors confined to the retina*

- All other tumors confined to the retina not in Group A
- Subretinal fluid (without subretinal seeding) ≤3 mm from the base of the tumor

**Group C**

*Local subretinal fluid or seeding*

- Local subretinal fluid alone >3 to ≤6 mm from the tumor
- Vitreous seeding or subretinal seeding ≤3 mm from the tumor

**Group D**

*Diffuse subretinal fluid or seeding*

- Subretinal fluid alone >6 mm from the tumor
- Vitreous seeding or subretinal seeding >3 mm from tumor

**Group E**

*Presence of any or more of these poor prognosis features*

- More than 2/3 globe filled with tumor *
- Tumor in anterior segment
- Tumor in or on the ciliary body
- Iris neovascularization
- Neovascular glaucoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

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A – 11. International Retinoblastoma Staging System

**Group I.**
- a. Patients (eyes) treated conservatively
- b. Patients (eyes) enucleated with completely resected tumors

**Group II.** Incompletely resected
Resected tumor with microscopic disease with microscopic residual

- N0. No tumor in optic nerve
- N1. Prelaminar invasion
- N2. Retrolaminar invasion
- N3. Resection margin and/or subarachnoid invasion
- NX. Unknown

- C0. Choroid negative
- C1. Minor choroid invasion
- C2. Massive choroidal invasion

- S0. No scleral involvement
- S1. Microscopical extension into sclera
- S2. Microscopical extension through sclera into the orbit

**Group III.** Regional extension
- a. Overt orbital disease
- b. Pre-auricular or cervical lymph node extension

**Group IV.** Metastatic disease
- a) Hematogenous metastasis
  - 1. Single lesion
  - 2. Multiple lesions
- b) CNS extension
  - 1. Prechiasmatic lesion
  - 2. CNS mass
  - 3. Leptomeningeal and CSF disease