Definition

- Retinoblastoma is a primary malignant neoplasm of the retina that arises from immature retinal cells.
- It is the most common primary intraocular malignancy of childhood.
What is so special about Retinoblastoma?

- Retinoblastoma has a strong tendency to invade the brain via the optic nerve and metastasize widely.
- Untreated children typically die of their disease within 2–4 years of the onset of symptoms.
Pathogenesis

• Retinoblastoma is of 2 types:
  1. Congenital Retinoblastoma.
  2. Sporadic Retinoblastoma.
• These 2 types of Retinoblastoma have 2 different pathogenesis.
Role Of RB Gene In Cell Cycle

GROWTH INHIBITORS (TGF-β, p53, others)

Stimulate

CDK Inhibitors
p16 (INK4a)

Inactivate

Cyclins D/CDK4,6
Cyclin E/CDK2

Activate

GROWTH FACTORS (EGF, PDGF)

Hyperphosphorylated RB

E2F

Histone deacetylase

Histone methyltransferase

E2F site

S phase genes

Transcriptional activation

Transcriptional block
Pathogenesis of Congenital RB [33%]

- In all of the patients of congenital RB, there is a germline mutation in the RB gene, that is, the mutation is present in all the cells of the body.
- For this reason, these patients are also at a greater risk of developing tumors elsewhere in the body.
- These patients usually develop Retinoblastoma in both the eyes [bilateral].
- Within the eyes, several tumors may be identified. Then it is called “Multifocal Retinoblastoma”.
Pathogenesis Of Sporadic RB [67%]

• In these patients, the mutation in the RB GENE is not germline, but they appear only in one cell of the retina.
• So, the risk of developing tumor elsewhere in the body [as in congenital RB] is not there.
• Patients usually develop unilateral tumor, only in one eye.
What is Trilateral RB?

- Children who have germinal retinoblastoma have a strong tendency to develop non-retinoblastoma malignancies.
- Around the time of diagnosis of the intraocular disease, a primary non-retinoblastoma intracranial malignancy (Pineoblastoma/Ectopic intracranial retinoblastoma) is the most common neoplasm encountered.
- Presenting features of such a tumor include somnolence, headache and other neurological symptoms.
Trilateral RB Continued......

• Central nervous system imaging studies show a solid tumor that involves the suprasellar or parasellar regions of the brain.
• Because this type of tumor usually occurs in children who have germinal retinoblastoma and bilateral disease, this association is commonly referred to as trilateral retinoblastoma.
• The intracranial malignancy has a strong tendency to seed the cerebrospinal fluid and thereby spawn implantation tumors along the spinal cord. This malignancy is usually fatal.
MRI showing a cystic enhancing mass of the pineal gland [Suspicious for Pineoblastoma] in a patient with hereditary retinoblastoma: A case of Trilateral Retinoblastoma.
Clinical Manifestations

• The most common presenting manifestation of retinoblastoma is a white glow in the pupil (leukokoria).

• This appearance is caused by reflection of light from the white intraocular tumor.
• The second most common presenting manifestation is strabismus.
• It should be noted that strabismus is a medical condition in which both eyes can’t look at the same place at the same time.
• It occurs when one eye turns in/ out/ up/ down.
• Common causes of strabismus are poor eye muscle control/ high amount of farsightedness.
• Because of the association between RB and strabismus, every child who has strabismus must undergo a complete ophthalmic examination to rule out RB.
About 25% of retinoblastoma is first noted as a result of strabismus
Less Common Ocular Manifestations Of RB

1. Red eye.
2. Excessive tearing.
3. Globe expansion (Buphthalmos).
5. Discoloration of the iris in the involved eye (usually caused by iris neovascularization).
6. Loss of the fundus reflex in the affected eye due to intraocular bleeding from the tumor.
7. Clumping/layering of white tumor cells on the iris/in the aqueous humor.
8. Spontaneous hyphema [Blood in angle of AC].
Diagnostic Tests

- Slit-lamp biomicroscopy.
- Indirect ophthalmoscopy.
- B-scan ultrasonography.
- Computed tomography (CT): Confirmation of diagnosis of an intraocular tumor.
- Magnetic resonance imaging (MRI) is the most useful and informative tool for evaluating the sellar and parasellar regions of the brain (to rule out ectopic intracranial retinoblastoma) and for studying the orbital soft tissues and optic nerve for evidence of extraocular tumor extension.
Fundoscopic view of a typical intraretinal retinoblastoma. Opaque, yellow-white macular tumor fed and drained by dilated, tortuous retinal blood vessels.
B-scan USG of Retinoblastoma showing solid, posterior intraocular mass contains strong particulate reflections attributable to intralesional calcification.
CT scan of unilateral intraocular retinoblastoma. Intraocular masses appear bright because of intrablastic calcification.
Contrast-enhanced T1-weighted MR image of a 34-month-old patient with nonhereditary retinoblastoma with a pineal cyst, with a diameter of 7 mm.
**Standard baseline clinical evaluation of children who have newly been diagnosed as Retinoblastoma**

- Complete pediatric history and physical examination.
- Blood for complete blood count (CBC).
- MRI or CT of brain, especially in bilateral or familial cases to look for ectopic intracranial Retinoblastoma.
- Lumbar puncture for CSF analysis[*].
- Bone marrow aspiration or biopsy[*].
- Bone scan[*].

*Currently advocated only for children with advanced intraocular disease or clinically extraocular disease at baseline.*
Retinoblastoma is characterized histopathologically by malignant neuroepithelial cells (retinoblasts) that arise within the immature retina.

- The retinoblasts typically appear to have a large basophilic nucleus and scanty cytoplasm.
- Cellular necrosis and intralesional calcification are frequent associations, especially in larger tumors.
Histopathologic examination of RB. Viable tumor cells clustered around blood vessels and small foci of necrotic cells between the larger masses of the cells.
Treatment Options

- Intravenous chemotherapy
- Enucleation
- External beam radiation therapy
- Plaque Radiation Therapy
- Laser therapy:
  1. Photocoagulation
  2. Transpupillary thermotheraphy (TTT)
- Cryotherapy.
Intravenous Chemotherapy

- Chemotherapy is currently the primary therapeutic option in most children with bilateral retinoblastoma.
- It is also employed as initial treatment in some children with unilateral disease when the affected eye is believed to be salvageable.
- The most common chemotherapeutic regimen in use around the world today consists of a combination of Carboplatin, Etoposide and Vincristine (CEV regimen).
• In some centers, **cyclosporine** is added to this regimen to reduce the multidrug resistance that occurs in many retinoblastomas.

• It is usually given as a cyclic treatment every 3–4 weeks for six or more cycles.

• Most intraocular retinoblastoma lesions (including intravitreal and subretinal seeds) regress substantially within the first two cycles.
Enucleation

• This treatment is particularly applicable to children who have unilateral advanced intraocular disease.

• Enucleation is sometimes recommended for both eyes in children who have bilateral far-advanced disease not amenable to any eye-preserving therapy.

• At the end of this presentation, there is a complete guide to Enucleation.
External Beam Radiation Therapy

- External beam radiation therapy is applicable to eyes containing one or more tumors that involve the optic disc, eyes that show diffuse intravitreal or subretinal seeding and eyes for which prior chemo-therapy or local treatments have been failed.
- Standard target doses of radiation to the eye and orbit are in the range of 40–50 Gy given in multiple fractions of 150–200 cGy over 4–5 weeks.
- External beam radiation therapy results in highly effective regression of vascularized retinal tumors.
- Even very large, cohesive retinoblastomas commonly show pronounced clinical regression within several weeks after treatment.
Plaque Radiation Therapy

• Plaque radiation therapy entails surgical implantation of a radioactive device (eye plaque) on the sclera overlying the intraocular tumor, leaving the plaque in place for a sufficient period of time (usually 2–5 days) to provide a predetermined radiation dose to the apex of the tumor, and subsequent surgical removal of the plaque.

• This form of therapy seems particularly applicable to eyes that contain a solitary medium to large tumor that does not involve the optic disc or macula and is associated with no more than a limited amount of adjacent intravitreal or subretinal tumor seeding.
Laser Therapy

• In *Photocoagulation*, a medical laser of appropriate wavelength (most commonly an argon green laser) is employed at sufficient power settings to produce almost instantaneous pronounced whitening of the target tissues.

• In *Transpupillary thermotherapy* (TTT), an infrared laser beam is directed at the retinal tumor using an operating microscope or indirect ophthalmoscope delivery system in series to produce dull white discoloration of the portion of the tumor covered by the spot.
Cryotherapy

- It is a focal treatment method that destroys targeted intraocular tissues by means of freezing.
- In this therapy, the ophthalmologist uses an insulated retinal cryoprobe to indent the sclera overlying the tumor and indirect ophthalmoscopy to monitor the position of the indentation in the fundus.
- Once the probe tip is positioned at the site of a retinal tumor, the ophthalmologist activates the probe to begin freezing.
- The ice ball that forms is allowed to encompass the entire tumor (if the tumor is small) or a portion of the tumor (if the tumor is larger) and extend into the overlying vitreous. The probe is then deactivated and the ice ball is allowed to thaw.
A Special Guide To Enucleation

- Definition
- Indications for Enucleation
- Preoperative work up and counseling
- Surgical procedure
- Post operative care
Definition

- Enucleation is defined as the removal of the entire globe with preservation of the eye muscles.
Indications for Enucleation

1. Blind painful eye.
2. Intraocular tumor.
4. Phthisis bulbi.
5. Microphthalmia.
6. Endophthalmitis/ Panophthalmitis.
7. Cosmetic deformity.
Preoperative Work Up

• Complete ophthalmological examination with unequivocal diagnosis of retinoblastoma based on clinical and radiological examination.
• Routine pre-anaesthetic workup.
• A minimum of 9-10 gms% of hemoglobin is mandatory. If the hemoglobin is lower, the same is built up with packed cell transfusions before surgery.
• Preoperative planning for placement of orbital implant.
**Pre-operative Counseling**

The parents of the child should be thoroughly counseled. The nature of surgery should be explained. Counseling should include detailed explanation that:

1. The eyeball cannot be replaced with a seeing eye.
2. The implants and prosthesis will be given to achieve cosmetic correction.
3. The enucleated eyeball requires histopathological examination and this will suggest further treatment plan and future follow up.
4. Informed special consent should be obtained from the parents for enucleation.
Surgical Procedure

- Eye is prepared and draped.
- Lid speculum is placed.
- 360° conjunctival peritomy is done.
360° conjunctival peritomy being done....
Tenon’s adhesions to sclera are cleared in all 4 quadrants with tenotomy scissors.

Pediatric muscle hook is used to hook the recti, one at a time.

Each rectus muscle is tagged with double-armed 6-0 vicryl sutures passed 3-4 mm beyond the insertion.

The rectus muscle is cut at the insertion leaving behind a small 1-2 mm stump attached to the sclera.
The inferior and superior oblique muscles are isolated and cut.
The hook is swept next to the globe and all other adhesions are lysed.
The speculum is next removed and the globe is prolapsed by pushing the lid margins backwards.
The optic nerve can be cut either from the temporal side or nasal side.
Globe is prolapsed upwards and enucleation guide is passed underneath while engaging the optic nerve after the extraocular muscles are cut from the globe....
Enucleation scissor is passed below the enucleation guide and optic nerve is cut as posteriorly as possible to get a long stump....
• The eye is removed after teasing away any surrounding tissues.
• The orbit is packed with wet gauze and firm pressure is applied to secure hemostasis.
• The implant is placed in the orbit (soak in antibiotic solution before placing the same).
• The preplaced 6-0 vicryl sutures attached to the recti will help anchor them.
• Conjunctiva and tenon’s capsule are closed in layers with 6-0 vicryl suture.
• Antibiotic ointment is instilled and a conformer is placed.
• Pressure pad and bandage is applied.
Globe is examined for extra scleral extension and adhesions. Optic nerve length and thickness at base is measured....
Implant is placed deep into the socket....
Post operative Care

• Post operative dressing is done.
• Topical antibiotic ointment is prescribed.
• Oral antibiotics are preferably given at the discretion of surgeon.
• Ocular prosthesis is given 4-6 weeks following surgery.
• Patient should be kept under close follow up till the histopathological report is available.
Thank You......

Courtesy:

• Yanoff’s Ophthalmology.
• Parson’s Disease Of The Eye.
• National Guidelines In The Management Of Retinoblastoma (India).
• Brain Abnormalities on MR Imaging in Patients with Retinoblastoma: A Report.
• Retinoblastoma: American Cancer Society.
• National Institute Of Health [NIH].