RETINOBLASTOMA
INTRODUCTION

» Most common intraocular malignancy of childhood arising from embryonic multipotent neural retinal cell.

» Seventh MC solid tumor in childhood.

» Unifocal/multifocal.

» Unilateral (70%) or bilateral (30%).

» Sporadic (94%) or familial (6%).

» Non hereditary (50-60%) or hereditary (40-50%).

» Congenital disease though usually not recognized at birth.
**HISTORY**

» First mentioned by Petras Pawius in Amsterdam in 1597.

» James Wardrop, a scottish surgeon first recommended enucleation for saving lives in patients of retinoblastoma in 1809.

» Verhoeff confirmed the origin from undifferentiated retinal cells, named retinoblastoma in 1900’s.

» American Ophthalmology Society first adopted the term retinoblastoma in 1926.
EPIDEMIOLOGY

» **Median age** –
  » Unilateral: 2 years, 80% cases are below 3 to 4 years.
  » Bilateral: < 12 months.

» **Incidence** –
  » 1 in 15,000-20,000 live births in the US, higher in developing countries including India (about 1532 cases per year, highest in the world).
  » No racial or gender predilection.

» **Congenital anomalies** –
  » Associated in 0.05% cases of retinoblastoma.
  » Cleft palate, dentinogenesis imperfecta, incontinentia pigmenti etc. with no mental impairment.
FORMS OF PRESENTATION

SPORADIC (Non-hereditary)
» Unilateral, unifocal.
» 60% of all cases.
» Present later.
» Children of the affected are normal.
» Chromosomal anomaly is a somatic mutation.
» Relatives have a low risk of RB development.

FAMILIAL (Hereditary)
» 85% bilateral, multifocal.
» 40% of all cases.
» Present earlier.
» Children of the affected have 45% chance of inheritance.
» Chromosomal anomaly is a germline mutation.
» Relatives have a high risk of RB development.
» Autosomal dominant with high penetrance.
GENETICS

» RB represents a prototypical model demonstrating genetic etiology of cancer.

» It is caused by mutation of the RB gene, a TSG on long arm of chromosome 13 (13q14.1-q14.2).

» Normal individual inherits two copies of this gene one from each parent.

ALFRED KNUDSON’S TWO HIT HYPOTHESIS (1971)
Two separate loss of function mutations are required to inactivate both the homologous loci of the RB gene for malignant phenotype to be expressed
Two mutations are required for the development of retinoblastoma.

**Sporadic retinoblastoma**

- Child starts with two wild type alleles (RB+/RB+).
- Both alleles must mutate to produce the disease (RB/RB).
- Probability of both mutations occurring in the same cell is low; only one tumor forms (e.g., one eye).
- First hit occurs after conception in utero or in early childhood in retinal cells.
- All cells in body are not affected as germ cells are not involved.
- Second somatic mutation results in loss of other normal allele.
Hereditary retinoblastoma

» Child starts with heterozygous alleles (RB/RB+).
» Only one mutation is required to produce disease (RB/RB).
» Mutations resulting in loss of heterozygosity (LOH) are more probable in rapidly dividing cells, and multiple tumors occur (e.g., both eyes).
» First hit occurs in utero in germ cells before conception or is inherited from a parent.
» All cells of body affected.
» Second hit occurs in any retinal cell.
» Increased risk for second malignancies
Hereditary retinoblastoma

Sporadic retinoblastoma

Single mutation

First mutation

Second mutation

Retinoblastoma

Retinoblastoma
MOLECULAR PATHOGENESIS

- RB1 protein: cell cycle regulator, checkpoint between G1 & S-phase.

- Key factor in RB protein functioning is the phosphorylation status.

- Normally unphosphorylated and suppresses entry into S-phase by binding to E2F (transcription apparatus).

- Phosphorylation by cyclin/cdk’s abolishes inhibition & causes dissociation of E2F which binds to DNA & promotes progression through cell cycle.
EVENTS IN CELL CYCLE

Note Rb Dephosphorylation

Note Rb phosphorylation
Phosphorylation of retinoblastoma protein by cyclin/cdk abolishes inhibition of gene transcription
GENETIC COUNSELLING

- Parents having a child with RB (at the time of enucleation or during treatment) & patients with family history of RB should undergo genetic counselling (blood sample only).
- Recommendation: examination at birth & 4 monthly thereafter until 4 years of age.
- Tumor tissue & blood required in sporadic cases while only blood sample sufficient in inherited cases.
- Molecular tests:
  - **Direct analysis** of the constitutional mutation of RB1 gene performed on constitutional DNA.
  - **Indirect analysis** of the allele carrying the mutation.
  - Tumor cell **LOH evaluation**.
- Patients should be informed about the risk of transmission and of second primary malignant tumor development (20% at 10 years, 50% at 20 years & 90% at 30 years).
PATTERNS OF GROWTH

TUMOR

ENDOPHYTIC
- Arises from inner layers of retina.
- Fills the vitreous cavity
- Anteriorly reaches aqueous venous channels
- May permeate through lymphatic channels
- Visual disturbance & white eye reflex.

EXOPHYTIC
- Arises from outer layers of retina.
- Fills the subretinal space.
- Posteriorly causes serous RD.
- Choroidal invasion through Bruch’s membrane.
- Proptosis & RD.

MIXED
- Most common growth pattern

DIFFUSE INFILTRATING
- No mass, only signs of endophthalmitis.
- Average age 6 years.
- Pseudohypopyon resembling inflammatory reaction.
- Diagnosis delayed & most difficult.
- UL & sporadic
Endophytic lesion

White eye reflex.

Exophytic lesion

Proptosis.
**NATURAL HISTORY**

- Rapidly progressive tumor.
- Untreated fills the eye & completely destroys the globe within 6 months i.e local extension is the rule.
- Metastasis (BM, bone, LNs and liver) is rare at presentation.
- Complete tumor regression may occur by unknown mechanism (occlusion of central retinal artery, severe inflammatory reaction and massive necrosis leading to pthisis bulbi).

**ROUTES OF SPREAD**

- Direct local Tumor infiltration
  - Choroid invasion
  - Scleral invasion
  - Orbital soft tissue, bone & brain invasion
- Subarachnoid Space Of optic nerve
- Anterior spread to Conjunctiva, Eyelids & Extra ocular tissue
- Hematogenous dissemination From orbital, bone or lymphatic invasion
- CSF dissemination To brain & spine
- Lymphatic dissemination
HISTOPATHOLOGY

- Composed of uniform small round or polygonal mitotically active cells.
- Vaible tumor cells surround blood vessels & form pseudorosettes.
- Cells are arranged in three characteristic types:
  - Flexner-Wintersteiner rosette: characteristic of RB but also seen in pineoblastoma & medulloepithelioma. Cells resembles retinoblasts of embryo.
  - Homer-Wright rosette.
  - Fleurette

Also –
- Calcification +++
- Necrosis ++
- Multifocality.
CLINICAL PRESENTATION

- Developed countries: present with signs rather than symptoms, IO tumor without local extension.
- Developing countries: diagnosed only after an enlarged eye or gross orbital extension.

1. **Leucokoria (60%)**: lack of red reflex of the eye in large tumors, RD, retrolental mass or vitreous opacification due to tumor cells which is often noticed by the mother.
2. **Strabismus (20%)**: disruption of fusional reflex due to loss of central vision from a tumor in the macula.
3. **Rubeosis iridis (17%)**: MC in advanced cases due to extensive tumor necrosis releasing angiogenic factors.
4. **Heterochromia**.
5. Spontaneous **hyphaema**
6. **Glaucoma**: neovascular or closed angle.
7. **Pseudohypopyon**: seeding of AC in endophytic or diffuse infiltrating tumors.
8. **Pain**: glaucoma or inflammation.
9. **Proptosis** of eye.
DIFFERENTIAL DIAGNOSIS

LEOCOKORIA

TOXOCARIASIS

• Congenital: trayd of convulsions, cerebral calcificaton & BL chorioretinitis + cataract + microphthalmus.
• Non congenital: in older children in UL eye due to localized inflammation by dead larvae.
• Diagnosed by ELISA IgM & angiography.
• Mimics endophytic RB.

PHPV

• Embryonal vessels do not regress resulting in anterior RD or posterior subcapsular cataract.
• Associated with retinal dysplasia.
• No H/O prematurity or oxygen administration.
• Mimics endophytic RB

COAT’S DISEASE

• Congenital retinal telangiectasias.
• MC in males UL in first or second decade.
• Peripheral localized fusiform dilations of retinal vessel.
• Exudation rich in lipids & foamy macrophages into subretinal space results in RD.
• Mimics exophytic RB.
DIAGNOSTIC EVALUATION

HISTORY: Administration of oxygen at birth, eating of dirt, association with dogs & FH of bone tumors or RB.

SYMPTOMS & SIGNS: Ocular as well as systemic.

OPHTHALMOSCOPIC EUA:

- Indirect ophthalmoscopy with pupillary dilation & general anesthesia.
- Number, size, location (anterior or posterior), laterality, disc diameter, subretinal fluid or seeds noted and degree of exophthalmos measured.
- Detailed mapping done with appropriate diagrams & description (relation with ora serrata, optic disc & macula).
- Creamy pink or snow white mass projecting into the vitreous.
- Poorly developed stroma gives way to tumor bits forming vitreal seeds
- RD, vitreal opacification & h’ge make diagnosis difficult.
STAGING

- Though most cases are diagnosed clinically, imaging is done:
  - Confirm diagnosis.
  - Estimate tumor size.
  - Document intralesional calcium.
  - Assess for spread of tumor into optic nerve, choroid, sclera & orbit.
  - Detect ectopic disease in pineal or suprasellar region.
- Differentiating RB from other ocular lesions in child presenting with atypical features (only RD or opaque vitreous, atypical mass).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular fundus under general anesthesia +</td>
<td>Any patient with retinoblastoma Schema, photographs, ultrasonography Reese grouping, new grouping</td>
</tr>
<tr>
<td>Brain and orbit CT scan or MRI +</td>
<td>Almost any patient with retinoblastoma (except neonatal screened patients with tumor respecting the head of optic nerve)</td>
</tr>
<tr>
<td>CSF cytology Bone marrow cytohistology +</td>
<td>When enucleation is necessary and shows histopathologic risk factors</td>
</tr>
<tr>
<td>Brain and spinal axis MRI Bone scan</td>
<td>Only in case of orbital, lymph node and/or distant metastatic diseases</td>
</tr>
</tbody>
</table>
OCULAR ULTRASOUND

- Demonstrates a mass more echogenic than the vitreous on B mode & highly reflective intrinsic echoes of fine calcifications on A mode.
- RD may also be seen in exophytic tumors.
- Accuracy: 80% (limited by vitreal opacities & RD).
- Limited evaluation of medial & lateral extension, extraocular disease.
- Colour doppler displays normal & tumor vasculature & differentiates subretinal or choroidal h’ge from neoplasms
CT/MRI

- 90% show calcification
- Dense homogenous
- Extension to choroid, vitreous & sclera not reliable.
- Detects intracranial disease

- 3D multiplanar capability.
- Hyperintense to vitreous on T1 & markedly hypointense on T2
- Delineation of ON, IO & EO spread
- Differentiates between tumor, RD & subretinal fluid.
ROLE OF FNAC

- Tissue biopsy confirmation not necessary: typical clinical & radiological findings.
- Resistance to performance of biopsy: may result in EO seeding & misdiagnosed as uveitis.
- FNAC with 30 G needle avoids vascularized conjunctiva of the limbus & the orbit, sclera & pars plana preventing possible spread of cells through the needle tract.
- Needle tract: peripheral cornea, AC, iris, ciliary body & tumor.
- Overall accuracy 95%
- Indicated only in selected patients:
  - diagnosis is ambiguous or
  - obvious EO extension.
### TABLE 14 Reese–Ellsworth classification for intraocular retinoblastoma

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Tumour characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I: very favourable prognosis</td>
<td>a: Solitary tumour, smaller than 4 disc diameters in size, at or behind the equator</td>
</tr>
<tr>
<td></td>
<td>b: Multiple tumours, none greater than 4 disc diameters in size, all at or behind the equator</td>
</tr>
<tr>
<td>Group II: favourable prognosis</td>
<td>a: Solitary tumour, 4–10 disc diameters in size, at or behind the equator</td>
</tr>
<tr>
<td></td>
<td>b: Multiple tumours, 4–10 disc diameters in size, all at or behind the equator</td>
</tr>
<tr>
<td>Group III: doubtful prognosis</td>
<td>a: Any lesion anterior to the equator</td>
</tr>
<tr>
<td></td>
<td>b: Solitary tumour, larger than 10 disc diameter, behind the equator</td>
</tr>
<tr>
<td>Group IV: unfavourable prognosis</td>
<td>a: Multiple tumours, some greater than 10 disc diameters</td>
</tr>
<tr>
<td></td>
<td>b: Any lesion extending anteriorly to the ora serrata</td>
</tr>
<tr>
<td>Group V: very unfavourable prognosis</td>
<td>a: Massive tumours involving more than half of the retina</td>
</tr>
<tr>
<td></td>
<td>b: Vitreous seeding</td>
</tr>
</tbody>
</table>

### TABLE 15 International Classification for Intraocular Retinoblastoma

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Tumour characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A: small intraretinal tumours away from fovea and disc</td>
<td>All tumours are 3 mm or smaller, confined to the retina, and are located further than 3 mm from the fovea and 1.5 mm from the optic disc</td>
</tr>
<tr>
<td>Group B: all remaining discrete tumours confined to the retina</td>
<td>All tumours confined to the retina not in group A</td>
</tr>
<tr>
<td></td>
<td>Tumour-associated subretinal fluid less than 3 mm from the tumour with no subretinal seeding</td>
</tr>
<tr>
<td>Group C: discrete local disease with minimal subretinal or vitreous seeding</td>
<td>Tumour(s) are discrete</td>
</tr>
<tr>
<td></td>
<td>Subretinal fluid, present or past, without seeding, involving up to one-quarter of the retina</td>
</tr>
<tr>
<td></td>
<td>Local subretinal seeding, less than 3 mm (2 disc diameters) from the tumour</td>
</tr>
<tr>
<td></td>
<td>Local fine vitreous seeding close to discrete tumour</td>
</tr>
<tr>
<td>Group D: diffuse disease with significant vitreous or subretinal seeding</td>
<td>Tumour(s) may be massive or diffuse</td>
</tr>
<tr>
<td></td>
<td>Subretinal fluid, present or past, without seeding, involving up to total retinal detachment</td>
</tr>
<tr>
<td></td>
<td>Diffuse subretinal seeding, may include subretinal plaques or tumour nodules</td>
</tr>
<tr>
<td></td>
<td>Diffuse or massive vitreous disease, may include ‘greasy’ seeds or avascular tumour masses</td>
</tr>
<tr>
<td>Group E: presence of any one or more of these poor prognosis features</td>
<td>Tumour touching the lens, neovascular glaucoma, tumour anterior to anterior vitreous face involving ciliary body or anterior segment, diffuse infiltrating retinoblastoma, opaque media from haemorrhage, tumour necrosis with aseptic orbital cellulitis, or phthisis bulbi</td>
</tr>
</tbody>
</table>
STAGING SYSTEMS-PATHOLOGICAL

St. JUDE’S STAGING
I: Tumor unifocal/multifocal confined to retina
   A. Occupying one quadrant or less
   B. Occupying two quadrants or less
   C. Occupying more than 50% of retinal surface.
II: Tumor unifocal/multifocal confined to globe
   A. With vitreous seeding
   B. Extending to optic nerve head
   C. Extending to choroid & optic nerve head.
   D. B+C
   E. Extending to emissaries.
III: Extraocular extension of tumor (regional)
   A. Extension beyond cut end of ON.
   B. Extension through sclera into orbital contents.
   C. Extension through choroid & beyond cut end of ON.
   D. Extension through sclera into orbital contents and beyond cut end of ON.
IV: Distant metastasis
   A. Extending through ON to brain.
   B. Blood borne metastasis to soft tissues & bone.
   C. Bone marrow involvement.

AJCC SYSTEM:
Clinical & Pathological

TABLE 16: Gubrowski and Abrahamson classification for intraocular and extraocular retinoblastoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour localisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Intraocular disease</td>
</tr>
<tr>
<td></td>
<td>a: retinal disease</td>
</tr>
<tr>
<td></td>
<td>b: extension to the lamina cribrosa</td>
</tr>
<tr>
<td></td>
<td>c: uveal extension</td>
</tr>
<tr>
<td>II</td>
<td>Orbital disease</td>
</tr>
<tr>
<td></td>
<td>Orbital tumour</td>
</tr>
<tr>
<td></td>
<td>a1: scattered epidermal cells</td>
</tr>
<tr>
<td></td>
<td>a2: tumour mass</td>
</tr>
<tr>
<td></td>
<td>Optic nerve</td>
</tr>
<tr>
<td></td>
<td>b1: optic nerve; line of section and meninges clear</td>
</tr>
<tr>
<td></td>
<td>b2: tumour at line of section or in the meninges</td>
</tr>
<tr>
<td>III</td>
<td>Intracranial metastasis</td>
</tr>
<tr>
<td></td>
<td>a: positive bone marrow alone</td>
</tr>
<tr>
<td></td>
<td>b: focal bone lesions with or without positive marrow</td>
</tr>
<tr>
<td></td>
<td>c: other organ involvement</td>
</tr>
</tbody>
</table>
PROGNOSTIC FACTORS

- Optic nerve invasion in the most important poor prognostic factor.
- Massive invasion of choroid, CB: increases possibility of hematogenous spread (60% risk of mets) & extension to extrascleral tissues (6 years DFS 90% in IO disease versus 10% for EO disease).
- Gross extraorbital extension has >90% risk of metastasis.
- Poorly differentiated tumor.
- Anterior chamber invasion, mortality 20 to 80%.
- Large tumor with vitreous seeding.
- Rubeosis iridis.
- Glaucoma.
- Bilateral tumors behave poorly as mortality resulta from second cancers & trilateral RB.
- Trilateral RB has almost 100% fatality.
<table>
<thead>
<tr>
<th>EXTENT OF INVASION OF ON</th>
<th>MORTALITY RATE</th>
<th>SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>10%</td>
<td>Similar to uninvolved ON 90%</td>
</tr>
<tr>
<td>Upto Lamina cribrosa</td>
<td>29%</td>
<td>60%</td>
</tr>
<tr>
<td>Posterior to Lamina cribrosa</td>
<td>42%</td>
<td>20%</td>
</tr>
<tr>
<td>Positive transected margin</td>
<td>80%</td>
<td>better</td>
</tr>
<tr>
<td>Stump of ON &gt;5mm</td>
<td>better</td>
<td>better</td>
</tr>
</tbody>
</table>
MANAGEMENT OF RB

» Complex issue.
» Multidisciplinary approach: Ocular oncologist, pediatric oncologist, radiation oncologist, radiologist and child psychologist.
» Treatment is tailored to each individual.
» Goals of treatment:
  » Save life.
  » Preserve vision or salvage eye (i.e. avoid enucleation).
  » Minimize any complications or side effects of therapy.
» Choice of therapy:
  » Risk of metastatic disease.
  » Systemic status.
  » Laterality of disease/size/location of tumor.
  » Visual prognosis.
  » Risk of second cancers.
**Disease:**

- **Unilateral**
  - Limited
  - Advanced

- **Bi-lateral**
  - Limited
  - Advanced

- **Metastatic**

**PRESENTATION**
TRADITIONAL TREATMENT OF RB

Unilateral

- Treated with enucleation, fellow eye observed till school age.

Bilateral

• More advanced side enucleation, less advanced side EBRT.
• BL enucleation if bilateral advanced disease.

metastatic

- Systemic CT, palliative treatment

- Treatment strategies have evolved over past few decades.
- Enucleation has decreased in number and trend towards vision/eye preservation.
- Multidisciplinary approach.
TREATMENT OPTIONS

» ENUCLEATION
» EXENTERATION
» EBRT

» FOCAL THERAPIES
  » PLAQUE RADIOTHERAPY
  » LASER PHOTOCOAGULATION
  » CRYOTHERAPY
  » THERMOTHERAPY
  » CHEMOTHERMOTHERAPY

» CHEMOREDUCTION
  » INTRAVENOUS
  » SUBCONJUNCTIVAL
  » TRANSPUPILLARY

» SYSTEMIC CHEMOTHERAPY
OF PATIENTS PREVIOUSLY TREATED WITH RADIO- THERAPY 60% REQUIRE FURTHER FOCAL THERAPY.

OF PATIENTS TREATED WITH EBRT 20% ULTIMATELY REQUIRE ENUCLEATION.
Fig 2: Guidelines for management of advanced unilateral RB

Evidence of Extraocular Dissemination

- No
  - Primary Enucleation
    - Low risk Histology
      - Observation
    - High risk Histology
      - Multimodality [EBRT ± CT]
- Yes
  - Neoadjuvant Chemotherapy
    - Response
      - Yes
        - Only orbital or p.a. node disease
      - No
        - CNS or systemic metastasis
          - Consider HDCT and ASCR

**Low Risk histology:** intraretinal extension, prelaminar optic nerve and isolated choroidal invasion (or both); patients with post-laminar optic nerve invasion and surgical margin free of tumor

**High Risk histology:** any degree of scleral invasion, post-laminar optic nerve (resection margin free of tumor) invasion with choroidal invasion. All patients with post-laminar optic nerve invasion beyond the cut end.

EBRT: external beam radiation therapy; CT: chemotherapy; p.a.: pre-auricular; CNS: Central nervous system; HDCT: high dose chemotherapy; ASCR: autologous stem-cell rescue.
Fig 3: Guidelines for management of Bilateral RB

Bilateral RB

Chemotherapy x 2 to 4 cycles

Good Response

- Yes
  - Amenable to local therapy
    - No
      - Further Chemoreduction
      - Shrinkage
      - Amenable to local therapy
    - Yes
      - Cryo/Photocoag
      - Cont. Chemo (total 6 to 12 cycles)
      - No response

- No
  - Potentially useful vision
    - Yes
      - EBRT
      - Chemotherapy
    - No
      - Brachytherapy
ENUCLEATION

INDICATIONS

» Unilateral or bilateral RB completely filling the globe with no hope of visual salvage due to damage to entire retina.

» Tumor invasion in optic nerve, choroid, AC, pars plana or orbit.

» Painful glaucoma with loss of vision.

» Tumor unresponsive to other forms of conservative treatment.

» Inability to examine retina secondary to vitreous h'ge or cataract following conservative therapy.

PROCEDURE

» Involves removal of the eye leaving behind lids and extraocular muscles but removing the longest possible segment (10 to 15mm) of optic nerve in continuity with the globe.

» Care should be taken to avoid perforation of the globe to prevent seeding.

  » Scleral perforation at the site of muscle insertions.

  » Traction sutures in the muscles.

» ON snares or clamps should be avoided to prevent crush artefact which may be misinterpreted as invasion by tumor.
ORBITAL IMPLANTS

- Historically not used due to potential interference with palpation of the socket and clinical detection of orbital recurrence.
- However CT/MR allow detailed orbital analysis despite an implant.
- PMMA, hydroxyapatite and polyethylene implants are commonly used 4 to 6 weeks after enucleation.
ROLE OF ADJUVANT THERAPY AFTER ENUCLEATION

ENUCLEATION by an experienced surgeon:
- sufficient resection optic nerve
- implant

HISTOPATHOLOGIC examination by an experienced pathologist:
- tumor sampling for molecular analysis
- complete examination of the eye

- microscopic extrascleral involvement
- involvement of the resection margin of the optic nerve

Chemotherapy
orbital irradiation

- massive choroidal involvement
  and/or
- retrolaminar involvement of the optic nerve
  and/or
- anterior chamber involvement

Chemotherapy (debated)

Specialized onco-ophthalmologic evaluation to discuss the indication of a conservative approach in case of:
- screening in familial RB
- young age of the patient
- small tumor
- lack of posterior pole tumor
- multifocal retinoblastoma

- no or minimal choroidal involvement
  and/or
- no or pretinal optic nerve involvement

No adjuvant treatment (debated)
CHEMOTHERAPY

GOALS OF CHEMOTHERAPY:
Reduction of tumor size → RD dealt with focal therapy is the standard of care in early stage disease.

1. Reduce the use of EBRT which reduces second malignancies and orbitofacial growth anomalies in early stage.
2. Reduce the need of enucleation in early stage.
3. Reduce the risk of local and systemic relapse in advanced stage.
4. Improve survival in metastatic disease.

» Neoadjuvant:
  » IORB - BL disease, UL disease not amenable to local therapy (6 to 12 cycles).
  » EORB – Orbit/bone involvement, TRB, metastatic spread (prolonged duration of CT 12 to 18 months).

» Adjuvant postoperative: High risk histopathological features.
» Salvage: recurrent disease in an only eye.
### TABLE 6. Comparison of EBRT, Enucleation, and Ocular Salvage Rate in Patients With Retinoblastoma Treated in the Current Study and in Studies Incorporating a 3-drug Chemotherapy Regimen and/or Etoposide, Plus Sequential Aggressive Local Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Eyes</th>
<th>% of Eyes Without EBRT or ENUC</th>
<th>Salvage Rate</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>27</td>
<td>59.3%</td>
<td>81.5%</td>
<td>32 eyes treated with vincristine + teniposide + carboplatin, 8 eyes treated with vincristine + teniposide; 5 of 40 eyes underwent EBRT and/or ENUC</td>
</tr>
<tr>
<td>Gallie et al, 1996</td>
<td>40</td>
<td>87.5%</td>
<td>N/A</td>
<td>3-drug chemotherapy (carboplatin + etoposide + vincristine) + SALT</td>
</tr>
<tr>
<td>Murphree et al, 1996</td>
<td>35</td>
<td>42.9%</td>
<td>42.9%</td>
<td>3-drug chemotherapy (carboplatin + etoposide + vincristine) + EBRT in all eyes; all eyes RE group Va or Vb</td>
</tr>
<tr>
<td>Kingston et al, 1996</td>
<td>28</td>
<td>0.0%</td>
<td>60.7% (10 ENUC + 1 patient who died w/o ENUC)</td>
<td>3-drug chemotherapy (carboplatin + etoposide + vincristine) + EBRT in all eyes; all eyes RE group Va or Vb</td>
</tr>
<tr>
<td>Beck et al, 2000</td>
<td>33</td>
<td>60.6%</td>
<td>81.8%</td>
<td>2-drug chemotherapy (etoposide + carboplatin) + SALT</td>
</tr>
<tr>
<td>Brichard et al, 2002</td>
<td>33</td>
<td>60.6%</td>
<td>60.6%</td>
<td>3-drug chemotherapy (carboplatin + vincristine + etoposide) + SALT</td>
</tr>
<tr>
<td>Shields et al, 2002</td>
<td>158</td>
<td>61.3%</td>
<td>76.6%</td>
<td>3-drug chemotherapy (vincristine + etoposide + carboplatin) + SALT</td>
</tr>
</tbody>
</table>

EBRT = external beam radiotherapy, ENUC = enucleation, SALT = sequential aggressive local therapy.
# EYE PRESERVATION AS PER STAGE

<table>
<thead>
<tr>
<th></th>
<th>EYES PRESERVED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RE I to III</td>
</tr>
<tr>
<td>EBRT ALONE</td>
<td>53%</td>
</tr>
<tr>
<td>EBRT + SALVAGE</td>
<td>96%</td>
</tr>
<tr>
<td>CT ALONE</td>
<td>29%</td>
</tr>
<tr>
<td>CT + SALVAGE</td>
<td>94%</td>
</tr>
<tr>
<td>CTRT</td>
<td>-</td>
</tr>
</tbody>
</table>

**Visual results Limited by**

- Macular involvement
- Tractional RD
- Hemorrhage
CHEMOREDUCTION NOT CHEMOTHERAPY

» Chemoreduction alone: not effective even for early lesions.
» Reese-Ellsworth eye groups 1, 2, or 3: systemic chemotherapy + local ophthalmic therapies can eliminate the need for enucleation or EBRT without significant systemic toxicity.
» Reese-Ellsworth eye groups 4 and 5: more effective therapy required
» Requirement RT: RE group V, tumor thickness >5 mm, VS, female gender, subretinal fluid, retinal tumor recurrence after previous chemoraduction.
» Enucleation requirement: RE group V, tumor base >15mm, thickness >5mm, age > 12 months, tumor proximity to foveola within 2mm.
» Cautious follow-up recommended: risk for late (upto 5 years) recurrent vitreous and subretinal seeds is substantial and proper treatment is critical for salvaging the eye.
» Chemoreduction averts the development of TRB.
Cryotherapy

- Under GA, pencil like probe is placed precisely on the sclera directly behind the intraocular focus of RB.
- Rapid freezing forms intracellular crystals which ruptures tumor cells and causes vascular occlusion.
- Fails if overlying VS present.
- 1 or 2 sessions at 1 month interval are required.
- **Indication:** Small primary or recurrent tumor in anterior retina i.e. equatorial and peripheral region or post EBRT residual tumor < 2mm thick and < 3.5 mm diameter.
- **Complications:** vitreous hemorrhage, choroidal effusion, retinal detachment, localized periretinal fibrosis and retinal tear.
PHOTOCOAGULATION

» Argon/Diode laser/Xenon arc.
» Light is focused through dilated pupil under GA and vessels are coagulated which results in involution of tumor.
» Indications:
  » Small primary or recurrent tumor in posterior part of retina < 2.5 mm thick and < 4.5 mm diameter.
  » Retinal neovascularization due to radiation retinopathy.
» Most tumors require 2 to 3 sessions to be cured.
» Contraindications:
  » Tumor located at or near macula or pupillary area.
  » Mushroom shaped tumors
  » Tumors arising from a vitreous base.
THERMOTHERAPY

» Ultrasound/microwave/infrared radiation used to deliver heat to eye.
» 42 to 60°C (which is below coagulation threshold) of heat produces a grey white scar but does not photocoagulate retinal vessels.
» Synergistic effect with CTRT
» Indications:
» Thermotherapy alone: small tumors outside retinal arcade < 3mm diameter and 2 to 3mm thick without vitreous or subretinal seeds produces control rates of 86%
» Thermochemotherapy (TCT): rest of the tumors after tumor shrinkage following 2 to 3 cycles when they satisfy above size criteria (thickness>4mm associated with higher recurrences).
THERMOTHERAPY

» Mechanism of action:
   » Membrane damage.
   » Protein denaturation.
   » Chromosomal damage.
   » Disruption of biochemical pathways.
   » Ischemic necrosis.

» Schedule:
   » Thermotherapy alone: 300MW power for $\geq10$ mins
     upto 45 to 600°C at 1 monthly interval for 3 sessions
     produces grey white scar.
   » TCT: 42 to 45°C for 5 to 20 mins depending on size
     (upto 15 mm diameter) produces a light grey scar.
THERMOTHERAPY

» Complications: focal iris atrophy and focal para axial lenticular opacity.

» Advantage: suitable for small tumors adjacent to fovea and optic nerve in which plaque therapy or laser photocoagulation would possibly induce more profound visual loss.

» Disadvantage: Time consuming, tedious process that requires careful observations, recordings, judgements and treatment adjustments in response to subtle tumor changes.
LOCAL ADMINISTERED CARBOPLATIN

- Being evaluated at present for advanced intraocular RB since achieves high concentration in vitreous humor.
- Subconjunctival: levels peak at 1 hr and diminishes thereafter slowly.
- Iontophoretic: levels slowly peak at 6 hrs.
- Could be combined with focal therapies and avoid systemic administration.

• Abramson DH. Ophthalmology 1999; 106:1947-50
• Hayden BH. Arch Ophthalmol 2000;118:1549-54
• Simpson AE. Arch Ophthalmol 2002;120:1069-74
SCLERAL PLAQUE THERAPY

» 1929: Foster, Moore and Scott used Ra seeds
» 1948: Henry Stallard pioneered and refined the technique, initial Ra applicator was replaced by cobalt 60 plaque.
   » Curved applicator to fit the eye with suture holes for fixing.
   » Left in place for 3 to 7 days to deliver 40 Gy to tumor apex and 100 to 200 Gy to tumor base.
   » Disadvantage: No external shielding resulting in high radiation dose to orbital bones and the surgeon.
» 1970-80’s: other radio-isotopes used e.g. I125, Ir192, Ru106

<table>
<thead>
<tr>
<th>Plaque</th>
<th>Energy</th>
<th>Half life</th>
<th>Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co60</td>
<td>1.33-1.7MV</td>
<td>5.2 years</td>
<td></td>
</tr>
<tr>
<td>I125</td>
<td>27-25Kev</td>
<td>60 days</td>
<td>upto 10mm</td>
</tr>
<tr>
<td>Ir192</td>
<td>295-612Kev</td>
<td>74 days</td>
<td></td>
</tr>
<tr>
<td>Ru106</td>
<td>3.5Mev (β)</td>
<td>368 days</td>
<td>upto 6mm</td>
</tr>
</tbody>
</table>
RESULTS $\beta$ AND GAMMA THERAPY

Table 5. Therapy outcome of $\beta$- and $\gamma$-ray brachytherapy of retinoblastomas

<table>
<thead>
<tr>
<th></th>
<th>Present study</th>
<th>et al. (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>23 (0.2–150)</td>
<td>12 (1–96)</td>
</tr>
<tr>
<td>Tumor diameter (mm)</td>
<td>7.5 (1.5–22)</td>
<td>7.7 (1–18)</td>
</tr>
<tr>
<td>Tumor height (mm)</td>
<td>3.7 (1–7.6)</td>
<td>4.1 (0.5–12)</td>
</tr>
<tr>
<td>Distance to optic disk (mm)</td>
<td>7.2 (0–21)</td>
<td>6.4 (0–17)</td>
</tr>
<tr>
<td>Retinal detachment (n)</td>
<td>22/175</td>
<td>31/208</td>
</tr>
<tr>
<td>Vitreous seeding (n)</td>
<td>37/175</td>
<td>15/208</td>
</tr>
<tr>
<td>Primary brachytherapy (n)</td>
<td>56/175</td>
<td>60/208</td>
</tr>
<tr>
<td>Mean duration of radiation (h)</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Mean dose apex/base (rounded) (Gy)</td>
<td>138/419</td>
<td>42/155</td>
</tr>
<tr>
<td>Tumor recurrence (%)/mean interval (mo)</td>
<td>6.3/9.7</td>
<td>17/8</td>
</tr>
<tr>
<td>Radiation retinopathy at 2/5 y (%)</td>
<td>19/22</td>
<td>21/27</td>
</tr>
<tr>
<td>Optic neuropathy at 5 y (%)</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Cataract at 5 y (%)</td>
<td>17.4</td>
<td>31</td>
</tr>
</tbody>
</table>

IJROBP 2006, Scheuler at al
# POOR PROGNOSTIC FACTORS

Table 4. Results of multivariate statistical analysis

<table>
<thead>
<tr>
<th>Investigated event</th>
<th>Risk factor*</th>
<th>Risk ratio (95% confidence limits)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eunucleation</td>
<td>Prior brachytherapy of the eye</td>
<td>2.3 (1.1–4.5)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Prior EBRT</td>
<td>2.0 (1.1–3.4)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Tumor diameter</td>
<td>1.4 (1.1–1.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Local tumor recurrence</td>
<td>Partial or complete fish-flesh regression</td>
<td>3.1 (1.2–7.9)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Vitreous tumor cell seeding before brachytherapy</td>
<td>2.1 (1.2–3.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Radiation optic neuropathy</td>
<td>Retinal detachment before brachytherapy</td>
<td>2.8 (1.5–4.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Radiation retinopathy</td>
<td>Vitreous tumor cell seeding before brachytherapy</td>
<td>1.6 (1.1–2.3)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Prior EBRT</td>
<td>1.9 (1.3–2.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cataract</td>
<td>Prior EBRT</td>
<td>4.0 (2.2–8.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Prior brachytherapy of eye</td>
<td>3.9 (2.1–7.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Distance between tumor and optic disk</td>
<td>0.8 (0.7–0.9)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Risk factors are significant at the 0.05 level.
I$^{125}$ CLAWS FOR WHOLE EYE-STANNARD

Fig. 1. $^{125}$I applicator; gold pericorneal ring and 4 gold claws each loaded with 3 $^{125}$I seeds.

Fig. 4. “Claw” being inserted between 2 rect muscles.

Fig. 5. Lateral X-ray of $^{125}$I applicator.
EBRT

- **Indications:**
  - Lesions close to macula or optic nerve.
  - Larger tumors with vitreous seeding.
  - Recurrent disease.
  - Adjuvant postoperative radiotherapy after enucleation in high risk pathologic features.
  - Palliative radiotherapy
  - Progression on chemoreduction

- **Target volume:** entire retina up to ora serrata and at least 1 cm of ON accepting the potential for cataract formation.
  - All retinal cells have neoplastic potential resulting in recurrences in retina as well as vitreous.
  - RB is a multifocal disease.
  - Tumor may even spread subretinally.
EBRT-TARGET VOLUME

Blach et al, IJROBP 1996
**TARGET VOLUME**

- EBRT does not prevent the appearance of new tumors in clinically uninvolved retina.
- Therefore, the traditional belief that external beam radiation can treat the retina “prophylactically” should be seriously questioned.
- Focal treatment modalities (plaque brachytherapy, photocoagulation and/or cryotherapy), when clinically feasible, should be considered the treatment of choice for intraocular retinoblastoma.
- EBRT should be considered only when focal treatment modalities are not clinically indicated.

Hernandez, IJROBP, 1996

### Table 4. Incidence of new tumor formation in previously uninvolved retina following external beam radiation for retinoblastoma

<table>
<thead>
<tr>
<th>Series</th>
<th>No. eyes treated</th>
<th>Percent of eyes developing new tumors (# eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedford et al. (4)</td>
<td>58</td>
<td>8% (5)</td>
</tr>
<tr>
<td>Salmonsen et al. (29)</td>
<td>361</td>
<td>13% (48)</td>
</tr>
<tr>
<td>Hopping (16)</td>
<td>&gt;300</td>
<td>16%</td>
</tr>
<tr>
<td>Abramson et al. (2)</td>
<td>37</td>
<td>32% (12)</td>
</tr>
<tr>
<td>Hadjistilianou (11)</td>
<td>16</td>
<td>19% (3)</td>
</tr>
<tr>
<td>Messmer (23)</td>
<td>127</td>
<td>27% (34)</td>
</tr>
<tr>
<td>Present study</td>
<td>34</td>
<td>23% (8)</td>
</tr>
</tbody>
</table>

**Incidence of new tumor formation in previously uninvolved retina following focal treatment of retinoblastoma.**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. eyes treated</th>
<th>Percent of eyes developing new tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Messmer (23)</td>
<td>102</td>
<td>20%</td>
</tr>
<tr>
<td>Abramson (2)</td>
<td>74</td>
<td>25%</td>
</tr>
<tr>
<td>Bedford (4)</td>
<td>63</td>
<td>20%</td>
</tr>
<tr>
<td>Rosengren and Tengroth (28)</td>
<td>17</td>
<td>23%</td>
</tr>
<tr>
<td>Stallard (37)</td>
<td>43</td>
<td>60%*</td>
</tr>
</tbody>
</table>

* Indirect ophthalmoscopy not available in this older series.
TOTAL DOSE

a) Group I & II lesions
   45Gy / 25# / 5wks (@1.8Gy / fr.) – Daily treatment
   45Gy / 18# / 6wks (@2.5Gy / fr.) – Alternate day treatment

b) Group III, IV, & V lesions
   50.4Gy / 28# / 6wks (@1.8Gy / fr.) – Daily treatment
   50.4Gy / 20# / 7wks (@2.5Gy / fr.) – Alternate day treatment

c) Post operative
   Microscopic residual disease
      45Gy / 25# / 5wks (@1.8Gy / fr.) – Daily treatment
      45Gy / 18# / 6wks (@2.5Gy / fr.) – Alternate day treatment
   Gross residual disease
      50.4Gy / 28# / 6wks (@1.8Gy / fr.) – Daily treatment
      50.4Gy / 20# / 7wks (@2.5Gy / fr.) – Alternate day treatment

d) Children <1 year of age, radiation dose should be reduced:
   Microscopic disease (post op radiotherapy) 39.6Gy/22#/ 4.5wks
   Gross disease (definitive radiotherapy) 45Gy/25#/ 5wks

---

Table 3. Hahnenmann/Wills guidelines for the treatment of retinoblastoma with external beam radiation

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;6 months</th>
<th>≥6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumors &lt; 16 mm</td>
<td>40–45 Gy in 1.5 Gy fr</td>
<td>45 Gy in 1.5–2.0 Gy fr</td>
</tr>
<tr>
<td>Any tumor ≥ 16 mm or localized vitreous seeding</td>
<td>48 Gy in 1.5 Gy fr</td>
<td>50 Gy in 1.5–2.0 Gy fr</td>
</tr>
<tr>
<td>Diffuse vitreous seeding or tumor involving ≥ 1/2 of retina</td>
<td>49.5 Gy in 1.5 Gy fr</td>
<td>50–54 Gy in 1.5–2.0 Gy fr</td>
</tr>
</tbody>
</table>
TECHNIQUES

1. Classic single temporal portal 3×4 cm, anterior border at lateral bony canthus with posterior 15° tilt (D-shaped field).


IAEA Pediatric Radiation Oncology Training
Dr Laskar Version 1 June 2009

Hernandez, IJROBP, 1996

- Anterior border at the limbus for lateral field.
- Half beam block anteriorly.
- 4 to 6 MV photon field.
- Eyes closed to spare minoe salivary glands and eyelids.
- Anterior field with electrons to prevent underdosing of AC and prevent exit dose.
3DCRT/IMRT/PROTONS

» Four non co-planar fields
» All anterior oblique field: sup, inf, med, lat.
» Less orbital hypoplasia.
» Minimize dose to opposite eye, optic chiasma, post. Pituitary, upper cervical spine.
» Tumor = 95% & orbit = 50%.
» More homogenous dose distribution.
» Less vitreal recurrence.
FOLLOW UP

• RECURRENCE OCCURS USUALLY WITHIN 3 YR.

• BUT FOLLOW UP DONE FOR INDEFINITE PERIOD FOR DIAGNOSIS OF SECND MALIGNANCY AND TUMOR CONTROL

OPHTHALMOSCOPIC EXAMINATION:

• First year: every 2-3 months.

• Second year: every 3-4 months.

• 3-5 years: every 6 months.

• > 5 years: every one year.
SECOND CANCERS

In the radiation field
- Osteosarcoma
- Fibrous histiocytoma
- Leiomyosarcoma
- Angiosarcoma
- Rhabdomyosarcoma
- PNET
- Meningioma
- Glioma
- Schwannoma
- Myoepithelioma

Outside the radiation field
- Osteosarcoma
- Renal cell carcinoma
- Ewing’s sarcoma
- Carcinoma of the tongue
- Medulloblastoma
- Malignant melanoma
- Hodgkin’s disease

Graphs showing incidence of second cancers over time after diagnosis of retinoblastoma.
SECOND CANCERS

- Subsequent cancer risk in 963 hereditary patients (SIR, 19; 95% CI, 16 to 21) exceeded the risk in 638 nonhereditary Rb patients (SIR, 1.2; 95% CI, 0.7 to 2.0).
- Radiation further increased the risk of another cancer in hereditary patients by 3.1-fold (95% CI, 2.0 to 5.3).
- Hereditary patients continued to be at significantly increased risk for sarcomas, melanoma, and cancers of the brain and nasal cavities.
- The cumulative incidence for developing a new cancer at 50 years after diagnosis of Rb was 36% (95% CI, 31% to 41%) for hereditary and 5.7% (95% CI, 2.4% to 11%) for nonhereditary patients.

Klienerman, JCO 2005