MANAGEMENT OF RETINOBLASTOMA
INTRODUCTION

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

Unifocal/ Multifocal.

Unilateral (70%)/ Bilateral (30%).

Sporadic (94%)/ Familial (6%).

Non hereditary (50-60%)/ Hereditary (40-50%).
EPIDEMIOLOGY

Median age
- Unilateral: 2 years, 80% below 3 - 4 years.
- Bilateral: < 12 months.

Incidence
- 1 in 15,000-20,000 live births in the US, higher in developing countries including India
- No racial or gender predeliction.

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.
• 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

\[\text{RB} \quad \text{RB}^+\]

Single mutation

\[\text{RB} \quad \text{RB}\]

Retinoblastoma

Sporadic retinoblastoma

\[\text{RB}^+ \quad \text{RB}^+\]

First mutation

\[\text{RB} \quad \text{RB}\]

Second mutation

\[\text{RB} \quad \text{RB}\]

Retinoblastoma
**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.
  - Older age 6 yrs.
  - Pseudohypopyon resembling inflammatory reaction.
  - Diagnosis delayed
  - UL & sporadic
NATURAL HISTORY

- Rapidly progressive tumor
- Untreated fills the eye & completely involves the globe.
- Metastasis (BM, bone, LNs and liver) is rare at presentation.

![Diagram of Routes of Spread]

**Routes of Spread**

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

- Primary Retinoblastoma of pineal & parasellar sites.
- Single tumor.
- Well differentiated: more rosettes, fleurettes & photoreceptor differentiation.
- Majority – familial retinoblastoma.
- Usually fatal due to meningeal spread, median survival of 9 months.
- Appear years (median time 40 months) after successful treatment of primary.
- Main cause of death in RB patients between 3 to 8 years.
- D/D: Metastatic or recurrent retinoblastoma.
HISTOPATHOLOGY

- Composed of uniform small round or polygonal mitotically active cells.

- Viable 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.

Leucokoria (60%): lack of red reflex of the eye in large tumors, RD, retrolental mass or vitreous opacification due tumor cells which is often noticed by the mother.

Strabismus (20%): disruption of fusional reflex due to loss of central vision from a tumor in the macula.

Rubeosis iridis (17%): in advanced cases due to extensive tumor necrosis releasing angiogenic factors.

Heterochromia.

Spontaneous hyphaema

Glaucoma: neovascular or closed angle.

Pseudohypopyon: seeding of ant. chamber in endophytic or diffuse infiltrating tumors.

Pain: glaucoma or inflammation.

Proptosis.
HISTORY: Administration of oxygen at birth, eating of dirt, association with dogs & Family history of 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).

| Ocular fundus under general anesthesia + | Any patient with retinoblastoma Schema, photographs, ultrasonography Reese grouping, new grouping |
| Brain and orbit CT scan or MRI +        | Almost any patient with retinoblastoma (except neonatal screened patients with tumor respecting the head of optic nerve) |
| CSF cytology Bone marrow cytohistology +| When enucleation is necessary and shows histopathologic risk factors |
| Brain and spinal axis MRI Bone scan     | Only in case of orbital, lymph node and/or distant metastatic diseases |
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.
- Color doppler displays normal & tumor vasculature & differentiates subretinal or choroidal h’ge from neoplasms.
CT SAN / MRI SCAN

- 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.
<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>
## International Classification for Intraocular Retinoblastoma

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Tumour characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong>: 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><strong>Group B</strong>: 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><strong>Group C</strong>: 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><strong>Group D</strong>: 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><strong>Group E</strong>: 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>
PROGNOSTIC FACTORS

- Optic nerve invasion.
- Massive choroidal invasion, CB: increased possibility of hematogenous spread (60%) & 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 result from second cancers & trilateral RB.
- Trilateral RB has almost 100% fatality.
<table>
<thead>
<tr>
<th>Extent of Invasion of Optic Nerve</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>60%</td>
</tr>
<tr>
<td>Positive transected margin</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Stump &gt;5mm</td>
<td>better</td>
<td>better</td>
</tr>
</tbody>
</table>
MANAGEMENT OF RB

- 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.
TREATMENT TECHNIQUES

- ENUCLEATION
- EXENTERATION
- EBRT
- FOCAL THERAPIES
  - Plaque Radiotherapy
  - Laser Photocoagulation
  - Cryotherapy
  - Thermotherapy
  - Chemothermotherapy
- CHEMOREDUCTION
  - Intravenous
  - Subconjunctival
  - Transpupillary
- SYSTEMIC CHEMOTHERAPY
UNILATERAL NONADVANCED DISEASE

Unilateral RE

- Amenable to local therapy
  - No
  - Yes
    - Chemotherapy x 2 to 4 cycles
    - Cryo/Photocoagulation Plaque

Good Response

- Yes
  - Amenable to local therapy
    - No
    - Yes
      - Further Chemoreduction

- No
  - Potentially useful vision
    - No
    - Yes
      - Epilation

Further Chemoreduction

EBRT: external beam radiation therapy.
UNILATERAL ADVANCED DISEASE

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
FLOW CHART: BILATERAL DISEASE

1. Bilateral RB
2. Chemotherapy x 2 to 4 cycles
3. Good Response
   - Yes: Amenable to local therapy
     - No: Further Chemoreduction
       - Shrinkage
         - Yes: Cryo/Photocoag
           - No response: EBRT**
         - No: Chemotherapy
       - No response: Cont. Chemo (total 6 to 12 cycles)
         - No: Further Chemoreduction
           - Yes: Cryo/Photocoag
             - No: Continue Chemo (total 12 cycles)
   - No: Potentially useful vision
     - Yes: EBRT**
       - No: Exucleation
     - No: Chemotherapy
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.

• Optic nerve 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.
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)

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

No adjuvant treatment (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
CHEMOTHERAPY

GOALS OF CHEMOTHERAPY

• Reduction of tumor size → RD dealt with focal therapy is the standard of care in early stage disease.
• Reduce the use of EBRT which reduces second malignancies and orbitofacial growth anomalies in early stage.
• Reduce the need of enucleation in early stage.
• Reduce the risk of local and systemic relapse in advanced stage.
• Improve survival in metastatic disease.

• Neoadjuvant
  – IORB - BL disease, UL disease not amenable to local therapy (6 to 12 cycles).
  – EORB – Orbit/bone involvement, metastatic spread
• Adjuvant: High risk histopathological features.
• Salvage: Recurrent disease in an only eye.
### 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 Retinal Detachment
- Hemorrhage
CRYOTHERAPY

- Rapid freezing forms intracellular crystals which ruptures tumor cells and causes vascular occlusion.

- Under GA, pencil like probe is placed precisely on the sclera directly behind the intraocular focus of RB.

- Fails if overlying vitreous seeding 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 the feeding 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 hyperthermia to tumor.

- 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 sub-retinal seeds produces control rates of 86%

- Thermochemotherapy (TCT): Useful for larger 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 $\geq 10$ mins up to 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, subjective and treatment adjustments required 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
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>
I\textsuperscript{125} CLAWS FOR WHOLE EYE-STANNARD

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**Fig. 1.** \textsuperscript{125}I applicator: gold pericorneal ring and 4 gold claws each loaded with 3 \textsuperscript{125}I seeds.

**Fig. 4.** "Claw" being inserted between 2 recti muscles.

**Fig. 5.** Lateral X-ray of \textsuperscript{125}I applicator.
EXTERNAL BEAM RADIOTHERAPY

• **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 after chemoreduction

• **Target volume:** Entire retina upto ora serrata and atleast 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 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.

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</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.

Hernandez, IJROBP, 1996
RADIOTHERAPY DOSE

a) Group I & II lesions
   45Gy / 25# / 5wks (@1.8Gy / fr.)

b) Group III, IV, & V lesions
   50.4Gy / 28# / 6wks (@1.8Gy / fr.)

c) Post operative
   Microscopic residual disease
   45Gy / 25# / 5wks (@1.8Gy / fr.)

   Gross residual disease
   50.4Gy / 28# / 6wks (@1.8Gy / fr.)

d) Children <1 year of age:
   Microscopic disease (post op RT) 39.6Gy/22#/ 4.5wks
   Gross disease (definitive RT) 45Gy/25#/ 5wks

TMH Recommendations

Hernandez, IJROBP, 1996
Described by Reese in 1930
Orthovoltage beams attempting lens sparing
High dose to bone: Bony deformities
Single En-Faced Megavoltage Beam
Ant. Border at Bony Orbital Margin
High Dose to Bony Orbit
1. Classic single temporal portal $3 \times 4$ cm, anterior border at lateral bony canthus with posterior $15^0$ tilt (D-shaped field).


Underdose of anterior structures of eye. Higher recurrences.

Cataract formation still higher.

Anterior border at the limbus for lateral field. Half beam block anteriorly. 4 to 6 MV photon field. Eyes closed to spare minor salivary glands and eyelids. Anterior field with electrons to prevent underdosing of AC and prevent exit dose.
3D-CONFORMAL RT

- 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.
INTENSITY MODULATED RT (IMRT)

RT DOSE: 45-50Gy
IMPORTANCE OF PROTOCOL TARGET DEFINITION ON THE ABILITY TO SPARE NORMAL TISSUE: AN IMRT AND 3D-CRT PLANNING COMPARISON FOR INTRAORBITAL TUMORS

Patrick A. Hein, M.D., David J. Gladstone, Sc.D., Marc R. Bellerive, M.Sc., and Eugen B. Hug, M.D.

Significant Reduction in Volume of Bony Wall of Orbit in High Dose Region
FOLLOW UP

Recurrence occurs usually within 3 yr.
Follow up done for indefinite period for diagnosis of second malignancy and tumor control

OPTHALMOSCOPIC 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

• 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.
Retinoblastomas should be treated by a group of specialists skilled in management of childhood malignancies.

Team should include Ophthalmologist, Medical Oncologists, Radiation Oncologists, Ocular surgeon, Genetic counselors

Multimodality treatment comprising Chemotherapy, Focal Therapies, Radiotherapy, & Surgery results in optimal outcomes

Customization of treatment is necessary based on disease status, risk factors, & Response to therapy

Radiation therapy in the form of plaque brachytherapy & EBRT are useful modalities for achieving local control

EBRT is extremely effective in palliation of locally advanced & metastatic disease