Orbital tumors and Retinoblastoma

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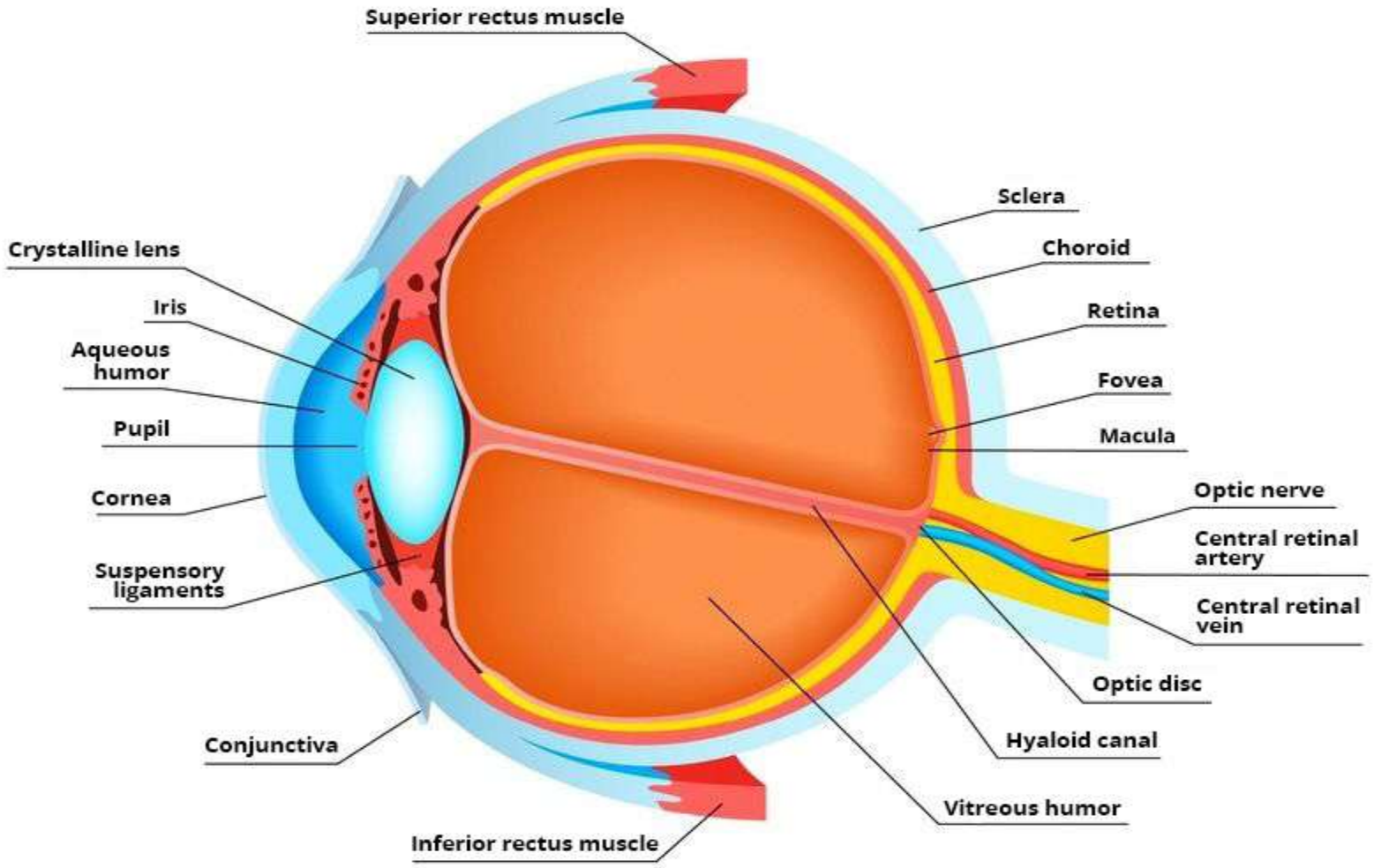
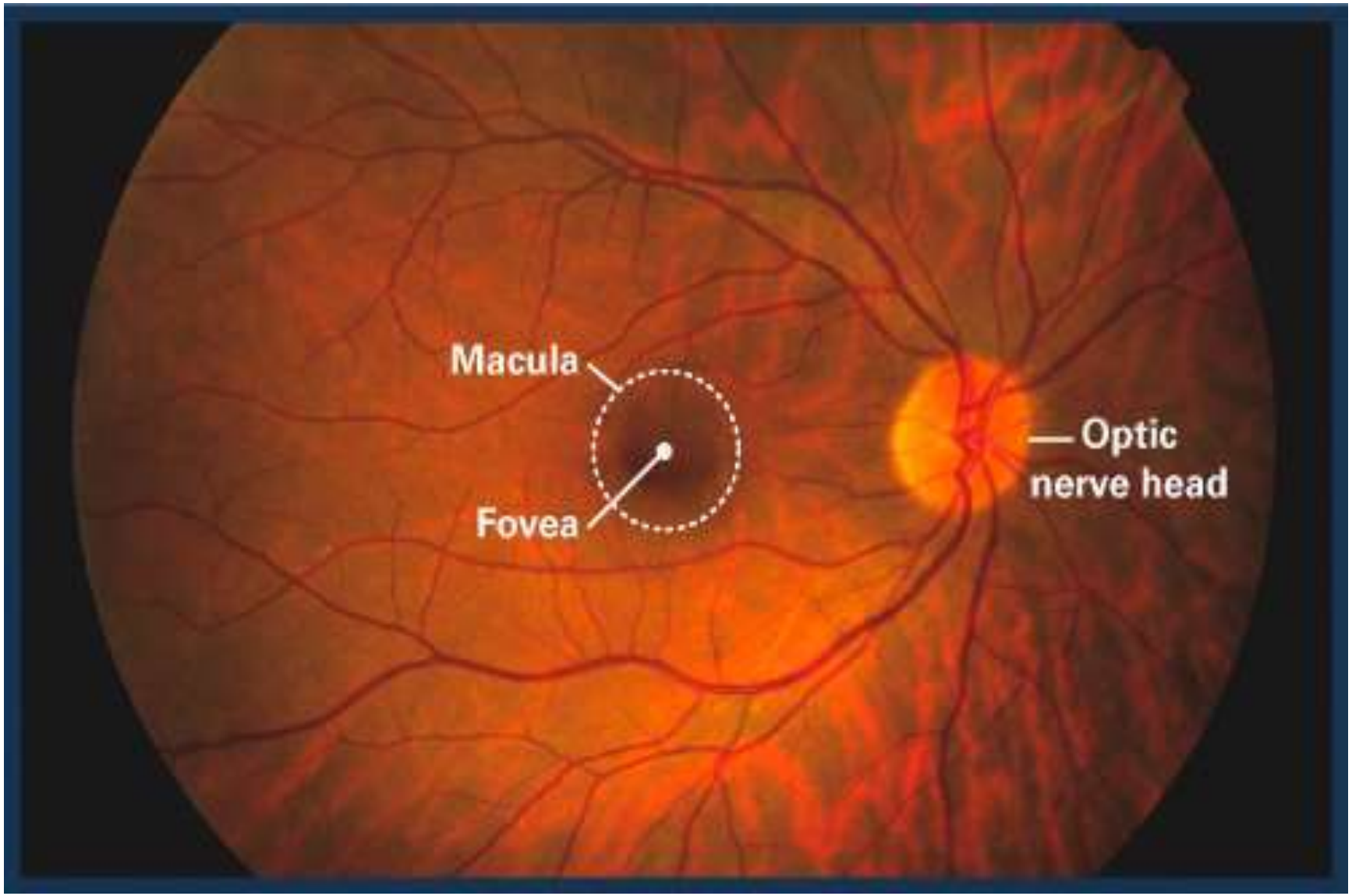
Orbital tumors in pediatric

Pediatric intra ocular tumor	Pediatric intra orbital tumor
1. Retinoblastoma	1. Rhabdomyosarcoma
2. Medulloepithelioma	2. Mets
3. Retinal astrocytic hamartoma	3. Optic pathway glioma
	4. Plexiform neurofibroma
	5. Lymphoproliferative disease.
	6. Dermoid and epidermoid inclusion cyst
	7. Leukemia
	8. LCH

- Retinoblastoma

EYE-Anatomy


Superior rectus muscle
Sclera
Choroid
Crystalline lens
Retina
Iris
Aqueous humor
Fovea
Pupil
Macula
Cornea
Optic nerve
Central retinal artery
Suspensory ligaments
Central retinal vein
Optic disc
Hyaloid canal
Conjunctiva
Vitreous humor
Inferior rectus muscle


Macula
Fovea
Optic
nerve head

Retinoblastoma- Epidemiology

1. Retinoblastoma is the most common Intraocular primary tumor of the eye in Children, Mexican data concluded with – RB is second solid tumor after CNS tumor in pediatric age

1. Mean age of diagnosis 2 years, in bilateral retinoblastoma is Earlier i.e 12 months and majority detected within 3 years

2. Unilateral (2/3rd) and Bilateral (1/3rd)

3. No predilection for sex, race or Right or Left eye

Current Opinion in Ophthalmology 2006, 17: 228-234
Br J Ophthalmol.2009.Jan;93(1):21-3

Retinoblastoma- Epidemiology

- **Incidence**
  - World: The Incidence of RB ranges from 1 in 14000 to 1 in 34000 live births-Worldwide
  - World: About 8000 children world wide every year
  - US has 200 new cases every years with 25% of them being bilateral
  - US- 11.8 cases per million live birth
  - Approximately 3-5 % of all Pediatric tumors
- 6% have orbital retinoblastoma at initial presentation

- India accounts for about 25% of RB in the World Incidence
- Incidence in India is 1500- 1800 every year
- In India 3.5 case / million live birth every year(world-3-42 per million)
- Majority of them advanced >70 , orbital in 20% of the cases

- *Current Opinion in Ophthalmology 2006, 17: 228-234*
- *Br J Ophthalmol.2009.Jan;93(1):21-3*

Retinoblastoma- Epidemiology

- Advanced tumor at initial presentation continues to be a barrier for eye salvage
- 60-80% pts treated in primary or secondary health care set ups **without any protocol based management - 50% failure rates**
- Visual outcome and survival : depends on early detection and appropriate referral to dedicated centers

**http://www.icmr.nic.in/ncrp/cancer_regoverview.htm*

#Ref: National Guidelines in the management of Retinoblastoma, ICMR 2010

Table 3. Analysis of unilateral versus bilateral disease at presentation

	Eyes, n^a	Globe salvage rate, %	Unilateral disease ($n = 316$)				Bilateral disease ($n = 151 \times 2$) (302 eyes)			
			eyes, n	recurrences, n	deaths, n^a	metastasis, $n^{a,b}$	eyes, n	recurrences, n	deaths, n^a	metastasis, $n^{a,b}$
Group A	22	100	–	0	–	–	22	0	–	–
Group B	58	100	2	0	–	–	56	0	–	–
Group C	20	94.7[b]	–	0	–	–	20	0	–	–
Group D	47	17.1	21	0	0	0	26	0	0	0
Group E	304	0	128	6	1	0	176	7	0	0
Extraocular disease	167	0	165	6	10	7	2	3	2	1
Total	618			12	11	7		10	2	1

[a] Outcome in bilateral disease was dependent on the grouping of the worst eye. [b] One patient was group C to begin with but subsequently required enucleation in view of progression.

Ocul Oncol Pathol 2018;4:23–32

Cell of origin of retinoblastoma

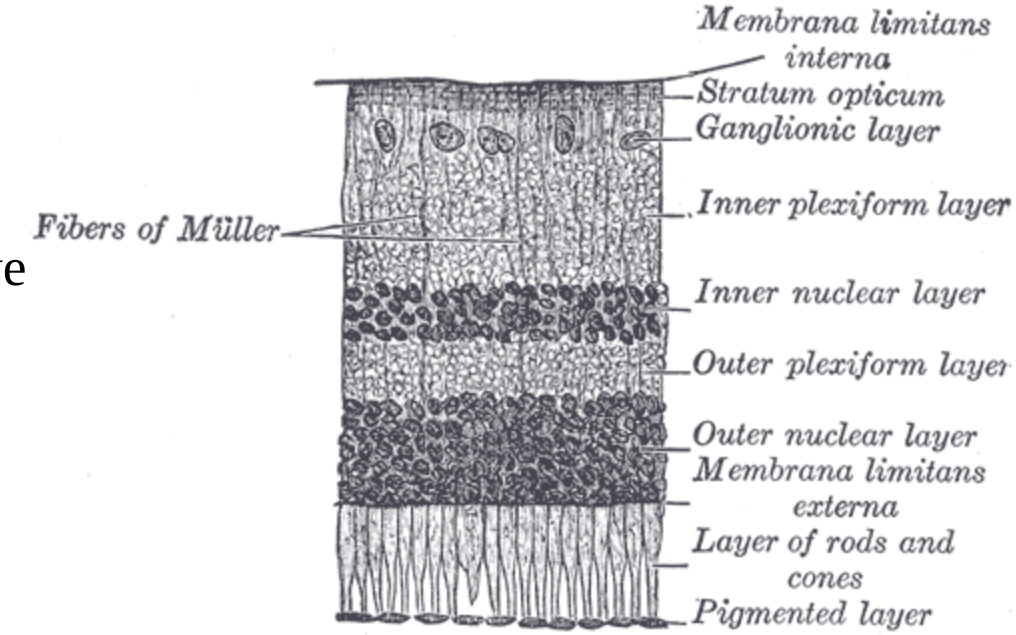
- The tumor is of neuroepithelial origin

- Basically - inner nuclear layer

- Can be unifocal/multifocal , involving single or both the eye

- The term was first adopted by American Ophthalmology society in 1926

- In early 1900s, Verhoeff concluded that the undifferentiated embryonic retinal cells called retinoblasts gave rise to RB



Retinoblastoma Registry in India

- Indian Council of Medical Research
- NATIONAL RETINOBLASTOMA REGISTRY
- Hospital Based Cancer Registry
- Commenced on **1st April 2009**
- 13 sites

Etiology

- Association with human papilloma virus (16), polyoma virus and adeno virus(2,5)
- The E7 protein of HPV known to inactivate the pRB
- This was proven by IHC studies where 75% of HPV positive RB did not express pRB
- Association of HPV with sporadic RB was studied
- HPV was detected in 20/83 cases (24%)
- Similar studies from Mexican and South American population reveal 28 and 82% HPV positivity in their sporadic RB

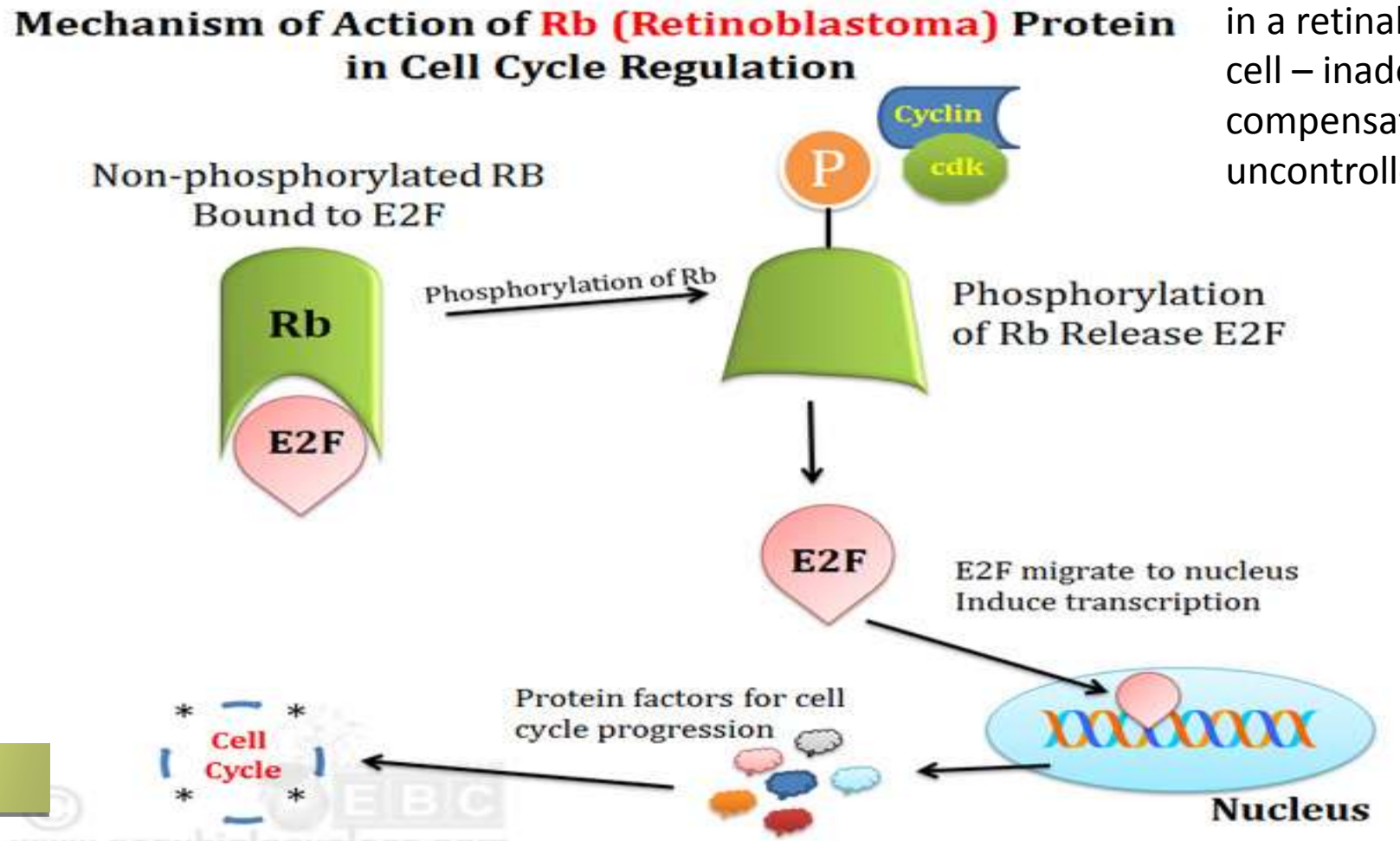
Bhuvaneshwari Anand et al, Prevalence of hogh risk HPV genotypes in RB, BR J Ophthal 2011;95;1014-1018.

Genetics

- Hereditary nature identified late 1962,-Retinoblastoma is the first cancer that had an established role in genetics
- Stallard noted deletion of D group chromosome, chromosome 13
- Locus of deletion 14 band on the long arm (q) of 13th
  Chromosome-RB1 gene resides on 13q14 ; encodes the pRB
- Regulates cell division – the first tumor suppressor gene discovered.
- Germline RB1 mutations carry risk of second cancers – osteosarcoma, melanoma and leiomyosarcoma

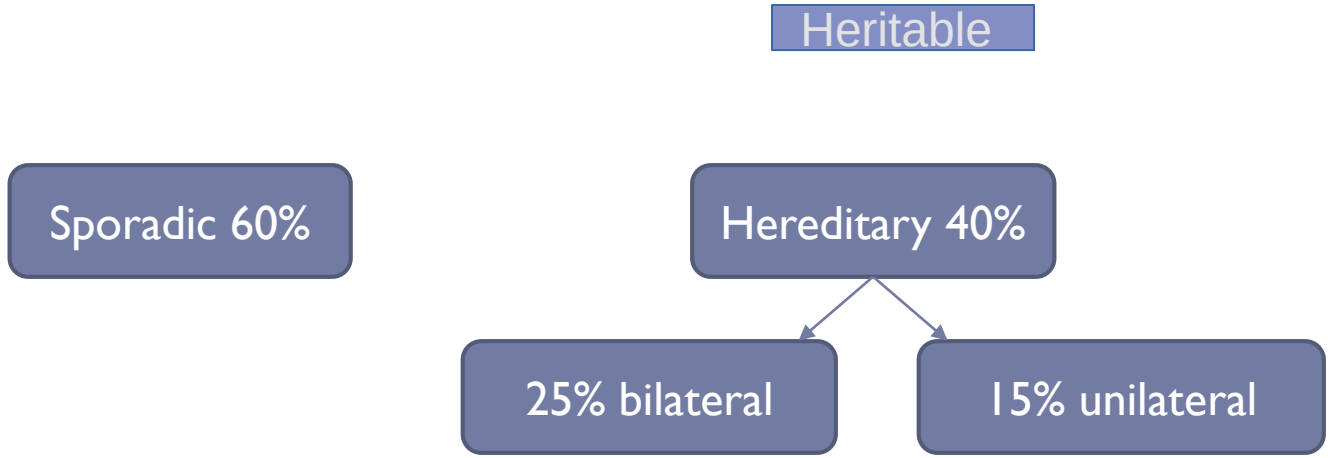
RB tumor suppressor gene

In many cell types loss of RB1 is compensated by overexpression of the other proteins , it does not happen in a retinal cone precursor cell – inadequate compensatory mechanisms – uncontrolled proliferation

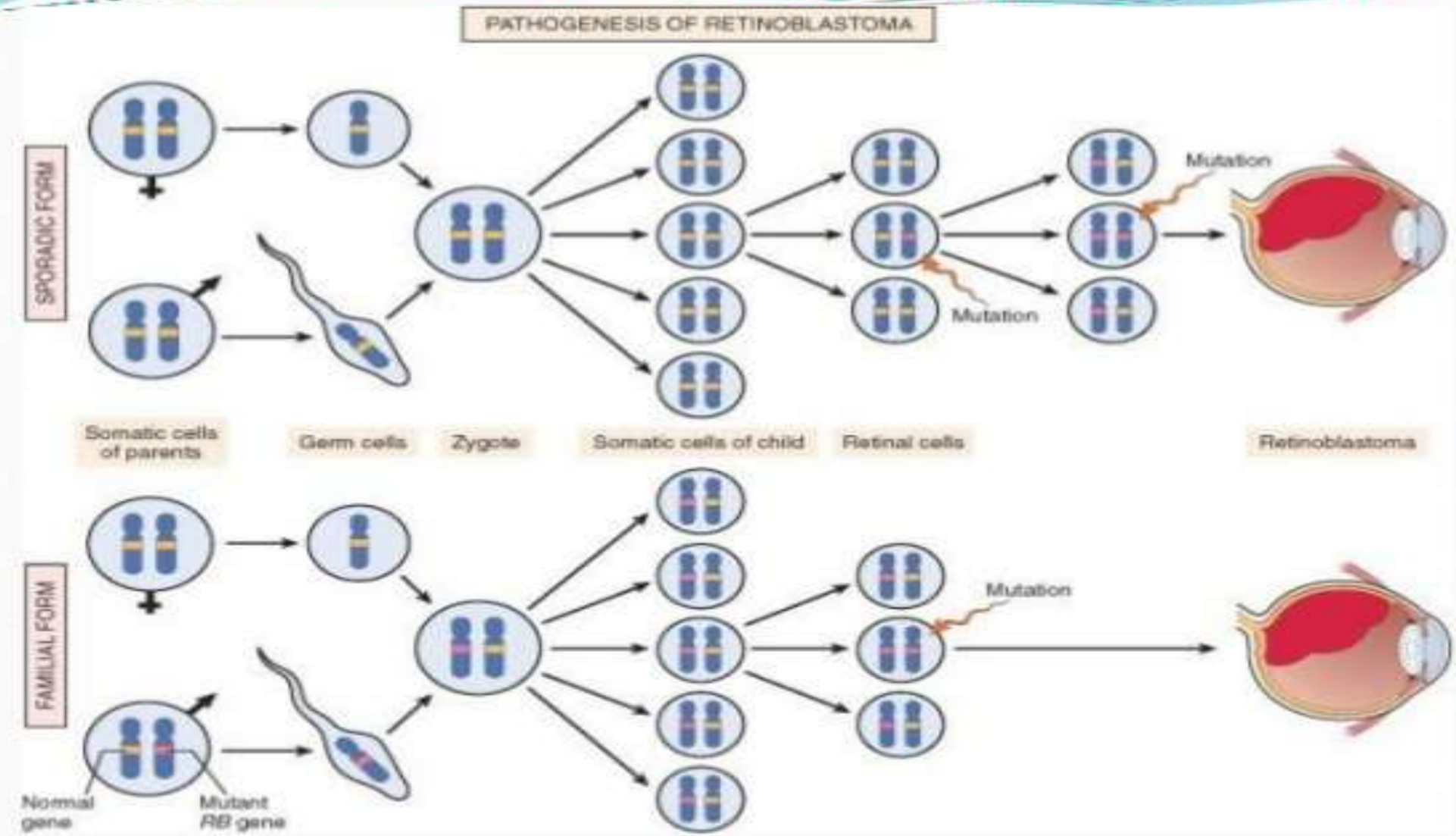


G1→S

- Can be unilateral/bilateral/ 5% of heritable cases can be trilateral



Knudson's 'two-hit' hypothesis



RB grouping and staging

- Reese Ellsworth-Grouping 1-V
- St Jude's-Staging
- Grabowosky-Staging
- Essen-Staging
- Chantada et al-staging
- NEW International Staging System- Staging 1-4
- International classification of retinoblastoma (Shields)- Grouping A_E
- International classificationof introcular classification of retinoblastoma (Murphee) group a-e
- TNM staging –Staging 1-4
- Abramson Grabowski Staging System -Extraocular RB stage 1-5

Reese Ellsworth classification RB

1. **Group I- Very favorable**
   A. Solitary tumor, < 4 disk diameters, at or behind the equator
   B. Multiple tumors, none >4 disk diameters, all at or behind the equator
2. **Group II –Favorable**
   A. Solitary tumor, 4-10 disk diameters in size, at or behind the equator
   B. Multiple tumors, none n4-10 disk diameters, behind the equator
3. **Group III- Doubtful**
   A. Any lesion anterior to the equator
   B. Solitary tumors larger than 10 disk diameters behind the equator
4. **Group IV- Unfavorable**
   A. Multiple tumors, some large than 10 disk diameters
   B. Any lesion extending anteriorly to the ora serrata
5. **Group V- Very unfavorable**
   A. Tumors involving more than half the retina
   B. Vitreous seeding

NEW International Staging System

Stage 0 **No enucleation**
(one or both eyes may have intraocular disease)

Stage I **Enucleation, tumor completely resected**

Stage II **Enucleation with microscopic residual** tumor

Stage III **Regional extension**

A. Overt orbital disease
B. Preauricular or cervical lymph node extension

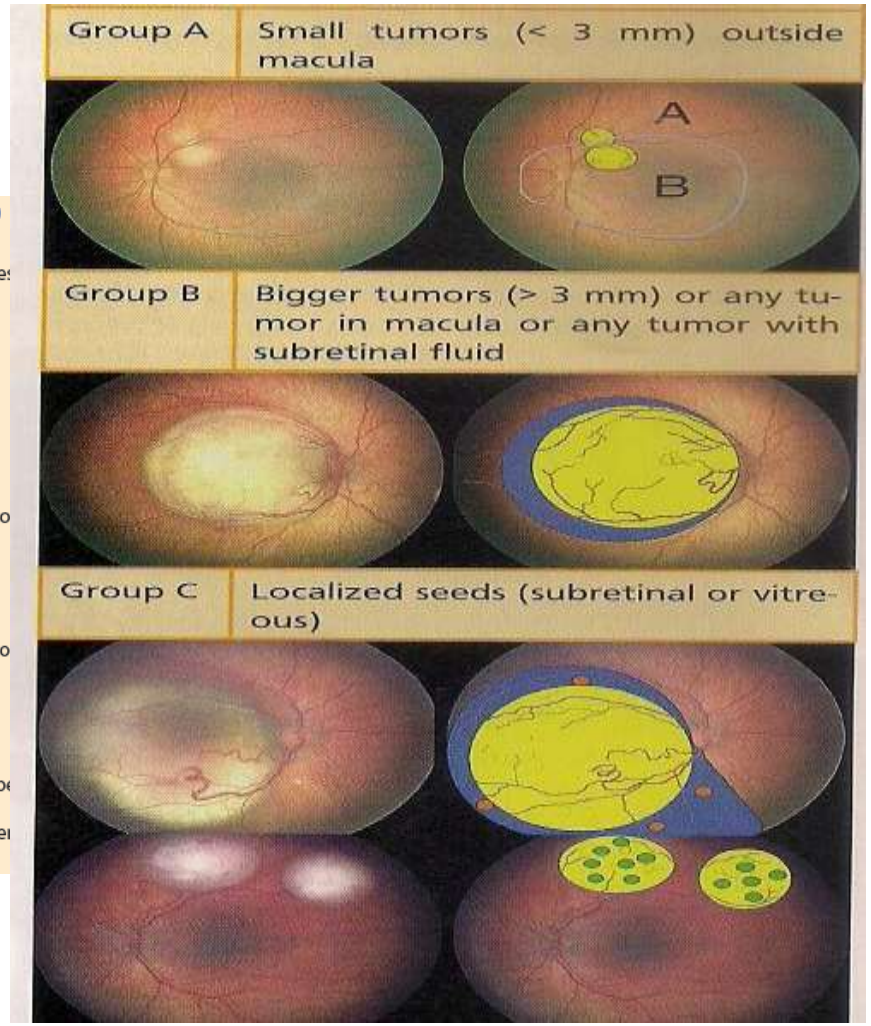
Stage IV **Metastatic disease**

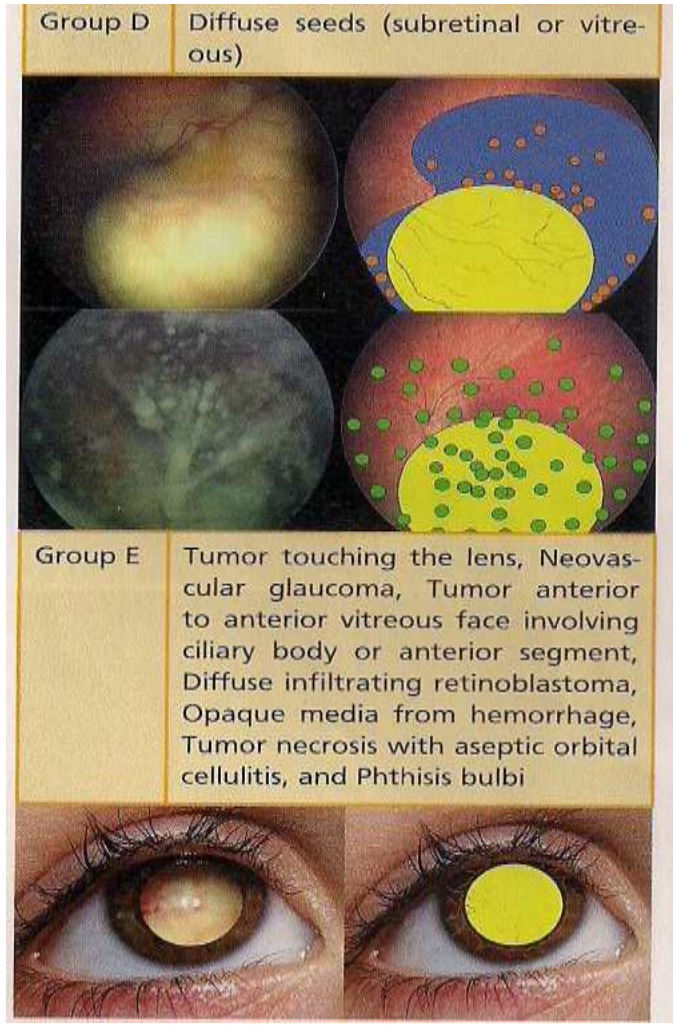
A. Hematogenous metastasis
1. Single lesion
2. Multiple lesions
B. CNS Extension
1. Prechiasmatic lesion
2. CNS mass
3. Leptomeningeal disease

Chantada G, Doz F, Antoneli CB, et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer. 2006:47;801-805.

Table 3. International Classification of Retinoblastoma (Shields)

Group A	Small tumor • Retinoblastoma ≤3 mm in size in basal dimension/thickne
Group B	Larger tumor • Retinoblastoma >3 mm in basal dimension/thickness • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to disc) • Clear subretinal fluid ≤3 mm from margin
Group C	Focal seeds • C1 Subretinal seeds ≤3 mm from retinoblastoma • C2 Vitreous seeds ≤3 mm from retinoblastoma • C3 Both subretinal and vitreous seeds ≤3 mm fro retinoblastoma
Group D	Diffuse seeds • D1 Subretinal seeds >3 mm from retinoblastoma • D2 Vitreous seeds >3 mm from retinoblastoma • D3 Both subretinal and vitreous seeds >3 mm fro retinoblastoma
Group E	Extensive retinoblastoma • Occupying >50% globe or • Neovascular glaucoma • Opaque media from hemorrhage in anterior chambe vitreous, or subretinal space • Invasion of postlaminar optic nerve, choroid (>2 mm), scle orbit, anterior chamber





Abramson Grabowski Staging System -Extraocular RB

Abramson/Grabowski—Extraocular

I. INTRAOCULAR DISEASE

- **a** Retinal tumor(s)
- **b** Extension into choroid
- **c** Extension up to lamina cribrosa
- **d** Extension into sclerae

II. ORBITAL DISEASE

- **a** Orbital tumor
  - **1** Suspicious (pathology of scattered episcleral tumor cells)
  - **2** Proven (biopsy-proven orbital tumor)
- **b** Regional nodes

III. OPTIC NERVE DISEASE

- **a** Tumor beyond lamina but not up to cut section
- **b** Tumor at cut section of optic nerve

IV. INTRACRANIAL METASTASES

- **a** Positive CSF only
- **b** Retinoblastoma mass in CNS

V. HEMATOGENOUS METASTASES

- **a** Positive marrow/bone lesions
- **b** Other organ involvement

Primary Tumour (T)

cTX: Primary Tumour cannot be assessed.

cT0: No evidence of primary tumour.

cT1: Tumours no more than 2/3 the volume of the eye, with no viteous or subretinal seeding:

- cT1a: No tumour in either eye is greater than 3mm in largest dimension, or located closer than 1.5mm to the optic nerve of fovea.
- cT1b: At least one tumour is greater than 3mm in largest dimension, or located closer than 1.5mm to the optic nerve or fovea. No retinal detachment or subretinal fluid beyond 5mm from the base of the tumour.
- cT1c: At least one tumour is greater than 3mm in largest dimension, or located closer than 1.5mm to the optic nerve or fovea, with retinal detachment or subretinal fluid beyond 5mm from the base of the tumour.

cT2: Tumours no more than 2/3 the volume of the eye with vitreous or subretinal seeding. Can have retinal detachment:

- cT2a: Focal vitreous and/or subretinal seeding of fine aggregates of tumour is present, but no large clumps or "snowballs" of tumour cells.
- cT2b: Massive vitreous and/or subretinal seeding is present, defined as diffuse clumps or "snowballs" of tumour cells.

cT3: Severe Intraocular Disease:

- cT3a: Tumour fills more than 2/3 of the eye.
- cT3b: One or more complications present which may include tumour-associated neovascular or angle closure glaucoma, tumour extension into the anterior segment, hyphema, vitreous hemorrhage or orbital cellulitis.

cT4: Extra-ocular disease detected by imaging studies:

- cT4a: Invasion of optic nerve.
- cT4b: Invasion into the orbit.
- cT4c: Intracranial extension not past the chiasm.
- cT4d: Intracranial extension past chiasm.

Regional Lymph Nodes (N)

cNX: Regional lymph nodes cannot be assessed.

cN0: No regional lymph node metastasis.

cN1: Regional lymph node metastasis involvement (preauricular, cervical, submandibular).

cN2: Distant lymph node involvement.

Distant Metastasis (M)

cMX: Presence of distant metastasis cannot be assessed

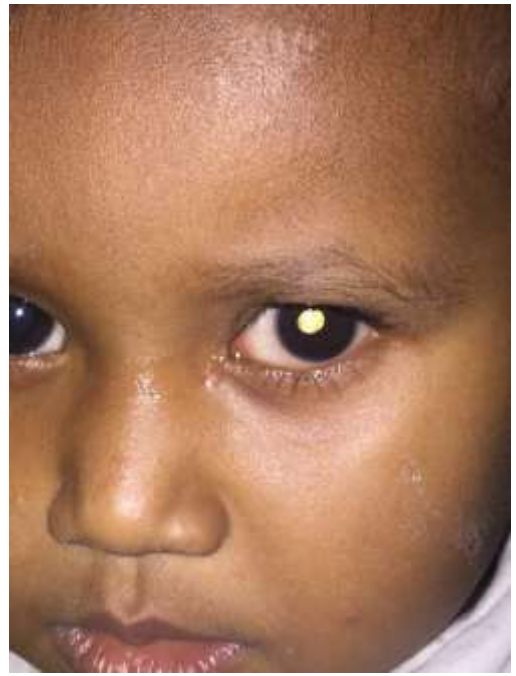
cM0: No distant metastasis

cM1: Systemic metastasis:

- cM1a: Single lesion to sites other than Central Nervous System.
- cM1b: Multiple lesions to sites other than Central Nervous System.
- cM1c: Prechiasmatic Central Nervous System lesion(s).
- cM1d: Postchiasmatic Central Nervous System lesion(s).
- cM1e: Leptomeningeal or Cerebro Spinal Fluid involvement.

Clinical presentations

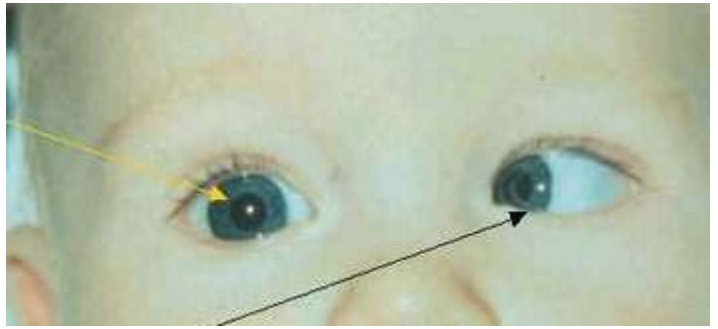
Manifestation	Percentage
Leucocoria	56
Strabismus	20
Red painful eye	7
Poor vision	5
Asymptotic	3
Orbital cellulitis	3
Unilateral mydriasis	2
Heterochroma iridis	1
Hyphema	1



Clinical presentation Indian data

Chief symptom	*n*	*(%)*
(1) Leukocoria	375	(60.6)
(2) Strabismus	105	(16.9)
(3) Hyperemia of eye	50	(8.1)
(4) Neovascularization	48	(7.8)
(5) Proptosis	27	(4.4)
(6) Glaucoma	3	(0.49)
(7) Others	10	(1.6)

Total N=467 patients (618 eyes



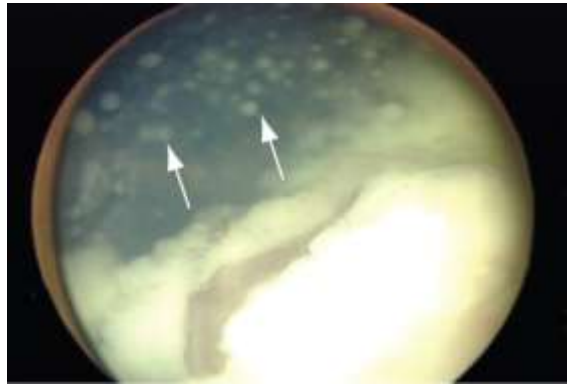
Ocul Oncol Pathol 2018;4:23–32

Clinical Presentation

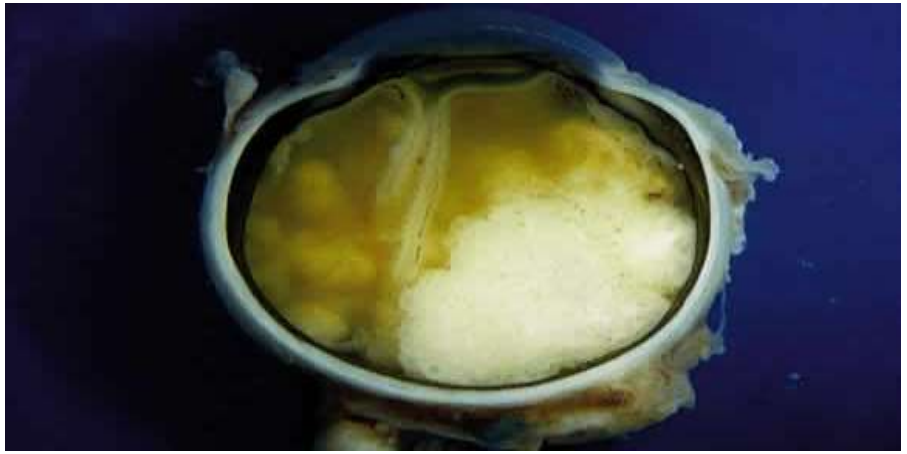
- -

Variants of RB

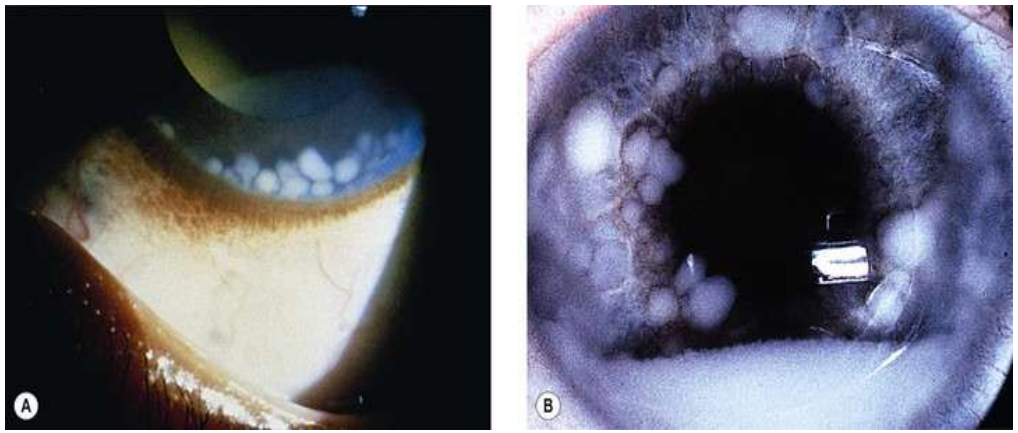
- Endophytic
  - Grows into the vitreous cavity
  - Increased predisposition for vitreous seeding
  - They are floating tumor spheres
  - White gray with a chalky appearance
  - Vitreous → anterior chamber → aqueous channels and conjunctiva → Lymph node metastasis



- Exophytic
  - They grow into the sub retinal space
  - Invade the choroid through the Bruch's membrane
  - Often associated with sub retinal fluid collection and serous detachment of the retina
  - Vessels appear prominent on the tumor surface on examination
  - Retinal detachment → vision loss



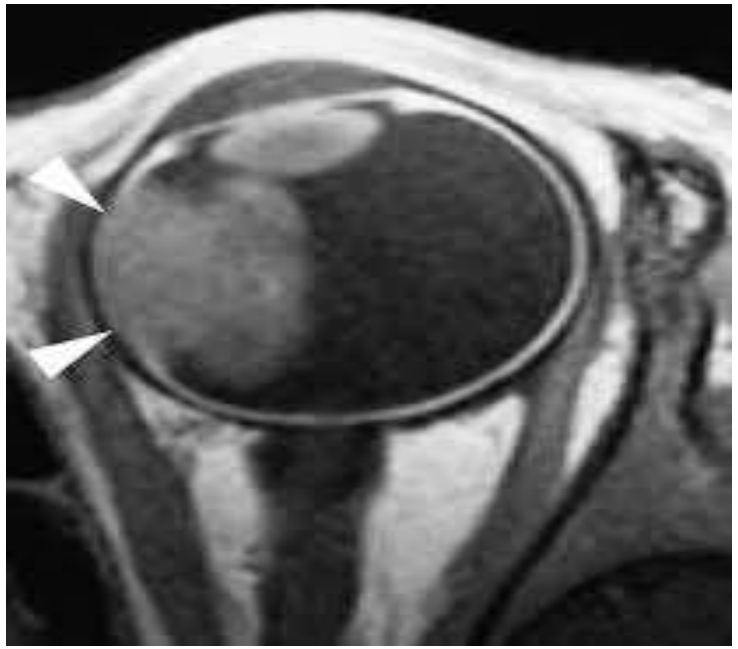
- Diffuse infiltrating
  - Diagnostically challenging
  - No mass seen
  - Average age of 6 years at diagnosis
  - Resembles an inflammatory process
  - Can lead to pseudohypopyon formation



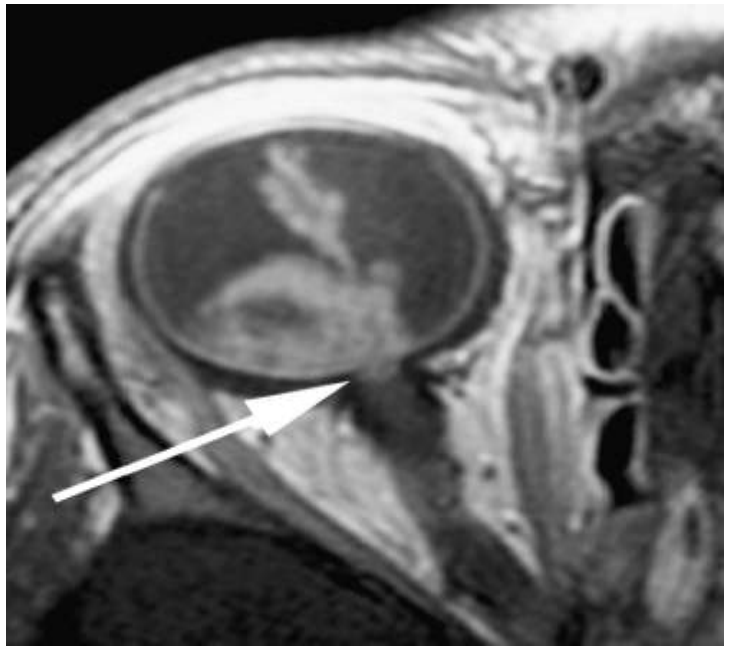
- Extensively necrotic
  - Severe inflammatory reaction with massive necrosis
  - Leads to pthisis bulbi if left untreated
  - Dispersion of iris pigment and conjunctival chemosis are common
  - Increased choroidal invasion and optic nerve involvement

High risk features in RB

Choroidal invasion

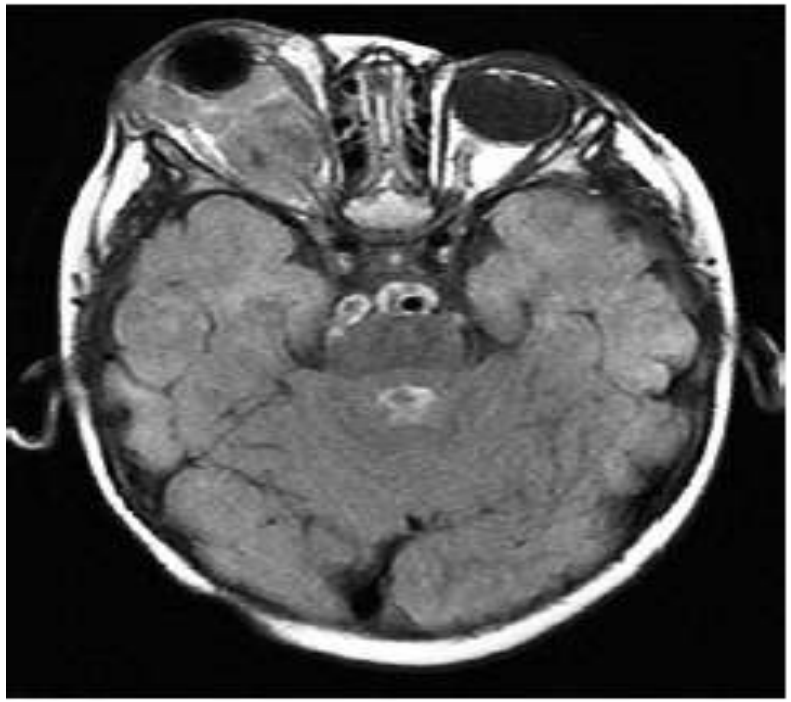


Optic nerve involvement

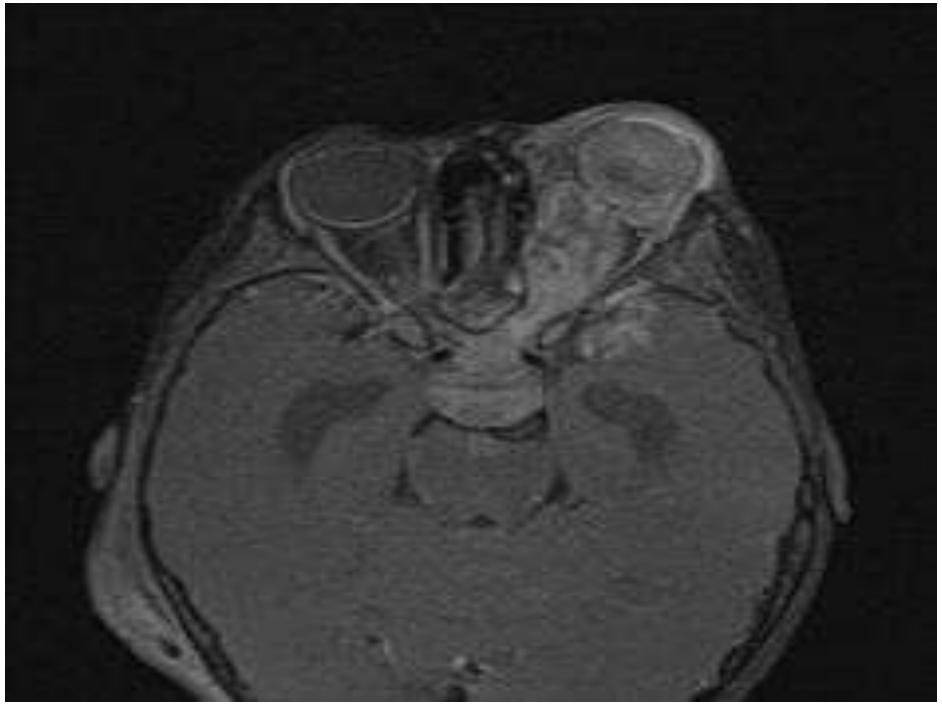


High risk features in RB

Invasion of orbital tissue



Intracranial spread



Modes of spread

- Direct infiltration through optic nerve into brain
- Choroidal invasion to sclera to orbital soft tissue involvement
- Tumor cell dispersion into subarachnoid space to CSF and contralateral optic nerve
- Hematogenous dissemination to bones
- Conjunctival/eye lid involvement to lymphatic spread and pre auricular lymph node metastasis

- Histologically metastasis are less differentiated than the intraocular tumors with occasional rosettes

Diagnosis of retinoblastoma

- Hemogram
- Biochemistry
- Serology
- Fundus examination
- B scan
- CT orbit
- MRI orbit and brain
- Metastatic work up – CSF analysis, BMA and MRI brain, CXR, CSF analysis

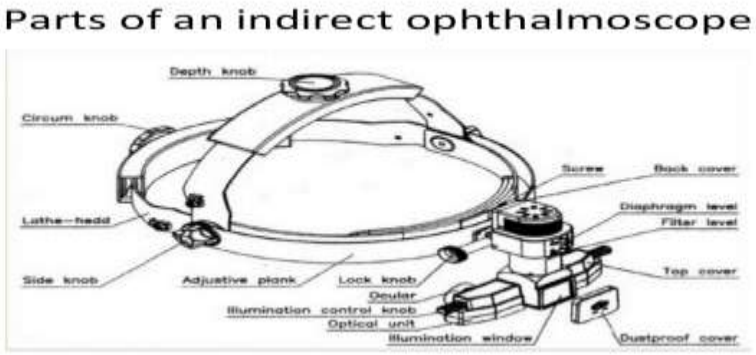
Fundus examination

- Easy and cost effective method
- Ideal for screening
- Direct and indirect ophthalmoscopy

Direct	Indirect
Monocular view	Binocular view
Limited field of view (10-15 degrees)	Wide field of view (35 degrees)
Poor view in hazy media	Better view in hazy media
One has to go very close to the patient	Working distance is about 35-40 cms
Drawing of retinal lesions is difficult & incomplete	Drawing of retinal lesions are easier
Difficult to use during surgery	Can be used for fundus examination during surgery
Illumination: 0.5 – 2 Watts	Illumination: 15 – 18 Watts
15 times magnification	2-5 times magnification
Virtual and erect image	Real and inverted image

Findings to be picked up

- Presence of tumor
- Number and size
- Involvement of anterior chamber
- Retinal detachment
- Sub retinal and vitreous seeds
- Hyphaema and neovascularisation

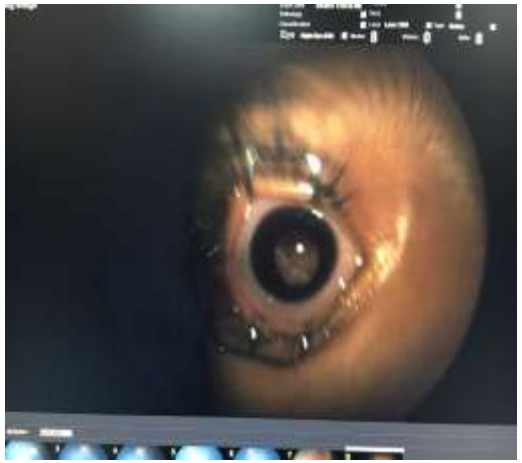


Retcam imaging

It is a wide-field imaging system (130 degree view).

useful in screening and follow up patients

Used in NACT monitoring helping in decision making



Ultrasonography

A-scan

•High starting spike

•V/W pattern s/o heterogeneous consistency with so lid and cystic areas

•High amplitude spikes from with in the tumour due to calcification

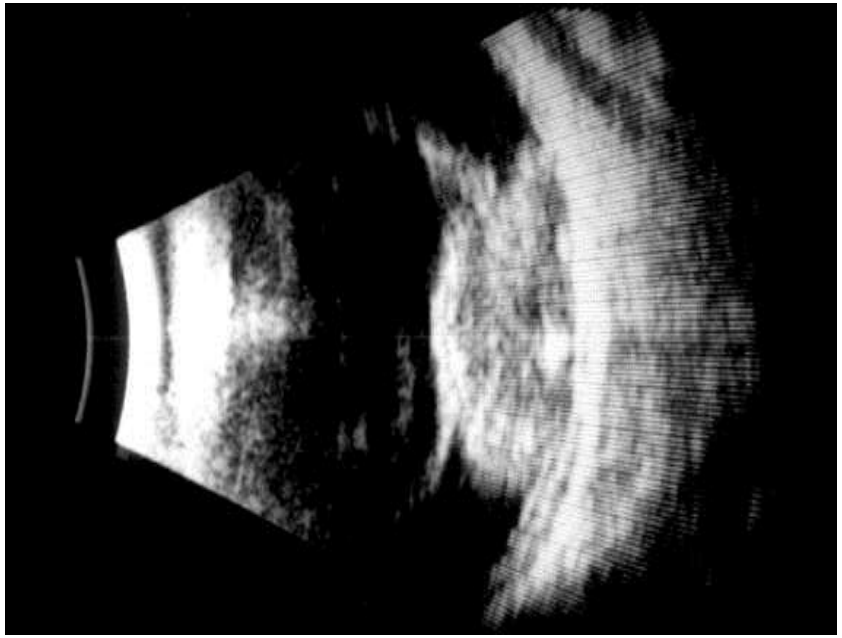
•No after movements / pulsatile activity

•Mod to high ref spikes from vitreous in case of vitreous seeding

B-scan

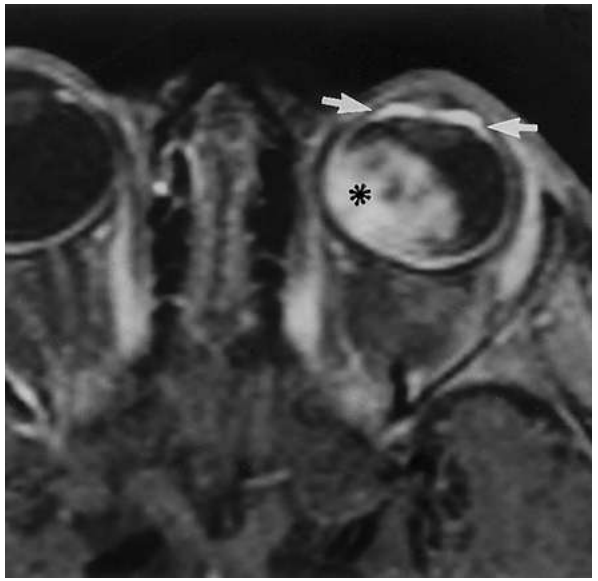
•Secondary orbital shadowing

- Presence of mass
- Calcification
- Type of tumor
- Can be used even in Opaque media
- Probe directly kept on the conjunctiva

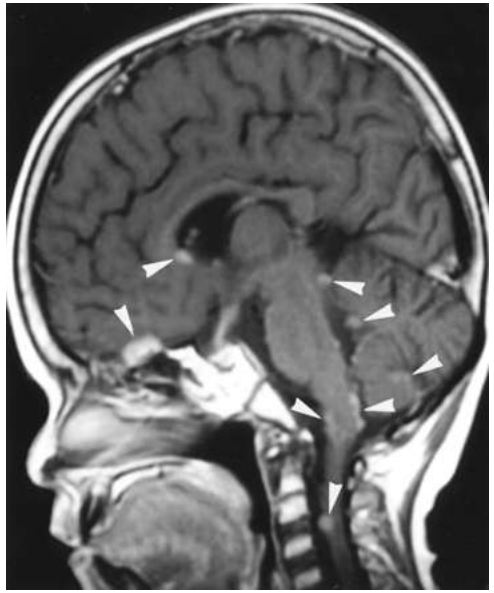


MRI

Fat suppressed, contrast enhanced MRI of brain and orbit – saggital, axial and coronal sections of 2mm cuts passing through optic nerve and pineal gland



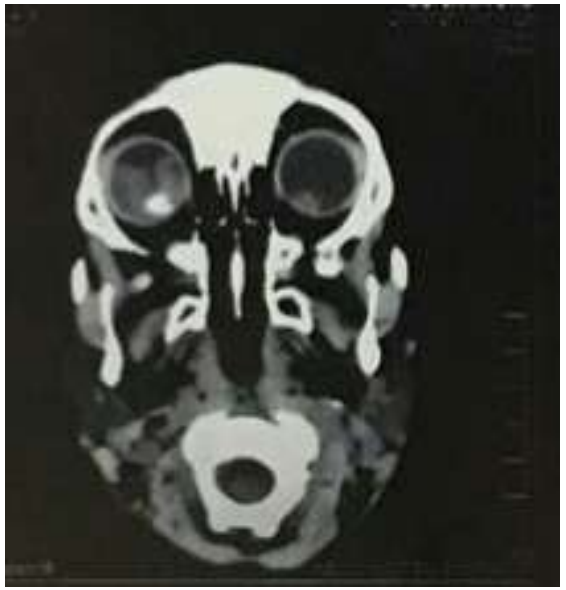
•All retinoblastomas can be visualised as hypointense to vitreous on T2 weighted images and slightly hyperintense to vitreous on plain T1 weighted images with a moderate enhancement after contrast application.



- Clear delineation of scleral breech
- Optic nerve involvement
- Presence of pineal gland involvement in the form of cystic changes/pinealoblastoma

- Intracranial extension

Computed tomography



Less significant after the advent of MRI

Use of CT scan – now controversial (↑ risk of second non ocular cancer)

•Significant only in detecting calcification in case of not being detected by USG/ diagnostic dialemma

- Easier to obtain
- Less time consuming
- Detects calcification in doubtful cases
- Optic nerve involvement cannot be picked up always
- Trilateral retinoblastoma identification

Fnac

Intraocular FNAC for RB is controversial and has not gained universal acceptance

rarely done (tumor
seeding and orbital invasion)

•In cases of diagnostic dilemma

Metastatic work up

- 2-5 % of retinoblastomas are metastatic at presentation

- If child has been symptomatic for 6 months without the commencement of treatment, likely to have metastatized

- Bone, CNS and bone marrow are common sites
- Baseline work up – hemogram, biochemistry
- Bone scan, bone marrow evaluation and chest X ray are recommended
- CSF analysis

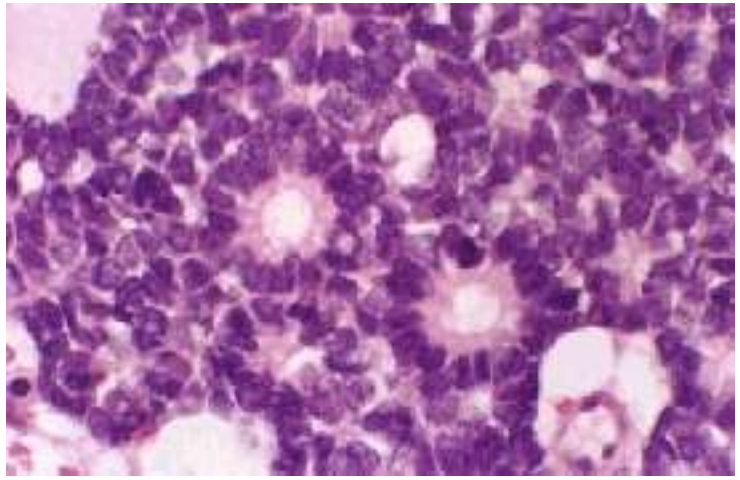
Distant metastatic retinoblastoma without central nervous system involvement , Mohammad Javed Ali, Santosh G. Honavar, and Vijay Anand Reddy[1] Indian J Ophthalmol. 2013 Jul; 61(7): 357–359.

Histopathology

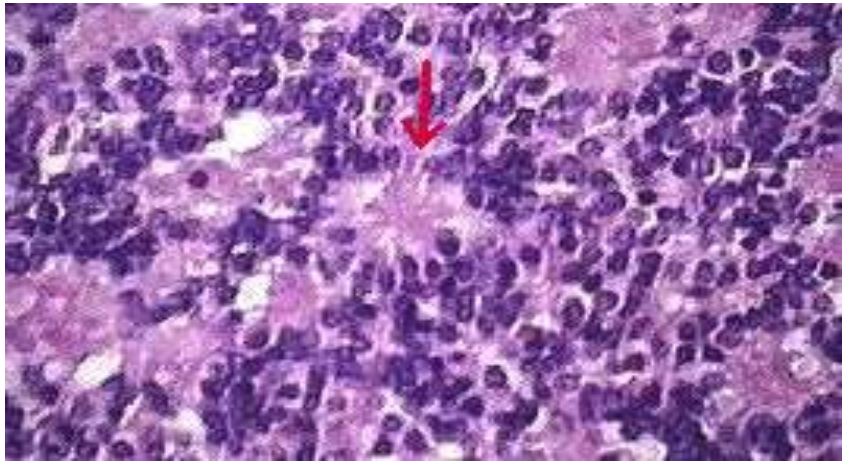
Under the microscope, RB contains deep blue cells with little cytoplasm
•Rosettes, pseudorosette & Fleurette,

•The following features are commonly seen in all retinoblastomas

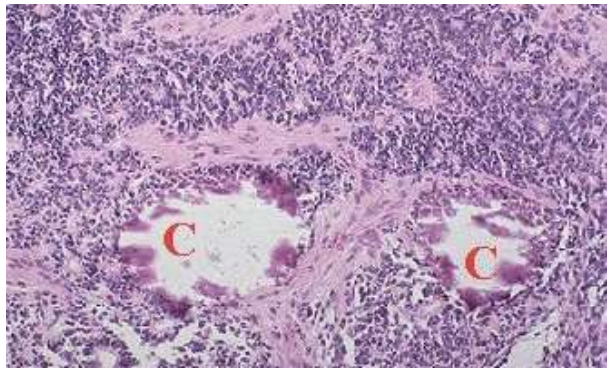
•the type of growth
•the presence or absence of vitreous or subretinal seeding
•rosettes and fleurettes
•Necrosis
•Calcification
•Iris neovascularization
•Invasion of the anterior chamber, iris, choroid, optic nerve and sclera



Flexner Wintersteiner rosettes: clusters of cuboidal or short columnar cells arranged around a central lumen.

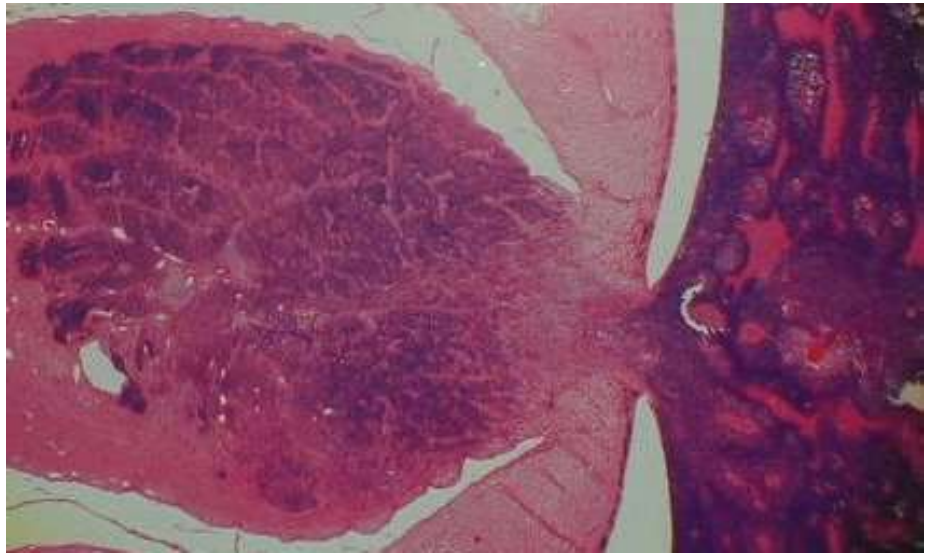


Fleurette (arrowed): photoreceptor differentiation



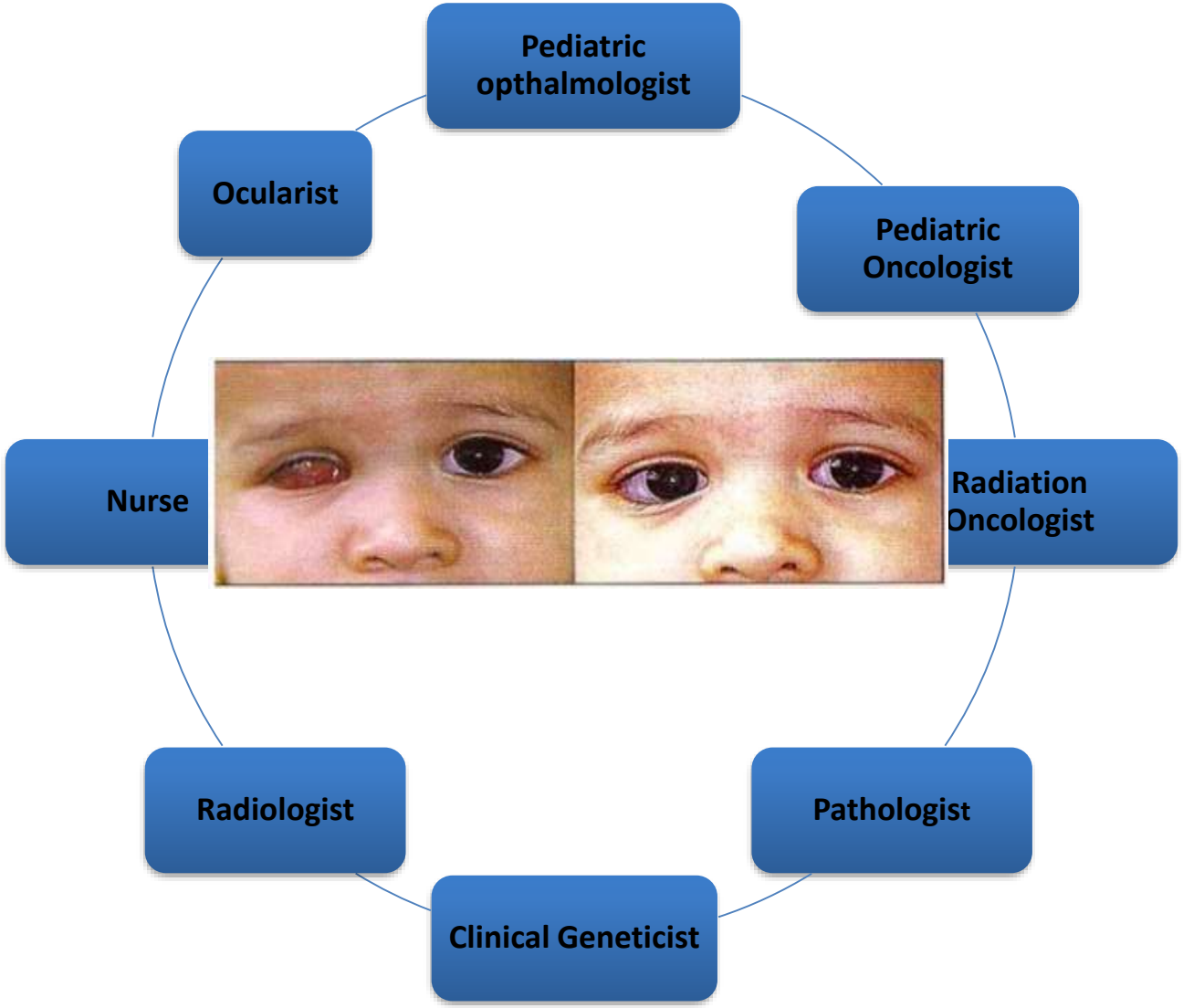
Retinoblastoma with areas of necrosis (the pink areas) and two areas of calcification (C)

Optic nerve (left) infiltrated by retinoblastoma (right). Note the presence of retinoblastoma (dark blue) in the optic nerve substance.



MANAGEMENT

TEAM APPROACH



Management

- Primary goal –Survival of the child (Save LIFE)
- Secondary- save eye and vision (save ORGAN and Function)
- Finally- reduce the long term side effects – fascial deformity, 2ndary malignancy etc

Management of retinoblastoma is highly individualized and is based on several considerations –

-Age at presentation-Laterality

-Tumor location

-Tumor staging

-Visual potential of the involved eye after treatment

-Systemic condition, family and societal perception.

-The overall prognosis and cost-effectiveness of treatment in a given economic situation.

Treatment participations

Original Paper

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Retinoblastoma: A Sixteen-Year Review of the Presentation, Treatment, and Outcome from a Tertiary Care Institute in Northern India

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Keywords
Intraocular retinoblastoma · Extraocular retinoblastoma · Enucleation · Chemotherapy

Abstract
Purpose: To study epidemiology, demographic profile, clinical characteristics, and outcome in pediatric patients with retinoblastoma. ***Methods:*** This was a retrospective review of retinoblastoma patients of a tertiary institute from January 1st 1998 to December 31st 2014. ***Results:*** The study included 467 patients (618 eyes) with a mean age of 34.7 ± 24.6 months (median = 30; 15 days to 144 months). Retinoblastoma was bilateral in 151 (32.3%) and there were 61.7% males. Intraocular disease was seen in 301 patients (451 eyes [72.9%]) and extraocular in 166 patients (167 eyes; 27.0%). Out of the 347 (74.3%) who received treatment, primary treatment was chemoreduction in 228 (65.7%) and enucleation in 117 (33.7%), while 25.6% of patients refused treat- ... rate of metastasis, recurrence, and death between the two. ***Conclusions:*** The majority of retinoblastoma patients in our study had advanced disease, and nearly a third had extraocular extension. There were a significant number of therapy refusals and dropouts. Chemoreduction led to a significant decrease in the histopathological risk factors without affecting the outcomes.

Introduction

Retinoblastoma is the most common primary intraocular malignancy of childhood. Despite advances in diagnosis and management, retinoblastoma still remains a considerable challenge especially in the developing world. More than 50% of patients die from the disease, and those who seek treatment are already at an advanced stage [1]. Survival in cases of extraocular retinoblastoma is even

Pediatr Blood Cancer 2013;60:771–775

Causes, Outcome and Prevention of Abandonment in Retinoblastoma in India

Archana Kumar, MD,[1]* Nirmalya Roy Moulik, MD,[1] Ravi Krishna Mishra, BAMS,[1] and Dipak Kumar, MS[2]

TABLE III. Reasons Behind Abandonment

Reason for abandonment	Number (% of responses)[a]
Financial constraints	24 (30)
Not willing for enucleation	16 (20)[b]
Family problems	15 (18.5)
Perception that disease was cured	15 (18.5)
Planned to get treated elsewhere	5 (6.5)
Superstitions or faith in alternate therapy	5(6.5)[c]

KCI data (2012-2014)

Total number of cases	53
Male: Female	1.2:1
B/L Retinoblastoma	21 (39.6%)
Intraocular RB	22 (41.6)
Extraocular RB	31 (58.4)
High risk features Optic nerve invasion Choroidal invasion Intracranial extension Orbital involvement	13 12 6 5 5
Bone marrow involvement	3
CSF	6
No of patients consented for treatment	29
No of patients completed the treatment	21
No of patients refused the treatment	24

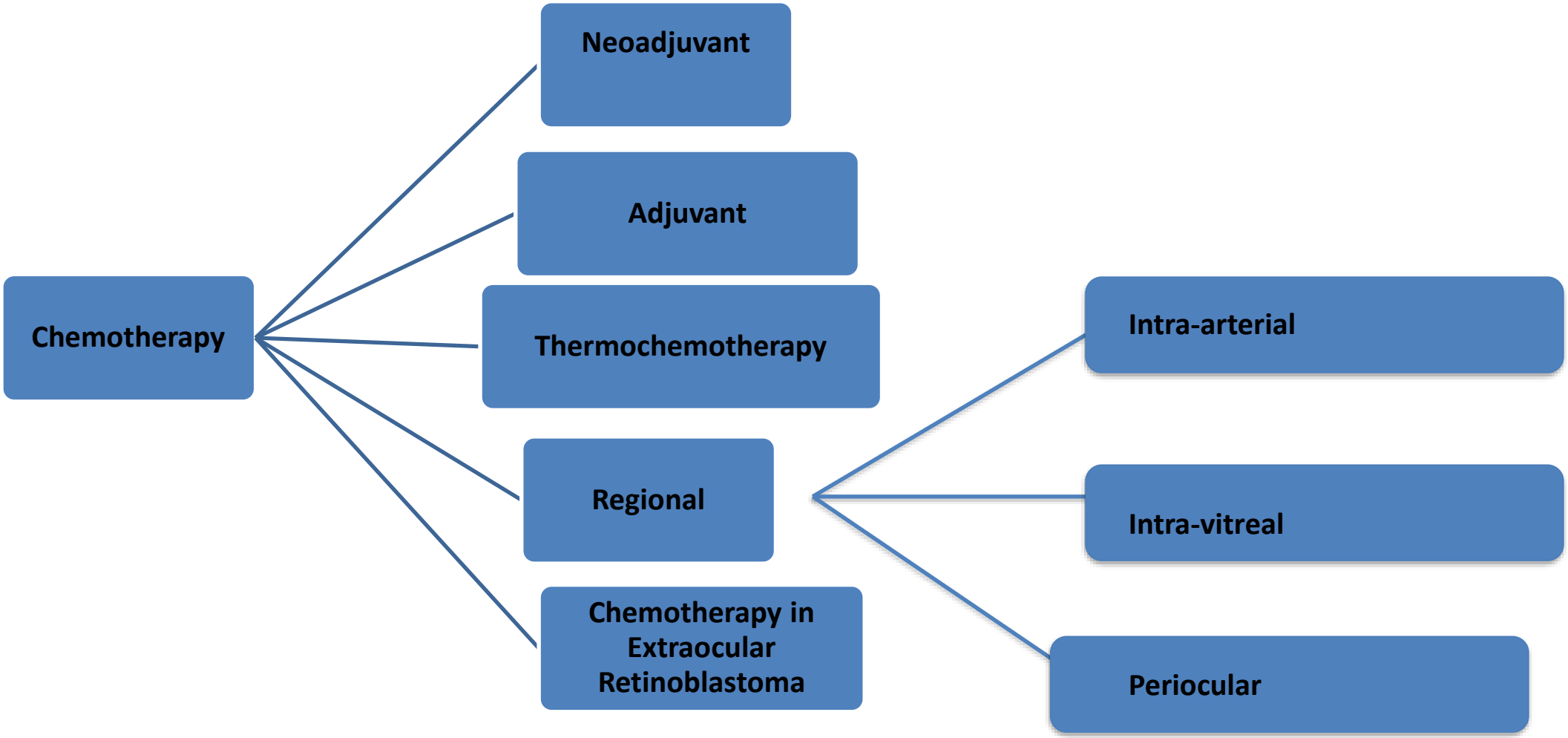
MANAGEMENT OF RETINOBLASTOMA

GROUP		Treatment Options
Group I, Group II	EARLY	Cryotherapy • Thermotherapy • Laser photocoagulation
Group II, III, GROUP IV	INTERMEDIATE	Chemoreduction + Local Therapy • Plaque brachytherapy • External beam radiotherapy
GROUP V	LATE	Enucleation • Adjuvant therapy – Chemo / EBRT • Orbital exenteration

TREATMENT OPTIONS FOR RETINOBLASTOMA

1. Surgery
   - Enucleation
   - Exenteration
2. Radiotherapy
   - External Beam Radiotherapy
   - Scleral Plaque Brachytherapy
3. Chemotherapy

TREATMENT OPTIONS FOR RETINOBLASTOMA



Focal Therapy

Trans pupillary thermotherapy

• Application of Infrared diode laser (810 nm) heat directly to the tumor.

A temperature rise is below the coagulative threshold and therefore spares retinal vessels from coagulation

- Large spot
- Long duration burns
- 6-10^0 temp raise

Tumors confined to the retina

No vitreous seeds

No exudative RD / choroidal invasion

<2 mm thick; <3-4mm in diameter,

Mechanism Direct cytotoxic effect of heat on tumor cells and heat-induced alteration of tumor microenvironment, expression of heat shock protein.

Advantages ➢ Tumors adjacent to the fovea or the optic nerve can be treated.

Complications

➢ Focal iris atrophy.
➢ Focal paraxial lens opacity.
➢ Retinal traction and serous detachment.

Laser photo coagulation

Indication

➢ Small posterior tumors which are 4 mm in diameter and 2 mm in thickness

Mechanism

Photocoagulation using argon green laser (532 nm) delivered with anIndirect laser delivery system causes tumor apoptosis.The treatment destroys the tumor by restricting the blood supply to the tumor and also by hyperthermia. Typically the treatment is repeated every 3-4 weeks

Advantages➢Can be used when TTT is not available.

Disadvantages(1) Retinal traction and serous retinal detachment.(3) Retinal hole.(4) Iris burns and lens opacities. Big scaring and loses vascularisation

Thermo chemotherapy

Indication

➢ Lesions smaller than 8mm diameter and 5mm high.

- Diode laser 810 nm to entire tumor covered in 10-15 min within 2-3 hrs after chemotherapy infusion.

Mechanism Heat facilitate cellular uptake of the drug ,increasing its effectiveness.

Advantages ➢ Synergistic effect - Single agent (Carboplatin) + Focal transpupillary hyperthermia.

Disadvantages ➢ Focal iris atrophy

Cryotherapy

Indication

➢Peripheral tumors <4 mm in diameter and <3 mm in thickness
Subretinal seeds

•Transscleral triple freeze and thaw technique under visualization using indirect ophthalmoscopy every 3-4 weeks.

Mechanism

Cryotherapy induces the tumor tissue to freeze rapidly, and a temperature upto −90°C causes intracellular ice crystal formation, protein denaturation, pH changes and disruption of cell membranes.

Advantages ➢Treatment of focal vitreous seeds overlying the tumor .

Complications

➢Large area of retinal scarring.
➢Retinal breaks.
➢Vitreoretinal tractions.
➢Lid and conjunctival edema.

Chemotherapy

CHEMOTHERAPY DRUGS

- Drugs used are

1.Vincristine	6.Cisplatin
2. Etoposide	7. Topotecan
3.Carboplatin	8. Thiotepa
4.Doxorubicin	9.Idarubicin
5.Cyclophosphamide	10. Cyclosporine

Chemotherapy regimen

VEC protocol	**Inj. Vincristine 1.5 mg/m2 day 1 (0.05 mg/kg BW <36 months age)** **• Inj. Etoposide 150 mg/m2 day 1&2 (5 mg/kg BW <36 months age)** **• Inj. Carboplatin 560 mg/m2 day 1 (18.6 mg/kg BW <36 months age)**	**3 - 4 weekly, 6 cycles, EUA before each cycle**
VEC protocol High dose chemo protocol	•Vcn 1.5mg/m2; Etop 250mg/m2; Carb 750mg/m2	
Shield's Protocol	Inj. Carboplatin 560 mg/m2 day 1 (18.6 mg/kg BW <36 months age) Inj. Etoposide 150 mg/m2 day 1 and day 2 (5 mg/kg BW <36 months age) Inj. Vincristine 1.5 mg/m2 day 1 (0.05 mg/kg BW <36 months age)	3 - 4 weekly, 6 cycles • EUA before each cycle •Chemocryotherapy and SALT
Shield's Protocol High dose chemo protocol	VCR 1.5mg/m2; Etop 250mg/m2; Carb 750mg/m2	

Global salvage – new initiatives

- Intra arterial chemotherapy
- Peri ocular chemotherapy
- Intra vitriol chemotherapy

Intra arterial chemotherapy

Indications

➢ Eyes which have not achieved tumor control after intravenous chemotherapy.

➢ Recurrent retinoblastoma or subretinal

Drugs Melphalan is the most extensively used drug.
Topotecan is added if extensive vitreous seeding.
In advanced cases, three drugs including carboplatin

• One-drug regimen: melphalan (3-7.5 mg)• Two-drugs regimen: melphalan (3-7.5 mg) + topotecan (1-2 mg)
• Three-drugs regimen: melphalan (3-7.5 mg) + topotecan (1-2 mg) + carboplatin (15- 50 mg)

Advantages

• High intraocular concentration of the drug without associated systemic adverse effects of the drugs

• Shorter time for tumor control

. Disadvantages

• Expensive
• Difficulty with catheterizations
• Vitreous hemorrhage
• Branch retinal artery obstruction
• Ophthalmic artery spasm with reperfusion
• Ophthalmic artery obstruction
• Partial choroidal ischemia
• Optic neuropathy
• Risk for brain vascular events, hypoxia, hypotension, and bradycardia.

Periocular chemotherapy

Indication

➢Advanced groups D or E with diffuse vitreous seeds in which a higher local dose of chemotherapy is desired

Drugs•Carboplatin (1.5-2.0 mg)•Topotecan (1 mg)

Procedure•
In the quadrant closest to the location of the vitreous seeds.

Intravitreal chemotherapy

Pioneered by Ericson & Rosengren in 1960

Indication
Recurrent or Persistent diffuse or focal vitreous seeds

Drugs
Melphalan is the most widely used drug in IVitC.Topotecan is generally added if there is extensive vitreous seeding.
• Melphalan (20-30 μg)• Topotecan (20-30 μg)• Combination: Melphalan (20-30 μg) + Topotecan (20-30 μg)

Radiation therapy

Radiotherapy

- RT- Why
- Indication
- RT dose
- Type- brachy/EBRT
- EBRT- ? IMRT/VMAT/SRT/PRT

In The

RE	Ellsworth 1977 EBRT	Hungerford 1995 EBRT	Shields 2003 CTRT+SALT	LVPEI 2005 CTRT+SALT*
I	93	100	100	100
II	82	84	100	100
III	81	82	100	100
IV	62	43	75	90
V	29	36	50	75

Radiation therapy

- Conventional EBRT in the megavoltage era
  Local control rates of 41–56%,
  Eye survival rates of 60–100%.

- Local control rates RE groups I–II- 79% and
  RE groups III–V - 20% for eyes.

  Eye survival rate RE groups I–III -80-90%
  RE Groups IV-V- 60%

  Failure rate - 40–60% of patients, with with other focal modalities, resulting in long-term eye survival rates of around 80%.

Failure rates at the primary site differed for tumors <15 mm and >15 mm in diameter (50% vs. 21%).

Results of chemoreduction

Table 4. Treatment Outcomes of Chemoreduction

Authors	Patients	Chemotherapy	Focal treatment	Outcome*
Shields, et al.[18]	158 eyes of 103 patients (364 tumors)	6 cycles (vincristine, etoposide, and carboplatin)	Cryotherapy, thermotherapy, or plaque radiotherapy	Treatment failure rate at 5 yrs RE groups I–IV: EBRT required in 10% Enucleation required in 15% RE group V: EBRT required in 47% Enucleation required in 53%
Shield, et al.[32]	249 eyes of 163 patients	6 cycles (vincristine, etoposide, and carboplatin)	Thermotherapy or cryotherapy	Treatment success rate ICRB group A: 100% ICRB group B: 93% ICRB group C: 90% ICRB group D: 47%
Künkele, et al.[33]	56 eyes of 40 patients	6 cycles (vincristine, etoposide, carboplatin, and cyclophosphamide)	Thermotherapy, laser coagulation, cryotherapy, or brachytherapy	Treatment failure rates ICRB group A: 25% ICRB group B: 15% ICRB group C: 33.3% ICRB group D: 83.3%

RE, Reese-Ellsworth; ICRB, International Classification of retinoblastoma.
*Failure defined as progression requiring enucleation or external beam radiotherapy (EBRT).

Radiotherapy in intensive Chemoreduction era

- **unilateral RB** (21 group C, 40 group D, 40 group E by ICRB) - intensified chemotherapy with periocular carboplatin resulted in eye salvage in 20 (95%) group C, 34 (85%) group D, and 23 (57.5%) group E eyes.
- 33 patients requiring EBRT.
- An earlier study of EBRT alone found that the long-term globe salvage rate using doses of 42–45 Gy was 53%, with local control in 50% of patients with ICB group E and RE group VB RB

» Manjandavida FP, Honavar SG, Reddy VA, Khanna R. Management and outcome of retinoblastoma with vitreous seeds. Ophthalmology 2014;121:517-24.

Results of chemoreduction

- **bilateral RB** who received primary chemotherapy and focal treatments, 36 eyes of 22 patients failed and required salvage EBRT.
- Of the 36 eyes, 24 eyes (66.7%) were controlled by EBRT of 40–44 Gy over 20–22 fractions and required no further treatment.
- Overall, 30 out of 36 eyes (83.3%)34 were preserved at 40 months.

» Chan MP, Hungerford JL, Kingston JE, Plowman PN. Salvage external beam radiotherapy after failed primary chemotherapy for bilateral retinoblastoma: rate of eye and vision preservation. Br J Ophthalmol 2009;93:891-4.

Radiotherapy in intensive Chemoreduction era Pros vs. Cons

Table 5. Comparison of Chemoreduction, Chemoreduction Plus Radiotherapy (RT) and Chemoreduction Plus Lower Dose Prophylactic RT in Advanced Retinoblastoma

Treatment modality	Chemoreduction alone	Chemoreduction+RT	Chemoreduction+lower dose prophylactic RT
Pros	Avoid or delay enucleation or RT	Higher tumor control than chemoreduction alone or lower dose RT	Less recurrence than chemoreduction alone Lower risk of RT related toxicity is expected than therapeutic RT
Cons	30–50% eventually required RT for globe salvage[18,28]	Late complication of radiation such as orbital bone hypoplasia or secondary malignancy	Exact risk of lower dose of RT is not known Prospective study may needed
Globe salvage rate	Group D: 11–47%[15,35] Group E: 53% at 2 yrs, 48% at 5 yrs[16]	RE groups IV–V: 28.6–62.5% at median F/U of 40 months[34]	Group D: 82% at 1 yr, 68% at 5 yrs[15] Group E: 91% at 2 yrs, 80% at 5 yrs[16]

RE, Reese-Ellsworth.

Shields CL, Ramasubramanian A, Thangappan A, Hartzell K, Leahey A, Meadows AT, et al. Chemoreduction for group E retinoblastoma: comparison of chemoreduction alone versus chemoreduction plus low-dose external radiotherapy in 76 eyes. Ophthalmology 2009;116:544-51.

Radiotherapy- indications

- Brachytherapy- primary or adjuvant to CT
  8mm depth and 16mm diameter

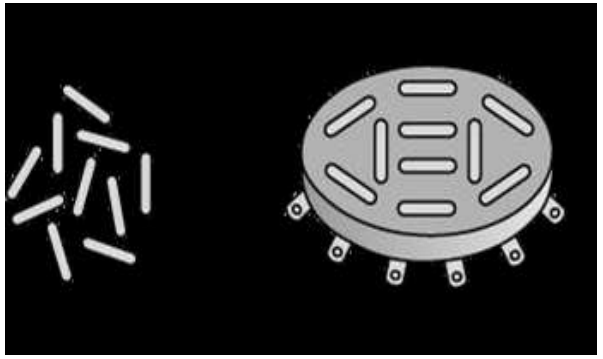
  EBRT- Definitive
  Multifocal RB with diffuse seed fail to responsd to CT
  Residual disease after Group II and IV

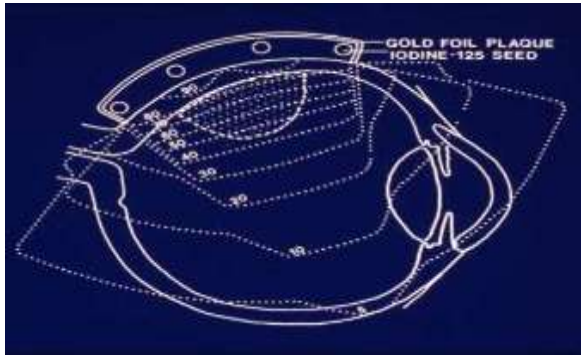
  EBRT- Adjuvant

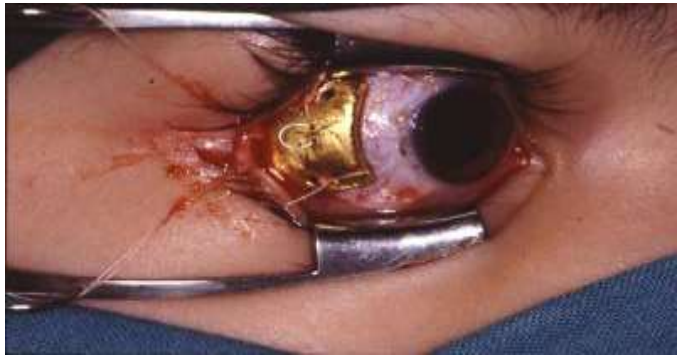
  EBRT in metastatic cases

Focal Plaque Brachytherapy

- Plaque brachytherapy involves placement of a radioactive implant on the sclera corresponding to the base of the tumor to transsclerally irradiate the tumor
- Indication in tumors < 16 mm in basal diameter and < 8 mm thickness. It could be the primary or secondary modality of management
- I-125 applicator, ‘claws’, developed by Sealy.
- It consists of four ‘claws’ loaded with I-125 seeds that are placed between each of the extraocular muscles and attached anteriorly to a pericorneal ring, which is itself attached to the four extraocular muscles.







Focal Plaque Brachytherapy

- A dose of 40Gy is given to the centre of the eye over 4 days.
- excellent results - local control and retention of vision in 85% in group A–C eyes and a local control rate of 58% in group D eyes with eye retention in 39%.
- The design of the ‘claws’ applicator ensures considerable protection of the bony orbit. This results in good long-term cosmesis and there is no recorded incidence of second non-ocular malignancy

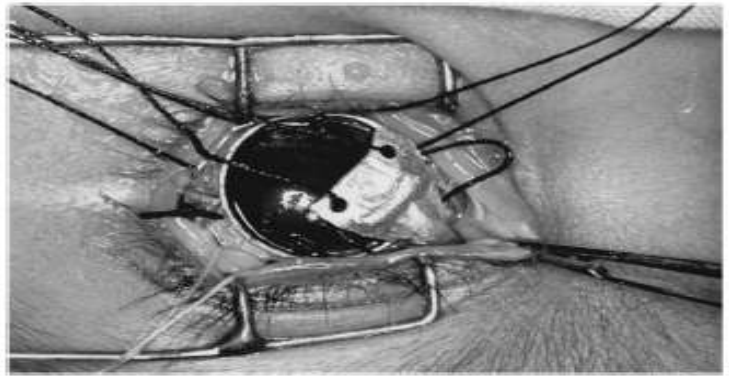


Figure 10 Insertion of one of the ‘claws’ of an I-125 applicator between the extraocular muscles and to be attached to the pericorneal ring, which is itself attached to the extraocular muscles. Reprinted with permission from Elsevier.[24]

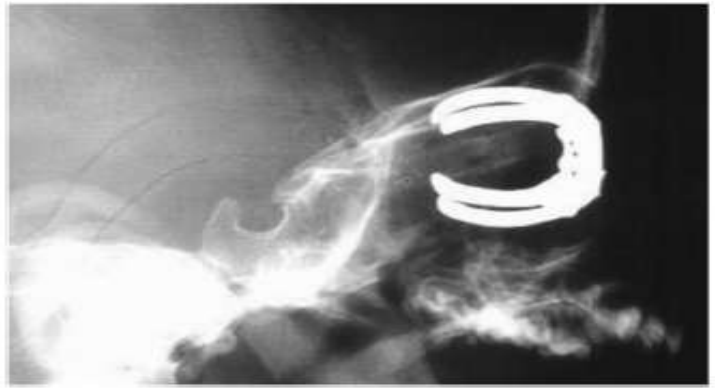


Figure 11 X-ray of ‘claws’ applicator. Reprinted with permission from Elsevier.[24]

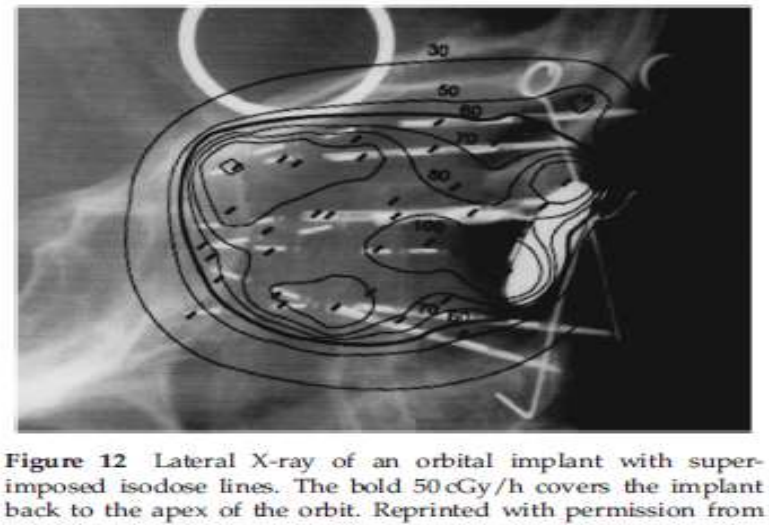


Figure 12 Lateral X-ray of an orbital implant with superimposed isodose lines. The bold 50 cGy/h covers the implant back to the apex of the orbit. Reprinted with permission from

3358

Eye Plaque Brachytherapy for Retinoblastoma—A Uni-Institutional Retrospective Analysis of 40 Eyes in 38 Patients Treated From 2001 to 2014

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Purpose/Objective(s): This study has the primary objective to evaluate the local control of retinoblastoma patients treated with ophthalmic plaque at our institution; and secondary objective of evaluating the impact of factors associated with disease and treatment, as control rate and local recurrence.

Materials/Methods: This is a retrospective study, single-institutional, with 40 eyes analysis in 38 consecutive patients who underwent brachytherapy with plaque of Ruthenium-106 (Ru-106) or iodine-125 (I- 125) between the years 2001 and 2014. It was described and analyzed data as laterality, thickness of the lesion dose treatment and outcomes. The Kaplan-Meier survival curves were calculated and statistically compared using the log-rank test.

Results: The follow-up and the median age were 82 and 27 months, respectively. Thirty three plaques were used I-125 and 7 Ru-106. Seventy-two percent of patients were treated as salvage therapy and 27.5% as a primary treatment. There were 2.5% loss of follow-up. Sixty percent of the lesions were bilateral. The median dose at the apex and base were respectively 46.9 Gy and 135.9 Gy. The actuarial local control at 1 year was 58.2% and for five years was 47.3%. Regarding the factors associated with local recurrence, the dose at the apex above 47 Gy resulted in better control, with 63.2% ($P = 0.103$). The previously untreated patients had a local Control 77.8%, far higher compared with the patients treated as salvage, only 40% ($P = 0.05$).

Conclusion: Eye plaque brachytherapy remains as an important therapeutic modality for intraocular retinoblastoma, particularly as primary therapy. The data obtained from patients treated as salvage raises issues related to the profile of these and, maybe, less favorable condition in our community, resulting in little or no response to proposed treatments.

Author Disclosure: **B.B. Silva**: None. **L. Sapienza**: None. **D.G. Castro**: None. **D.D. Ferreira**: None. **C.R. Leão**: None. **D.F. Neves**: None. **B. Silva**: None. **A. Aiza**: None. **A.C. Scintini**: None. **C. Pellizzon**: None. **M. Regalin**: None.

Abstract

Background/Aims To report visual outcomes, survival outcomes and complications following episcleral brachytherapy (EB) for retinoblastoma.

Methods Retrospective review of retinoblastoma cases treated with EB in a single institution. Survival outcomes were analysed using the Kaplan-Meier method.

Results Eleven tumours of 11 eyes were treated with either iodine-125 or ruthenium-106 EB with a mean apical dose of 44 Gy. The tumours were classified as group B in 5 (46%), C in 3 (27%) or D in 3 (27%) eyes, respectively. Mean follow-up time was 75.4 months. EB served as primary treatment in 3 eyes (27%) and secondary treatment in 8 eyes (73%). Final visual acuity was better than 20/200 in 70% of cases. Globe preservation was achieved in 9 (82%) eyes. Local recurrence occurred in 18% of cases at a mean onset of 17.4 months after EB. Two group D tumours that recurred after secondary EB underwent enucleation. Mean onset of radiation retinopathy was 17.4 months following EB. No metastatic or fatal events were recorded. Kaplan-Meier analysis showed recurrence-free survival and ocular survival of 80% and overall survival of 100% at 5 years after EB.

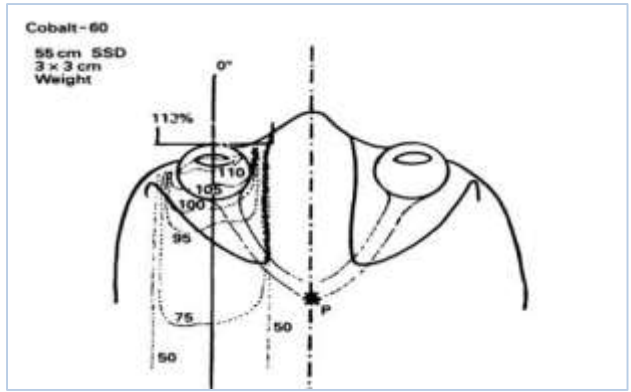
Conclusion EB is an effective primary or secondary treatment modality for selected retinoblastoma eyes (groups B and C). Advanced group D tumours may represent a risk factor for local recurrence. Visually significant complications such as radiation retinopathy should be anticipated.

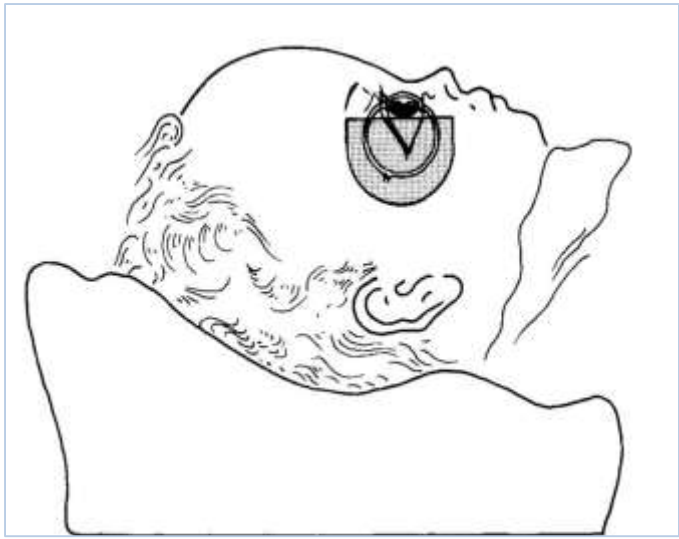
Role of EBRT

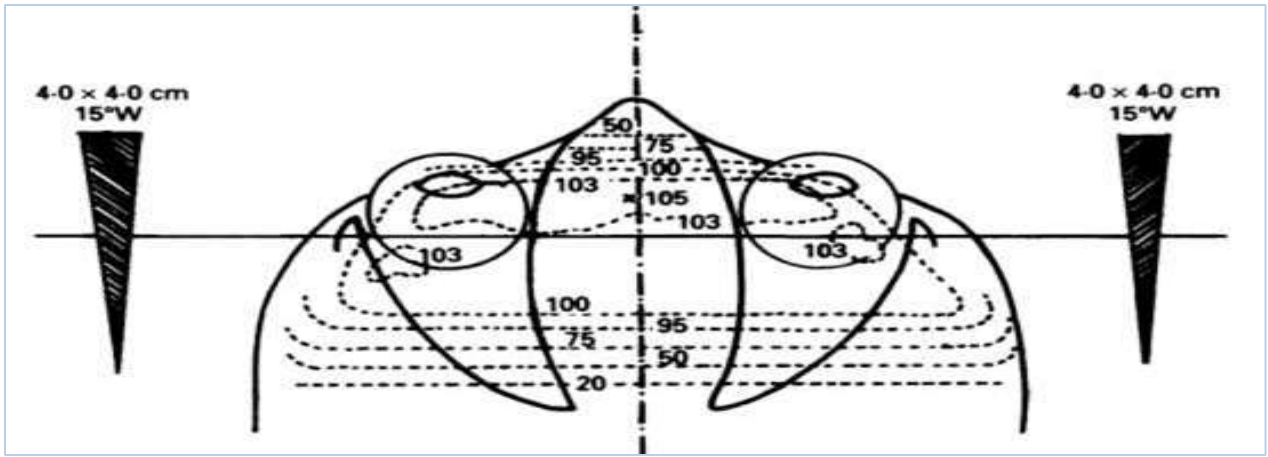
Table 4: Indications of External Beam radiotherapy.

1	Residual disease after chemotherapy and local therapy
2	Diffuse vitreous seeds
3	Recurrence after chemotherapy4
4	Post enucleation a. Sclera involvement b. Extraocular extension c. optic nerve involvement

EBRT- Conventional techniques

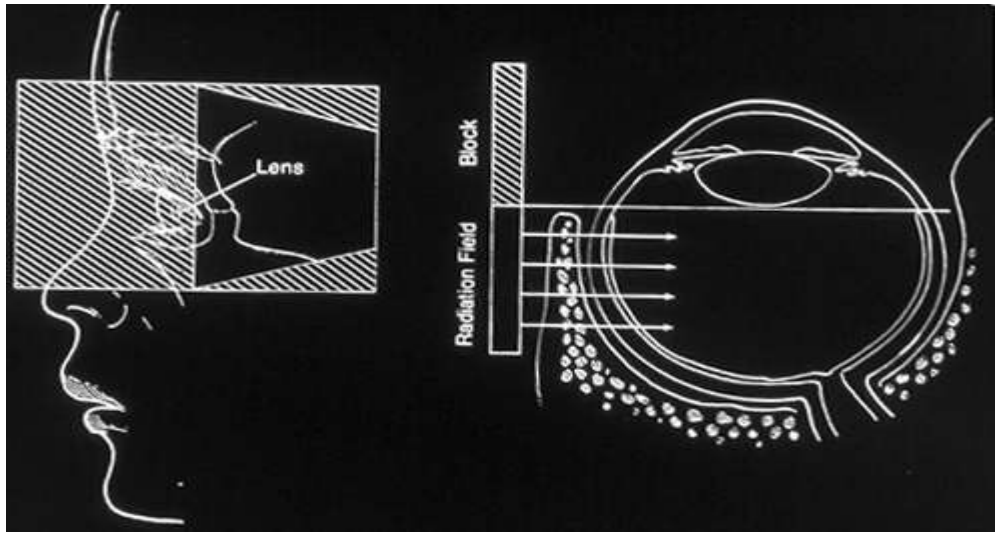


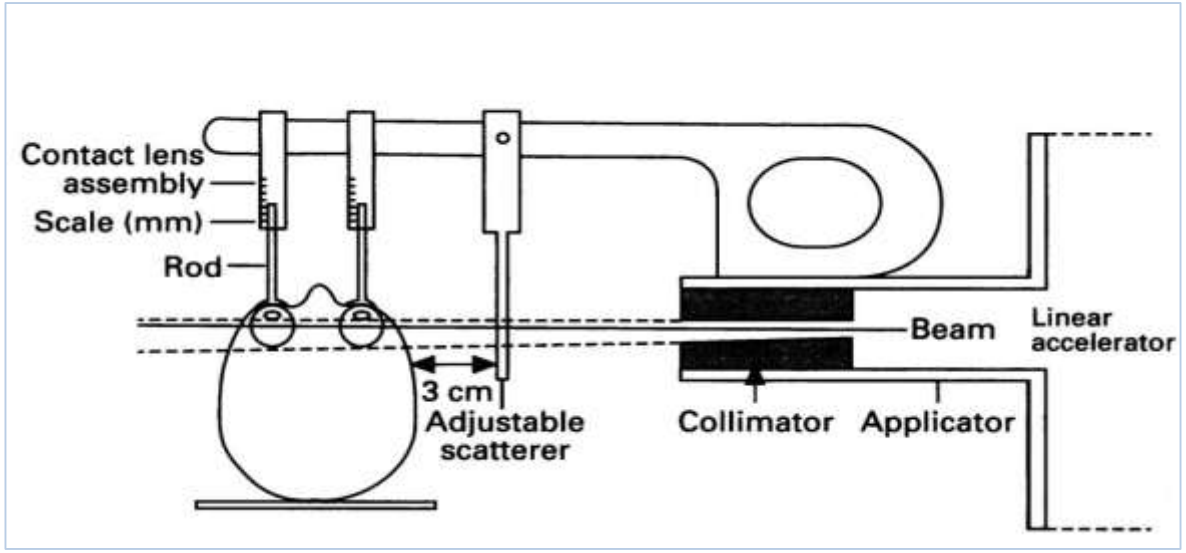


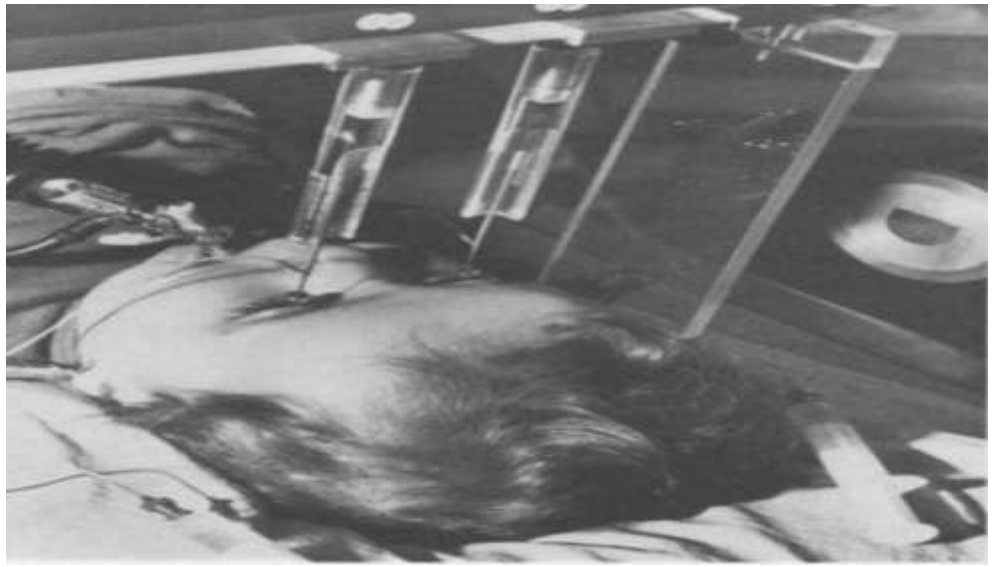


EBRT- Conventional techniques

- RT to the whole eye done with EBRT, using the Schipper technique to spare the lens and anterior eye.
- Suction contact lenses are placed on both eyes of the anaesthetised child and attached by rods to the extension of the D-shaped collimator of the linear accelerator so that the anterior edge of the beam, along the central beam axis, falls just posterior to the lens



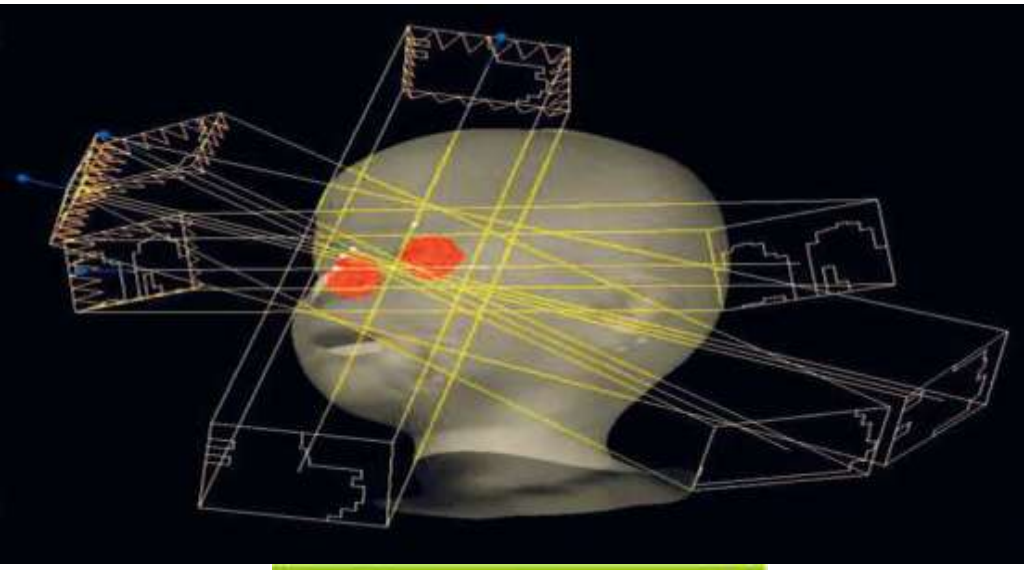




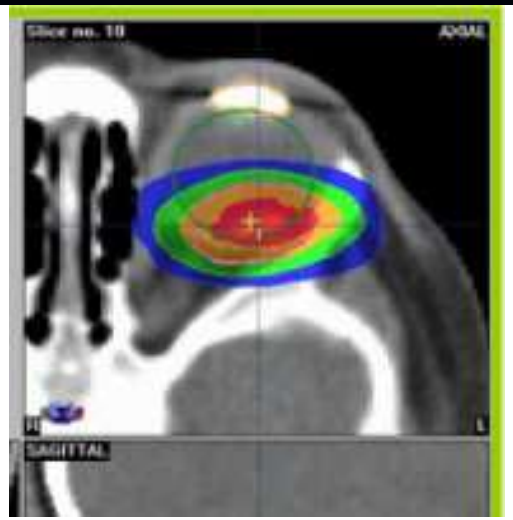
EBRT- Conformal techniques- Current practice

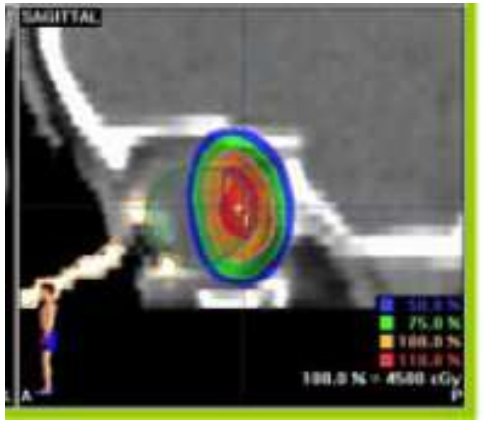
- 3DCRT/IMRT/VMAT/SRT/Tomotherapy/Proton/
- These innovations in the delivery of radiation permit safer treatment of retinoblastoma while trying to reduce the exposure of radiation to normal structures and bone.
- Intensity modulated radio therapy (IMRT) perhaps permits greatest reduction in the dosage of the radiation to the orbit and the lacrimal gland while permitting therapeutic dosage to the retina up to the ora serrata and the vitreous

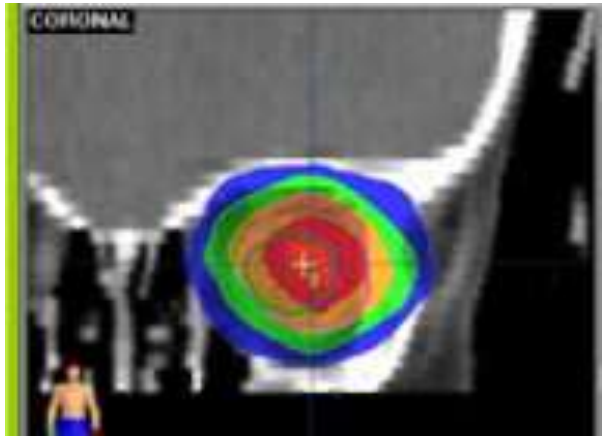
COMPARISION OF RT TECHNIQUES



- The volume of the bony orbit receiving >5 Gy was found to be 69% for IMRT, 25% for three-dimensional (3D) conformal electrons, and 10% for proton radiotherapy.
- volume of the ipsilateral bony orbit receiving at least 20 Gy (V20 GY) was much lower for arc-based IMRT than for 3D-conformal radiotherapy (56% vs. 90%).







PROTON THERAPY

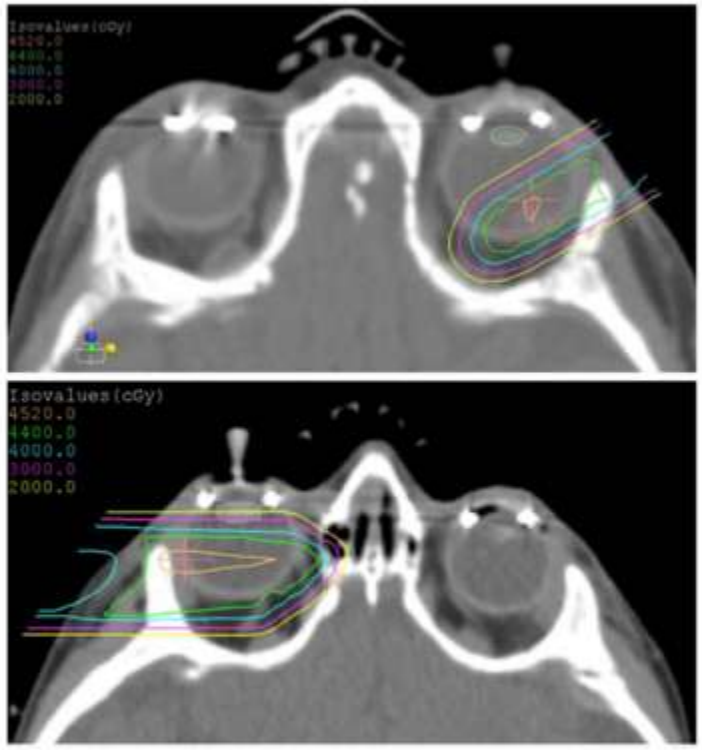


Figure 1.
Representative axial CT slice from two PRT plans. A. For small tumors without seeding, a single anterior oblique beam was used to minimize dose to the bony orbit (prescription dose 44 Gy[RBE]). The tumor is outlined in red, and the lens is outlined in pale green. B. For larger tumors, or if seeding was present, the posterior chamber was targeted with a single lateral beam (prescription dose 45 Gy[RBE]).

Int J Radiat Oncol Biol Phys. 2014 November 15; 90(4): 863–869. doi:10.1016/j.ijrobp.2014.07.031.

Table 2

Follow-Up Details

Median length of follow-up (range)	8 yrs (1 -24 yrs)
Median age at last follow-up (range)	9 yrs (2 - 24 yrs)
No. irradiated eyes enucleated	11/60 (18%)
Stage A-B	3/11
Stage C-D	7/11
Stage unknown	1/11
Enucleation location	
Our institution	6 (55%)
Outside institution	5 (45%)
Median time elapsed between PRT and enucleation (range)	10 mo (5 - 44 mo)
Median time when enucleation at our institution	20 mo
Median time elapsed when enucleation at outside institution	7 mo
Indication for Enucleation	
Progressive disease	8/11
Ocular complications	2/11
Unknown	1/11
Non-enucleative ocular complications requiring procedure	
Cataracts	4
Radiation retinopathy	3
Glaucoma	1
Neovascularization/Hemorrhage	1
Other	2
Multiple	1
No. patients with metastatic disease	0

Enucleation

Oldest form of treatment for retinoblastoma, and is still indicated in advanced cases.

- ➢ The myoconjunctival technique with a silicone orbital implant is a safe and cost-effective procedure

Indication
Tumor occupying >75% vitreous volume
Necrotic tumor with secondary orbital inflammation
Tumors associated with hyphema or vitreous hemorrhage
Advanced unilateral tumor
Secondary glaucoma
pars plana invasion
anterior segment seeding
Worse eye in advanced bilateral

Enucleation

Special Considerations

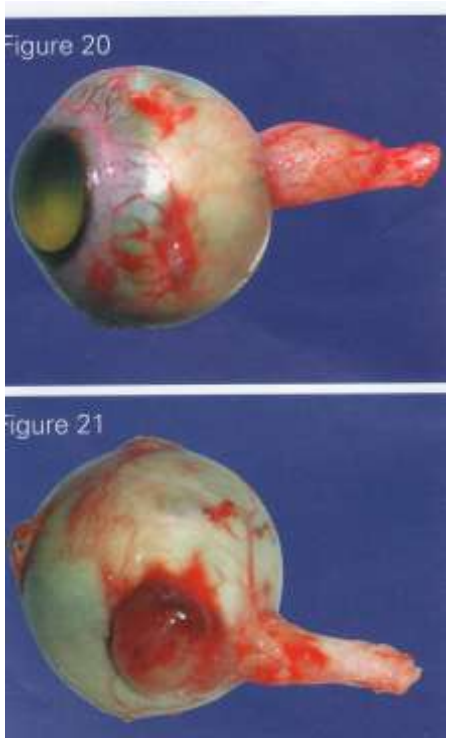
➢Minimal manipulation

➢Avoid perforation of eye

➢Harvest long (>15mm)optic nerve stump

➢Inspect the enucleated eye for macroscopic extraocular extension and optic nerve involvement

➢Avoid biointegrated implant if postoperative radiotherapy is necessary



Adjuvant radiation therapy

- Indications

- Optic nerve invasion @ cut end
- Scleral / extraocular extension
- Inadvertent ocular perforation
- Intraocular surgery in unsuspected retinoblastoma

Adjuvant RT

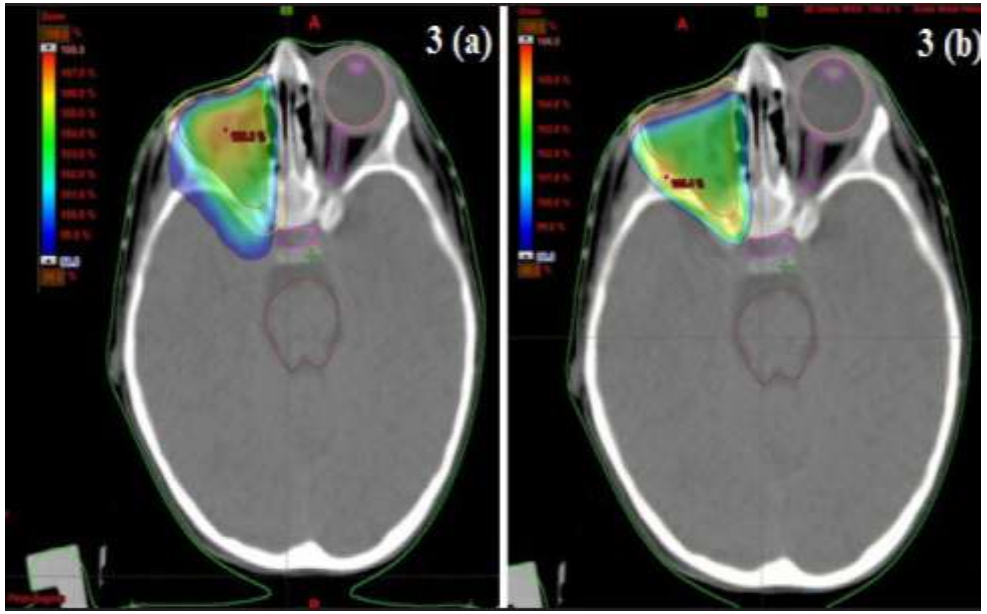


Table 1: Dosimetric parameters of three dimensional conformal radiotherapy and intensity modulated radiotherapy pla

Dosimetric parameter	3DCRT	IMRT
PTV 95%	99%	97.7%
99%	96%	92%
Lt eye (Dmax)	1.4 Gy	17.9 Gy
Lt lens (Dmax)	0.3 Gy	6.2 Gy
Lt optic nerve (Dmax)	2.3 Gy	25.97 Gy
Brainstem (Dmax)	34.99 Gy	30.08 Gy
Optic chiasm (Dmax)	46.1 Gy	49.1 Gy
Pituitary gland (Dmax)	45.24 Gy	46.48 Gy
Brain (Dmean)	7.24 Gy	7.02 Gy
Integral dose of brain	12.6 J	12.9 J
Homogeneity index	1.10	1.14
Conformity index	1.54	1.40

Dose- 40-45 Gy in 1.8Gy/fractions

Summary of Chemoradiation era Eye Salvage Rates

RE	Ellsworth 1977 EBRT	Hungerford 1995 EBRT	Shields 2003 CTRT+SALT	LVPEI 2005 CTRT+SALT*
I	93	100	100	100
II	82	84	100	100
III	81	82	100	100
IV	62	43	75	90
V	29	36	50	75

GLOBE SALVAGE WITH VARIOUS MODALITIES OF TREATMENT

Table 27.4 Percentage of Globes Salvaged Using External Beam Radiotherapy Alone, External Beam Radiotherapy and Salvage Treatment, and Chemoreduction and Focal Adjuvant Treatment

Reese-Ellsworth Group	EBRT alone Ellsworth[273] (1965–1972)	EBRT + Salvage Rxb Hungerford[268] (1970–1985)	CRDc + ATd Shields[228] (1994–1996)
I	91%	100%	100%
II	83%	84%	100%
III	82%	82%	100%
IV	62%	43%	100%
V	29%	66%	78%

EBRT, external beam radiotherapy; Rx, treatment; CRD, chemoreduction using vincristine, etoposide, and carboplatin; AT, adjuvant treatment (laser photocoagulation, cryotherapy, thermotherapy, chemothermotherapy, plaque radiotherapy, external beam radiotherapy).

Shields CL, Shields JA, Needle M, et al. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma Ophthalmology 1997;104:2101–2111

Indian results

Studies in India	Place	Main variable studied	Salient finding
Chawla B et al, 2015	New Delhi	Survival of retinoblastoma	• The Kaplan-Meier survival probability was 83%, 73% and 65% at 1 year, 2 years and 5 years, respectively. • Extra ocular invasion was predictive of low survival (HR 5.04, p<0.001).
Dhir SP et al, 1981	Chandigarh	Survival of retinoblastoma	Patients with orbital involvement had significantly (p <0.01) poor survival than those with intra, ocular disease alone. No significant difference was seen in survival between various modes of therapy.

During every follow up visit..

- 3 monthly follow up for 1 year, 4 monthly in 2nd year and 6 monthly in 3rd year
- Examination of the fellow eye
- Examination of the ophthalmic socket and mobility of the implant
- A thorough physical examination for possible distant metastasis
- Second malignancies in cases of heritable retinoblastoma

National guidelines in management of Retinoblastoma . ICMR

summary

- Retinoblastoma is one of the curable disease if diagnosed early
- Needs proper multimodality approach- if not available- good referral service to he expert center.
- In India- majority of the cases diagnosed at advanced cases, initiative need strengthen the early screening and diagnosis.
- In well maintained set up- Group-A with focal therapy and group B-D- chemoreduction and SALT- eye salvage is 100%
- CT is the main stay of the treatment- Over 80% of tumors are too large or too advanced at presentation for this strategy. Thus, EBRT remains the primary treatment option to preserve the eye and vision in these patients

Summary

- With recent advances in RT techniques (IMRT and PBT) radiation could be delivered more safely with a reduced dose to adjacent normal organs, resulting in a dramatic reduction of late complications.

- Meticulous planning by a multidisciplinary team of EBRT, beginning at the initial stage of treatment, can optimize therapeutic outcomes in patients with RB.

Orbital tumors

Pediatric intra ocular tumor	Pediatric intra orbital tumor
1. Retinoblastoma	1. Rhabdomyosarcoma
2. Medulloepithelioma	2. Neuroblastoma mets
3. Retinal astrocytic hamartoma	3. Optic pathway glioma
	4. Plexiform neurofibroma
	5. Lymphoproliferative disease.
	6. Dermoid and epidermoid inclusion cyst
	7. Leukemia
	8. LCH

MEDULLOEPITHELIOMA

- Rare congenital neuroepithelial tumor
- Arising from non pigmented ciliary epithelium of ciliary body
- Within first decade of life
- Clinically appear as amelanotic or lightly pigmented cystic mass in ciliary body with erosion into anterior chamber and iris root.
- They are cytologically malignant but distant mets are rare
- Nodal mets can occur with prediction for lymph nodes of parotid gland
- Local excision followed by adj RT is recommended
- Also treated with I 125 plaque brachytherapy in combination with surgical resection
- If metastatic then chemotherapy also given along with RT.

RETINAL ASTROCYTIC HAMARTOMA

- Glial tumor of retinal nerve fiber layer that arise from astrocytes
- Cream white, elevated, well circumscribed, can be multiple or solitary
- Found in conjunction with Tuberous sclerosis
- Usually clinically asymptomatic
- If symptomatic Rx – argon laser coagulation.

Rhabdomyosarcoma

- The most common orbital malignancy of childhood
- Associated with Li Fraumeni syndome, Beckwith-Weidemannn syndrome, NF2, MEN-2
- 2 types-alveolar type –more aggressive, less common
  - embryonal type – less aggressive, more common
- Rapidly growing painless mass, proptosis in m/c – superomedial quadrant of orbit for embryonal type and inferiorly for the alveolar type.
- The rapid growth and aggressive nature of the tumor frequently resulting in invasion of the adjacent bone and soft tissue; lymph node mets and intracranial invasion are relatively rare .
- Hematogenous mets to m/c - lungs and bones.

- The treatment of orbital rhabdomyosarcoma has changed drastically over the last 20 years from primary orbital exenteration to more conservative – combining systemic CT and RT.
- Local control can be achieved with 45Gy.
- Orbital rhabdomyosarcomas have 10 year survival rate of 87%.
- Patients routinely receive chemotherapy with vincristine and d-actinomycin.

NEUROBLASTOMA METASTASES

- M/c extracranial solid tumor of childhood
- Arises from neural crest cells.
- Median age of diagnosis was one year with 42% presenting at < 1 yr.
- M/c primary childhood cancer to metastasize to the orbits
- 2% of all cases have orbital involvement which can be primary manifestation of the tumor.
- M/c clinical presentation is unilateral or bilateral proptosis and periorbital ecchymosis(raccoon eyes)
- Treatment of mets neuroblastomas based on age at presentation staging specific tumor biological markers that include histopathological analyses,chromosomal abnormalities and expression of MYCN oncogene

- The prognosis of disseminated NB is better in infants – 80% 5 year survival, more than 1year – 45% 5 year survival.
- Requires multimodality therapy including CT, RT, myeloablative therapy with stem cell transplant, immunotherapy.

OPTIC PATHWAY GLIOMA

- Categorized as juvenile pilocytic astrocytoma, usually WHO grade 1 or 2 ,low grade.
- Account for 4 - 6 % of all brain tumors in children.
- Median age of Dx is 5-9 yrs.
- Half of patients with optic pathway glioma have NF1,mostly bilateral.
- Incidence among patients with NF1 – 30 – 58%.
- Slow growing unrecognized for long time.
- Present with decreased visual acuity, optic disc edema, pallor, atrophy, RAPD.
- Treatment only indicated in symptomatic cases.
- Radiation therapy with conventional or radiosurgery can be used.
- In patients with progressive disease chemotherapy is the mainstay of treatment with carbplatin and vincristine.
- Surgery is also an option in aggressive disease with no vision in the affected eye.

Plexiform neurofibroma

- Hamartoma of neuroectodermal origin
- 1-2% of orbital tumors.
- First decade of life.
- Presence of PNF is diagnostic of NF1.
- Can involve any peripheral nerve but usually sensory nerves in the orbit or eyelid, can cause widening of superior orbital fissure, dysplasia of greater sphenoid wing.
- Eyelid PNF have S shape due to thickening and fat deposition.
- Orbital involvement can cause globe proptosis, bony expansion, sphenoid dysplasia can lead to temporal lobe herniation and pulsatile exophthalmos .
- Treatment is directed at the relief of specific symptoms generally complete surgical excision of the PFN is not possible.
- Surgical debulking and frontalis suspension procedures can reduce proptosis and allow for binocular vision.

Orbital tumors

- Lymphoproliferative Disease
- Leukemia
- Langerhans Cell Histiocytosis of the Orbit
- Dermoid and Epidermoid Inclusion Cysts

Thank you