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Radiation therapy for Retinoblastoma


Kathi Arts
শ্বাস
(A Breath)
Based on a true story... From India
Shwaas

Contents

Introduction

- The most frequent intraocular neoplasm of childhood despite being a rare disease.
- The incidence rate below five years of age

India: Six cases per million

Worldwide: 11.8 cases per million.

- Bilateral cases : generally detected early, before 12 months of age
- Unilateral cases: At around 24 months

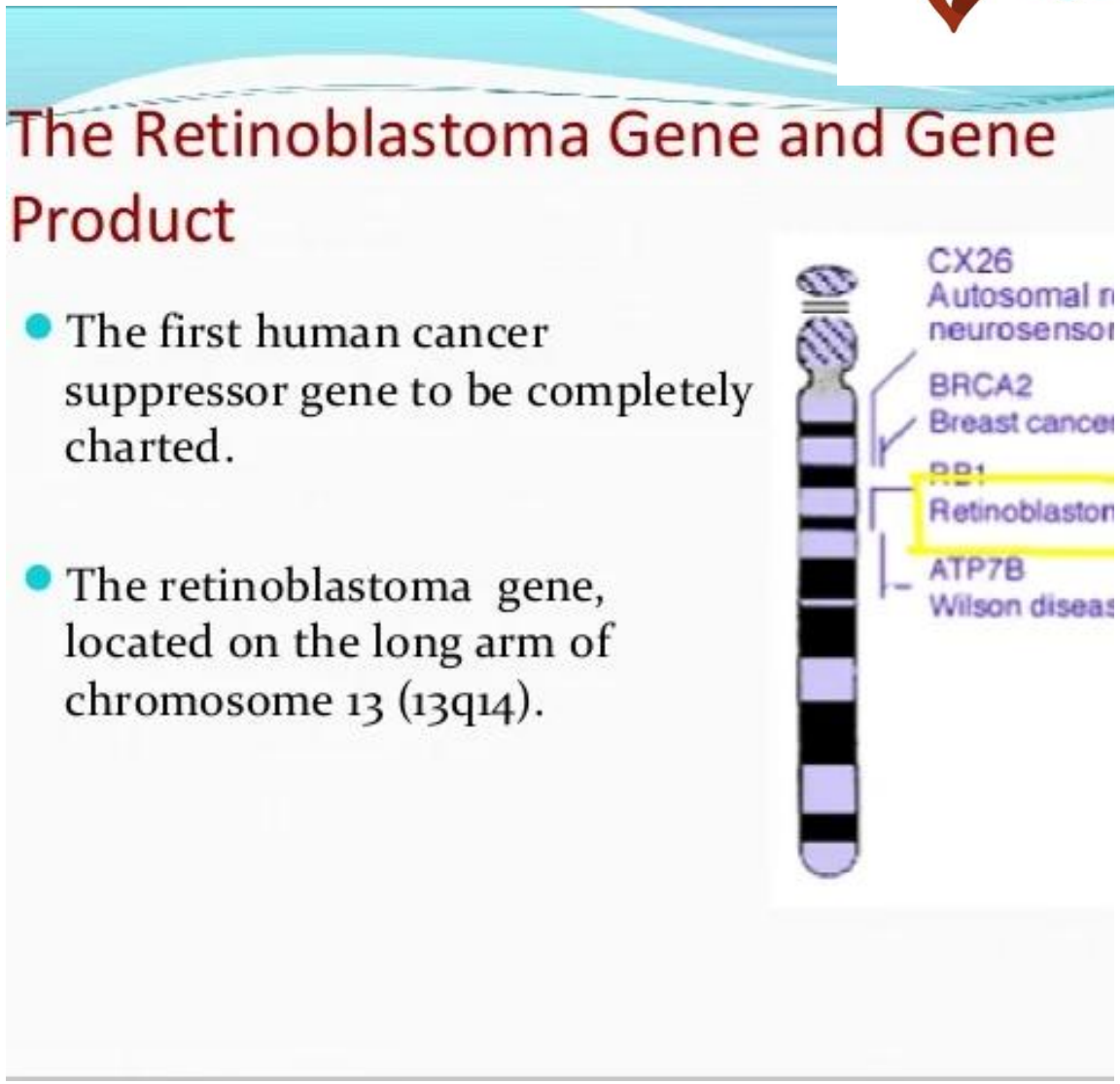
Genetic basis of retinoblastoma

- Two-hit model of tumour suppressor gene inactivation in 1971 by Knudson

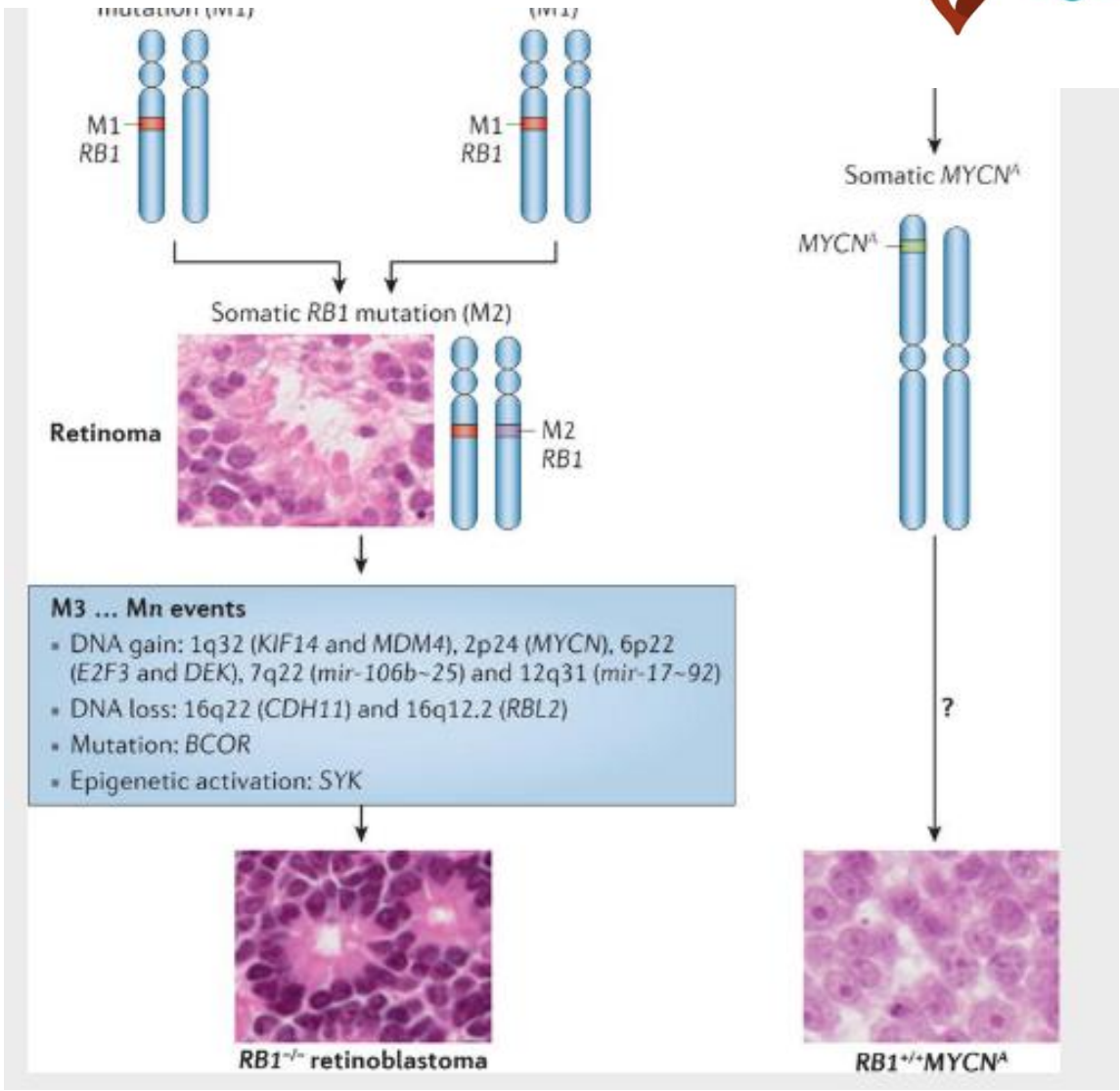
Three genetic subtypes

1. Heritable retinoblastoma : 40% are hereditary

- due to germline mutations in the biallelic RB1 tumor-suppressor gene
- present at earlier age,
- at higher risk of developing bilateral disease
- more likely to develop a secondary malignant tumor.



- -Inactivating mutation (M1) in the RB1tumor suppressor gene present in all cells of the body
  - A second, somatic mutation (M2) in a susceptible retinal cell can lead to benign retinoma.
  - Further genetic and/or epigenetic events (M3…Mn) are required to transform to retinoblastoma
- 2. Non-heritable: progress similarly, except both M1 and M2 occur in one susceptible retinal cell.
  - Roughly 60% of tumors are sporadic
  - present with unilateral, more advanced disease at diagnosis



- 3. RB1+/+MYCN-amplified (RB1+/+MYCNA) : rare, non-heritable subtype driven by amplification of MYCN with normal RB1,

- Aggressive & unilateral

- Seen in very young infants

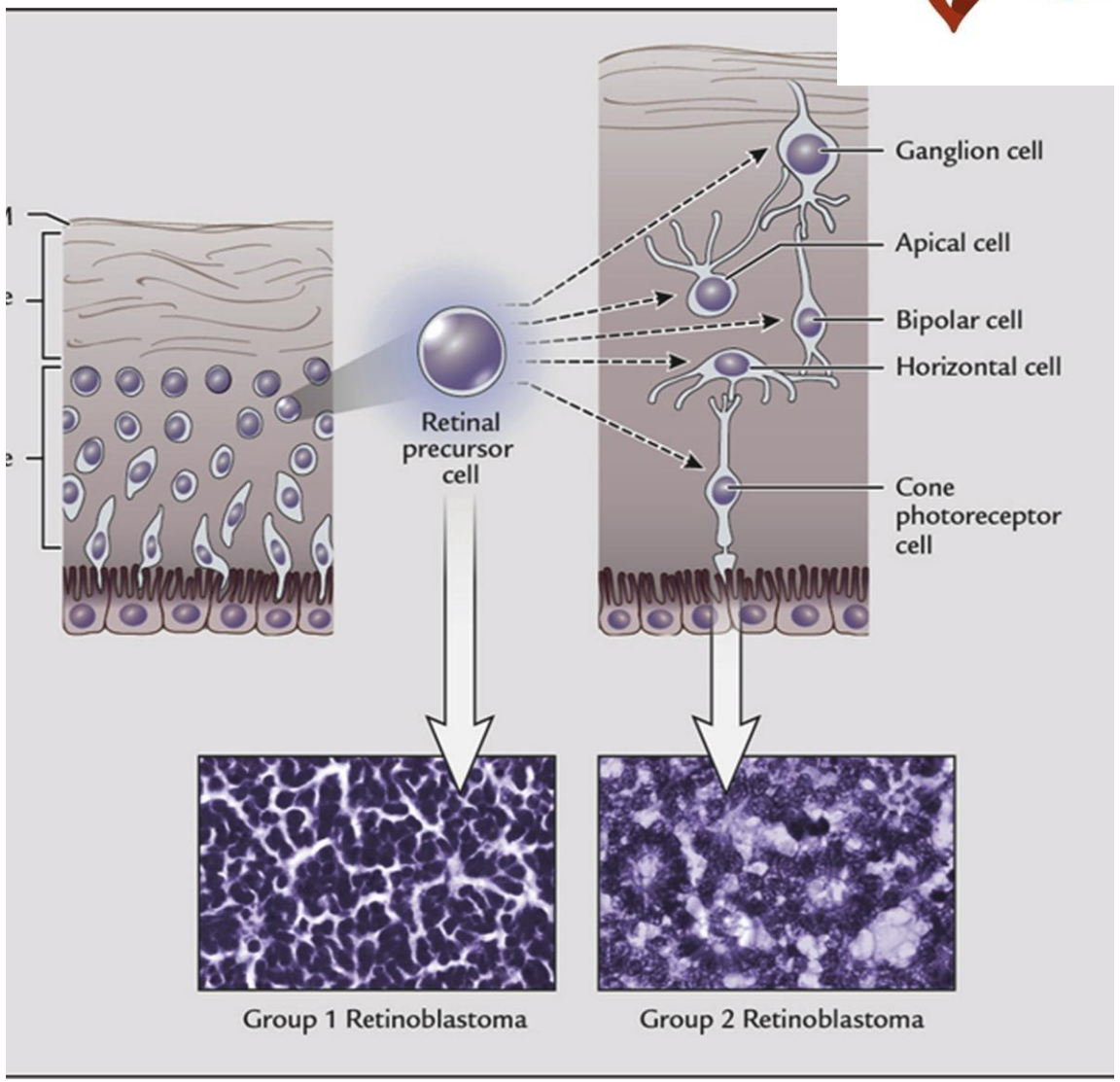
- Another 1.5% of unilateral non-familial retinoblastomas are unexplained and have apparently normal RB1 and MYCN genes

- Promoter hypermethylation of RB1

- Resemble sporadic

The retinoblastoma cell of origin

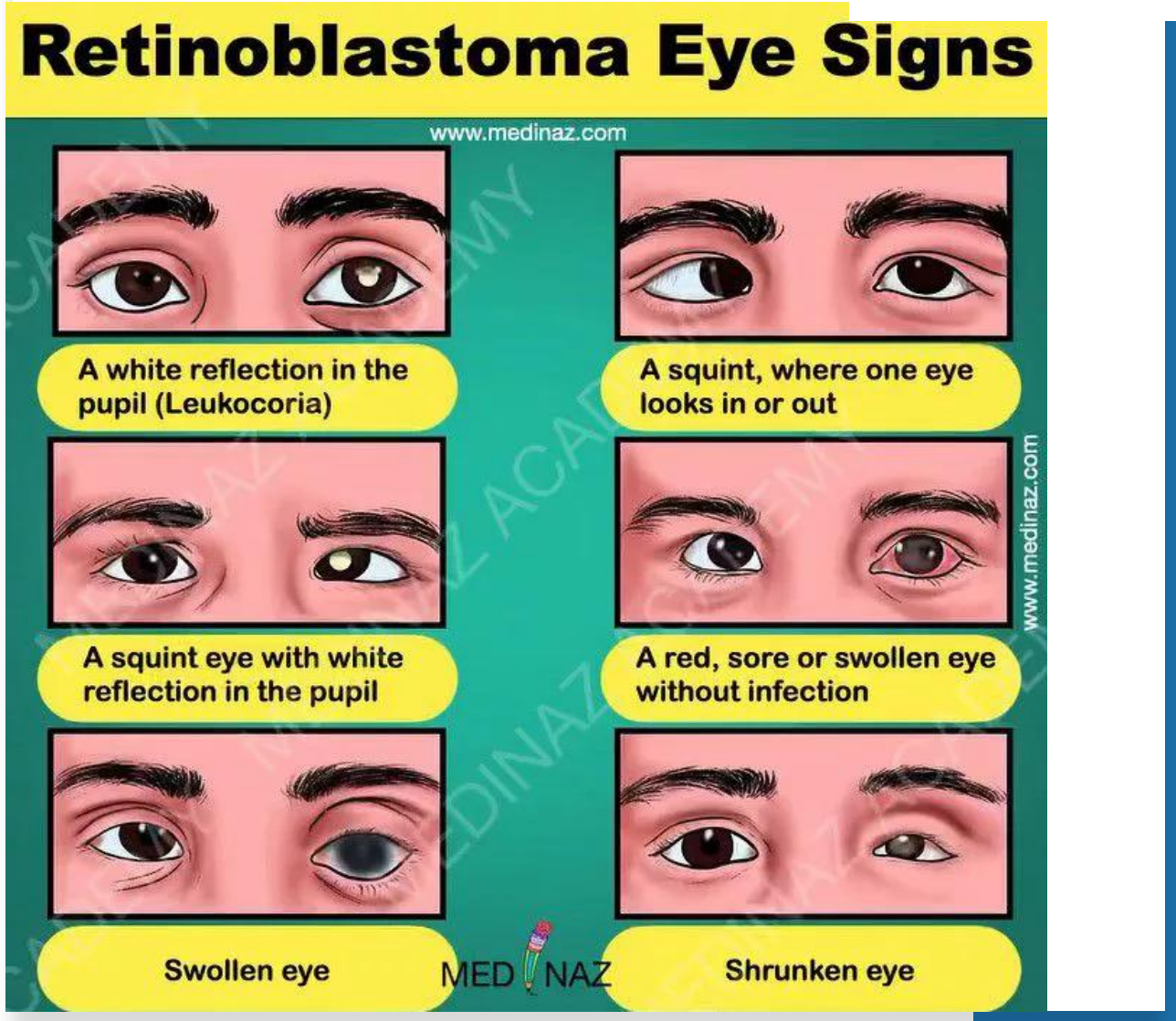
- Retinoblast, or primitive retinal progenitor or precursor cell (RPC):
- Cone precursor



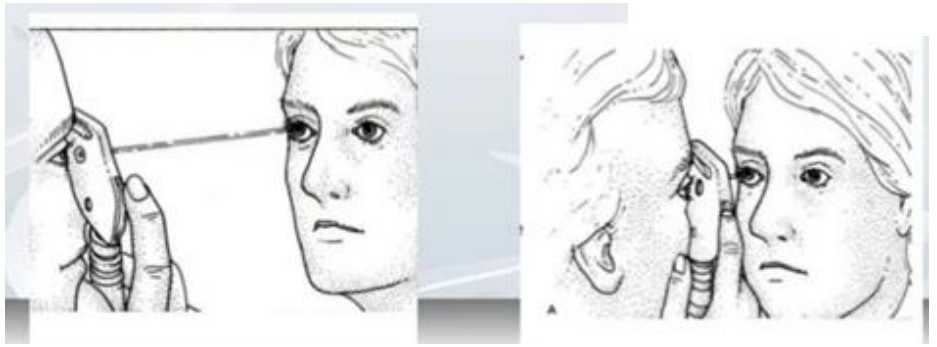
CLINICAL EVALUATION

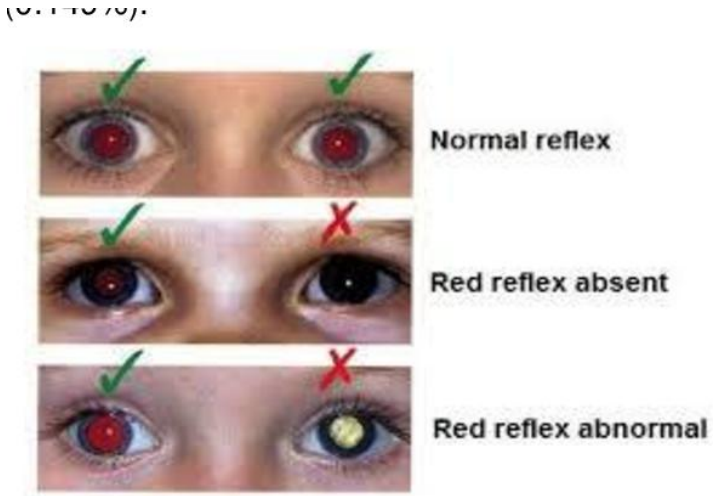
Symptoms

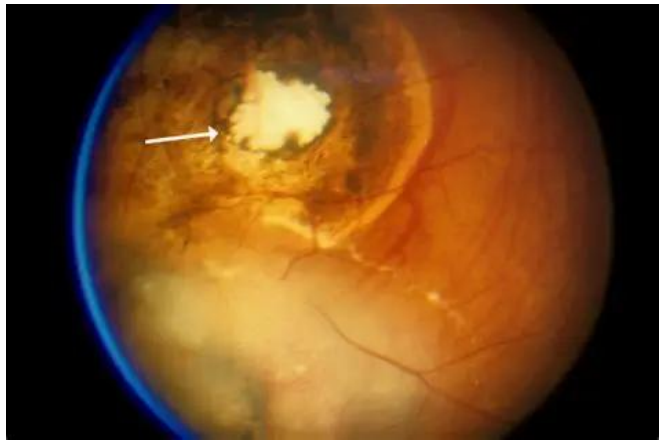
- White eye reflex (leukocoria): is a white pupillary reflex, often reported by parents as a "white spot" in the eye when light shines on it, occurs in 60% to 80% of cases and serves as the hallmark sign of retinoblastoma
- Squint
- Diminished vision
- Red eye
- Proptosis



- Family History - Ocular malignancies and other malignancies is crucial
- A comprehensive ocular examination both eyes
- For pupil examination: leukocoria is best observed in dim light using a direct ophthalmoscope or during red reflex testing





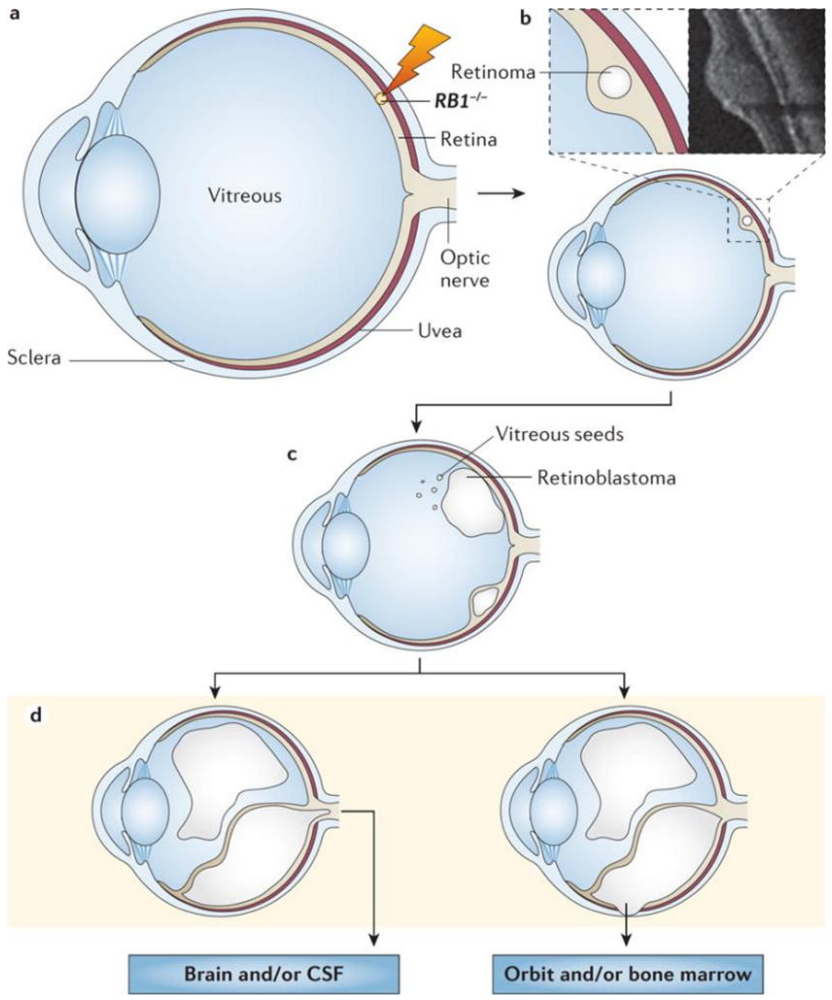


- A slit-lamp examination: in cases of advanced disease. For iris neovascularization or tumor invasion of the anterior segment.
- A dilated fundus examination with indirect ophthalmoscopy:
  Lesions typically presents as a white, chalky retinal mass with or without calcifications.

Tumor size- and oDD (disc diameter)
Accurate mapping with diagrams & description. Associated features examined, retinal detachment, vitreous or subretinal seeding, and tumor vessels supplying the lesion.

- Evaluation Under Anesthesia(EUA) :to facilitate a comprehensive assessment.

- Regional neck nodes: Cervical or preauricular lymphadenopathy
- Systemic examination: to rule out hepatomegaly or other signs of systemic involvement. The neurological examination for signs of CNS involvement or metastasis.
- Skeletal abnormalities must also be assessed for bone pain

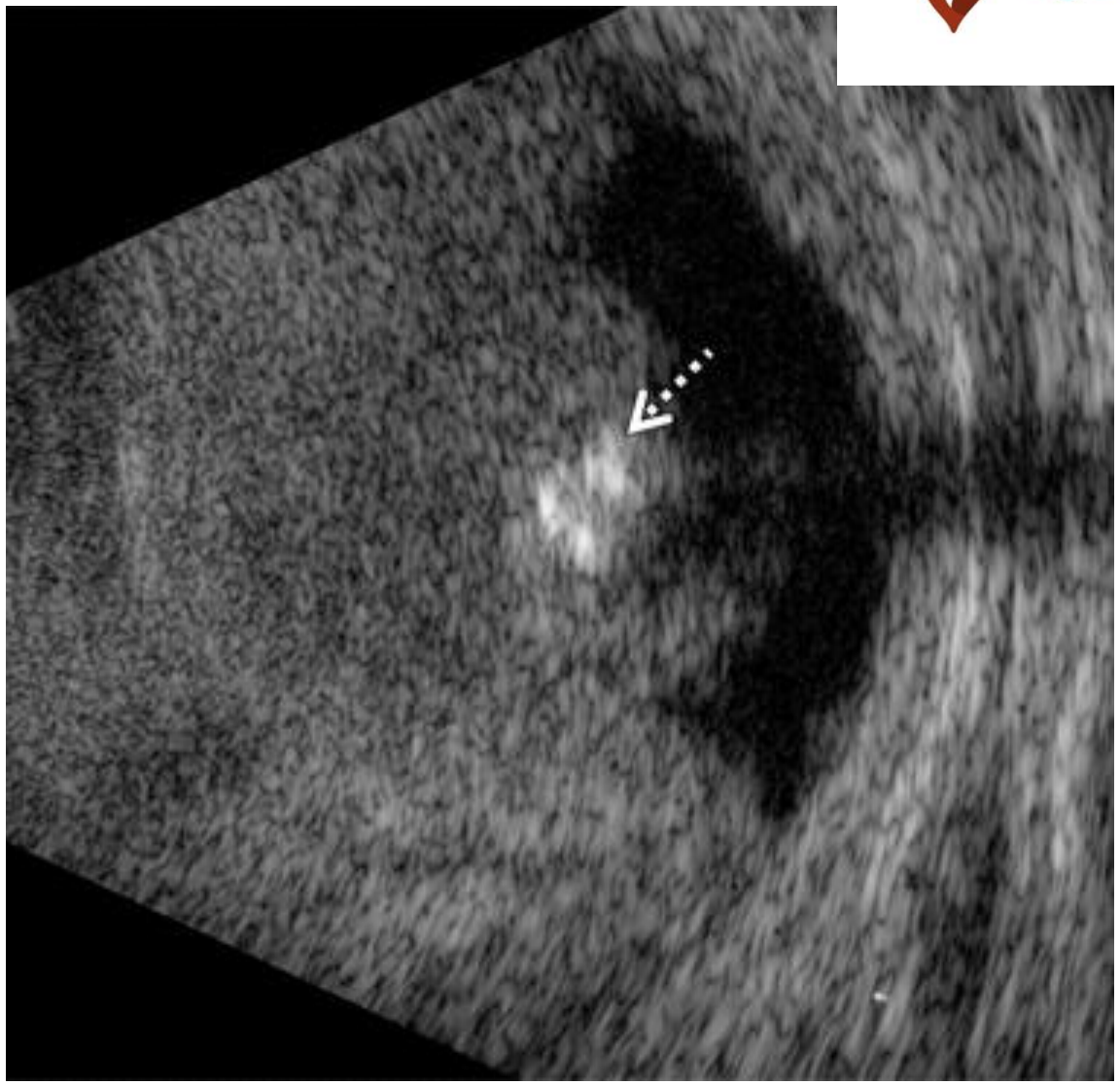


Investigations

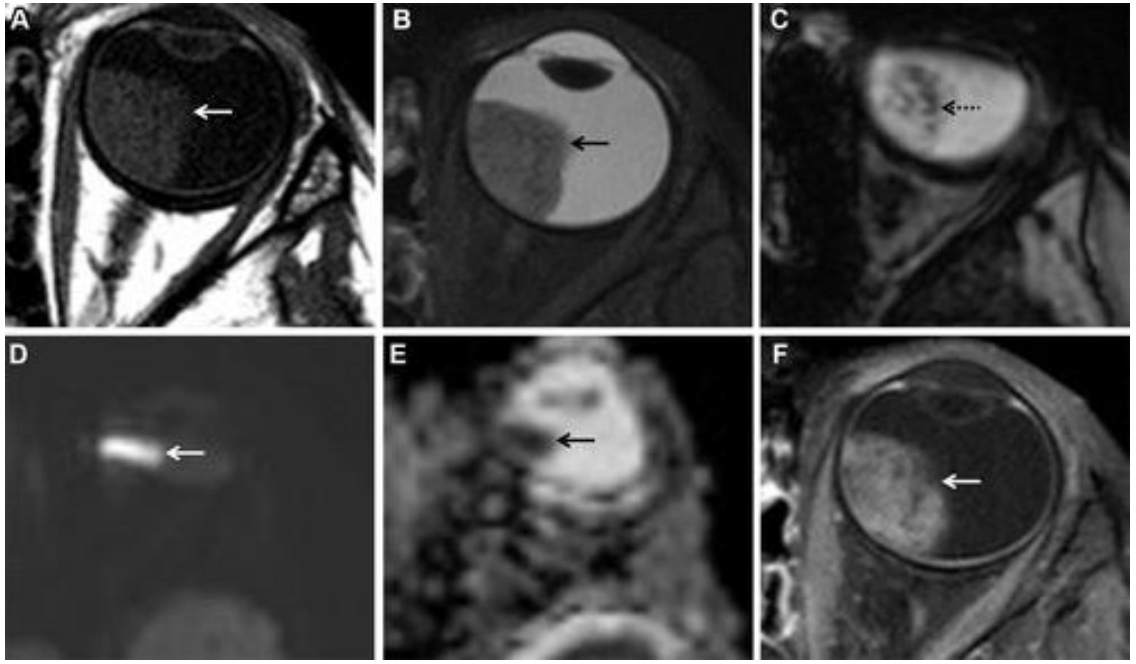
- Hematological evaluation : Complete blood count (CBC)
- Liver Function Tests (LFT)
- Renal Function Tests (RFT)
- Erythrocyte Sedimentation Rate (ESR)
- In advanced disease, bone-marrow examination or lumbar puncture in patients if there is concern for extraocular extension, to rule out cerebrospinal fluid (CSF) or bone-marrow metastases
- Genetic & Molecular studies (when asked for).

Imaging Studies

- Wide-field photography: specialized camera to capture high-resolution images of the retina and provide a panoramic view of the fundus.
- Ocular Ultrasonography with color doppler- A scan B scan: High-frequency B-scan: an echogenic mass with high internal reflectivity, a feature commonly associated with calcification, which is a hallmark of retinoblastoma.



Radiological investigation



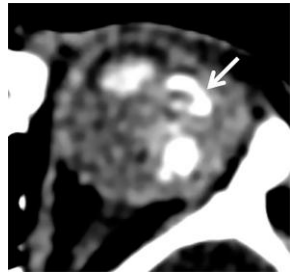
A: Axial T1-weighted image
B: Axial fat-saturated T2-weighted image
C: Axial gradient-echo MR image shows foci of blooming (arrow) corresponding to areas of calcification.
D, E : Axial diffusion-weighted and apparent diffusion coefficient
F: Axial contrast-enhanced fat-saturated T1-weighted MR image shows avid nearly homogeneous enhancement within the retinoblastoma

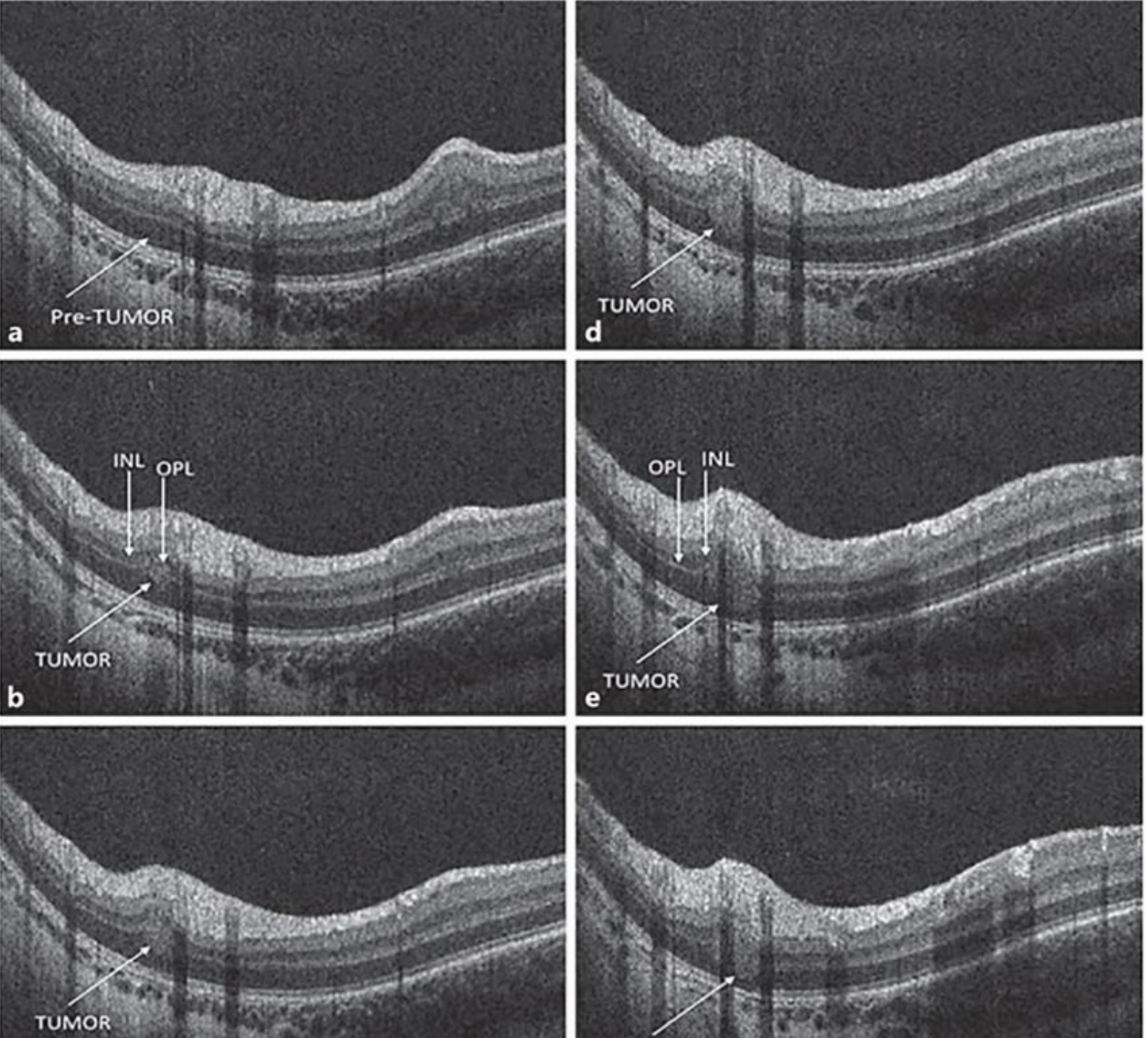
MRI: To assess → optic nerve invasion → extraocular extension

extraocular extension → presence of trilateral retinoblastoma (pinealoblastoma and primitive neuroectodermal intracranial tumours associated with RB1 mutations)

presence of trilateral retinoblastoma (pinealoblastoma and primitive neuroectodermal intracranial tumours associated with RB1 mutations) → intracranial metastasis

presence of trilateral retinoblastoma (pinealoblastoma and primitive neuroectodermal intracranial tumours associated with RB1 mutations) → CT was historically used to detect ocular calcifications but has largely been replaced by ultrasound and MRI due to concerns regarding pediatric radiation exposure.

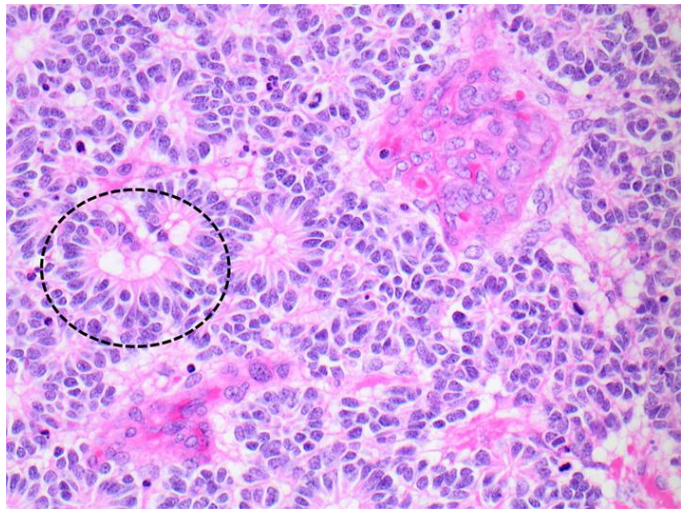




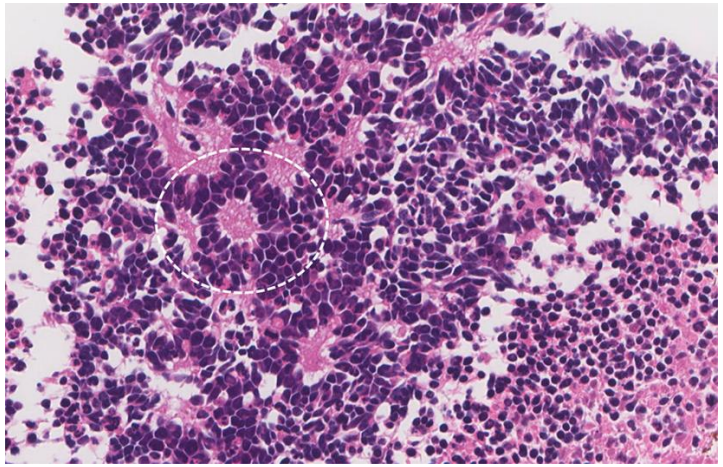
OCT images of a 17-week-old male with a germline retinoblastoma mutation.

- Very useful are high frequency (50 MHz) ultrasound biomicroscopy and OCT to discover invisible tumours in infants with familial disease

Pathology



Flexner-Wintersteiner



Homer Wright rosettes

Gross Pathology: As a white, friable intraocular mass arising from the retina. The tumor may exhibit areas of calcification, necrosis, and hemorrhage.

Microscopic Features:composed of small hyperchromatic cells with a high nuclear-to-cytoplasmic ratio. Tumor cells may be arranged in a spoke-wheel pattern around a central core, known as rosettes, with Flexner-Wintersteiner rosettes (cuboidal cells surrounding a central lumen) and Homer Wright rosettes (tumor cells surrounding a tangle of neural filaments) being pathognomonic.

RB1+/+MYCNA retinoblastoma have a distinct morphology with rounded nuclei and prominent nucleoli related to the high MYCN protein

Immunohistochemistry

Differentiate it from other small round blue cell tumors

Synaptophysin: stain positively for this marker, indicating the tumor cells' neuroectodermal origin.

Neuron-specific enolase: positive staining supports retinal differentiation.

Ki-67: The high proliferative index reflects the tumor's aggressiveness.

S-100 Protein: This marker is positive in some cases and may suggest certain forms of differentiation.

Glial fibrillary acidic protein: This molecule may be expressed in areas of glial differentiation within the tumor.

Vimentin: Positive staining in undifferentiated tumor

Prognostic Features

High-risk features include

- Optic nerve invasion beyond the lamina cribrosa
- Massive choroidal invasion, scleral or orbital extension
- The presence of tumor cells at surgical resection margins.

Differential Diagnosis

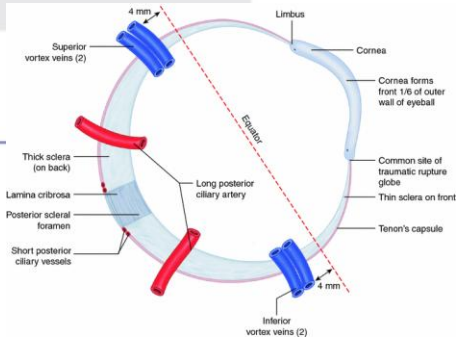
- Medulloepithelioma: which originates from the nonpigmented ciliary epithelium
- Embryonal rhabdomyosarcoma: typically involving the orbit rather than the retina, also shares some histological features
- Primary intraocular lymphoma: which usually affects older patients and involves the uvea or vitreous rather than the retina, can also resemble but is differentiated based on patient age and tumor site

Classification and staging

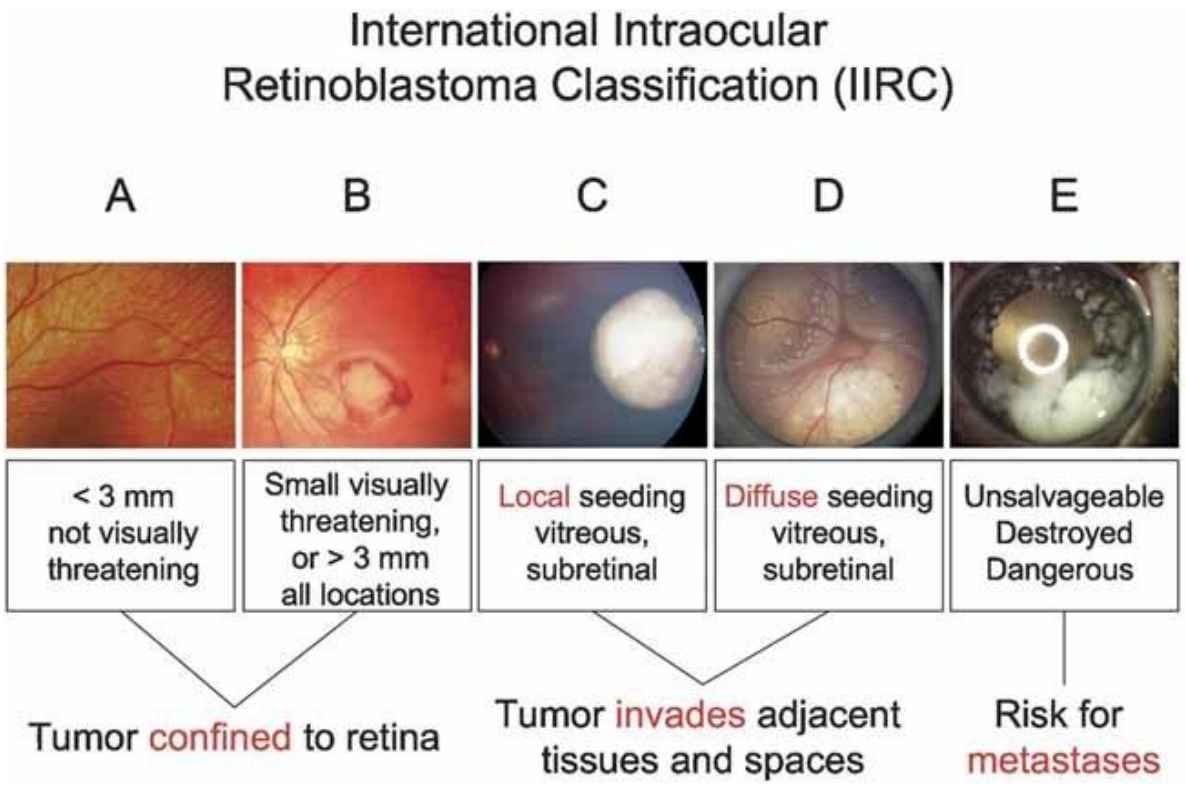
Table 1. Reese-Ellsworth Classification of Intraocular Retinoblastoma

Group likelihood of globe salvage	Subgroup	Description
I: very favorable	1A	Solitary tumor <4 DD at or behind the equator
	1B	Multiple tumors, none >4 DD, all at or behind the equator
II: favorable	IIA	Solitary tumor, 4–10 DD, at or behind the equator
	IIB	Multiple tumors, 4–10 DD, at or behind the equator
III: doubtful	IIIA	Any lesion anterior to the equator
	IIIB	Solitary tumor >10 DD behind the equator
IV: unfavorable	IVA	Multiple tumors >10 DD behind the equator
	IVB	Any lesion extending anteriorly to the ora serrata
V: very unfavorable	VA	Massive tumors involving more than half the retina
	VB	Vitreous seeding

DD, disc diameter.



- Created in 1963 to predict rates of tumor control and globe preservation following photon radiation therapy using lateral beams.



- When intravenous chemotherapy for intraocular retinoblastoma was introduced in the 1990s, a new classification scheme, the International Intraocular Retinoblastoma Classification (IIRC) scheme, was developed.
- The IIRC scheme groups tumours from A-E, depending on their size, location, and additional features, including the presence of retinoblastoma ‘seeds’ and/or retinal detachment.

Shields and colleagues developed a modified scheme, the Intraocular Classification of Retinoblastoma (ICRB), which differed from the IIRC mainly in the definitions of the advanced groups, D and E. In 2006, the ICRB scheme was found to successfully predict the outcome of intravenous chemotherapy

Table 2. International Classification for Retinoblastoma

Group A: small intraretinal tumors away from the foveola and disc	All tumors ≤3 mm in greatest dimension, confined to the retina, and located >3 mm from the foveola and >1.5 mm from the optic disc
Group B: all remaining discrete tumors confined to the retina	All other tumors confined to the retina not in group A Tumor-associated subretinal fluid <3 mm from the tumor with no subretinal seeding
Group C: discrete local disease with minimal subretinal or vitreous seeding	Tumor(s) are discrete Subretinal fluid, present or past, without seeding, involving up to one-quarter of the retina Local fine vitreous seeding may be present close to discrete tumor Local subretinal seeding <3 mm (2 DD) from the tumor
Group D: diffuse disease with significant vitreous or subretinal seeding	Tumor(s) may be massive or diffuse Subretinal fluid present or past without seeding, involving up to total detachment Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumor masses Diffuse subretinal seeding may include subretinal plaques or tumor nodules
Group E: presence of any one or more of these poor prognosis features	Tumor touching the lens Tumor anterior to anterior vitreous face involving the ciliary body or anterior segment Diffuse infiltrating retinoblastoma Neovascular glaucoma Opaque media from hemorrhage Tumor necrosis with aseptic orbital cellulitis Phthisis bulbi

DD, disc diameter.

Table 3. TNM Classification of Retinoblastoma

Category	Subcategory	Description
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor <2/3 of eye, with no vitreous or subretinal seeding
	T1a	Tumor <3 mm or <1.5 mm from the optic nerve or fovea
	T1b	Tumor >3 mm or >1.5 mm from the optic nerve or fovea Subretinal fluid <5 mm from the base of the tumor
	T1c	Tumor >3 mm or <1.5 mm from the optic nerve or fovea Subretinal fluid >5 mm from the base of the tumor
T2		Tumor <2/3 of eye with vitreous or subretinal seeding
	T2a	Focal vitreous and/or subretinal seeding
	T2b	Massive vitreous and/or subretinal seeding
T3		Severe intraocular disease
	T3a	Tumor >2/3 of the eye
	T3b	Presence of neovascular glaucoma, anterior segment extension, hyphema, vitreous hyphema, vitreous hemorrhage or orbital cellulitis
T4		Extra-ocular disease detected by imaging studies
	T4a	Invasion of the optic nerve
	T4b	Invasion into the orbit
	T4c	Intracranial extension not past the chiasm
	T4d	Intracranial extension past the chiasm
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node involvement
N2		Distant lymph node involvement
MX		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1		Systemic metastasis
	M1a	Single lesion at sites other than the CNS
	M1b	Multiple lesions at sites to other than the CNS
	M1c	Prechiasmatic CNS lesion(s)
	M1d	Postchiasmatic CNS lesion(s)
	M1e	Leptomeningeal or CSF involvement

CNS, central nervous system; CSF, cerebrospinal fluid.

American Joint Committee on Cancer TNM staging takes into account systemic disease and includes the statuses of both extraocular and intraocular involvement

The recently published 8th edition includes a hereditary (H) component for Rb, making it the cTNMH scheme (c for clinical). The cTNMH categories are based on whether the tumour burden is determined to be intraretinal, intraocular, advanced intraocular or extraocular. The TNM scheme also has a pathological (pTNM) sub-classification which is widely used by ophthalmic pathologists.

St Judes staging

I. Tumor (unifocal or multifocal) confined to retina

A. Occupying 1 quadrant or less.

B. Occupying 2 quadrants or less.

C. Occupying more than 50% of retinal surface.

II. Tumor (unifocal or multifocal) confined to globe

A. with vitreous seeding

B. Extending to optic nerve head.

C. extending to choroid and optic nerve head

D. Extending to emissaries.

III. Extraocular extension of tumor (regional)

A. extending beyond cut end of optic nerve (including sub-arachnoid extension)

B. Extending through sclera into orbital contents.

C. extending to choroid and beyond cut end of optic nerve (including sub-arachnoid extension)

D. extending through sclera into orbital contents and beyond cut end of optic nerve (including sub-archnoid extension)

IV. Distant metastases

A. Extending through optic nerve to brain

B. Blood-borne metastases to soft-tissues and bone marrow metastases

Table 3: Grabowski and Abramson staging for intra- and extra-ocular retinoblastoma

Intraocular disease
a. Retinal disease
b. Extension to lamina cribrosa
c. Uveal extension
Orbital disease
a. Orbital tumor
1. Scattered episcleral cells
2. Orbital invasion
b. Optic nerve
1. Invasion upto cut end
2. Invasion beyond the cut end
Intracranial metastasis
a. Positive cerebrospinal fluid alone
b. Mass lesion in the central nervous system
Hematogenous metastasis
a. Positive bone marrow alone
b. Focal bone lesions with/without bone marrow disease

Genetic diagnosis

- Enables precise screening of relatives and subsequent generations
- Of unilateral patients, 85% will test negative
- In familial retinoblastoma, prenatal screening can be performed on DNA obtained from amniotic fluid.

Table 1: Risk of developing retinoblastoma in siblings and off springs of patients

Subjects	Probability of disease %
Subjects with carriers of RB1 gene mutation	90
Offspring of patient	45
Sibling of patient (if either parent is affected)	45
Sibling of patient with bilateral disease	2
Sibling of patient with unilateral disease	1

Management

Management strategies are tailored based on factors

- Tumor size
- Laterality (unilateral or bilateral)
- Disease extent (intraocular or extraocular, systemic)
- Age and genetic predisposition.
- Overall health of the child
- Socioeconomic circumstances
- Access to expert care.

Treatment Goals

The primary goal : to save life.

The secondary goal: to preserve vision and, when possible, maintain the eye.

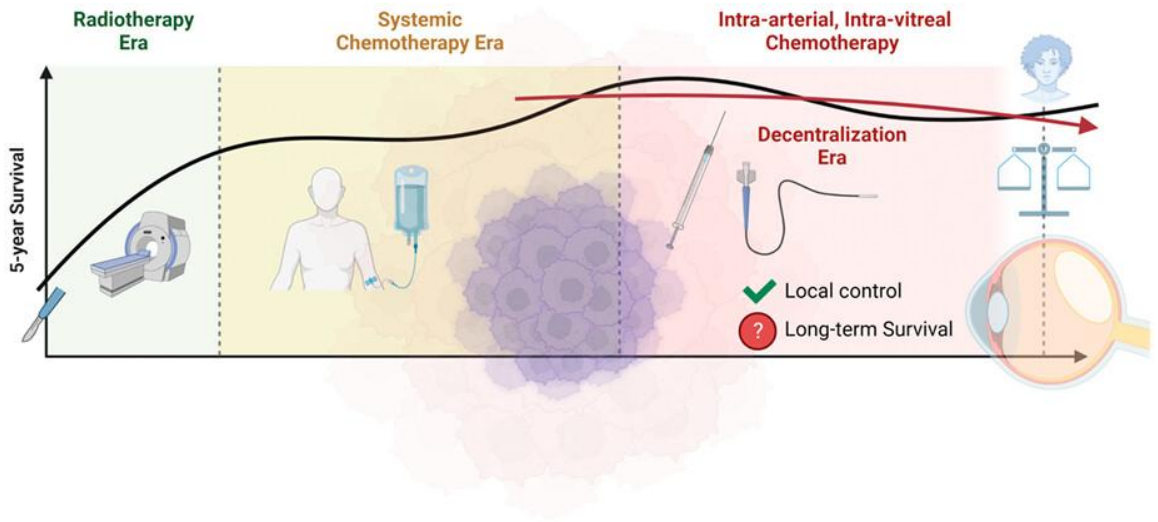
A tertiary goal: to minimize treatment-related morbidity, including the risk of secondary malignancies and adverse effects.

Multidisciplinary team Involvement

- Ophthalmologist: Detailed ocular assessments and managing localized treatments
- Radiologist
- Pathologist
- Pediatric oncologist / Medical oncologist
- Radiation Oncologist
- Surgical oncologist
- Geneticist

Evolution of treatment

- The treatment of retinoblastoma has evolved significantly over the past few decades, shifting from traditional methods like enucleation and external beam radiation to more advanced, targeted therapies that prioritize eye preservation and minimize long-term complications.



Treatment options	
Local therapy	Laser photocoagulation (Green laser) Transpupillary thermal therapy(Diod laser) Cryo therapy
Chemotherapy	Local chemotherapy • Intravitreal • Intracameral • Periocular Intravenous chemotherapy Intra-arterial chemotherapy Intrathecal chemotherapy
Radiation therapy	Plaque radiation therapy(Brachytherapy) External beam radiation therapy Proton beam therapy
Surgery	Enucleation (Intraocular) Exenteration (Extraocular)

Tumor Classification	Treatments
Groups A and B	Focal therapies (laser, cryotherapy, TTT) ± systemic chemotherapy
Group C	Systemic chemotherapy + focal therapies
Group D	Systemic chemotherapy, IAC, ± IVC
Group E	Enucleation ± systemic chemotherapy for high-risk features
Extraocular	Systemic chemotherapy, radiation therapy, ± high-dose chemotherapy with stem cell rescue
Metastatic	High-dose chemotherapy, stem cell rescue, or palliative care

Localized Therapies

Laser photocoagulation: is commonly used for small, posteriorly located tumors.

This technique uses laser energy to coagulate the blood vessels supplying the tumor, resulting in tumor necrosis.

Primarily indicated for group A tumors or small group B tumors.

Cryotherapy: involves tumor destruction through cycles of freezing and thawing, often using the triple freeze-thaw technique.

This procedure is most effective for small anteriorly located tumors, such as those near the ora serrata.

Unsuitable for larger or posterior tumors

Thermotherapy (transpupillary thermotherapy, TTT): utilizes heat delivered via an infrared diode laser to destroy tumor cells.

Although mainly used for focal consolidation following chemotherapy, it can also be used as an isolated treatment.

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Systemic Chemotherapy

Used as

Primary therapy: in higher risk RB, which includes bilateral groups D and/or E.	Chemoreduction: used in combination with local therapies (good initial responses to chemotherapy to be consolidated with local therapy typically classified as group B or C)

- The most common chemotherapy regimen is the combination of vincristine, carboplatin, and etoposide (VCE), which is the standard triple-drug therapy for retinoblastoma.

Table 4: Chemotherapy vincristine, etoposide, and carboplatin protocol

A. Drugs
Vincristine 1.5 mg/m^2 day 1 (0.05 mg/kg for children <3 years and max dose 2 mg)
Carboplatin 560 mg/m^2 day 1 (18.6 mg/kg for children <3 years)
Etoposide 150 mg/m^2 days 1 and 2 (5 mg/kg for children <3 years)

B. Cycles
Every 3-4 weeks;
Ensure ANC >1000 and platelets >100,000/mm^3

C. Number of Cycles
2-6 cycles for chemoreduction
6 cycles for chemoprevention
6-12 cycles for systemic disease

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).

Local: Intraarterial chemotherapy

Shown to be effective in locally controlling 80–100% of patients with groups C, D and E when used in combination with systemic chemo therapy

Involves the insertion of a catheter into the femoral artery, which is advanced toward the ophthalmic artery.

Delivers high concentrations of chemotherapy drugs, such as melphalan, topotecan, and carboplatin, directly to the affected eye.

The main advantage is the high drug concentration to tumor cells while significantly reducing systemic toxicity.

Additionally, highly effective for treating vitreous seeds.

However, the procedure carries risks such as vascular complications, orbital edema, and retinal toxicity.

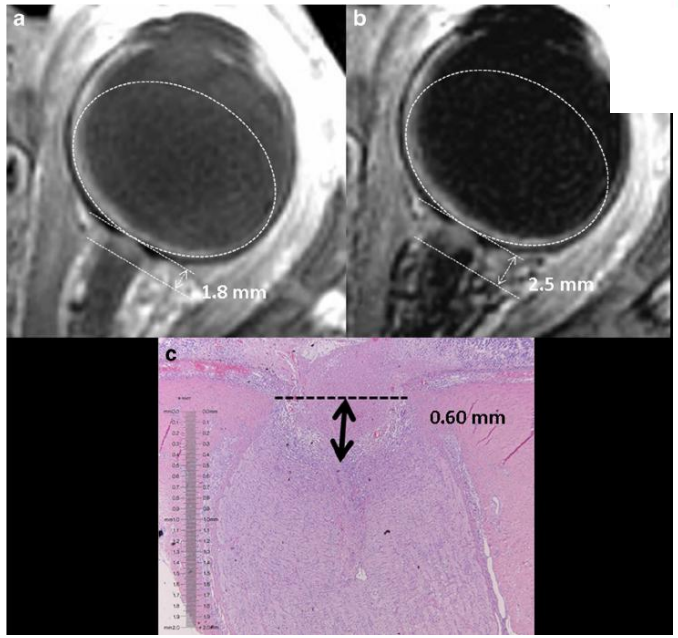
Intravitreal chemotherapy

- In IVC, chemotherapy drugs like melphalan and topotecan are injected directly into the vitreous cavity to address vitreous seeding, when persist after systemic treatment or IAC.
- However, one of the risks is the potential for extraocular spread, which may be minimized with the proper technique

Table 6: Post-enucleation specimen (histopathological criteria for chemoprevention)

Indications for chemoprevention
Anterior chamber seeding
Iris infiltration
Ciliary body infiltration
Massive choroidal infiltration
Invasion of optic nerve lamina cribrosa
Retrolaminar optic nerve invasion
Invasion of optic nerve transection*
Scleral extension*
Indications for no additional chemotherapy
Intraretinal extension
Prelaminar optic nerve invasion

*These require additional EBRT as this is considered as extraocular disease limited to orbit



CHEMOTHERAPY FOR RETINOBLASTOMA POST ENUCLEATION (CHEMOPREVENTION)

Brachytherapy

- Has been used to treat intraocular tumors since 1930
- Modern plaques currently include assemblies of gold shells with low-energy photon seeds (125I, 103Pd, and 131Cs) or solid beta (106Ru and 90Sr) plaques
- Remains a valuable and necessary tool to treat focal primary tumors, secondary resistant and recurrent tumors after chemoreduction and tumors not amenable to other local treatment modalities
- The ABS-Ophthalmology Oncology Task Force recommends (Level 2 Consensus) that ideal tumors for primary brachytherapy are located anterior to the equator and in unilaterally affected children.
- For secondary treatment, residual or recurrent tumors are treated irrespective of location. Exceptions include anterior segment involvement (typically an indication for enucleation)

Episcleral plaque brachytherapy (EPB)

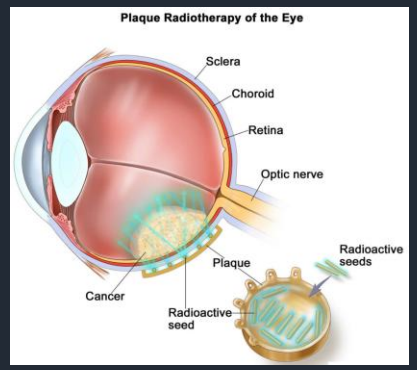
Can be considered for the treatment of groups B or C when the tumor diameter is <16 mm, tumor thickness is 4–9 mm, and vitreous seeding is limited

Excellent treatment for small isolated tumors located far from the optic nerve or macula

The recommended dose to the tumor apex is 45 Gy.

Reported local control rates range between 79% and 94% at five years.

Radiation retinopathy is the most common visually threatening complication, especially in those patients undergoing chemotherapy.



Plaque treatment planning

- Team: Radiation oncologist, ophthalmic oncologist, and medical physicist
- The fundus diagram should be created
- the tumors clock hour orientation within the eye
- its longitudinal and transverse diameters
- its largest basal diameter
- It should include measurements from the tumor to the fovea, optic nerve, lens, and opposite eye wall.
- From the ophthalmic examination, ultrasound findings, and photographic images.
- Pre planning

Patient: Mariyamma, Left eye, ∫T = 39.82 hrs, 604534/21, Plan-110

Plaque Simulator Treatment Plan

Plaque 1 CAX (mm)	Avg. dose rate (cGy/hr)	Total Dose (Gy)	
0.00 (external sclera)	202.1	80.48	
1.00 (inner sclera)	172.1	68.51	
2.00	132.8	52.87	
3.00	100.6	40.04	
4.00	73.62	29.31	
5.00	52.29	20.82	
6.00	36.01	14.34	
7.00	24.13	9.610	
8.00	15.56	6.196	
9.00	9.696	3.861	
10.00	5.763	2.295	
Critical Site	Avg. dose rate (cGy/hr)	Total Dose (Gy)	Dist. from plaque (mm)
Prescription point	100.4	39.99	3.001 Tumor 1 Apex @ 2.00 mm
Sclera	172.1	68.51	1.000 (from plaque center)
Optic disc	0	0	21.99 (center to center)
Opposite retina	0	0	23.00 (from plaque center)
Lens	24.33	9.689	9.212 (center to center)
Eye origin	1.649	0.657	12.00 (from plaque center)
Macula (posterior pole)	0	0	20.84 (center to center)
Tumor apex	100.4	39.99	3.001 (from plaque center)

Dose calc. mode: Standard, Point, F[Ø], A[R], Pexp, Shell

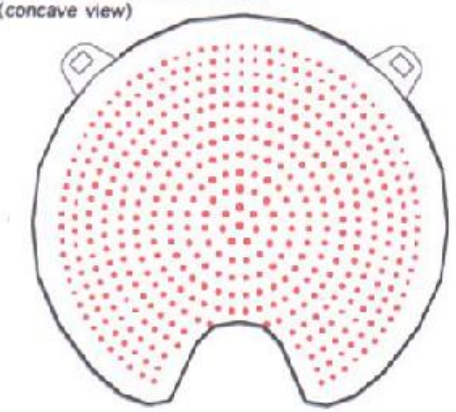
Insertion:	Thursday, April 15, 2021 3:00 PM
Removal:	Saturday, April 17, 2021 6:49 AM
Duration:	39.817 (hours)

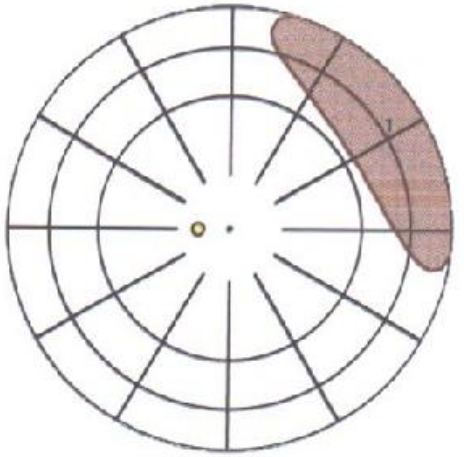
Isotope in plaque #	1
Total:	4.390MBq
Avg. per source	0.010MBq
Ref. date:	Thursday, April 15, 2021

Plaque #	1
Name of plaque:	COB 1250_Correc.iplq
Nominal diameter:	18.70 mm
Number of seeds:	450
Scleral offset:	0.00 mm

Tumor #	1
Apex of tumor:	2.00 mm
Radial (COMS BM):	12.00 mm
Circumferential:	12.00 mm
Longest dimension:	12.00 mm
Nominal width:	12.00 mm
Surface area:	121.97 mm^2
% of retinal surface:	8.25 %
Approx. volume:	0.12 cc

FRONT: COB 1250_Correc.iplq
(concave view)





Plaque Simulator Summaries

Dose summary: Distance from center of plaque #0 to:	Dist.(mm)	Gy
Apex of tumor	3.00	39.994
Center of lens	9.21	9.689
Optic disc	21.99	0.000
Opposite retina	23.00	0.000
Fovea	20.84	0.000
Center of eye	12.00	0.657
Prescription point	3.00	39.994
Central axis of plaque #0	**Dist.(mm)**	**Gy**
External sclera	0.00	80.477
COMS sclera	1.00	68.505
	2.00	52.872
	3.00	40.039
	4.00	29.315
	5.00	20.821
COMS 5mm point	6.00	14.339
	7.00	9.610
	8.00	6.196
	9.00	3.861
	10.00	2.295

Calculation summary: Plaque#	1	2	3	4
COMS Calc.				
Anisotropy	•			
Linear sources				
Carrier correction T(r)				
Scatter modifier B[r]				
Air interface A[R]	•			
Partial exposure	•			
Penumbra				
Slot collimation				
Shell lip collimation	•			
Analyze lip	•			
Circular lip				

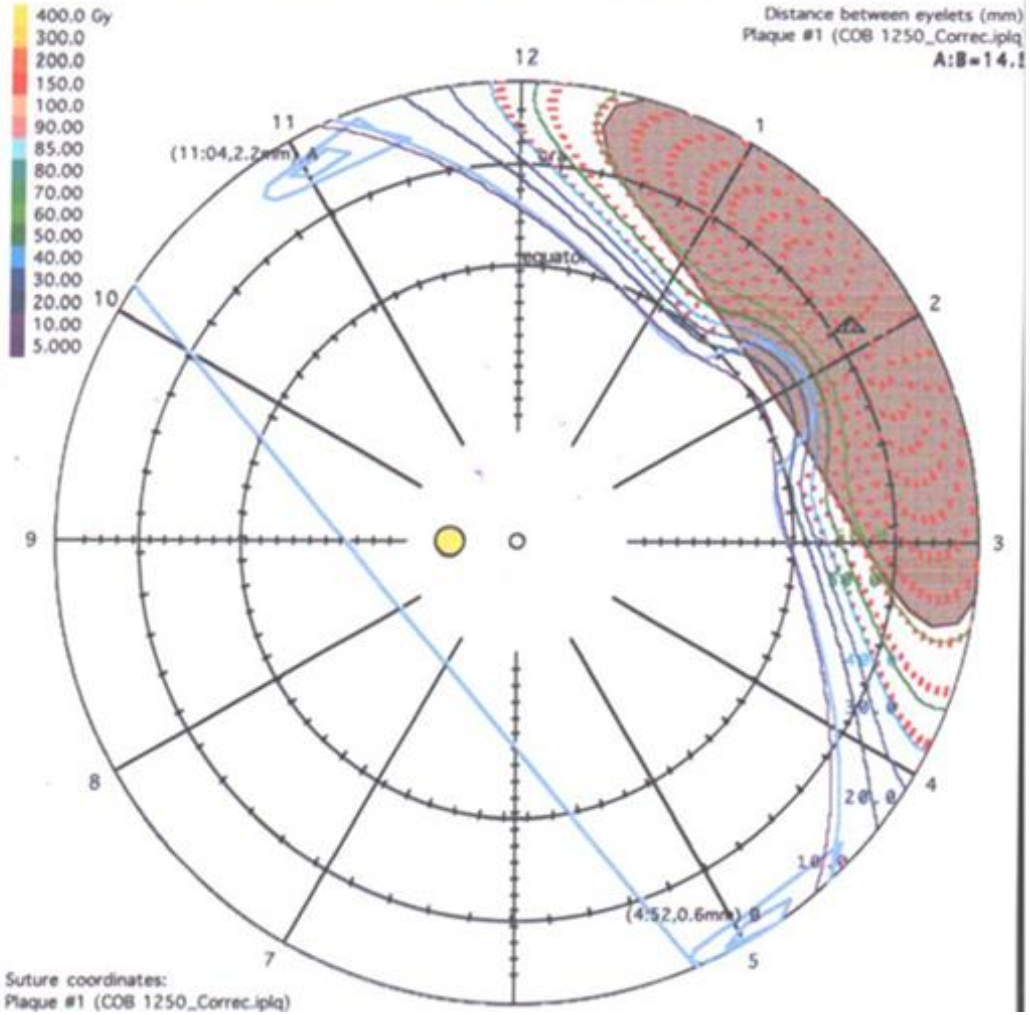
Plaque Simulator Summaries

Isotope summary: Plaque#	1	2	3	4
Isotope	Ru-106 (2001)			
Inventory name	COB 1250_Co...			
Number of sources used	450			
Assay date	4/16/19			
Avg. source strength @ assay	0.04 MBq			
Total strength @ assay	17.29 MBq			
Total strength @ implant	4.39 MBq			

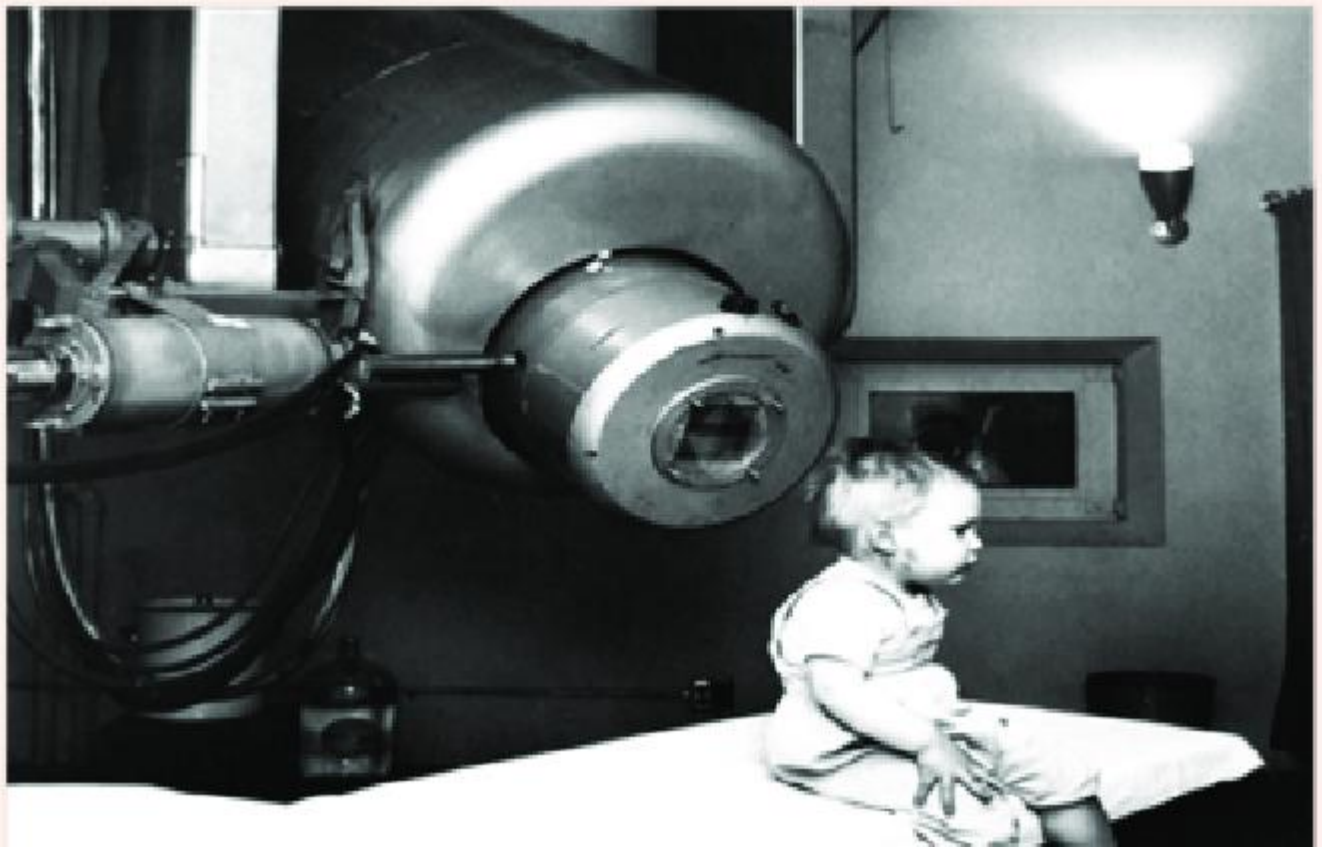
Tumor summary: Tumor#	1	2	3	4
MT - macula->tumor margin	16.41			
BM - base diameter in direction of macula	12.00			
DT - disc edge->tumor margin	17.29			
BD - base diameter in direction of disc	11.59			
Height (from internal sclera)	2.00			
Longest basal dimension	12.00			
Perpendicular to longest dimension	12.00			
Surface area (sq. mm)	121.97			
% of retinal surface	8.25			
Estimated volume (cc)	0.119			

Plaque Simulator Retinal Diagram

Current plaque	1 (COB 1250_Correc.iplq)
Dose matrix set	1 ()
Prescribed (Rx) dose	39.99 Gy to Tumor 1 Apex @ 2.00 mm
Dose matrix max	69.82 Gy




OT 4-SEHB
1970/01/31 20:18
360 degree Peritomy



Isaac Gordon: first pediatric patient treated for retinoblastoma linear accelerator in 1957.

CONVENTIONAL EXTERNAL BEAM RADIOTHERAPY

The use of EBRT to treat RB has decreased dramatically over the past four decades, more than for other types of pediatric cancer.

According to the National Cancer Institute's Surveil lance, Epidemiology, and End Results database of the nine original tumor registries (SEER-9), the use of EBRT for RB has declined from 30% of treatments in the period from 1973 to 1976 to 2% in the period from 2005 to 2008.

External beam radiotherapy (EBRT) is no longer recommended for first line therapy for primary intraocular retinoblastoma, since radiation, especially in the first year of life, imposes a high risk of secondary cancers when the patient carries an RB1 mutation.

Radiation was also found to affect the growth of the soft tissue and bone around the eye

Indications

Patients with multifocal RB

Tumors close to the macular or optic nerve with preserved vision.

Large tumors and those with vitreous seeding that do not respond to systemic chemotherapy.

EBRT serves as a salvage treatment for recurrent or resistant tumors, as well as for extraocular spread in selected cases.

Treatment volume

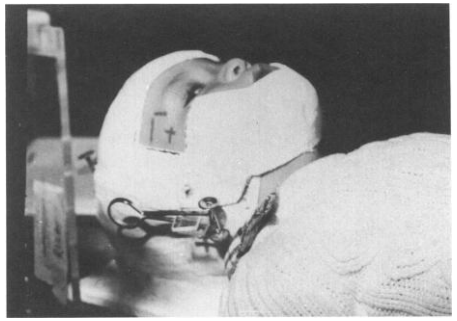
Treating the entire retina : due to concerns about new retinal lesions after EBRT was conventional practice.

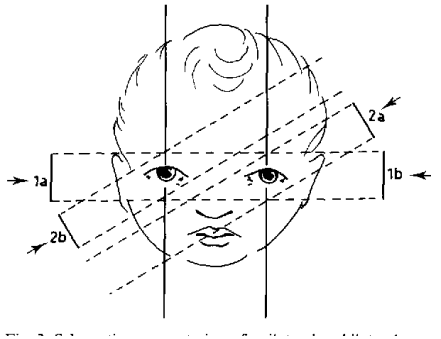
However, the rates of new lesions in the uninvolved retina were similar in patients who received focal and whole retinal treatment.

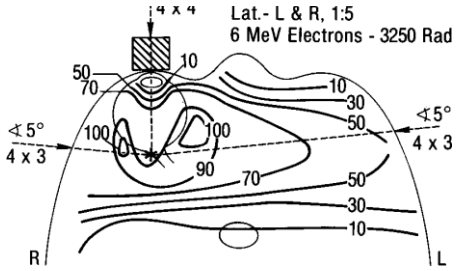
Avoiding irradiation of the uninvolved retina may reduce the rates of eye complications

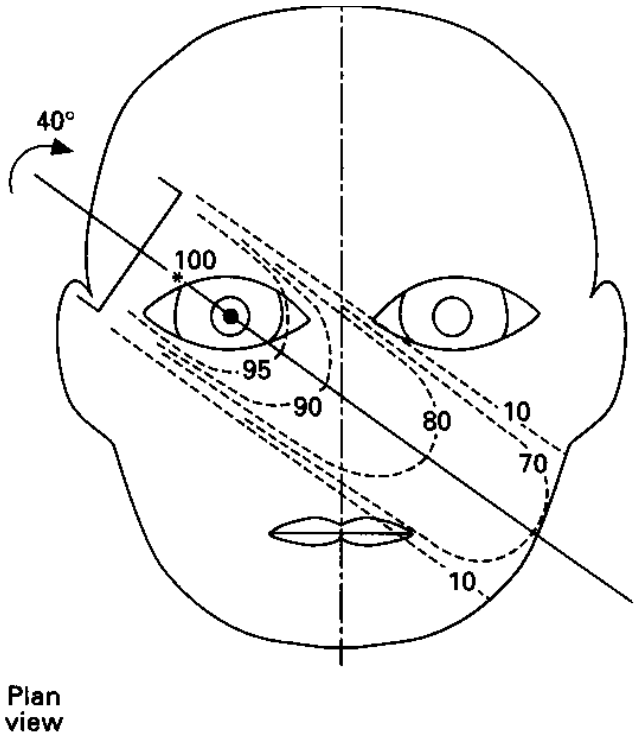
Whole retina treatment may be required for group D eyes as well as salvage therapy in eyes with vitreous or subretinal seeding unresponsive to chemotherapy.

- Traditionally, a single D-shaped lateral field with the anterior field border positioned at the lateral bony canthus was used.With this technique, the posterior pole of the lens was in the 30% isodose line
- In an effort to spare the lens and treat anterior retina, a number of techniques were developed to treat the anterior eye but shield the lens with a hanging block or a shielded contact lens.









cataracts. This technique was superseded by a method which employed a lateral photon beam with its anterior edge placed 2–3 mm posterior to the limbus together with superadded

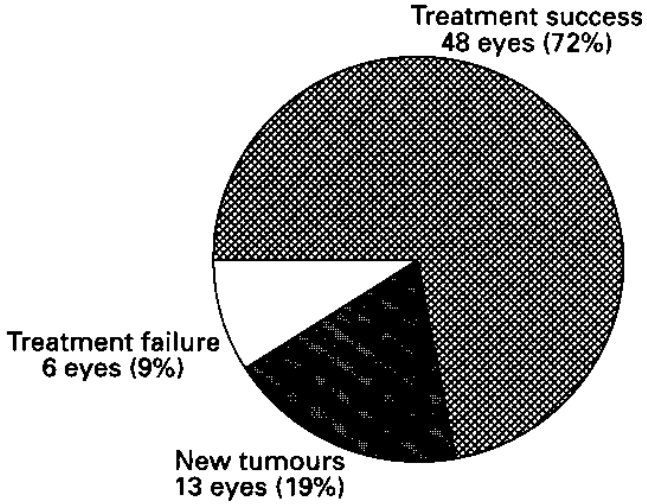
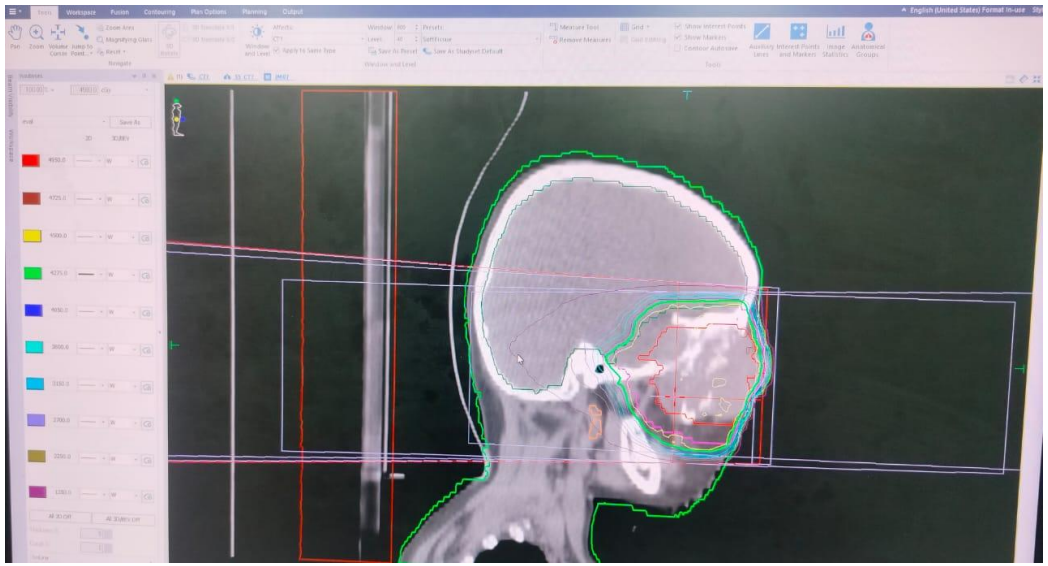
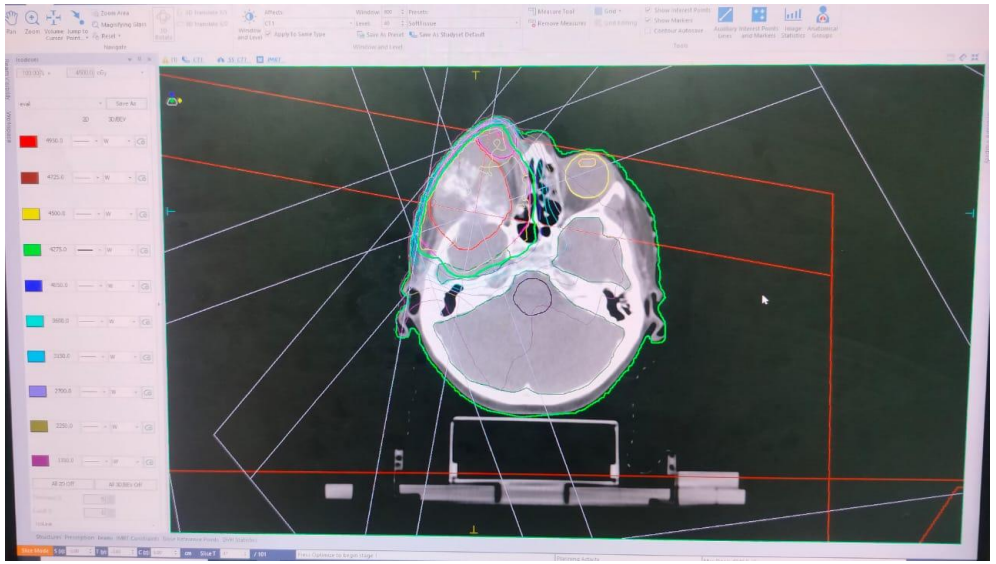
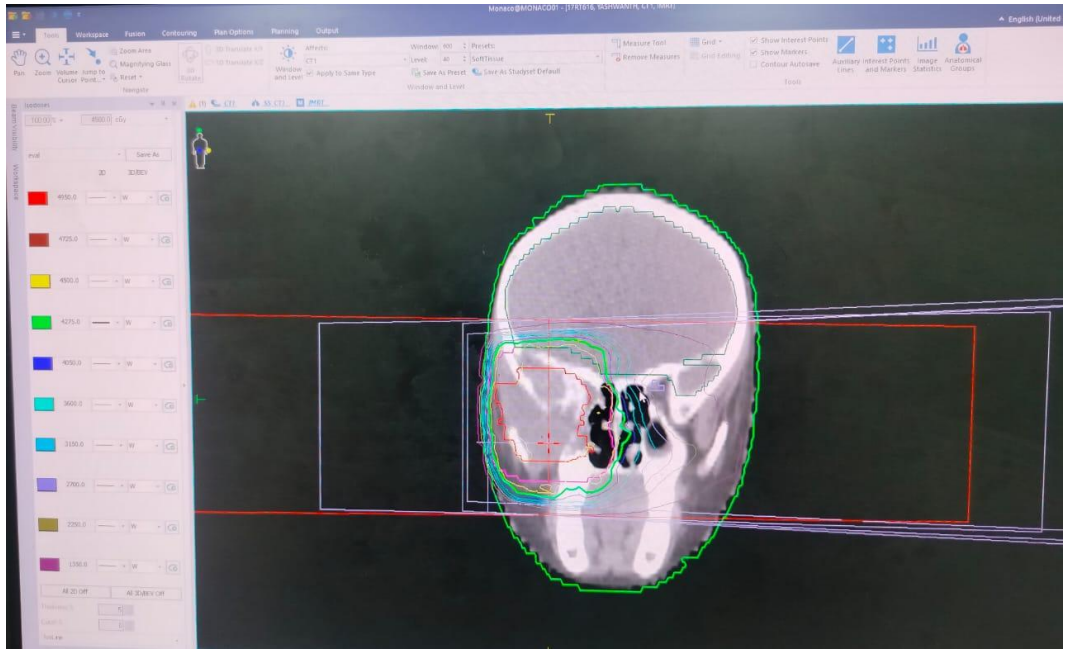


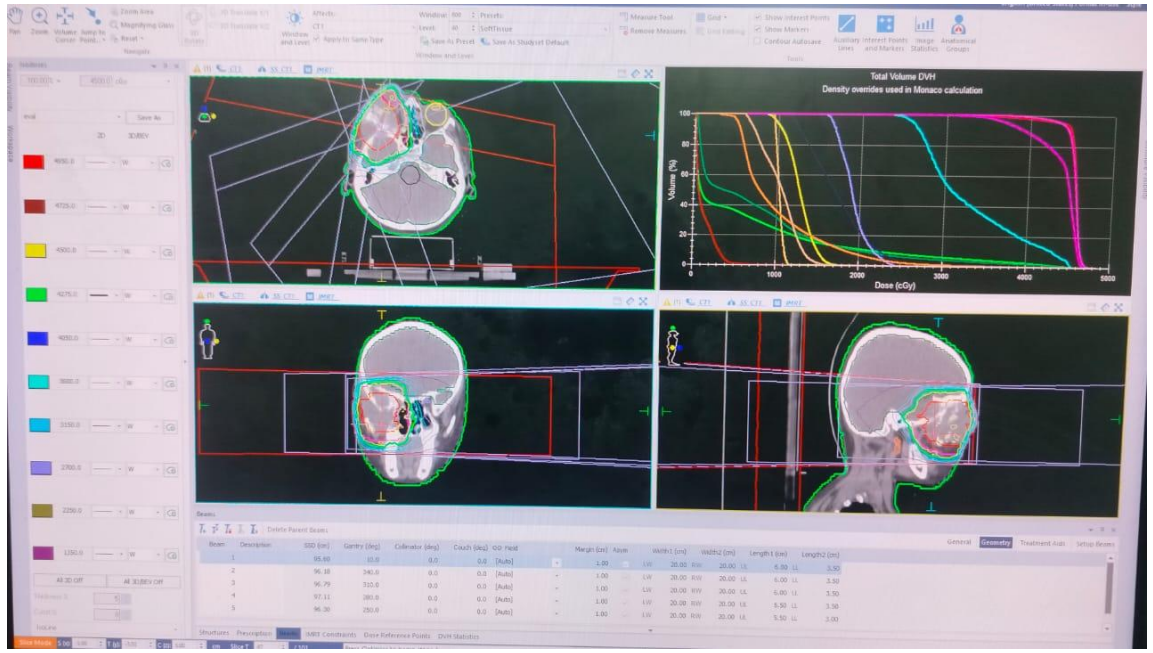
Figure 4 Initial results of lens sparing external beam

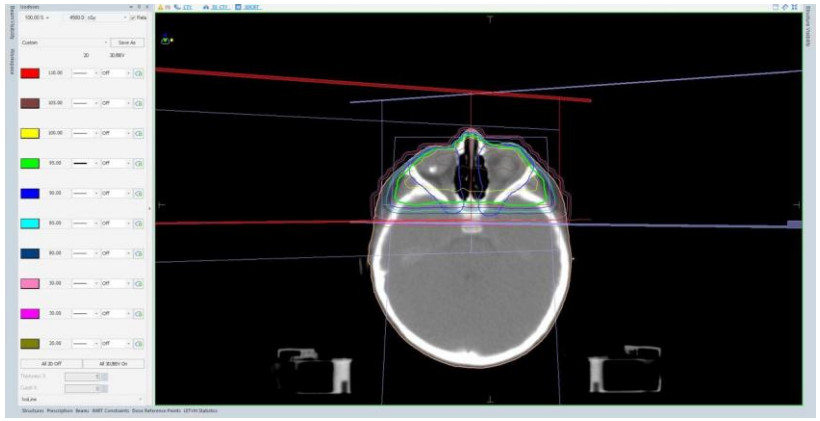


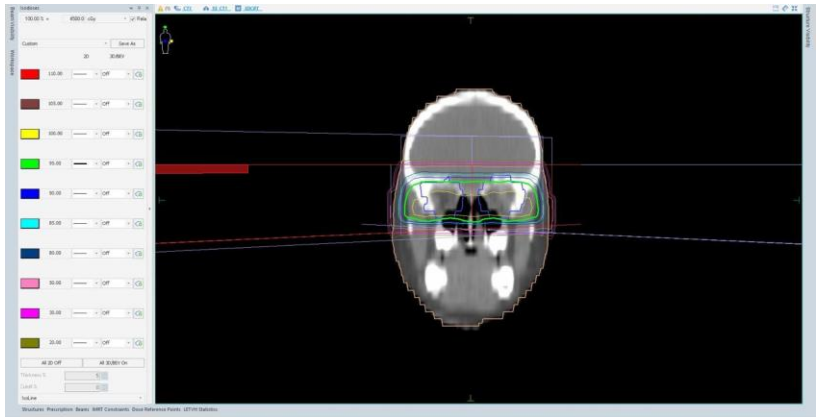


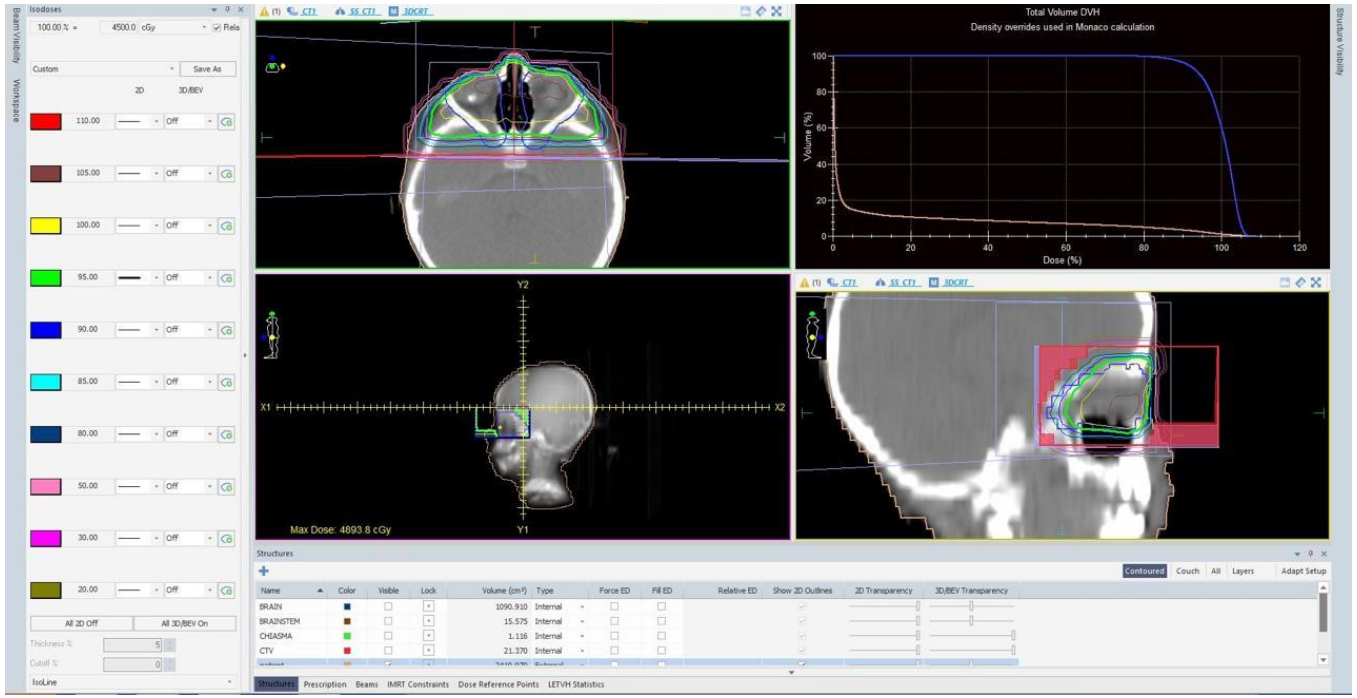
vydehi




Total Volume DVH
Density overrides used in Monaco calculation
Volume (%)
Dose (cGy)






Isodoses
100.00 % =
4500.0 cGy
Rela
Custom
Save As
2D
3D/BEV
110.00
105.00
100.00
95.00
90.00
85.00
80.00
50.00
30.00
20.00
Off
All 2D Off
All 3D/BEV On
Thickness %
Cutoff %
IsoLine
Total Volume DVH
Density overrides used in Monaco calculation
Volume (%)
Dose (%)
Y2
X1
X2
Y1
Max Dose: 4893.8 cGy
Structures
Contoured
Couch
All
Layers
Adapt Setup
Name
Color
Visible
Lock
Volume (cm³)
Type
Force ED
Fill ED
Relative ED
Show 2D Outlines
2D Transparency
3D/BEV Transparency
BRAIN
1090.910
Internal
BRAINSTEM
15.575
Internal
CHIASMA
1.116
Internal
CTV
21.370
Internal
Structures
Prescription
Beams
IMRT Constraints
Dose Reference Points
LETVH Statistics

Radiotherapy dose

The traditional therapeutic dose of EBRT is 45 Gy

Modern precision radiotherapy techniques, such as IMRT and stereotactic radiotherapy using a hypofractionated dose schedule, aim to achieve conformal dose distribution to the eye tumor.

However, IMRT results in a high integral dose by delivering low doses to surrounding tissues, which may in crease the risk of secondary tumors.

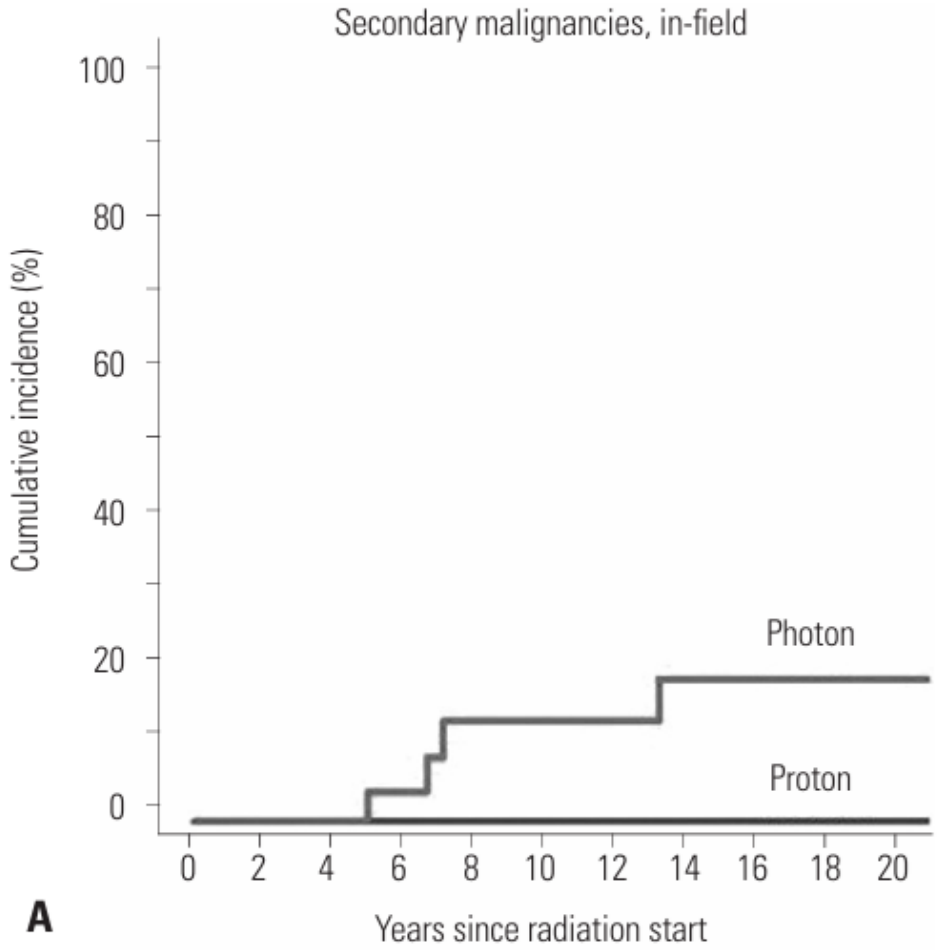
The volume of the bony orbit receiving >5 Gy was found to be 69% for IMRT, 25% for three-dimensional (3D) conformal electrons, and 10% for proton radiotherapy.

PROTON BEAM THERAPY

By reducing the radiation dose to the bone surrounding the eye, proton beam therapy (PBT) is expected to reduce the in incidence of secondary sarcoma.

A retrospective analysis of patients with RB treated with PBT at Massachusetts General Hospital or photon RT at Boston Children's Hospital showed that the former significantly reduced the rate of secondary malignancy [0/55 (0%) vs. 4/31 (13%)]

However, since the median follow-up period was shorter for PBT than for photon RT (6.9 years vs. 13.1 years) and the number of RB patients treated with PBT was relatively small, this finding requires confirmation in larger patient cohorts.



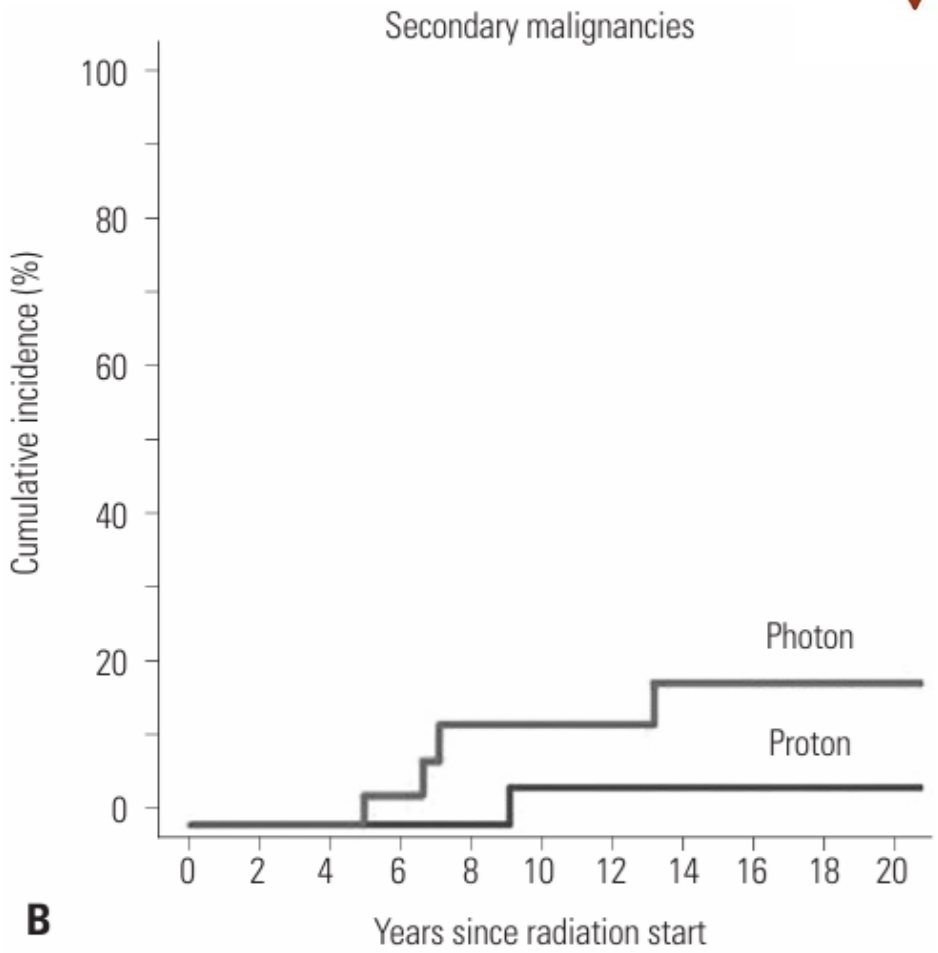
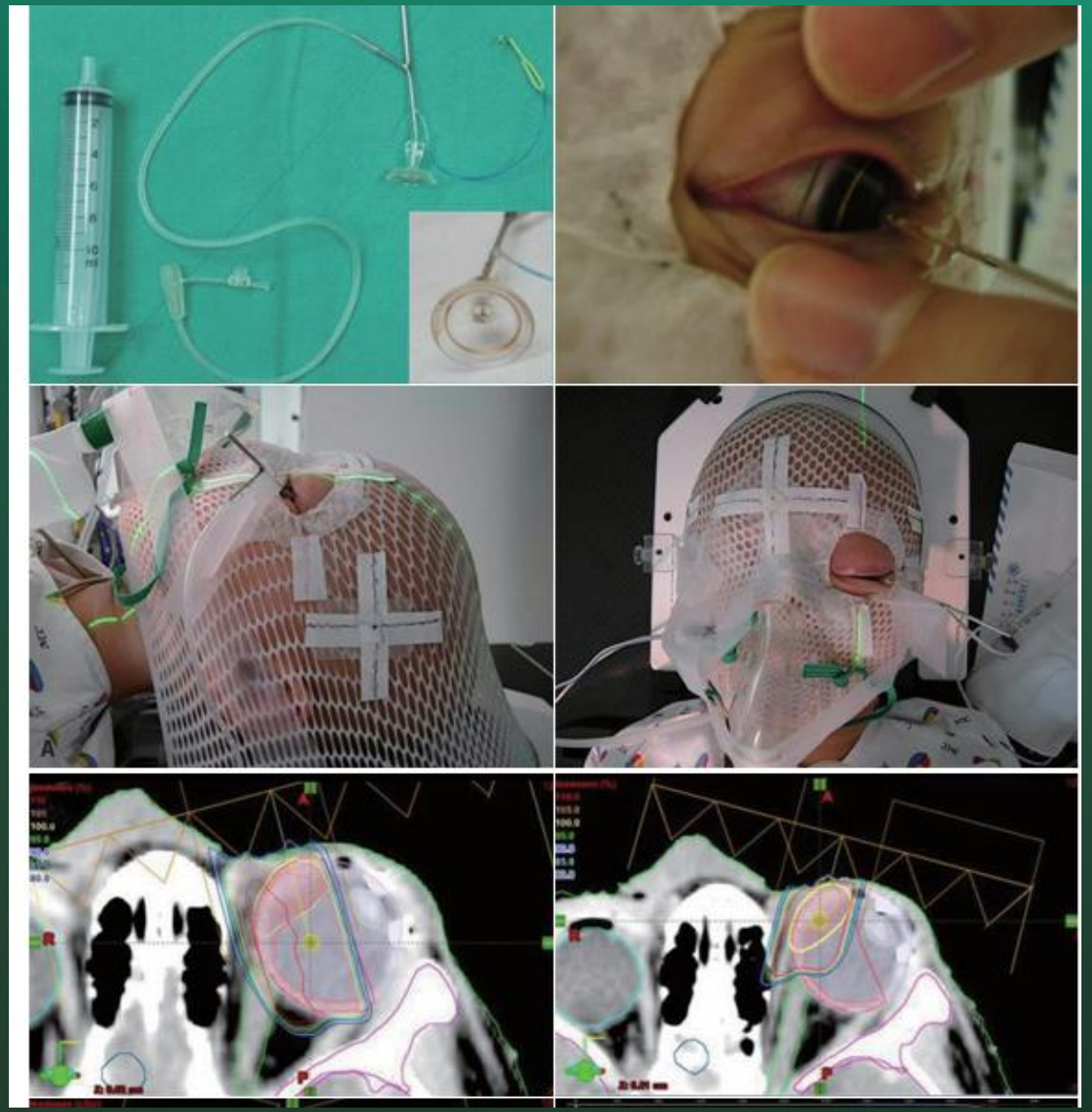


Fig. 1. Cumulative rates of (A) "in-field" or "radiation-induced" secondary malignancies and (B) all secondary malignancies in patients treated with proton beam therapy and photon radiotherapy.



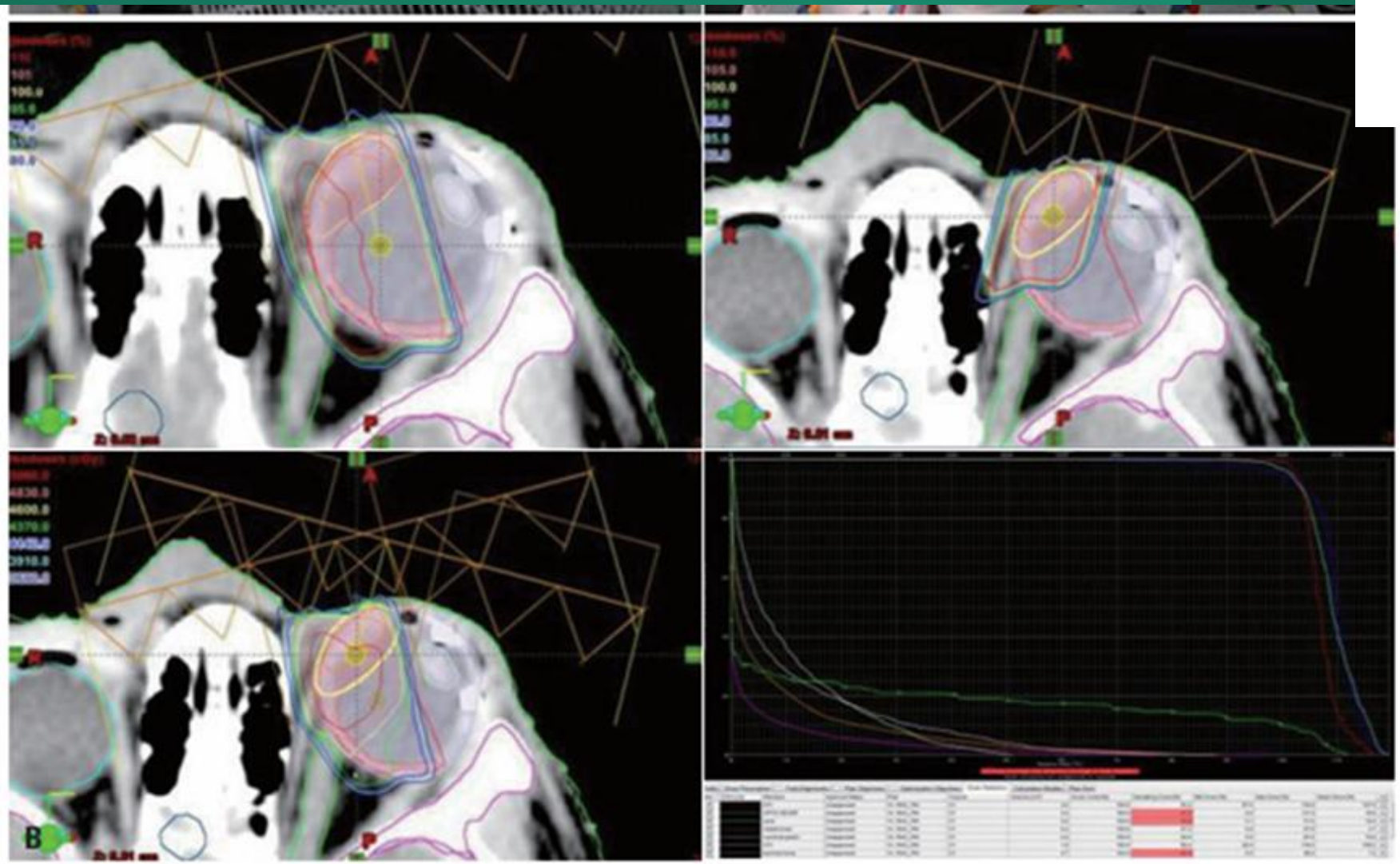
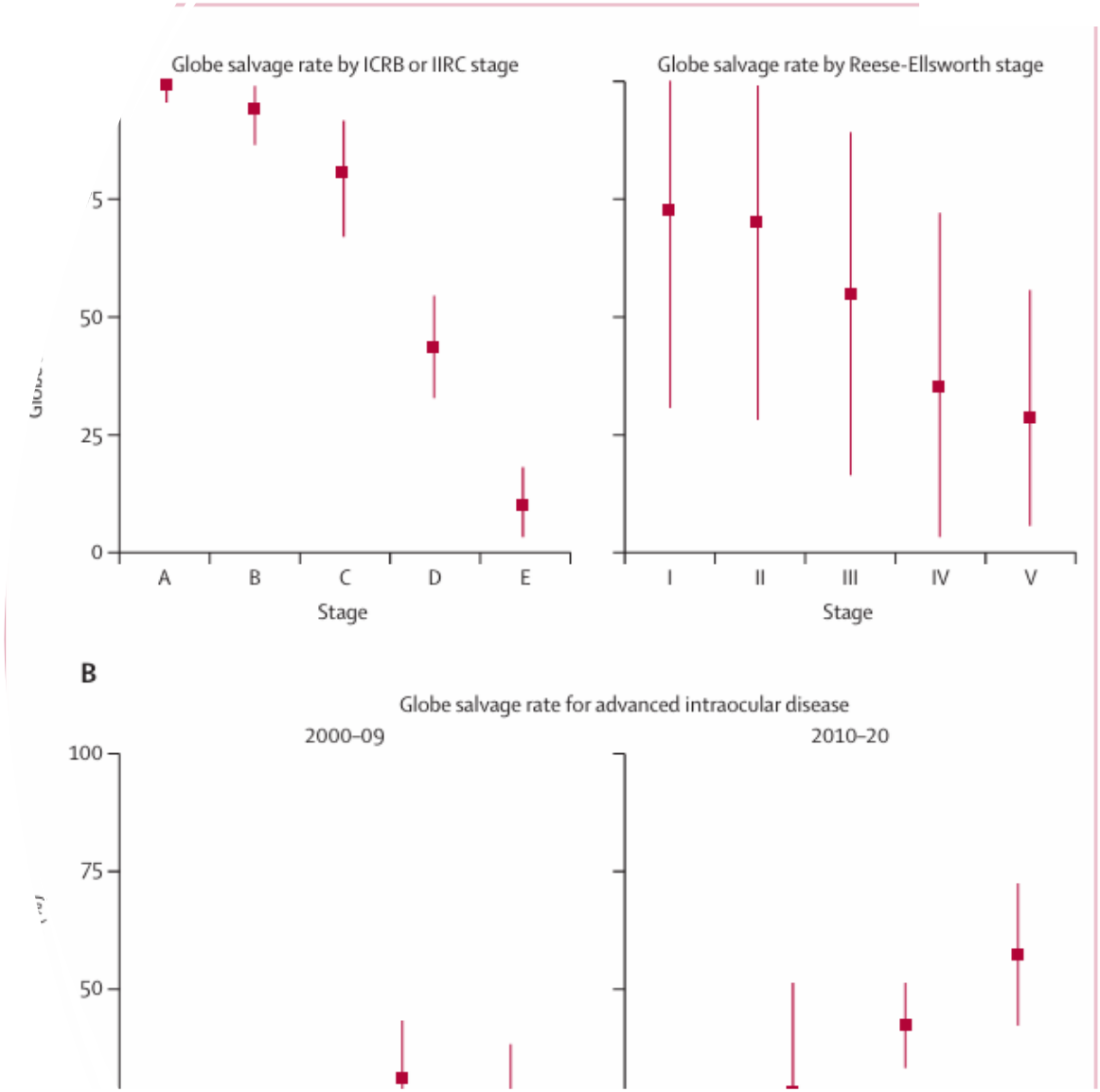


Fig. 2. Practices at National Cancer Center, Korea. (A) Under anesthesia, a small suction cup is placed on the cornea and the eyeball is rotated so tha the proton beam can maximally avoid the orbital bone while covering the retinal target. (B) Dose distribution in proton beam therapy–initial field (le upper), boost field (right upper), summation of both fields (left lower) and corresponding dose volume histogram for the entire plan (right lower).

Results:
www.thelancet.com/lancetgh
Vol 10 March 2022

- Global retinoblastoma survival and globe preservation: a systematic review and meta-analysis of associations with socioeconomic and health-care factors



Indian J Ophthalmol. 2025 Aug 1;73(8):1116-1123. doi: 10.4103/IJO.IJO_3033_24. Epub 2025 Jul 28.

Survival outcomes and globe salvage rates of retinoblastoma in India – A systematic review

Shreyasi Das [1], Amita Mahajan [1], Sima Das [2], Santosh G Honavar [3]

Affiliations + expand

PMID: 40719712 PMCID: PMC12416596 DOI: 10.4103/IJO.IJO_3033_24

- The total number of patients was 4147.
- Median age at diagnosis was between 24-36 months of age.
- The overall globe salvage rates ranged from 13% to 54.7%, with early intraocular disease having greater rates of vision preservation.
- A higher proportion of vision salvage (>50%) was found in recently concluded studies, mainly due to the use of intra-arterial chemotherapy after 2019.
- The pooled 5-year overall survival (OS) was 78.7%. Reported relapse rates ranged from 7% to 36%.
- Treatment abandonment rates varied between 10% to 58%.

Complications

- Dryness of the eye
- Cataract: During the megavoltage EBRT era, cataract developed in about 20–30% of eyes about 2–3 years after radiotherapy. The incidence is higher in patients treated with orthovoltage X-rays:
- Orbital hypoplasia
- Glaucoma, neovascularization, and hemorrhage sometimes require enucleation after EBRT

Indications for enucleation

- Unilateral advanced tumors (particularly with extensive seeding) with negligible visual potential (group D or E)
- A blind eye with recurrent disease following chemotherapy and/or radiation
- Any eye with suspected optic nerve, anterior segment, choroidal, scleral, or extraocular tumor involvement
- If the active tumor in the eye and cannot be followed due to obscured media (e.g., vitreous hemorrhage or phthisis).
- Exentration when persistent extraocular component after high dose chemo

Screening

- Vision screening and eye examination
- Red-eye reflex examination
- Awareness to all health professionals
- An innovative study called PhotoRed in India trained healthcare professionals to use flash photography to identify childhood eye diseases, including retinoblastoma

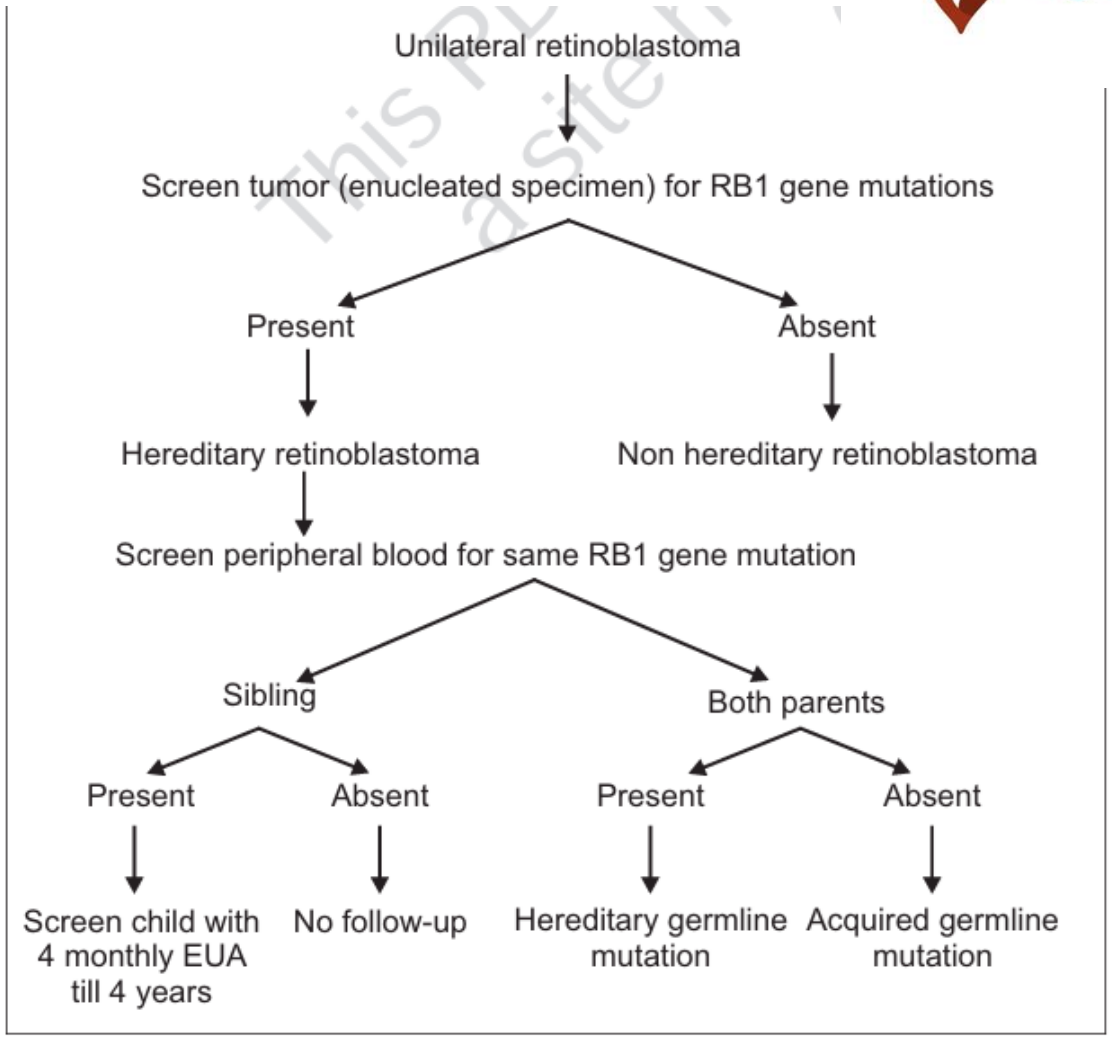


Figure 1: Algorithm for genetic studies in unilateral retinoblastoma

Surveillance

- Surveillance screening for second cancers (including leiomyosarcoma, osteosarcoma, melanoma, lung and bladder cancer) with and without radiation is a pressing need in the opinion of retinoblastoma survivors.

Take home message

- The most frequent intraocular neoplasm of childhood
- White eye reflex (leukocoria) serves as the hallmark sign of retinoblastoma
- Accurate mapping of fundus with diagrams & description is essential
- CT scan to be avoided in suspected RB gene mutations
- Primary goal of the management is to save life and secondary to save vision
- Group A to C treated with focal therapies with and without systemic/ local chemotherapy
- Episcleral plaque therapy can be used in Group B & C
- Use of EBRT declined, used for extraocular and as salvage treatment for recurrent or resistant tumors
- Proton therapy is emerging as the preferred modality