Retinoblastoma Management: Update

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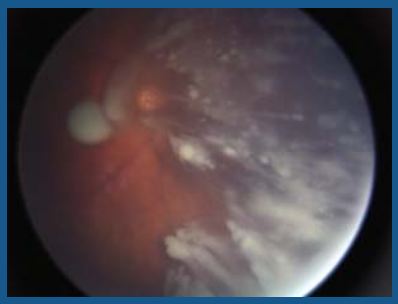
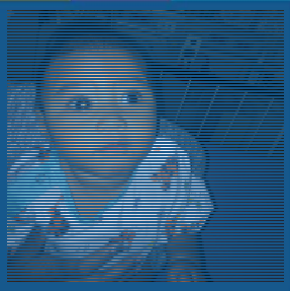
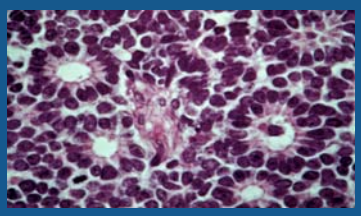
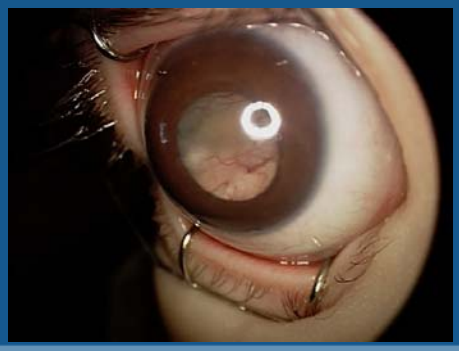
Retinoblastoma







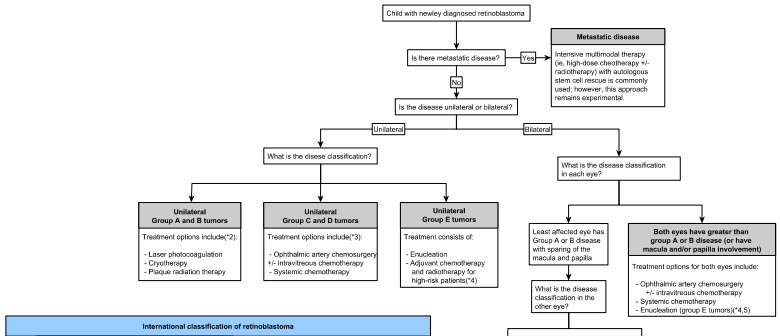


Retinoblastoma: Background

- Most common primary intraocular tumor in children
- Second only to uveal melanoma as most common primary IO malignancy
- Rare disease: 1/15,000 live births= 350 cases/year in US
- No sex or racial predilection
- New mutations in 90% of cases, family history 10%
- Average age at diagnosis:
  - Average 18 months
    - Bilateral 12 months, Unilateral 24 months

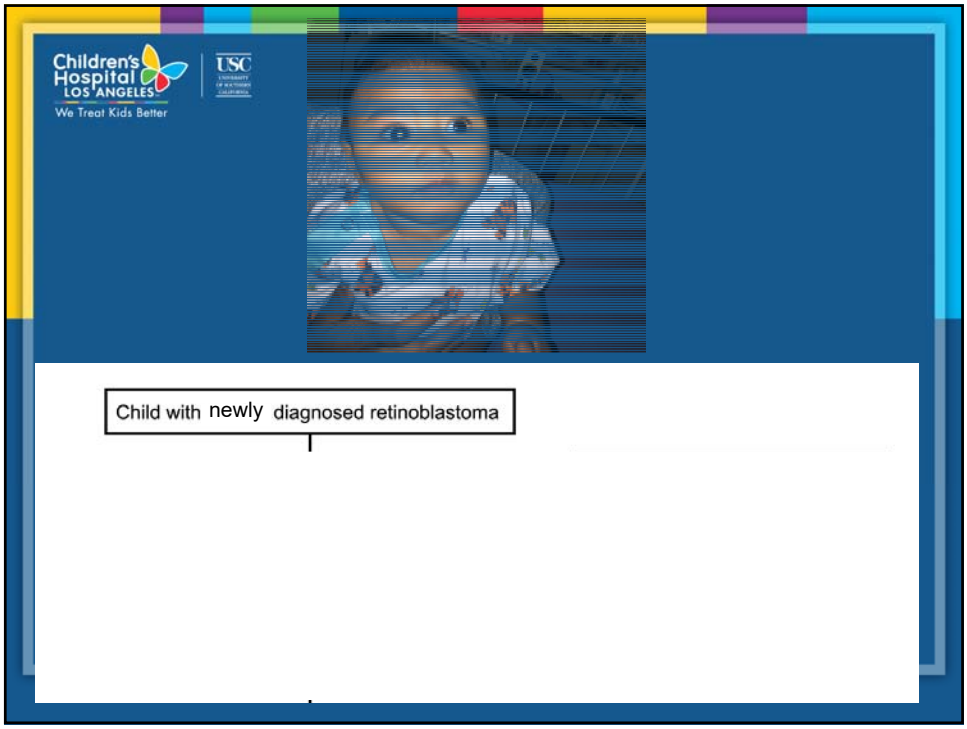
Hey Dr. Berry, How do you treat this?

Algorithmic overview of initial treatment options for children with newly diagnosed retinoblastoma based on disease classification(*1)



International classification of retinoblastoma

Group	Description:	Specific features
A	Very low risk: Eyes with small discrete tumors away from critical structures.	Tumor ≤3 mm in basal dimension or thickness
B	Low risk: Eyes with discrete retinal tumor of any size or location without vitreous or subretinal seeding.	Tumor >3 mm in basal dimension or thickness, or any of the following: • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to disc) • Clear subretinal fluid ≤3 mm from margin
C	Moderate risk: Eyes discrete retinal tumors of any size or location with only focal vitreous or subretinal seeding.	One of the following: • Subretinal seeds ≤3 mm from tumor • Vitreous seeds ≤3 mm from tumor • Both subretinal and vitreous seeds ≤3 mm from tumor • Less than one quadrant of subretinal fluid in the fundus
D	High risk: Eyes with massive nondiscrete tumors and/or diffuse vitreous or subretinal seeding.	One of the following: • Subretinal seeds >3 mm from tumor • Vitreous seeds >3 mm from tumor • Both subretinal and vitreous seeds >3 mm from tumor • Greater than one quadrant of subretinal fluid in the fundus
E	Very high risk: Eyes that have been destroyed anatomically or functionally by the tumor	Extensive retinoblastoma, or one of the following: • Neovascular glaucoma • Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space • Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber • Tumor anterior to the anterior vitreous face including the ciliary body or iris • Diffuse infiltrating tumor • Phthisis bulbi or orbital cellulitis



Presenting Signs

- Presenting signs/symptoms %
  - Leukocoria 56.2
  - Strabismus 23.6
  - Inflammatory Sx 8.9
  - Poor Vision 7.7
  - Family Hx 6.8
  - Routine Exam 2.8
- Rare disease + Leukocoria = Late diagnosis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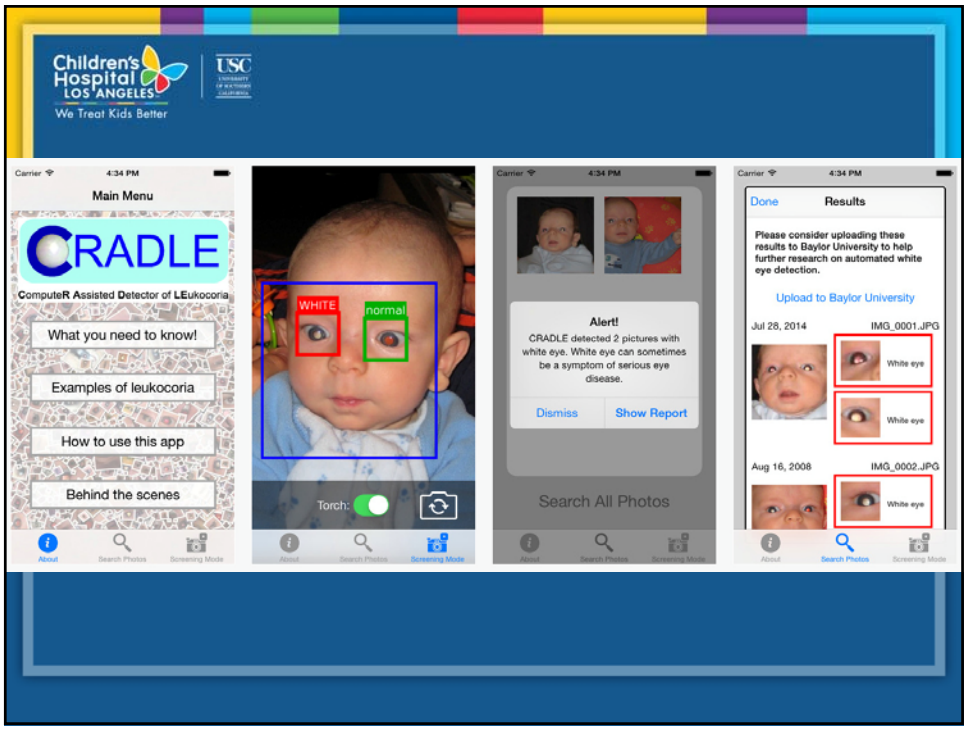
EVERY 60 SECONDS
A CHILD GOES BLIND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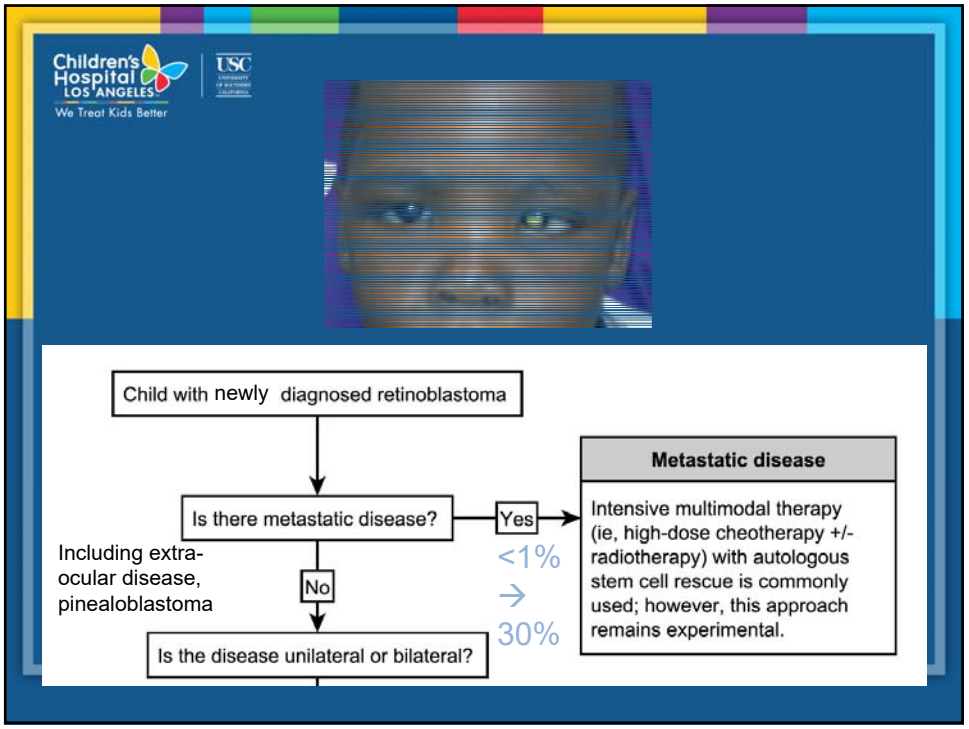
Main Menu
CRADLE
ComputeR Assisted Detector of LEukocoria
What you need to know!
Examples of leukocoria
How to use this app
Behind the scenes
WHITE
normal
Torch:
Alert!
CRADLE detected 2 pictures with white eye. White eye can sometimes be a symptom of serious eye disease.
Dismiss
Show Report
Search All Photos
Done
Results
Please consider uploading these results to Baylor University to help further research on automated white eye detection.
Upload to Baylor University
Jul 28, 2014
IMG_0001.JPG
White eye
White eye
Aug 16, 2008
IMG_0002.JPG
White eye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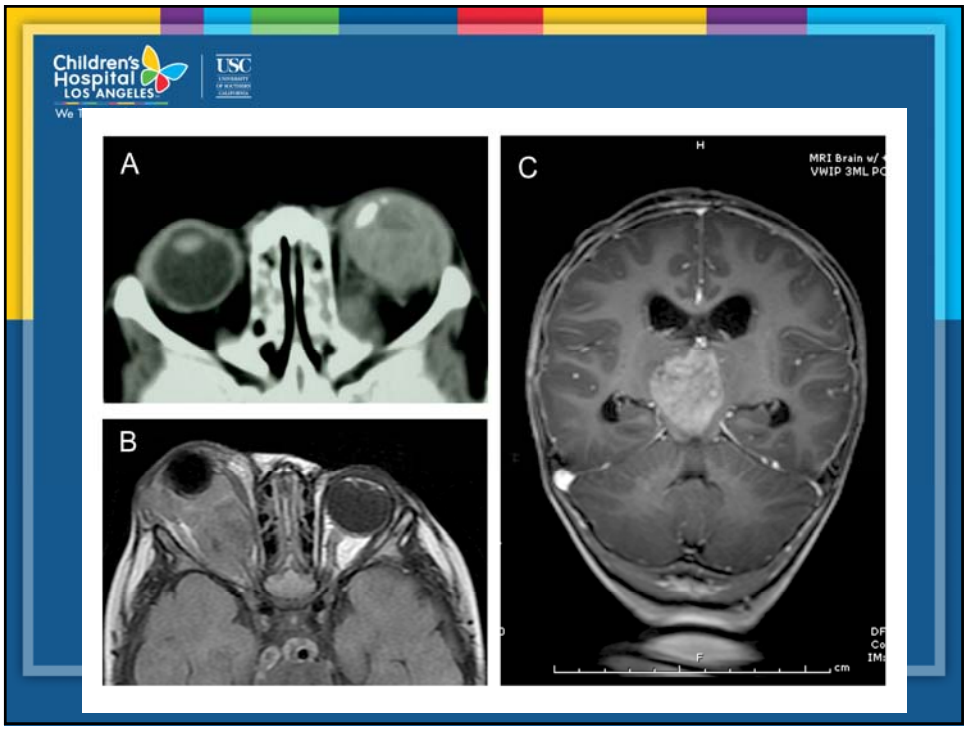
Child with newly diagnosed retinoblastoma
Is there metastatic disease?
Yes
<1%
→
30%
Metastatic disease
Intensive multimodal therapy (ie, high-dose cheotherapy +/- radiotherapy) with autologous stem cell rescue is commonly used; however, this approach remains experimental.
Including extra-ocular disease, pinealoblastoma
No
Is the disease unilateral or bilateral?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A
B
C
MRI Brain w/
VWIP 3ML PC

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2/3 Is the disease unilateral or bilateral? 1/3

Unilateral

Bilateral

What is the disese classification?

What is the disease classification in each eye?

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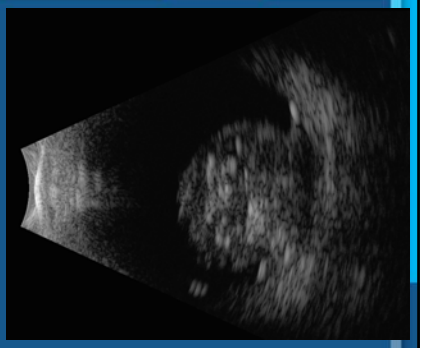
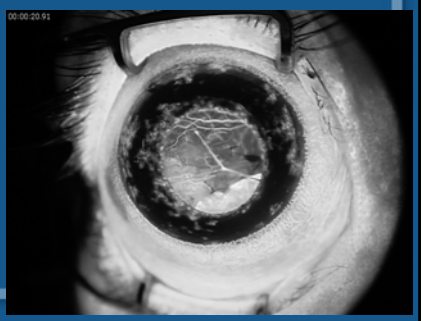
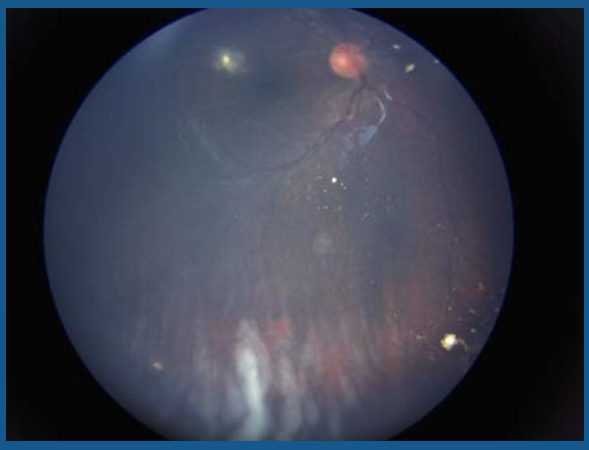
EUA





Two important features of RB: Seeding/Calcification



Intraocular calcification:

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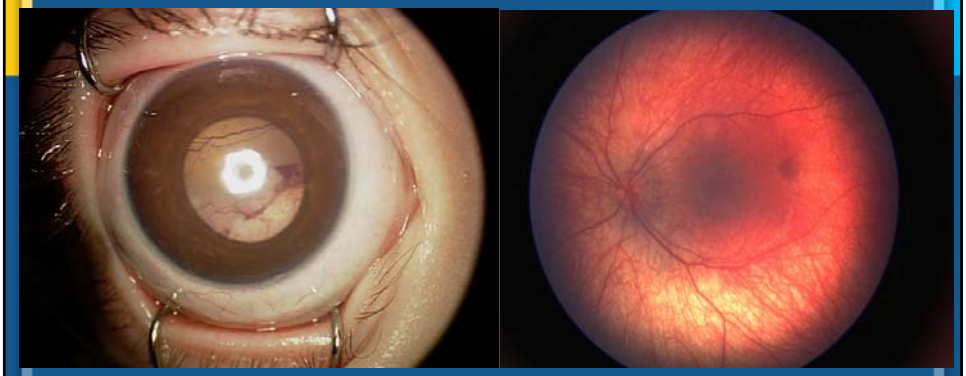
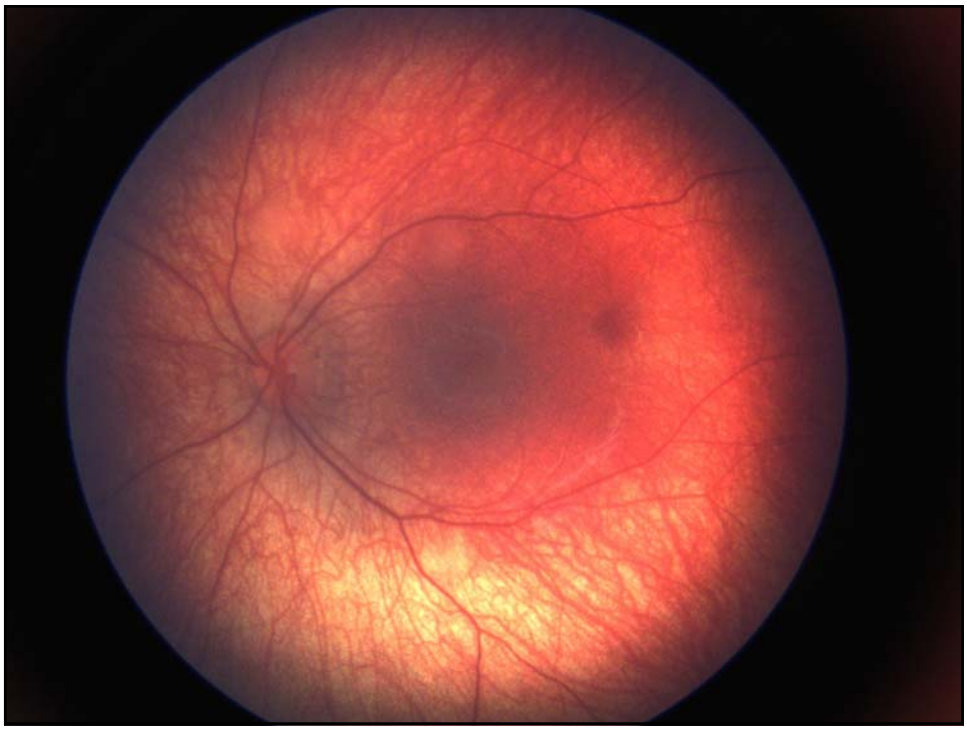
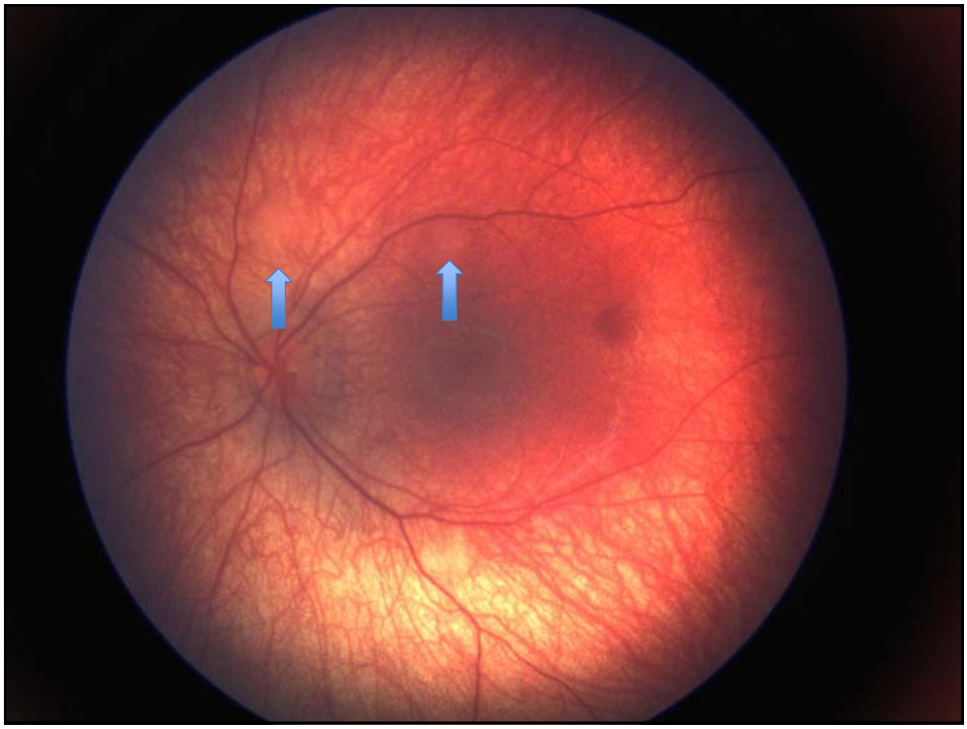
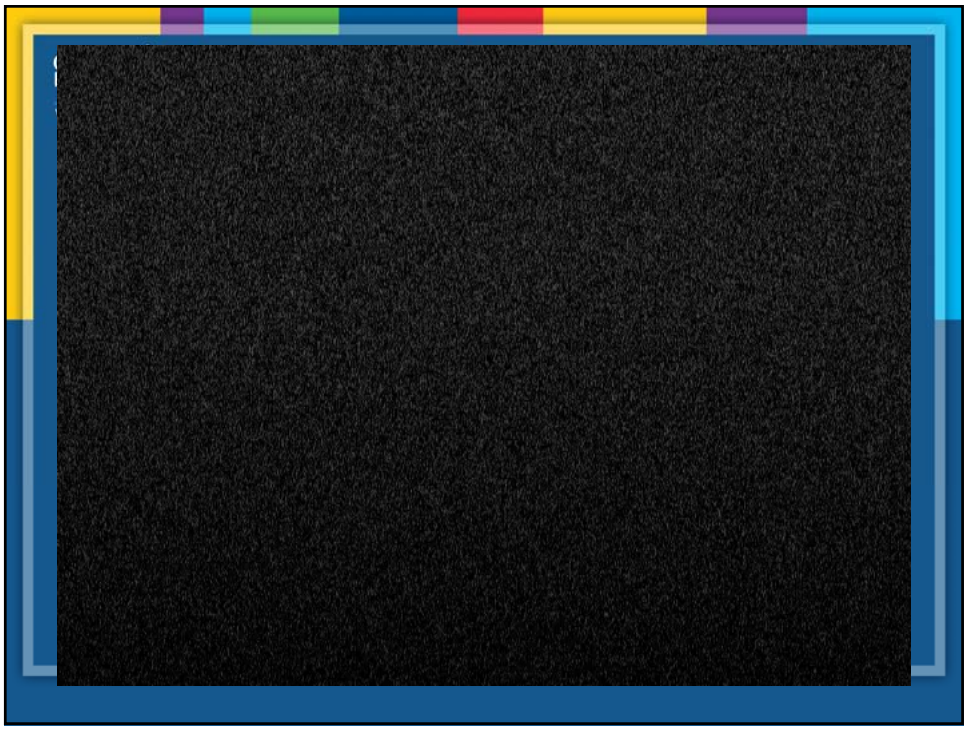
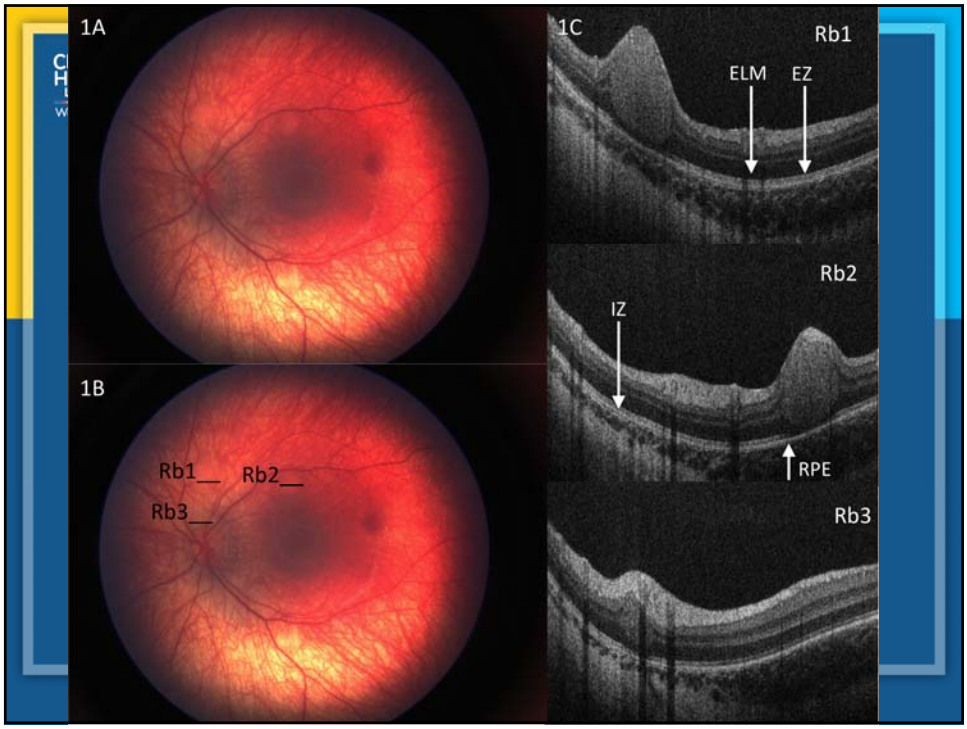
OCT for diagnosis

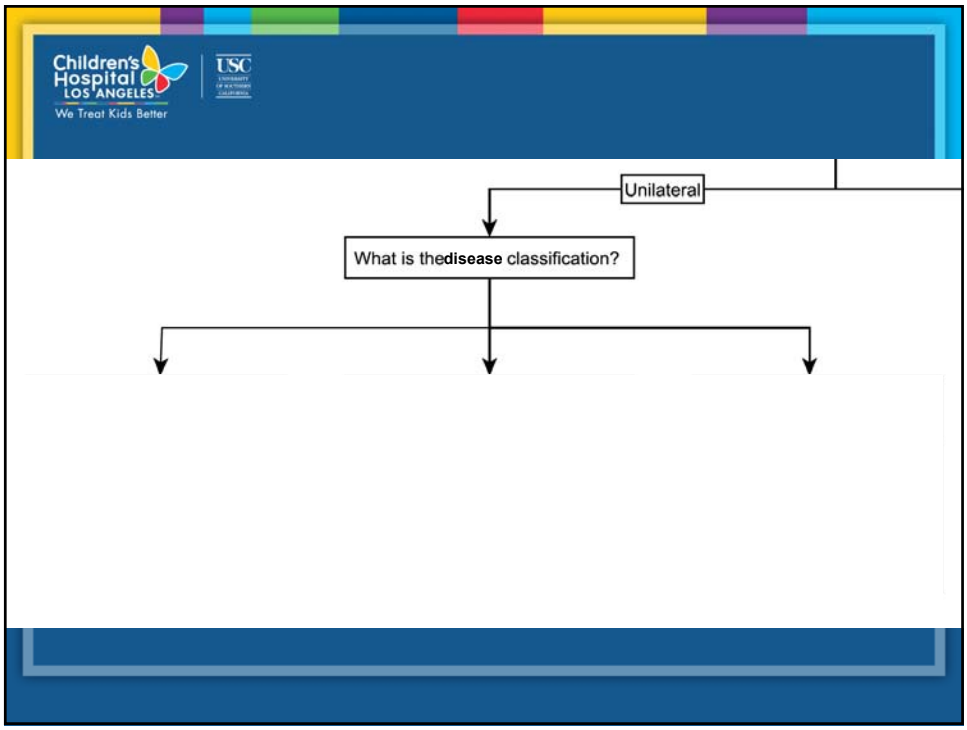









1A
1B
Rb1__ Rb2__
Rb3__
1C
Rb1
ELM
EZ
Rb2
IZ
RPE
Rb3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Unilateral
What is thedisease classification?

INTERNATIONAL CLASSIFICATION SYSTEMS FOR INTRAOCULAR RETINOBLAST

Group A
Small intraretinal tumors away from foveola and disc

- All tumors are 3 mm or smaller in greatest dimension, confined to the retina *and*
- All tumors are located further than 3 mm from the foveola **and** 1.5 mm from the optic d

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 less than 3 mm from the tumor with no subretinal see

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 1/4 retina
- Local fine vitreous seeding may be present close to discrete tumor
- Local subretinal seeding less than 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 retinal detachment
- Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumor mas
- 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 ciliary body or anterior segment
- Diffuse infiltrating retinoblastoma
- Neovascular glaucoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulites
- Phthisis bulbi

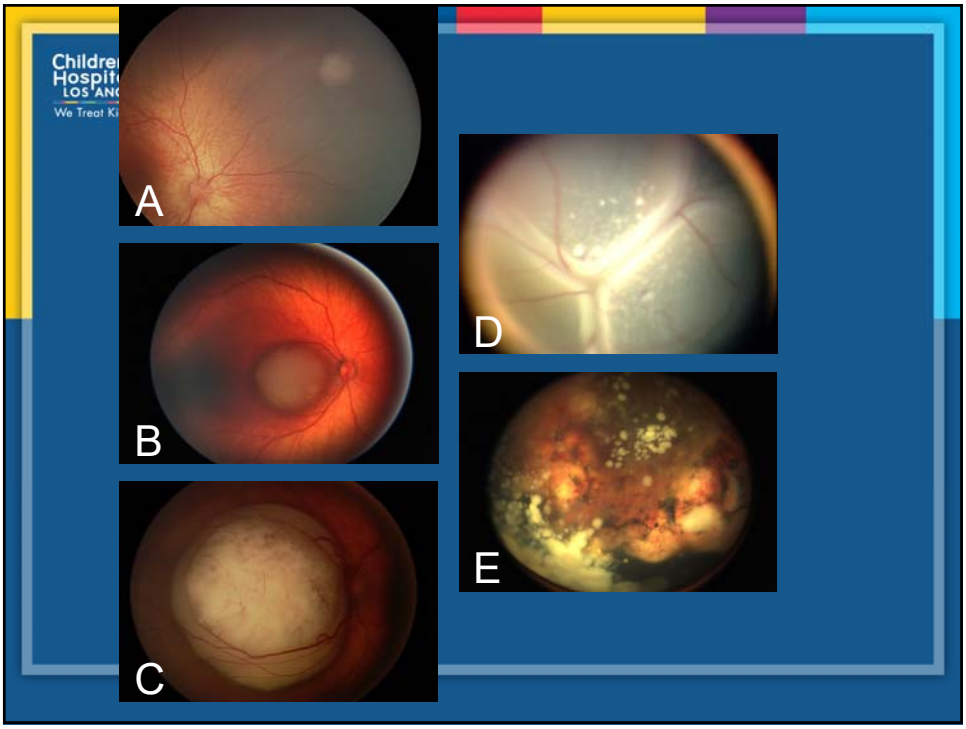
A: small and far

B: bigger and/or closer

C: seeding

D: diffuse seeding

E: everywhere



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Unilateral

What is the **disease** classification?

Unilateral Group A and B tumors

Treatment options include(*2):

- Laser photocoagulation
- Cryotherapy
- Plaque radiation therapy

Unilateral Group C and D tumors

Treatment options include(*3):

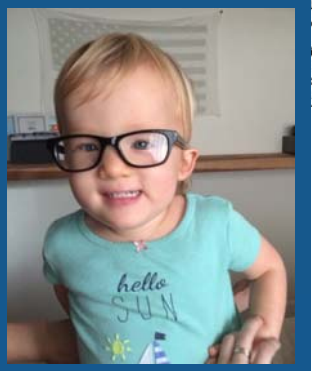
- Ophthalmic artery chemosurgery
+/- intravitreous chemotherapy
- Systemic chemotherapy

Unilateral Group E tumors

Treatment consists of:

- Enucleation
- Adjuvant chemotherapy and radiotherapy for high-risk patients(*4)

Age & size of the patient



Bilateral

What is the disease classification in each eye?

- Laser photocoagulation
- Cryotherapy
- Plaque radiation therapy

Treatment options for the second eye include:

- Ophthalmic artery chemosurgery
+/- intravitreous chemotherapy
- Systemic chemotherapy
- Enucleation (group E tumors)(*4,5)

age & size of the patient

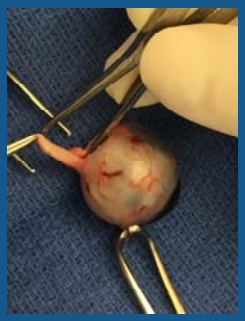
Modern Treatment Options for Intraocular Retinoblastoma:

- Enucleation
- Systemic Chemoreduction
- local chemotherapy: Intra-arterial/intravitreal
- Cryotherapy
- Transpupillary thermotherapy (Argon and Diode Laser)
- Brachytherapy
- External Beam Radiation (rare)

Enucleation

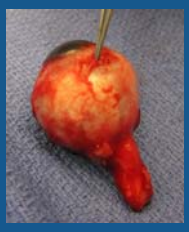
- One hour surgery, curative.
- Curative in 96% of cases

- Advanced Unilateral Cases, Group D or E
- Group E
  - Buphthalmos, NVG, anterior segment or CB invasion, orbital cellulitis, phthisis



Enucleation

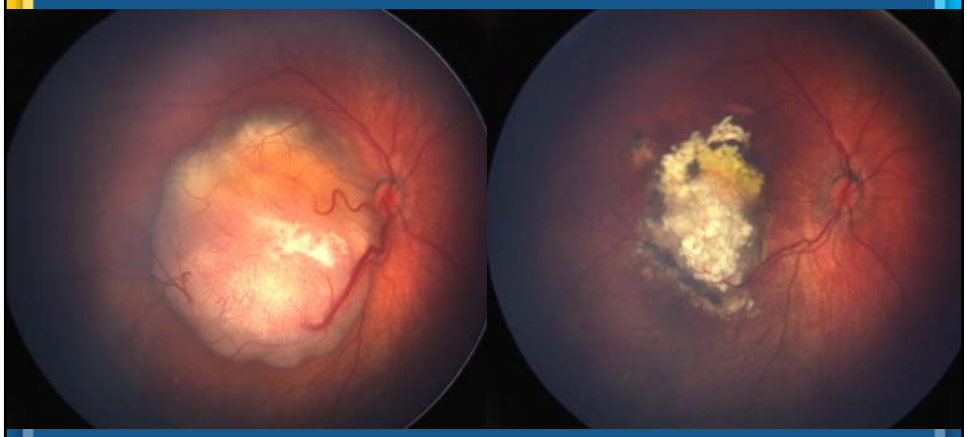
- Kim JW, et al BJO 2008
  - Tumor recurrence after enucleations 1914-2006
    - 71 pts/1674 pts undergoing enucleation (4.2%)
      - Overall, no downward trend in incidence over time
    - 97% in 12 months
      - Mean 6 months
      - never after 24 months
- bilateral Group E may treat
  - Zhou et al: Risk of masking high risk pathological features if enucleation after 3 months



Chemoreduction

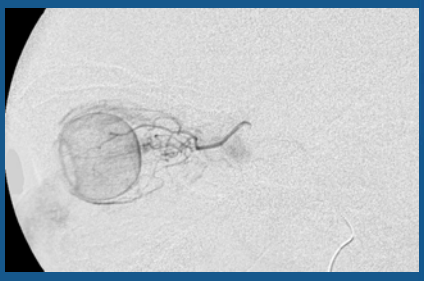
- Carboplatin + Vincristine + Etoposide
  - Bilateral disease: Group B or worse in least affected eye
  - 3 to 6 cycles (months) ** 3 at CHLA for Group B
- Results:
  - 90-100% cure rates for small tumors
  - <50% for Group D
  - Need additional treatment
- Problems:
  - Bone marrow suppression common
  - ? Risk of secondary leukemia
  - Cost/ duration of treatment

Chemoreduction: 6 cycles



Intra-arterial Chemosurgery

- MSKCC (adapted from Japanese technique)
- Infusion of chemotherapy directly into the ophthalmic artery
- Avoids systemic toxicity of drug/achieves higher levels within the globe
- ?local/regional toxicity

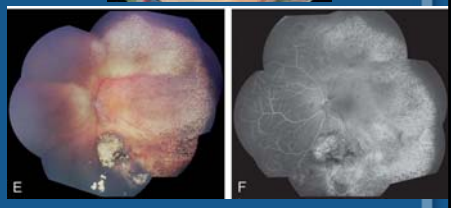


Intra-arterial Chemosurgery

- Melphalan, Topotecan, carboplatin
  - Unilateral disease: Group B or worse
  - recurrences
  - 3 cycles (months)
  - 3 months and 6 kilos otherwise bridge therapy
- Results:
  - >90% cure rates reported for primary therapy in Group D
  - >50% for recurrent disease post other therapy
  - Need additional treatment
  - Technical expertise with interventionalist

Local complications (Transient/Rare)

- Transient
  - Periorbital edema
  - Skin erythema/nasal lash loss
- Rare
  - Avascular retinopathy
  - Sectoral choroidal vascular occlusion
  - Stroke
  - Metastasis

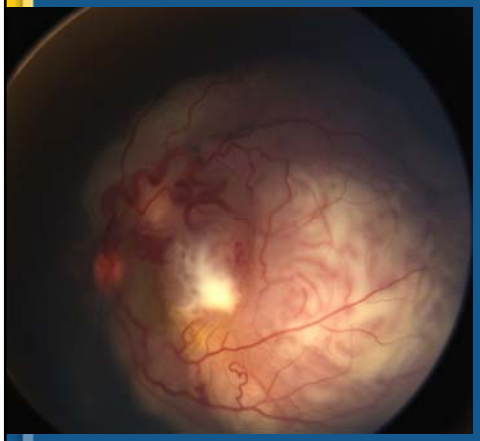


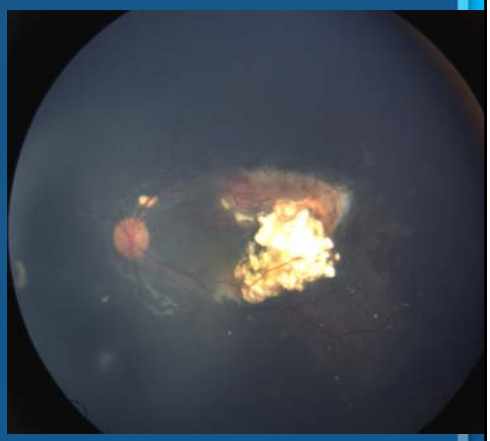
Intra-arterial Chemosurgery

Preliminary arteriogram

1.5 French Magic catheter in origin of left ophthalmic artery prior to infusion

Intra-arterial Chemosurgery: 3 cycles



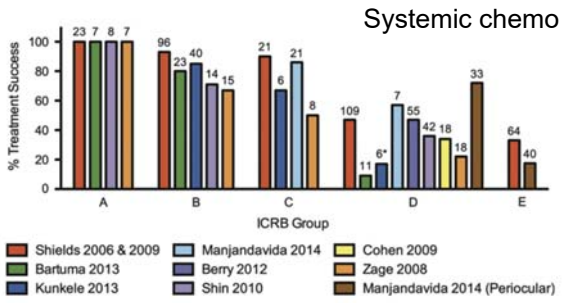


IA Chemo: Summary

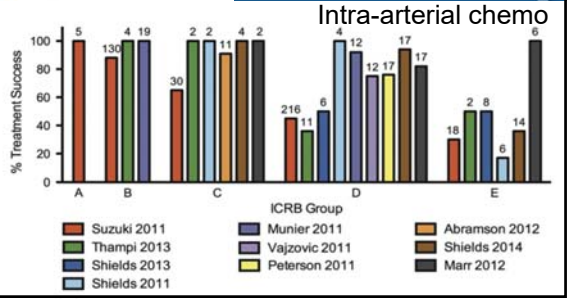
- As primary therapy, IA Chemo probably offers cure rates slightly higher than systemic chemotherapy
  - Higher rate of local side effects
  - Lower rates of bone marrow suppression
  - Toxicity in some cases probably explained by variability in blood flow to ophthalmic territories
- Technique dependent results
- Best candidates:
  - Older than 6 months
  - Primary: unilateral group C,D
  - Salvage: Unilateral retinal and vitreous recurrences

Systemic vs. Intra-arterial

Systemic chemo



Intra-arterial chemo



Chung et al. Retinoblastoma: Evidence of Stage-based Chemotherapy. International Ophthalmology Clinics 2015

Table 1. Chemoreduction protocol at CHLA

	Standard protocol	First cycle: 50% reduced-dose protocol		Subsequent cycles: 50–100% dose protocol[a]
		for infants <2 months	for infants >2 months	
Carboplatin				
Day 1	13 mg/kg (390 mg/m^2)	6.5 mg/kg (195 mg/m^2)	6.5 mg/kg (195 mg/m^2)	6.5–13 mg/kg (195–390 mg/m^2)
Day 2	13 mg/kg (390 mg/m^2)	6.5 mg/kg (195 mg/m^2)	6.5 mg/kg (195 mg/m^2)	6.5–13 mg/kg (195–390 mg/m^2)
Etoposide				
Day 1	5 mg/kg (150 mg/m^2)	2.5 mg/kg (75 mg/m^2)	2.5 mg/kg (75 mg/m^2)	2.5–5 mg/kg (75–150 mg/m^2)
Day 2	5 mg/kg (150 mg/m^2)	2.5 mg/kg (75 mg/m^2)	2.5 mg/kg (75 mg/m^2)	2.5–5 mg/kg (75–150 mg/m^2)
Vincristine				
Day 1	0.05 mg/kg (1.5 mg/m^2)	not given	0.025 mg/kg (0.75 mg/m^2)	0.025–0.05 mg/kg (0.75–1.5 mg/m^2)[b]
Day 2				

[a] Patients are increased to 100% if they (1) are >3 months of age, (2) show no grade III toxicity to the 75% dose, and (3) have inadequate tumor response to the 75% dose. [b] Only given to infants >2 months of age.

Table 1 Standard drug dosages used according to age

Drug	3–6 months	6–12 months	1–3 years	≥3 years
Melphalan (mg)	2.5	3	4	5
Topotecan (mg)	0.3	0.3	0.3	0.4
Carboplatin (mg)	25	30	30	30

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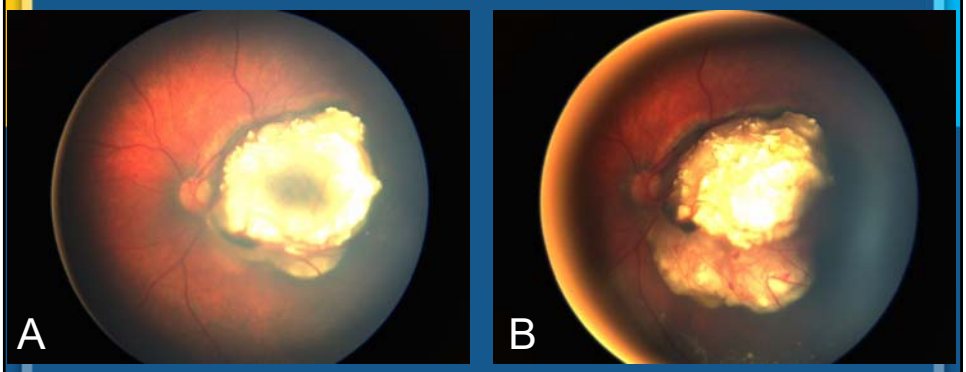
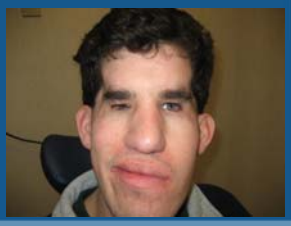
Recurrence: Retinal Primary



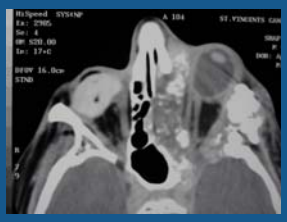
EBR

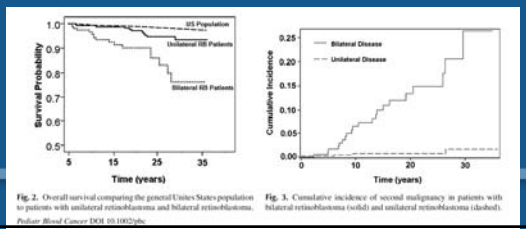
- Radiation: curative at dose well tolerated by human eye (40-45 Gy)
- Best modality for preserving vision (treats entire eye)
- Side effects:
  - Cataract
  - Bony hypoplasia
  - Second cancers
- Contraindicated in kids <12 months
- Used to be used for seeding
- Best for retinal recurrence in only eye



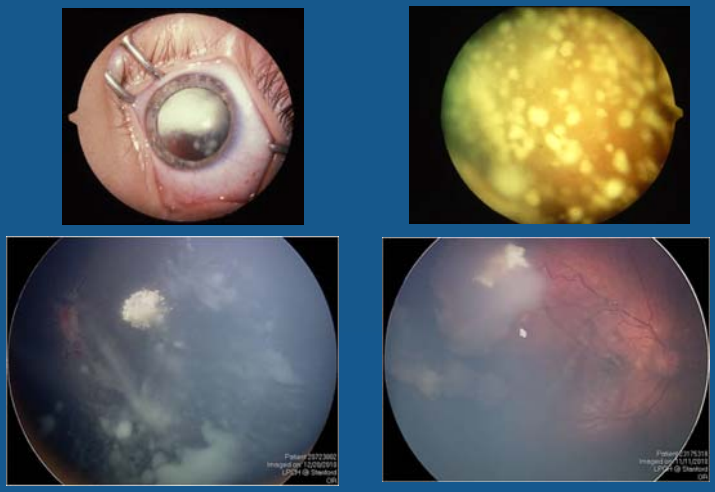
EBR: Second Cancers

- Risk of second cancer at 50 years:
  - Germinal 36%
  - Somatic 6%
- Sarcomas, brain cancers, melanomas
- Risk greatest for EBR treated germline patients < 12 months of age





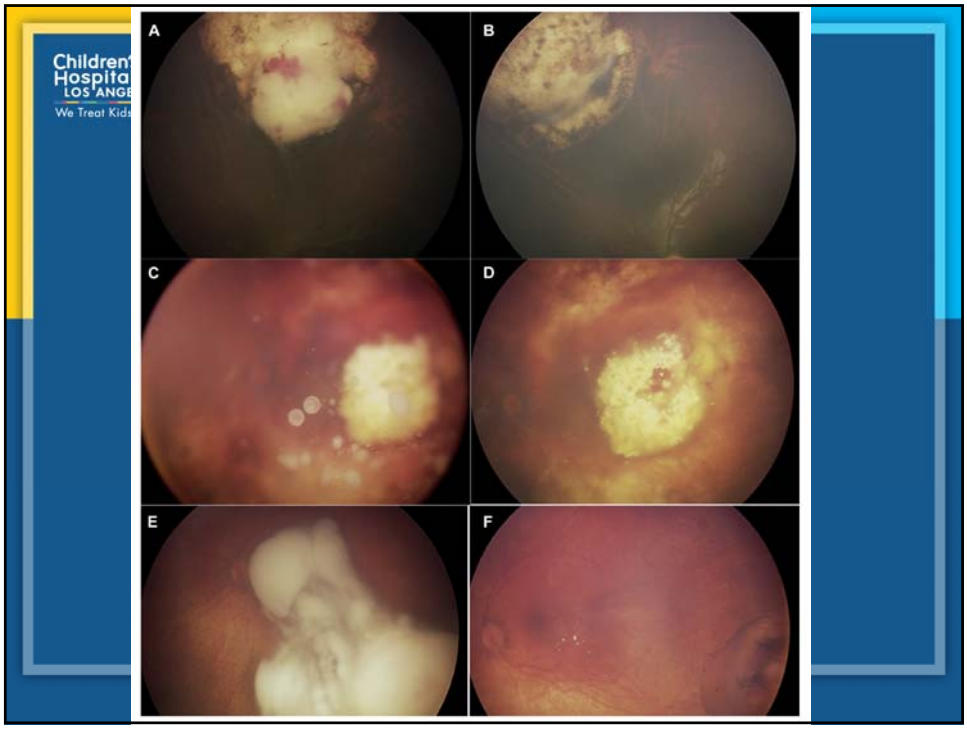
Recurrence: Seeding



Seeding Classification

Table 1. Summary of Vitreous Seed Classification and Clinical Findings

Class	Type	Description	Regression Characteristics	Median Time to Regression (wks)	Median No. of Injections	Median Melphalan Dose (μg)
Type 1	Dust	Small granules of vitreous opacities Can be seen as a vitreous haze overlying tumor	Typically regress to type 0 (not visible)	2–3	3	20
Type 2	Spheres	Spherically shaped opacities within vitreous Dust may be present around spheres Can be homogenously opaque or have a translucent outer shell with relatively transparent or whitish center	Initially disperse (pseudo-growth) and then disappear, but can become calcific (type I), amorphous (type II), or a mixture of types I and II (type III)	6–7	5	30
Type 3	Cloud	Dense collection of punctate vitreous opacities Can appear as a sheet or globule of seed granules and often with wispy edge Dust and spheres are sometimes also visible	Initially disperse (pseudo-growth), become calcific, or disappear, but can remain calcific (type I) or amorphous (type II)	12–14	8	33



Seeding Classification

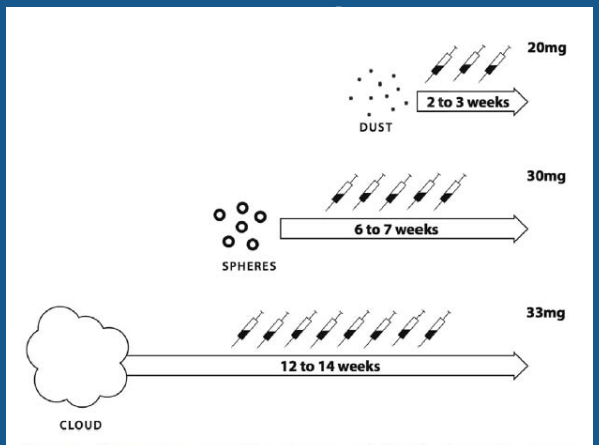


Figure 1. Illustration summarizing vitreous seed classification and response to intravitreal melphalan: number of injections received, time to response, and mean dose of melphalan per injection.

Vitreous seeding pre-2012

- Unilateral Group B
- After 3 cycles CEV, tumor recurrence noted with vitreous seeding
- Treated with 2 cycles systemic topotecan/cyclophosphamide
- Retinal tumor regressed but the vitreous seeding showed no response

Vitreous seeding pre-2012

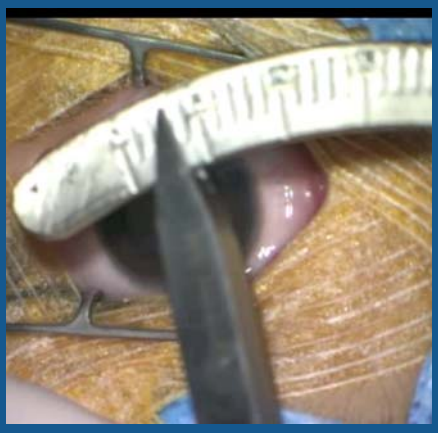
- 2 sessions of IAC
  - 5 mg melphalan
  - 8 mg melphalan
- No response by vitreous seeding
- Left eye was enucleated

Intravitreal chemotherapy injection: Munier 2012

- IVC protocol for RB
  - Melphalan 20-30 ug
  - UBM at injection site, 180 degrees away from seeding
  - 32 ga needle
  - Only for isolated vitreous seeding

Intravitreal Melphalan: Injection Technique

- Mark the injection site 3.25-3.5mm posterior the limbus



Intravitreal Melphalan: Injection Technique

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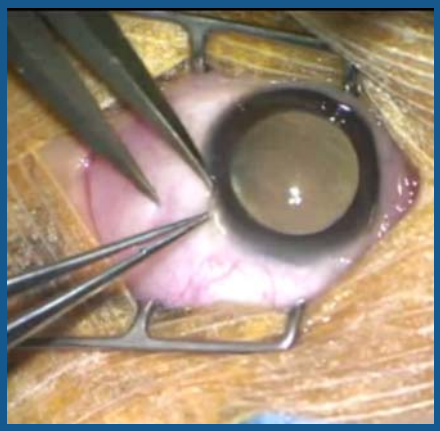

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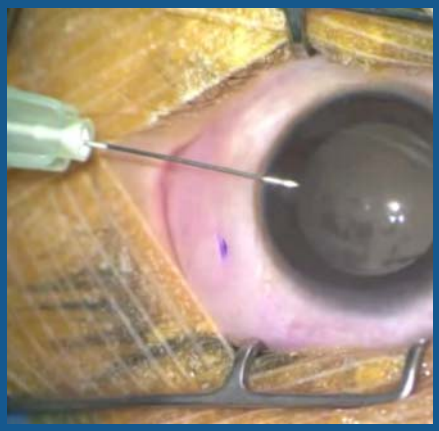
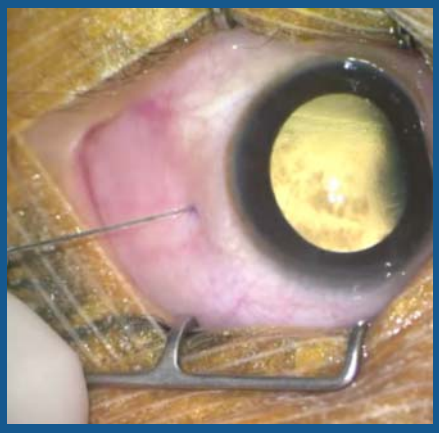
Intravitreal Melphalan: Injection Technique

- Mark the injection site 3.25-3.5mm posterior the limbus
- Paracentesis is performed withdrawing 0.1 cc of aqueous humor



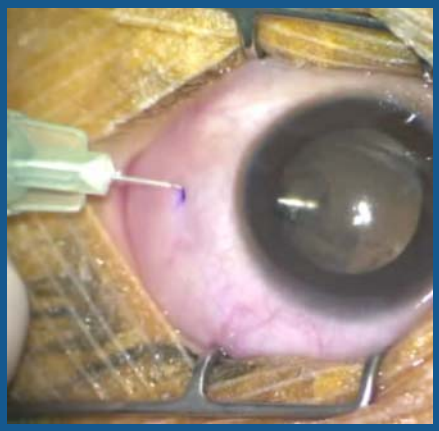
Intravitreal Melphalan: Injection Technique

- Mark the injection site 3.25-3.5mm posterior the limbus
- Paracentesis is performed withdrawing 0.1 cc of aqueous humor
- An injection is done with a 32 G needle in a quadrant of the eye free of tumor



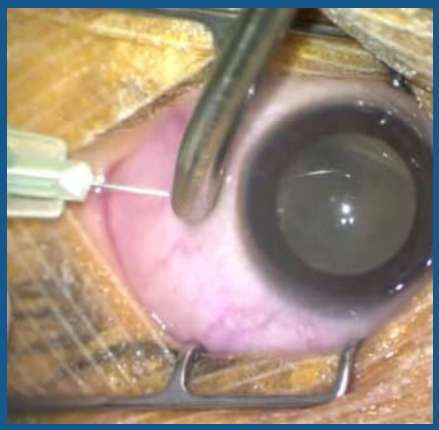
Intravitreal Melphalan: Injection Technique

- Mark the injection site 3.25-3.5mm posterior the limbus
- Paracentesis is performed withdrawing 0.1 cc of aqueous humor
- An injection is done with a 32 G needle in a quadrant of the eye free of tumor
- The needle is visualized behind the lens



Intravitreal Melphalan: Injection Technique

- Mark the injection site 3.25-3.5mm posterior the limbus
- Paracentesis is performed withdrawing 0.1 cc of aqueous humor
- An injection is done with a 32 G needle in a quadrant of the eye free of tumor
- The needle is visualized behind the lens
- Cryotherapy is applied as the needle is withdrawn
- The eye is then shaken to distribute the chemotherapy
- Surface is bathed in sterile water

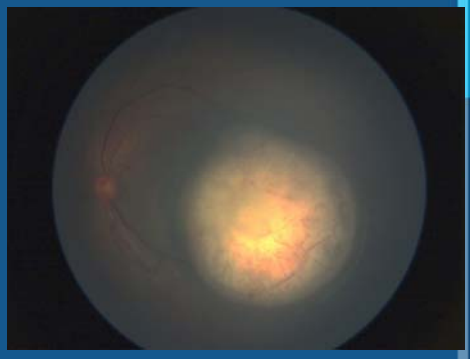


Review of IVC complications: Smith SJ BJO 2014

- 10 published studies on IVC for RB
  - 295 patients, 1287 injections, mean F/U 74 months
    - 38 patients with ocular side effects
      - 17 major (2 with RD)
      - 21 minor (IOP, cataract)
    - 1 patient with extraocular spread in Japan
    - 395 injections in 71 patients outside Japan with no extraocular spread

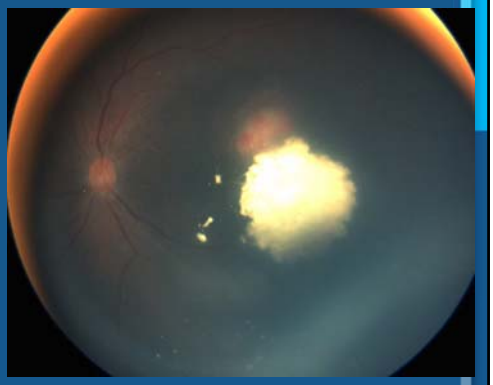
Intravitreal Melphalan:Case 1

- A 2-month-old girl presented to CHLA with bilateral retinoblastoma:
  - OD: Group D
  - OS: Group B
- She was started on systemic chemotherapy with consolidation laser therapy



Intravitreal Melphalan:Case 1

- S/p 4 cycles of chemotherapy and consolidation laser therapy pt had persistent active vitreous seeding OU
- She underwent 2 IVM injections OU (1 week apart) w/ no apparent intra-op or post operative complications

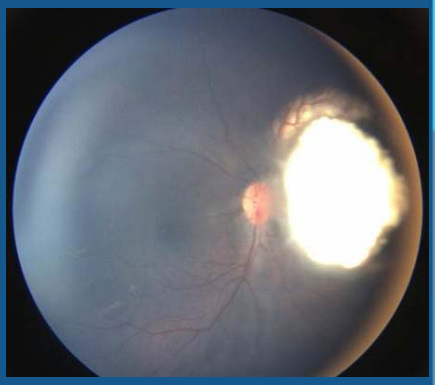


Intravitreal Melphalan:Case 2

- A 6-month-old boy presented to CHLA with unilateral Group D retinoblastoma OD
- He was started on systemic chemotherapy with consolidation laser therapy

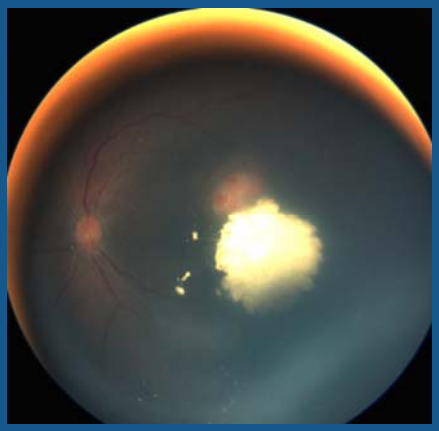
Intravitreal Melphalan:Case 1

- S/p 6 cycles of chemotherapy and consolidation laser therapy pt had persistent active vitreous seeding
- He underwent 2 IVM injections OD (1 week apart) w/ no apparent intra-op or post operative complications

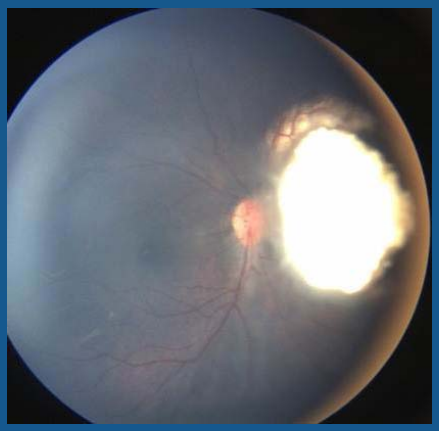


Intravitreal Melphalan: Cases 1&2

Case 1



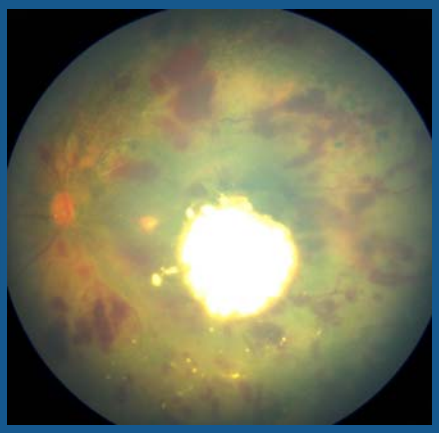
Case 2



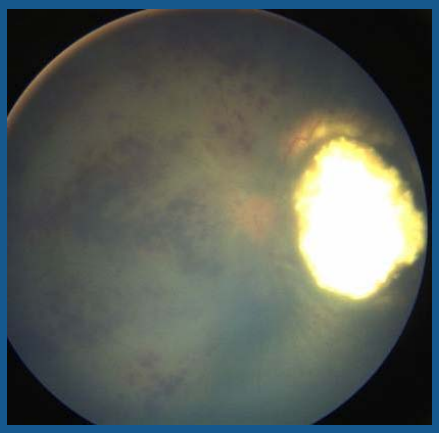
1 week s/p 1st IVM injections

Intravitreal Melphalan: Cases 1&2

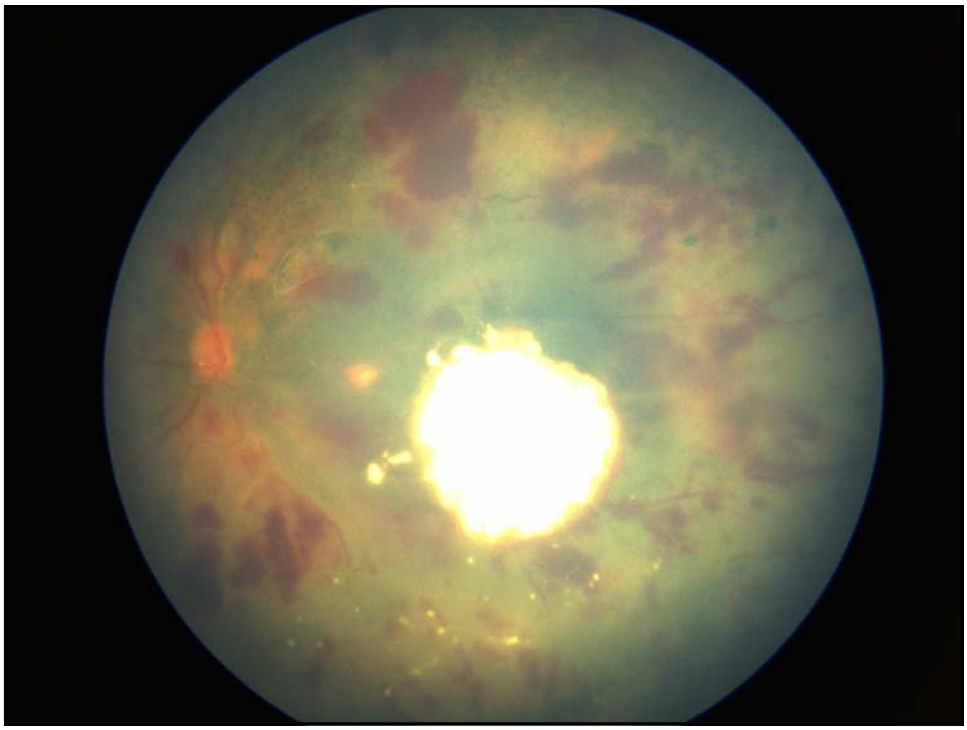
Case 1

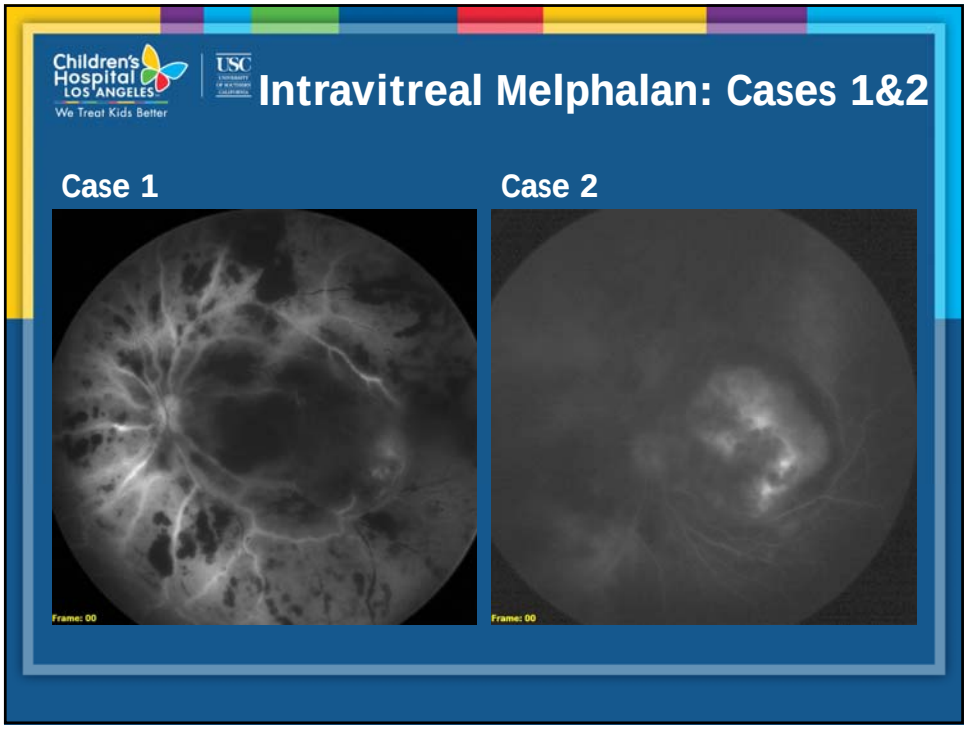


Case 2



1 week s/p 2nd IVM injections

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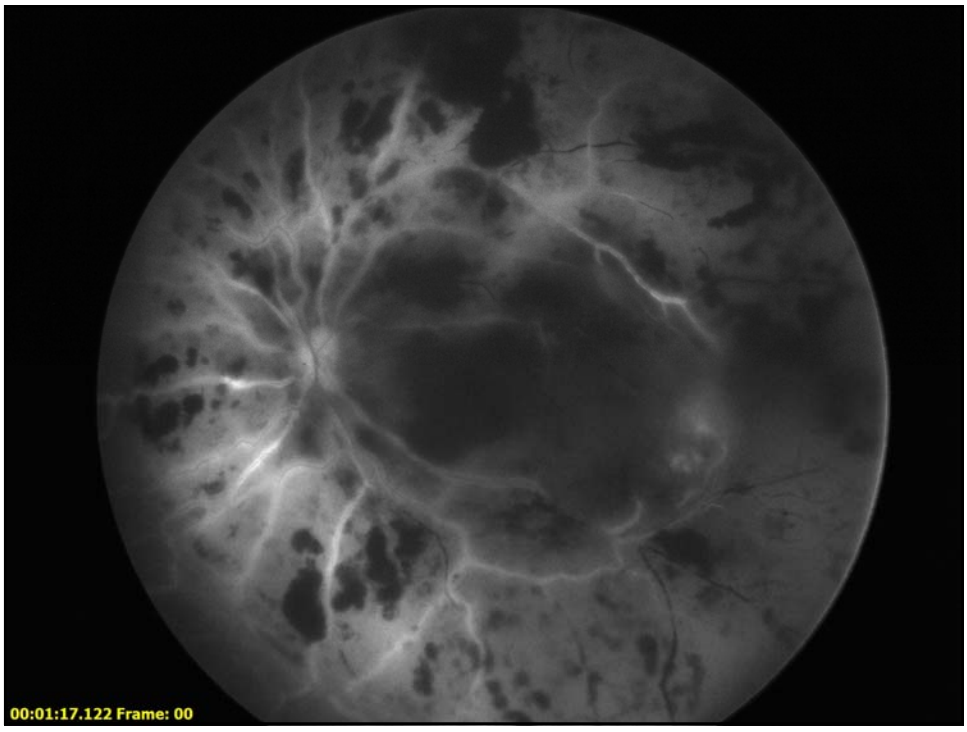
Intravitreal Melphalan: Cases 1&2
Case 1
Case 2
Frame: 00
Frame: 00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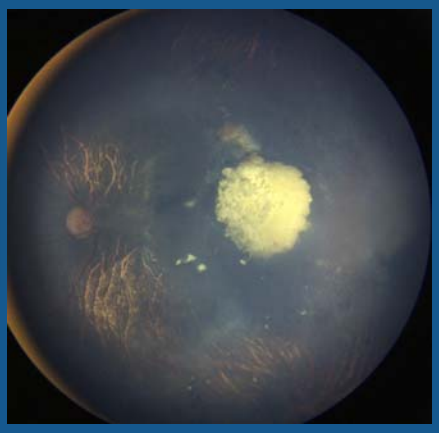
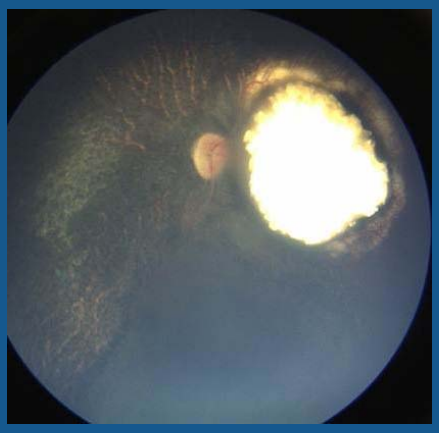
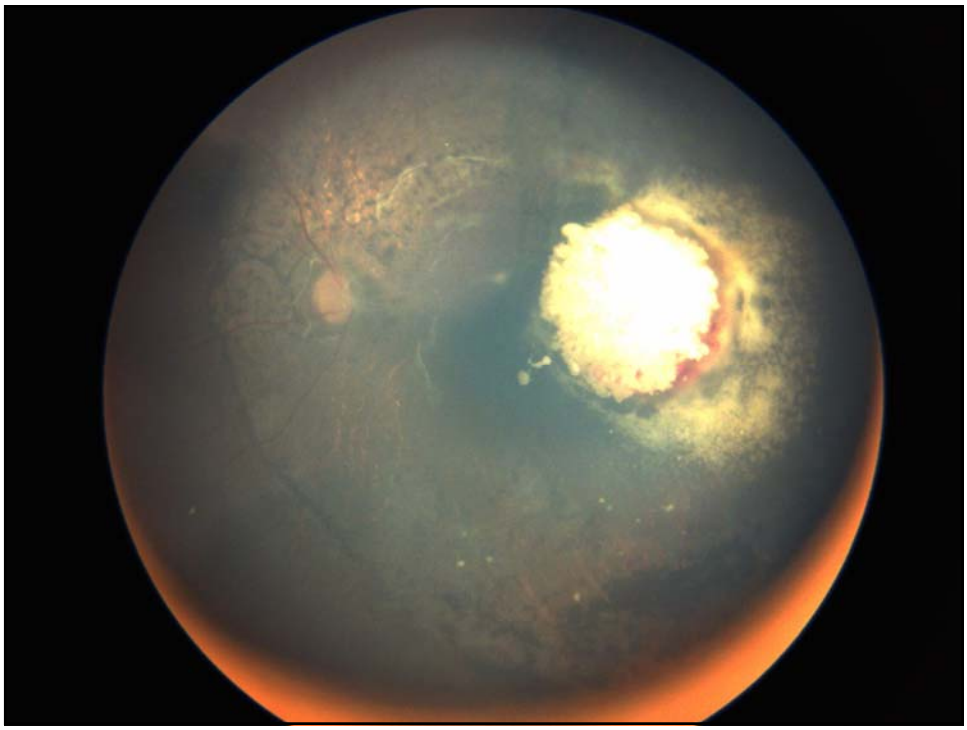
Intravitreal Melphalan: Cases 1&2

Case 1

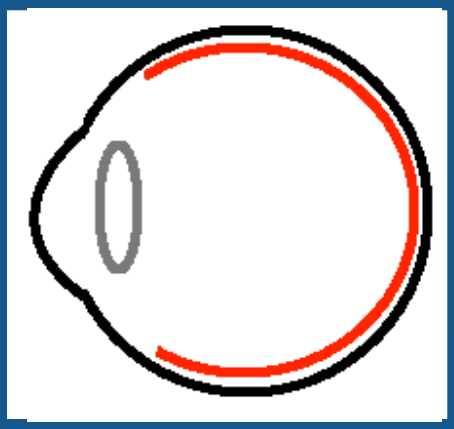


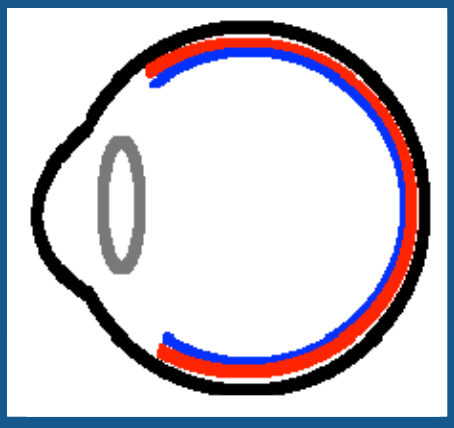
Case 2

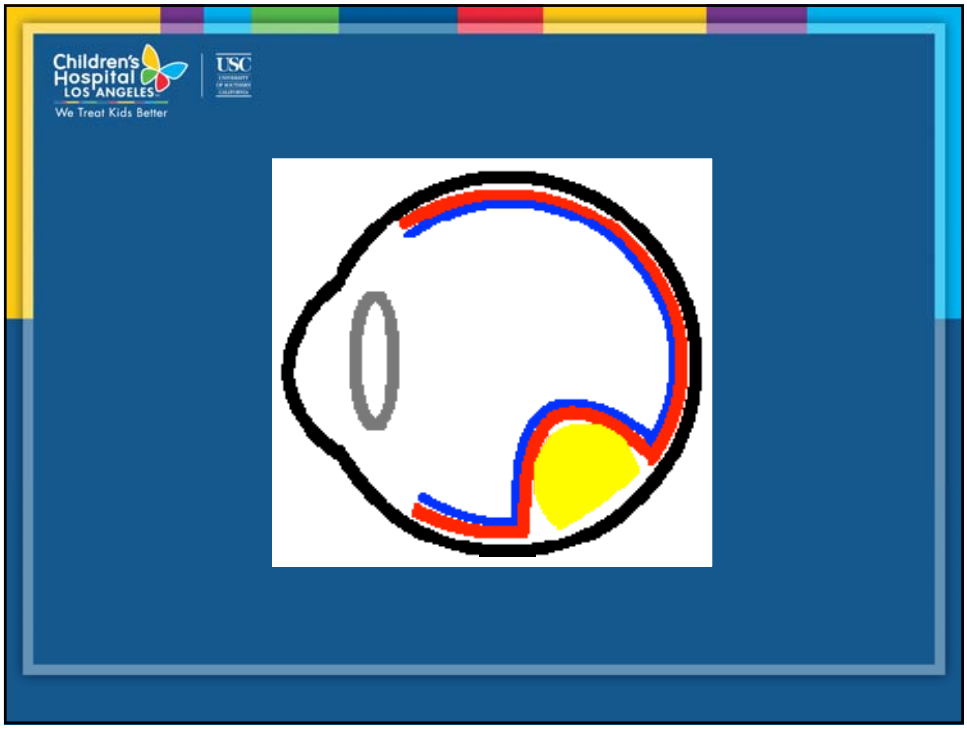




Proposed Hypothesis



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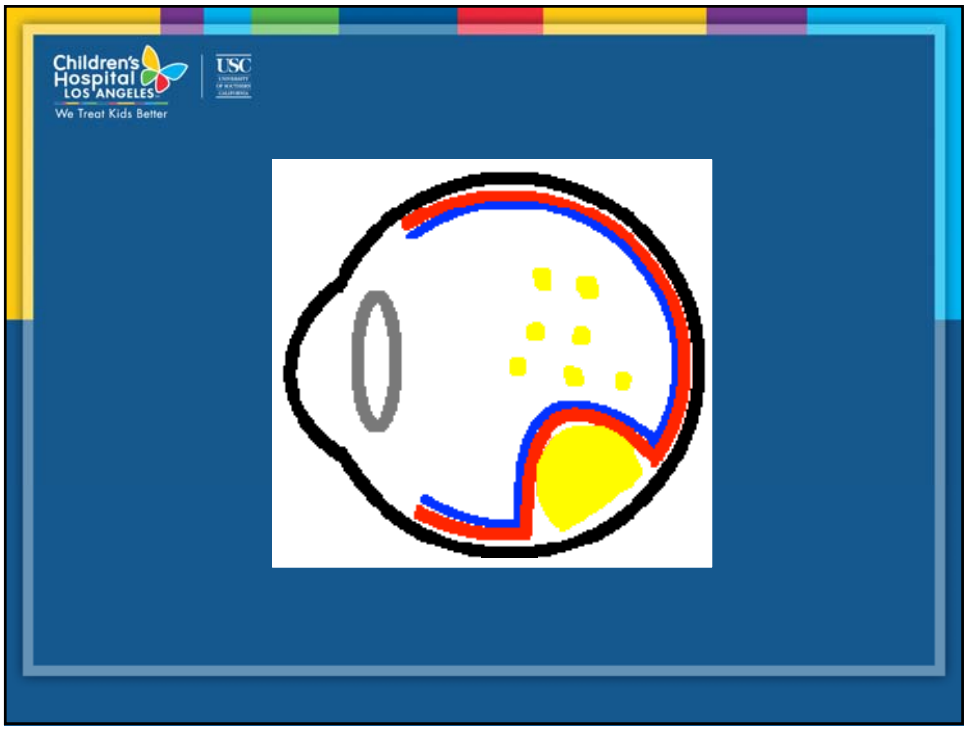
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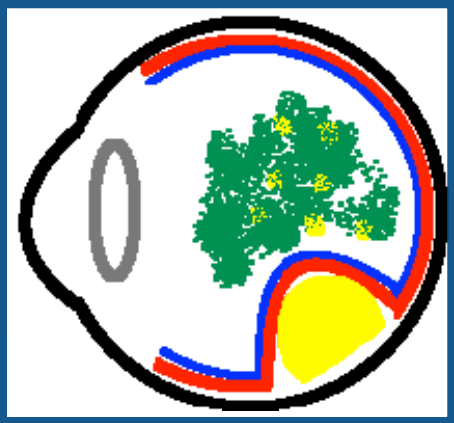
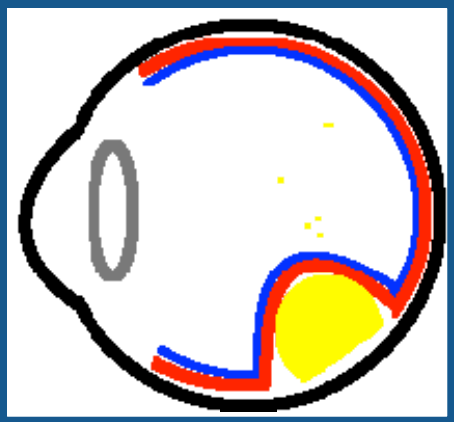
Treatment goal

Treatment goal

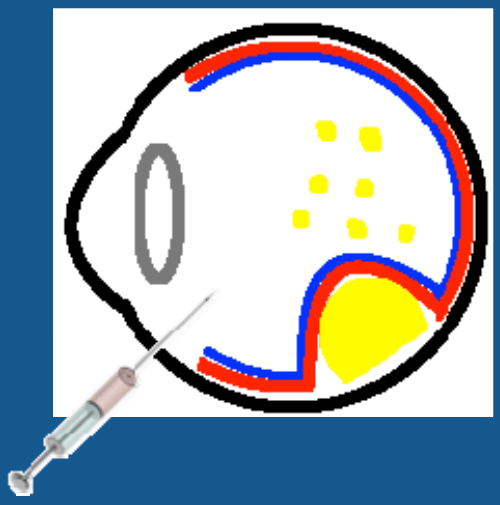
Treatment goal



Treatment goal



Proposed hypothesis



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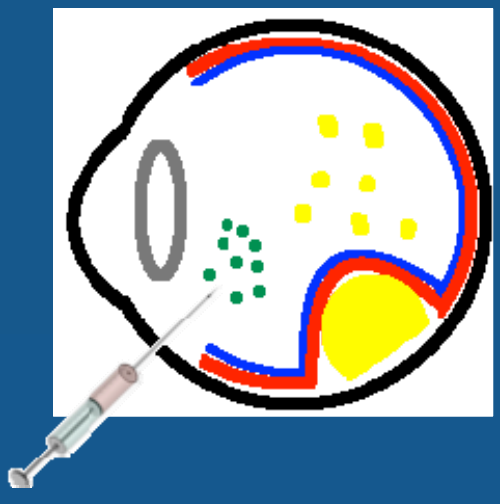

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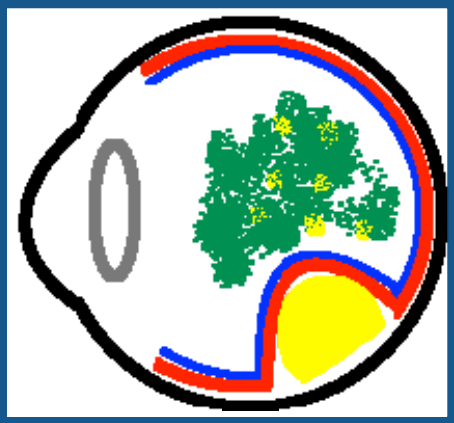

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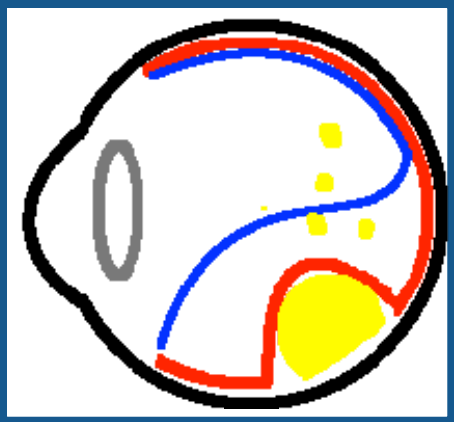

Proposed hypothesis

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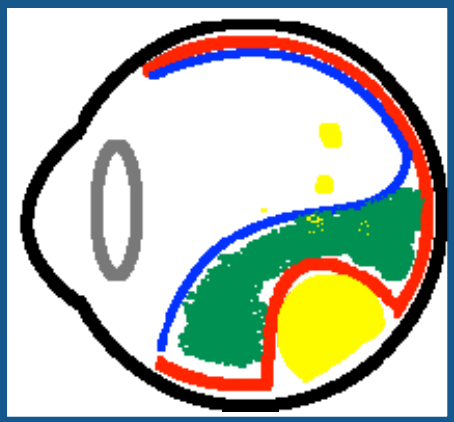


Proposed hypothesis

Proposed hypothesis

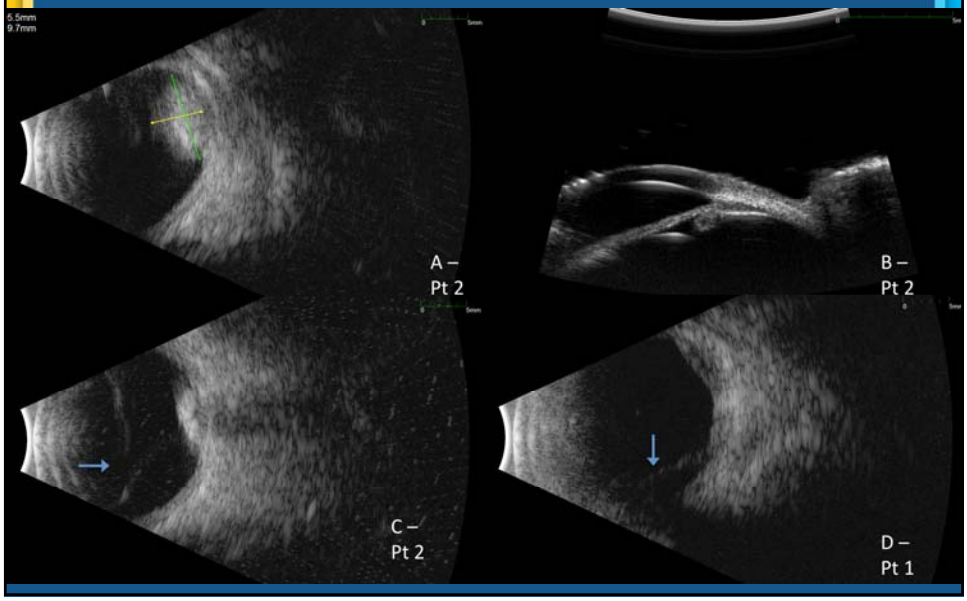
Intravitreal injections induce induce a PVD in 24% of adults

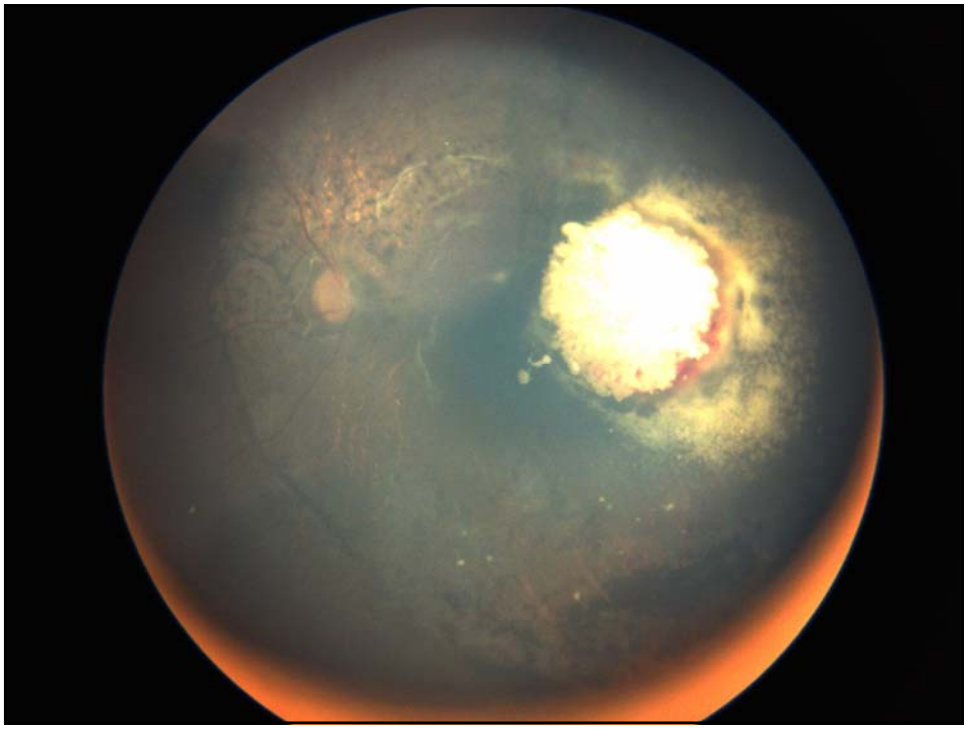
Geck et al. Eye 2012

Proposed hypothesis

In the phase III ocriplasmin study, PVD could be observed by injecting 0.1 ml of a sham-solution in 10.1 % of control patients

Stalmans et al. NEJM 2012



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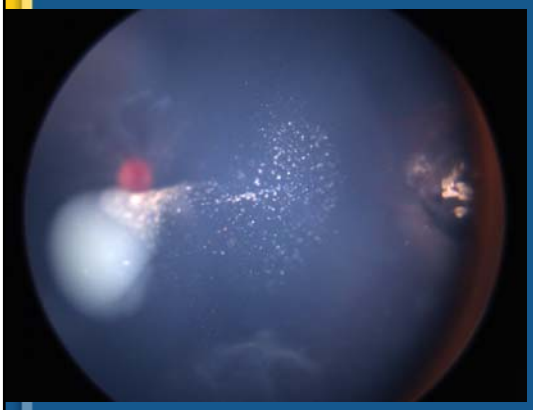
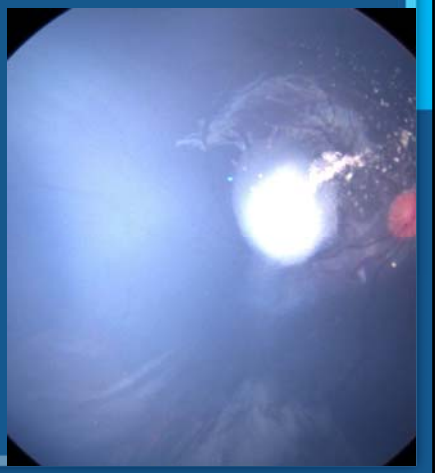
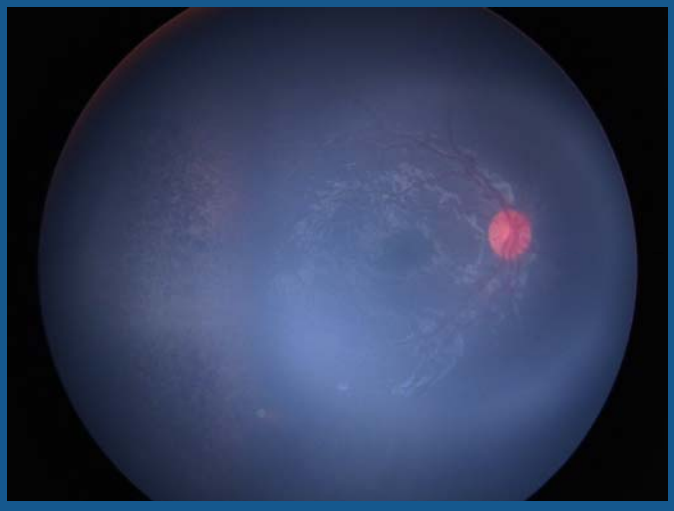
A
B

Group B eye with diffuse vitreous seeding following systemic chemotherapy



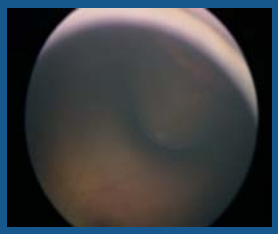
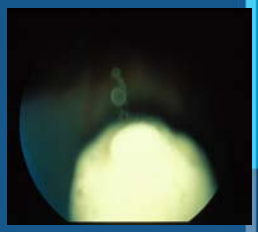


After 6 IVC injections



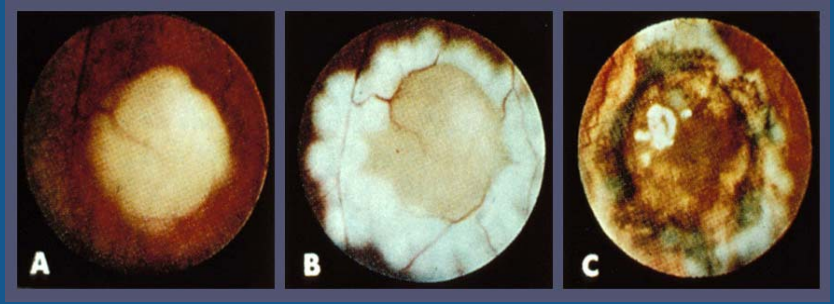
Local: Cryotherapy for RB

- Best modality for small, peripheral tumors
- Mechanism of action:
  - Cell death through formation of ice ball, apoptosis
- Technique: probe used to indent sclera


Local Therapy: Photocoagulation

- Useful for small (<3mm), posterior tumors
- Options:
  - Argon (photocoagulation)
  - Diode 810 nm (TTT)



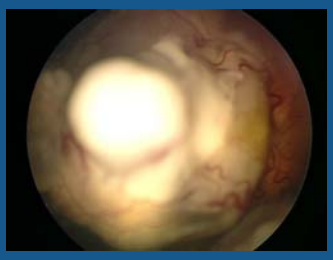
Brachytherapy: Focal tumors too large for laser or cryotherapy

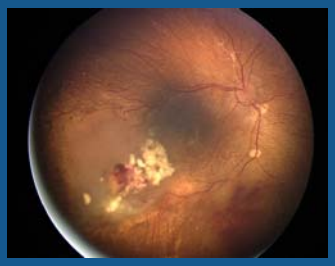
Treatment options for RB

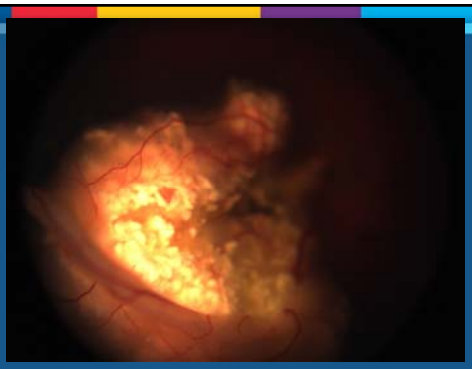
- Enucleation
  - Unilateral, advanced tumors with poor visual potential
- Systemic chemotherapy
  - Small-medium sized tumors, bilateral cases
- External beam radiation
  - Systemic chemo failures, older than 12 months
- Laser/cryotherapy
  - Small, focal tumors
- Radioactive plaque
  - Large focal tumor
- Intra-arterial chemotherapy infusion
  - Large tumors with seeding (EBR contraindicated)

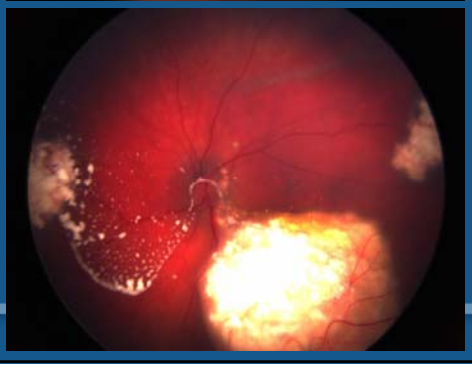
Retinoblastoma Summary

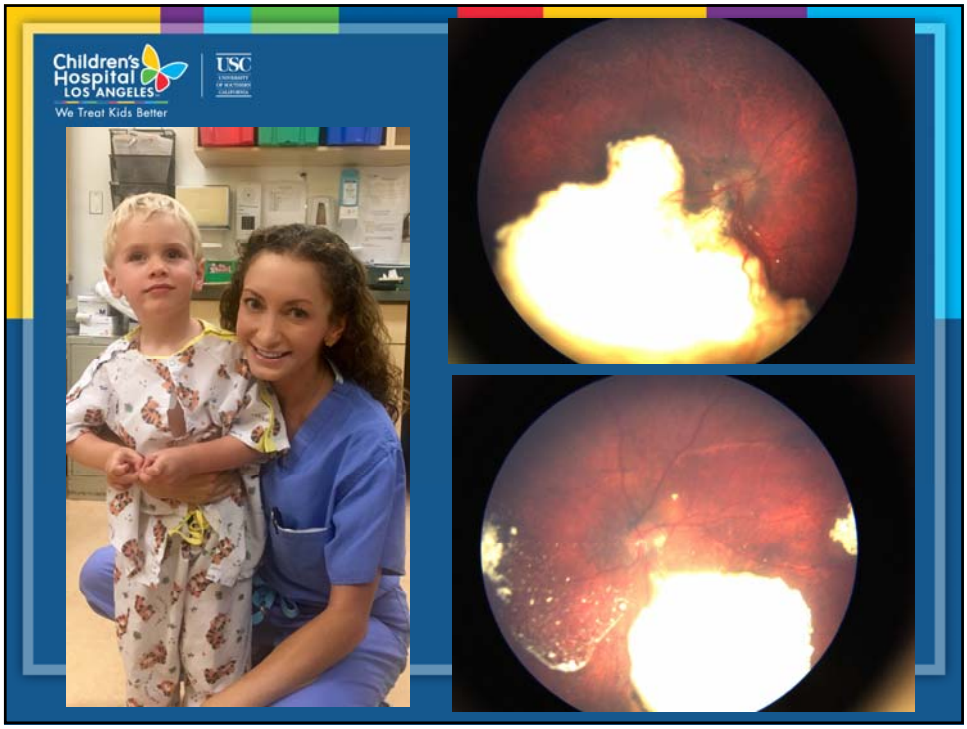
- Rare tumor
- Improving prognosis for eye salvage
- Various treatment modalities depending on the Age of patient and laterality of disease
- As well as size/location/extent of seeding of the tumor
- Local therapies are becoming common







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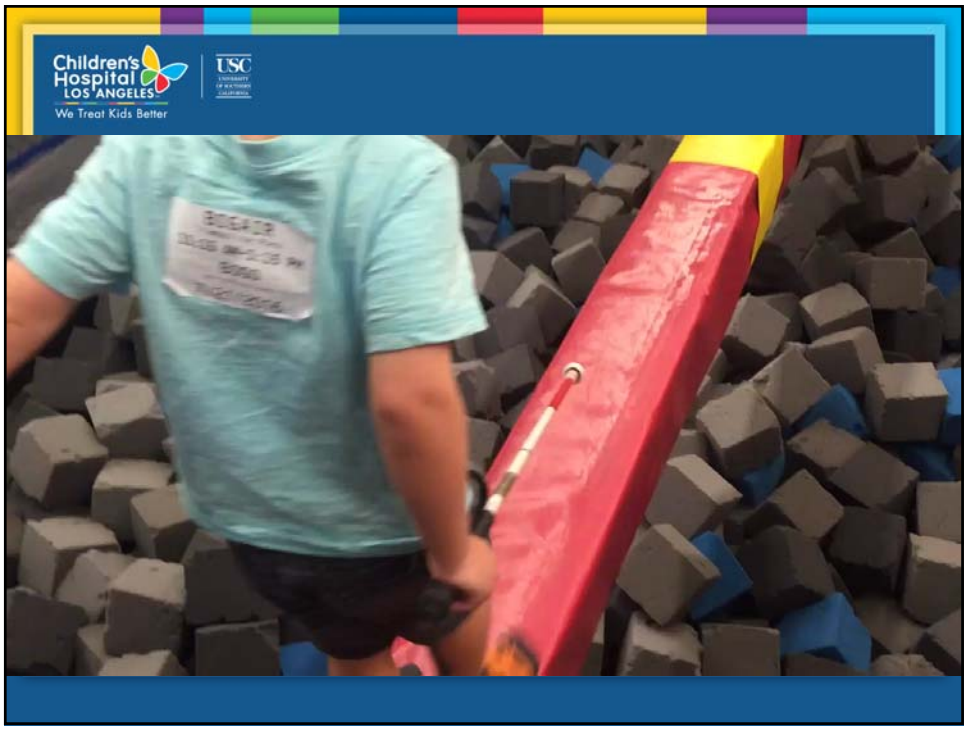
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Thank you!