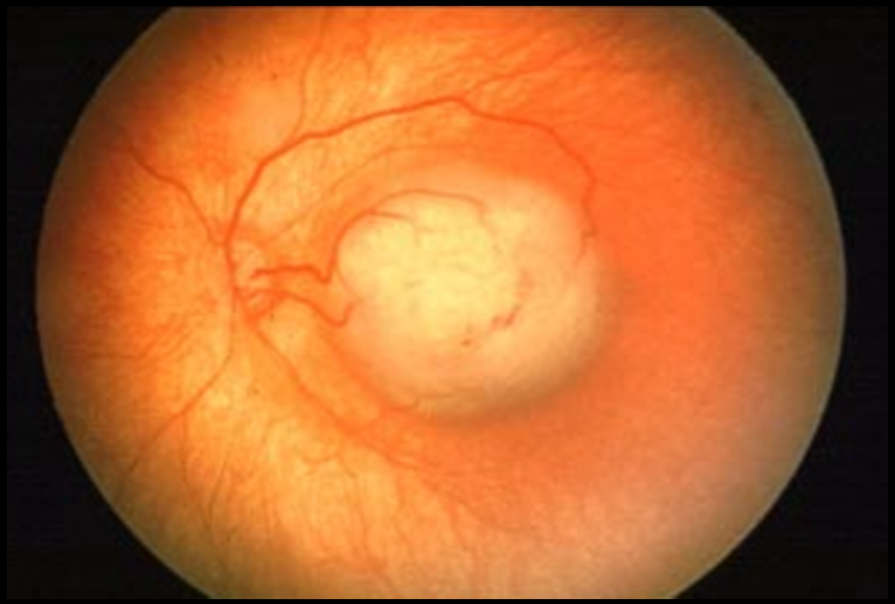
# Retinoblastoma

## Current Concepts of Management



Dr. P Vijay Anand Reddy

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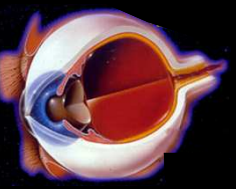
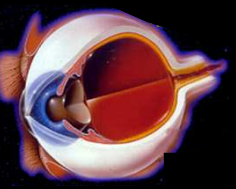


# Introduction

- **Global:** **2-4% of childhood malignancies (Europe, N America, Australia)**
- India: 5 - 7% of childhood malignancies
- **Global incidence :** **8-11 cases per million children <5 yrs**
- **India :** **19.6 per million 0-4 yrs age grp Annual incidence**
- **Global incidence:** **1 in 15,000 live births**


- **Bishop JO,Madson *EC.Surv Ophthalmol* 1975;19:342-366.**
- **Singh AD,Damato, Jacob Pe'er, A. Linn Murphree, Julian D. Perry. *Clinical ophthalmic oncology p414***



# Disease Burden: Global

- **2 - 4%** of childhood malignancies
  (Europe, N America, Australia)
- Global incidence :
  - **8-11 cases per million** children <5 yrs

*Ref: Indian Journal of cancer,Oct-Dec2010:Vol47,Is4:473-4*

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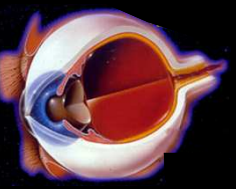
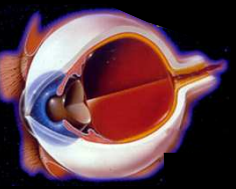


# Introduction

- India accounts for about 25% of RB in the World
- Incidence :1200-1500 cases per yr
- 6% have orbital retinoblastoma at initial presentation
- Advanced tumor at initial presentation continues to be a barrier for eye salvage



# Indian Picture

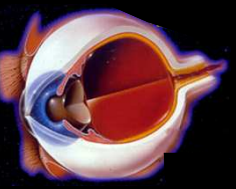
- 80-85% pts treated in primary or secondary health care set ups **without any protocol based management - 50% mortality**

- Visual outcome and survival :

  depends on early detection and appropriate referal to dedicated centers

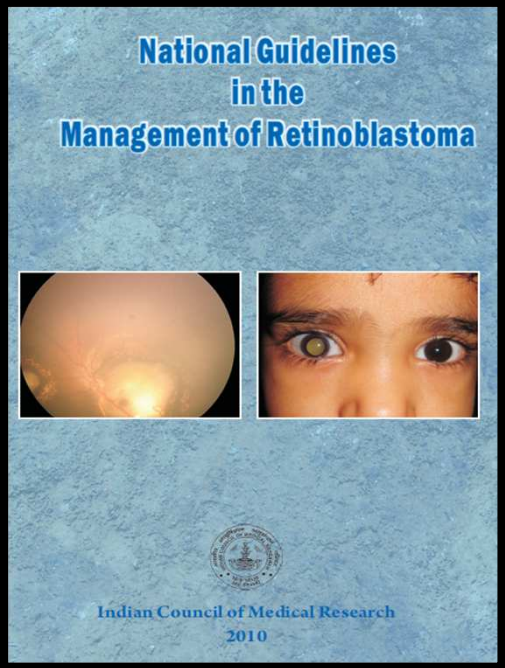
**http://www.icmr.nic.in/ncrp/cancer_regoverview.htm*

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



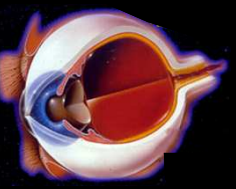
# Retinoblastoma Registry in India

- Indian Council of Medical Research
- Hospital Based Cancer Registry
- Commenced on **1st April 2009**
- 13 sites^
- Registered approx. 600 cases / year
- Approx 1100* registered so far



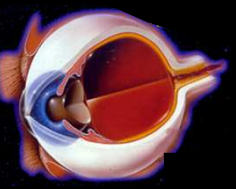

**Unpublished data, Personal communication with Dr Vasantha Thavaraj Deputy Director General (SG),Chair Child Health,Division Of RHN-ICMR*

^ Majenta -FINAL RB PROFORMA 2nd year.doc



# Epidemiology

- No racial predilection
- No sex predilection
- No eye predilection
- Mostly unilateral
- Bilateral in 25 to 35 % of cases



# Genetics

- Hereditary nature identified late 1962,
- Stallard noted deletion of D group chromosome, chromosome 13
- Locus of deletion 14 band on the long arm ( q) of 13$^{th}$ chromosome
- Intact gene protects against retinoblastoma
- Recessive tumour suppressor gene and for RB to occur both genes should be damaged

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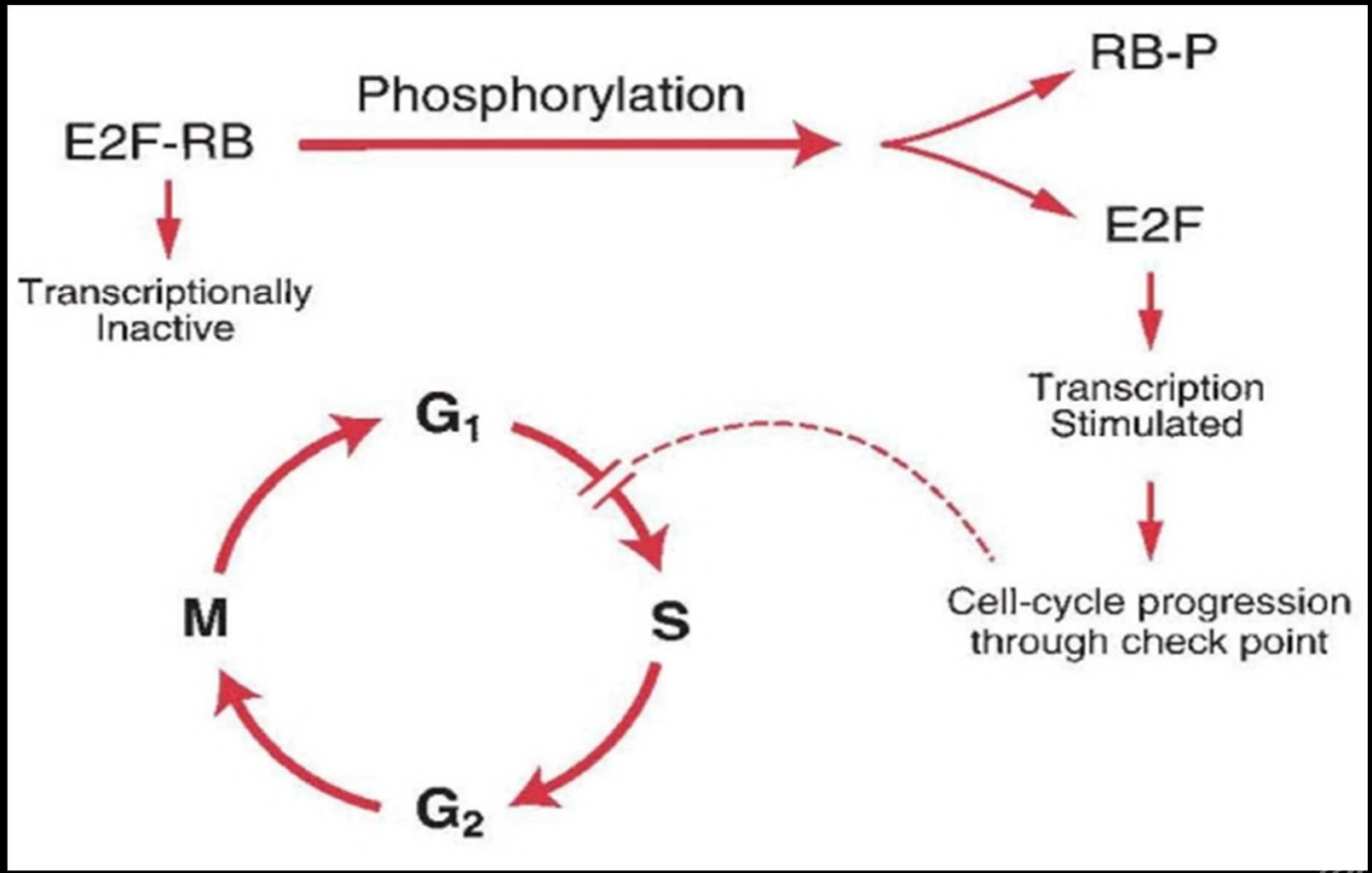
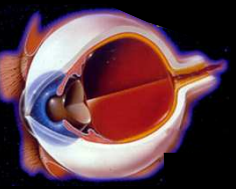
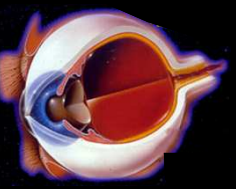
# Rb gene


RB-P
Phosphorylation
E2F-RB
E2F
Transcriptionally
Inactive
Transcription
Stimulated
G1
M
S
Cell-cycle progression
through check point
G2



# Genetics…

- Of all newly diagnosed cases
  - 6% familial
  - 94% sporadic
- Unilateral
  - 15 % are hereditary, 85 % non hereditary



# Genetics…

**1971, Knudson, 2 hit hypothesis**

**Hereditary retinoblastomas :**

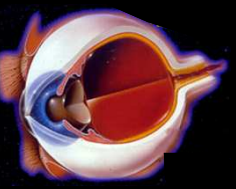
**1st hit germinal mutation, affects all cells,**

**2nd hit somatic retinal cells.**

- **Hence predisposition to second non-ocular tumours like osteosarcoma**

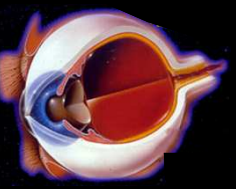
**Unilateral sporadic :**

- **both hits somatic mutations, no risk of second non-ocular tumours**

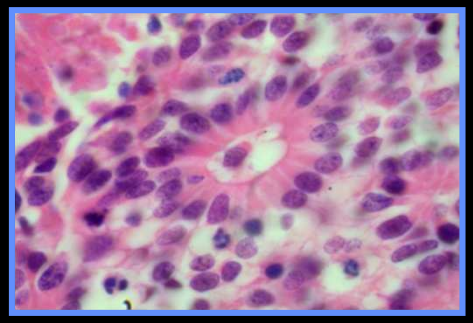


# Pathogenesis

- Derived from glial cells, called Glioma by Virchow in 1864
- Flexner 1891 and Wintersteiner 1897, believed it to be a neuroepithelioma due to rossettes
- Later, retinoblasts
- RETINOBLASTOMA term accepted in 1926 by American Ophthalmological society



# Pathology…



Microscopy…

Poorly differentiated tumours :

- small round cells with large hyperchromatic nuclei and scanty cytoplasm with mitotic figures

Well differentiated tumours : rosettes and fleurettes

1. Flexner-Wintersteiner : cells arranged around central lumen
2. Homer Wright : cells arranged around central neuromuscular tangle
3. Pseudorosette : cells arranged around blood vessels
4. Fleurettes : pear shaped eosinophilic structures

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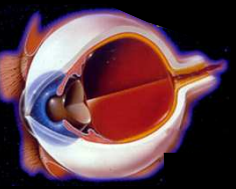
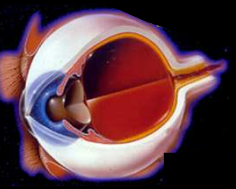


# RB Classifications

- Reese Ellsworth
- St Jude’s
- Grabowosky
- Essen
- Chantada et al
- NEW International Staging System



# 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

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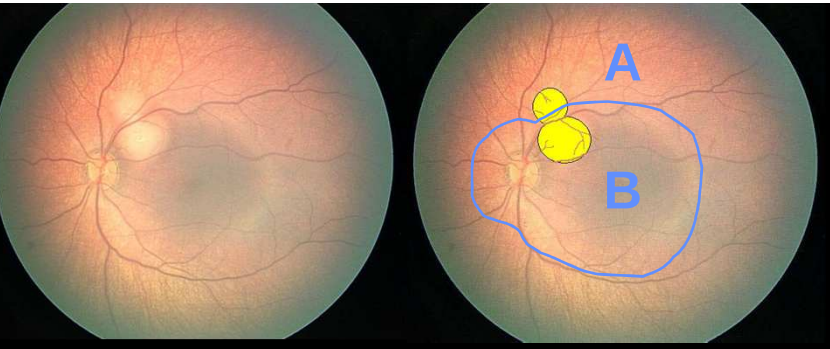
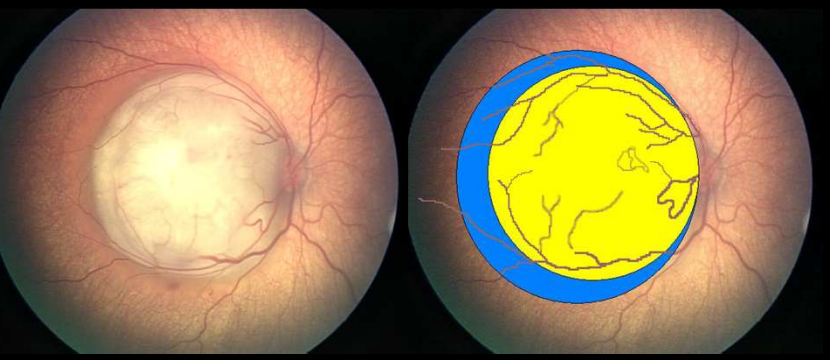
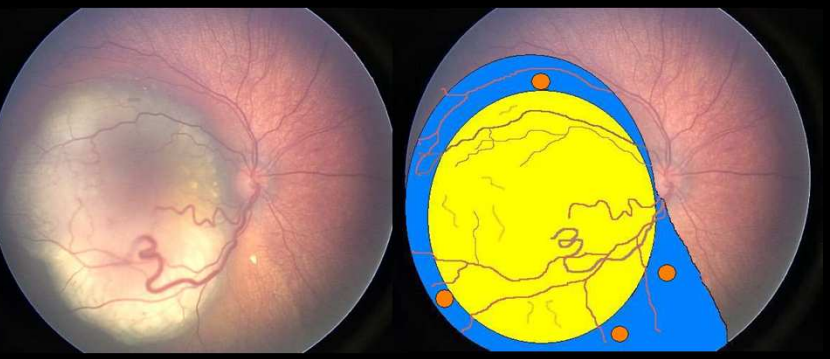



Group A
< 3 mm

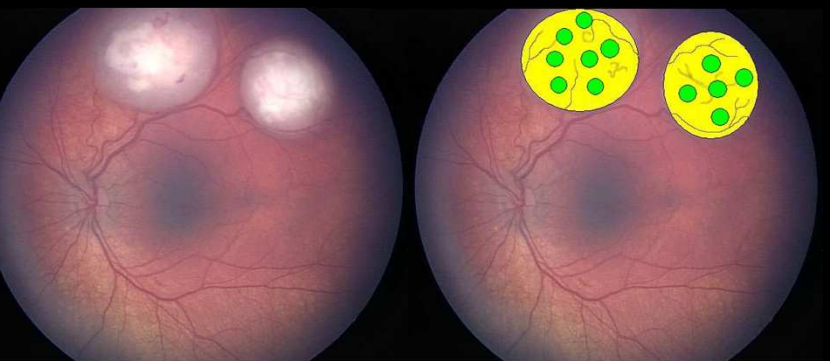
Group B
macula
> 3 mm



Group B
tumor + SRF

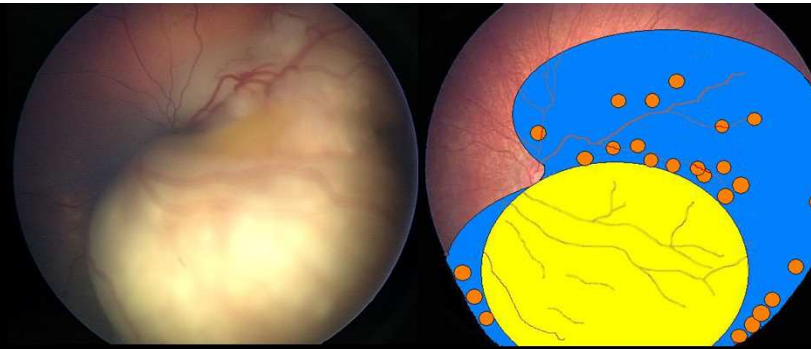


Group C
focal SR
seeds

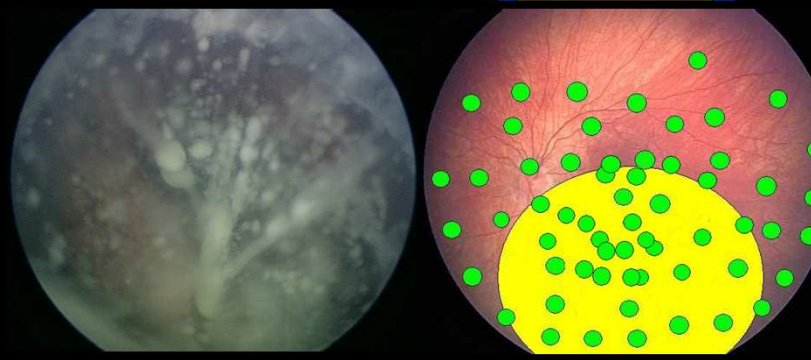


Group C
focal
vitreous
seeds

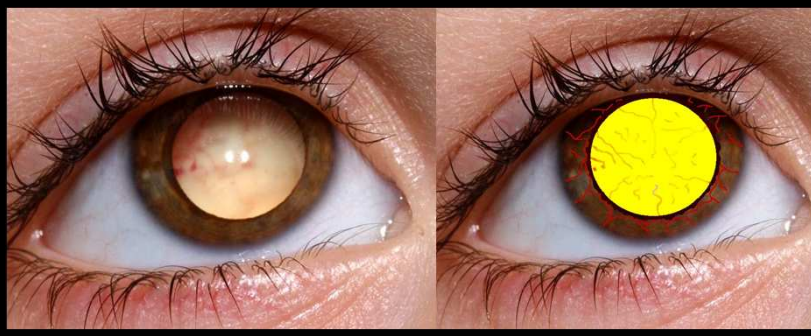
Group D
diffuse
SR seeds



Group D
diffuse
vitreous
seeds



Group E
high risk
• NVG
• blood
• invasion



# International Grouping of Intraocular Retinoblastoma

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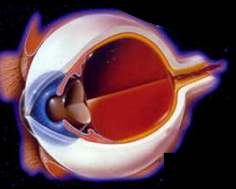

# NEW International Staging System

- **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.*

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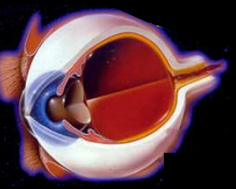

# Retinoblastoma in Hyderabad

## January 1988-December 2010

1543 eyes of 1067 patients

591 Unilateral

476 bilateral

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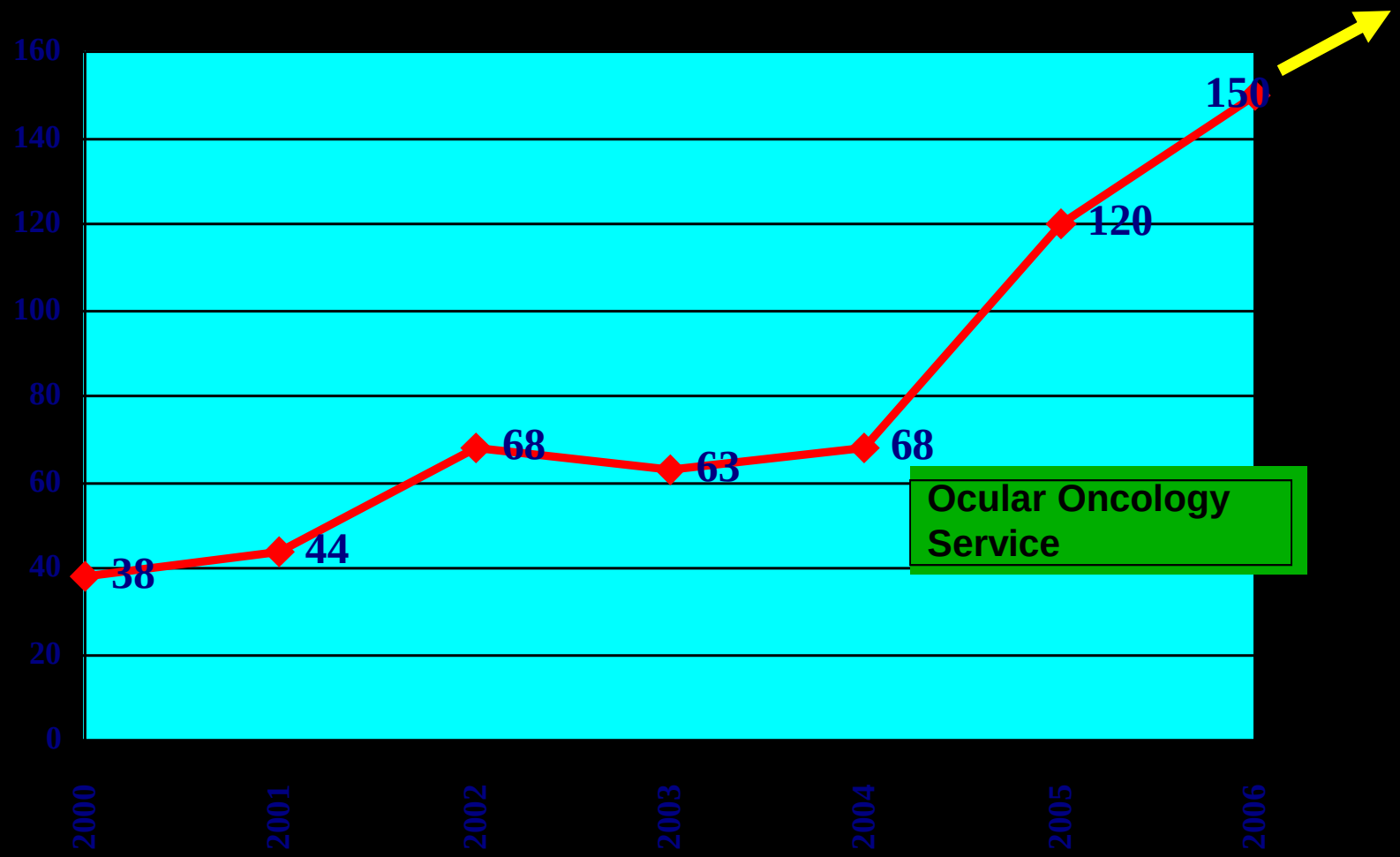
# RB Referrals 2000 - 2006




Increasing Referrals

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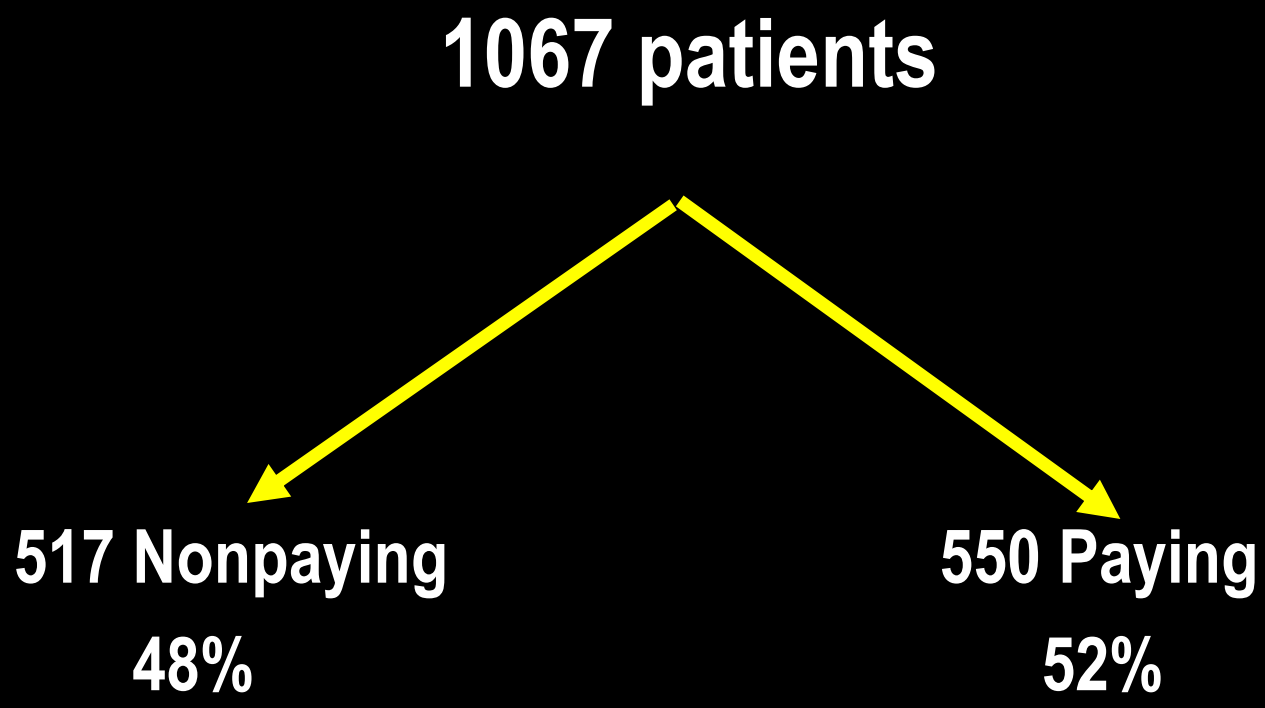
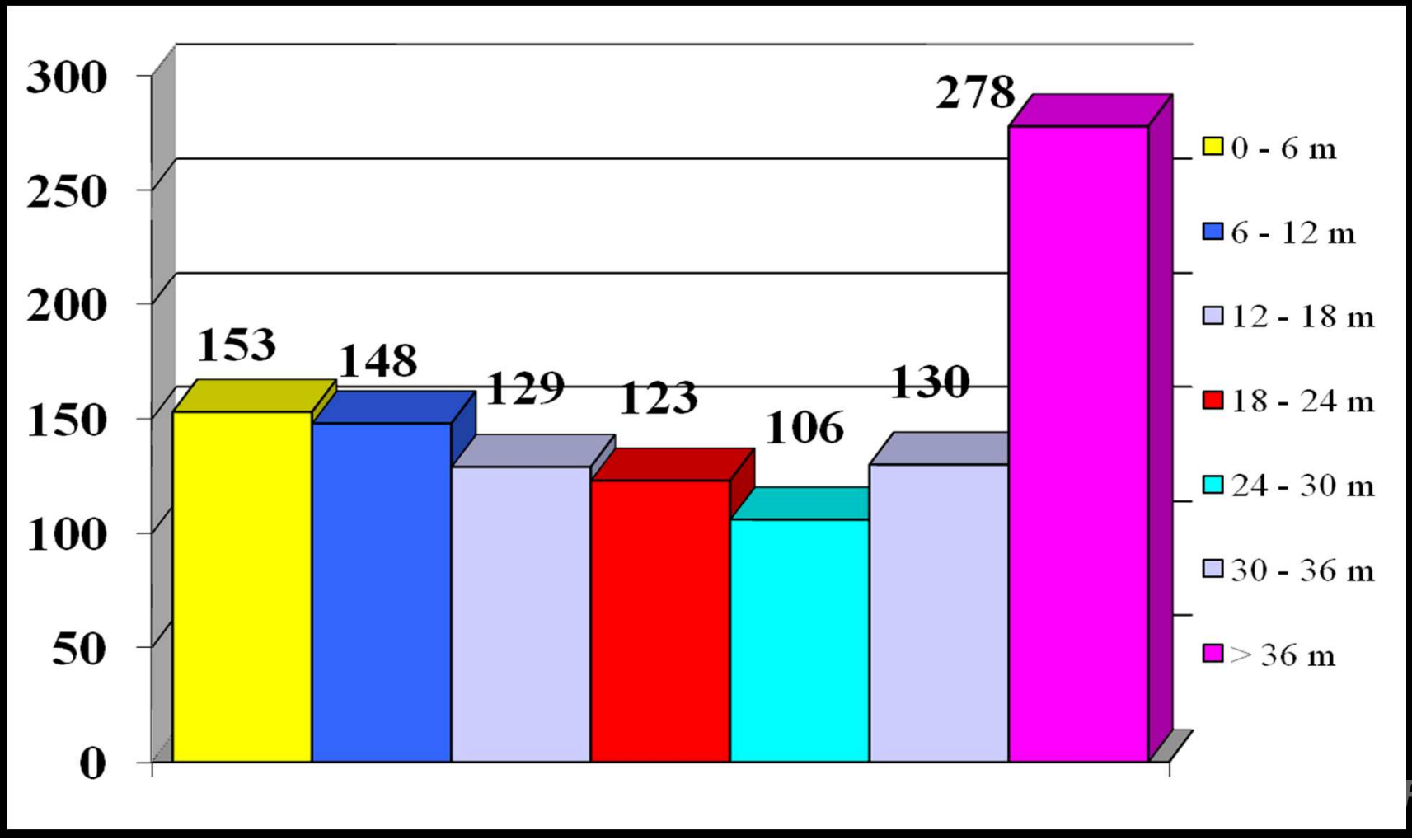
# Socioeconomic Status



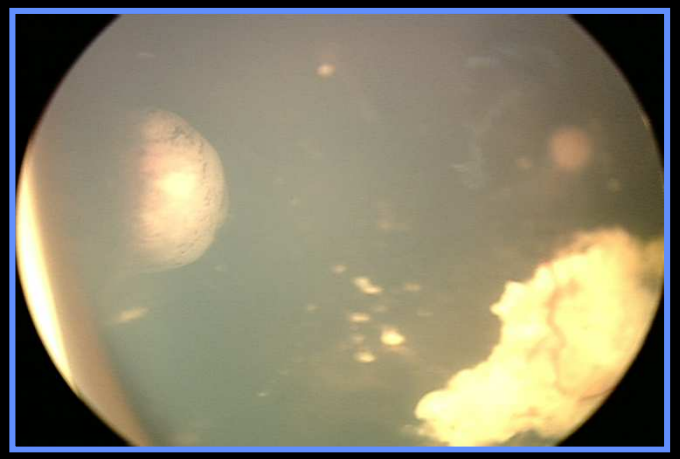
# Age at Diagnosis

N = 1067 patients



# Age at diagnosis

- Average 18 months
- Unilateral 23 months
- Bilateral 12 months

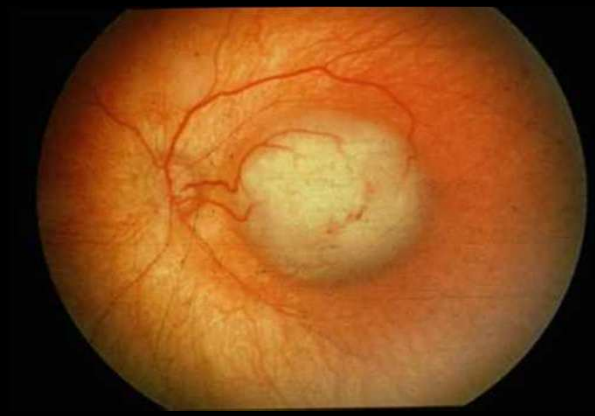
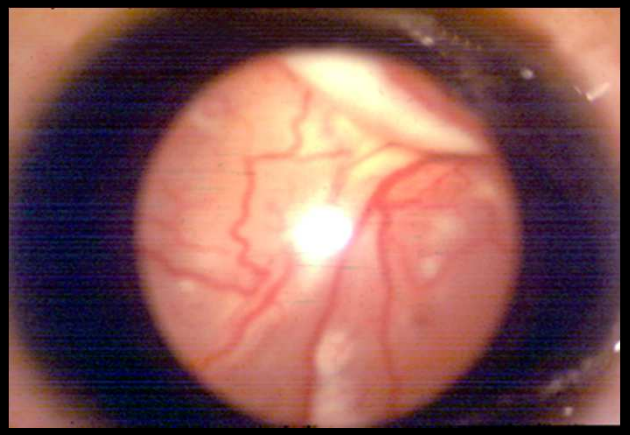
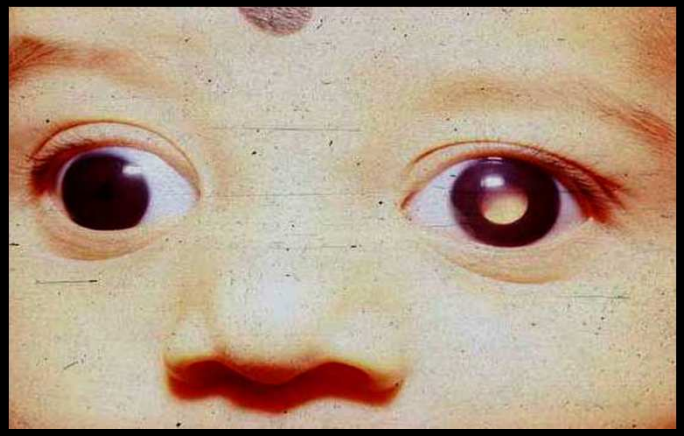


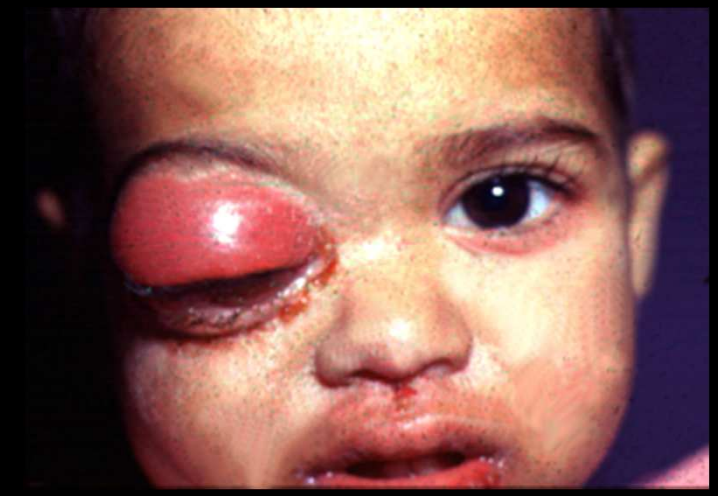
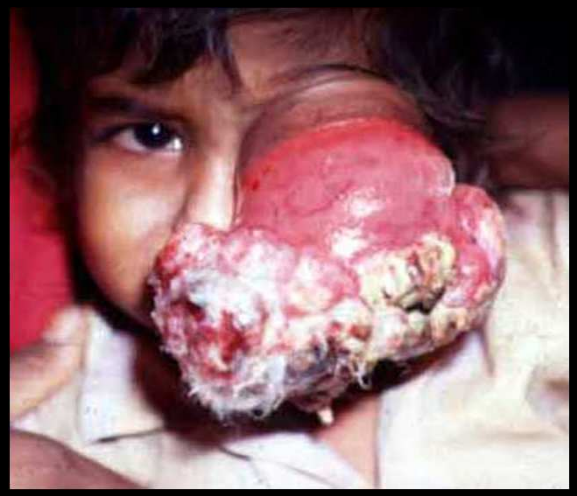
***Shields et al. Intraocular tumours, 1992.***

VAR

# Clinical Spectrum

*……Intraocular RB*

*Extra ocular RB……*

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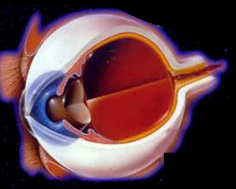
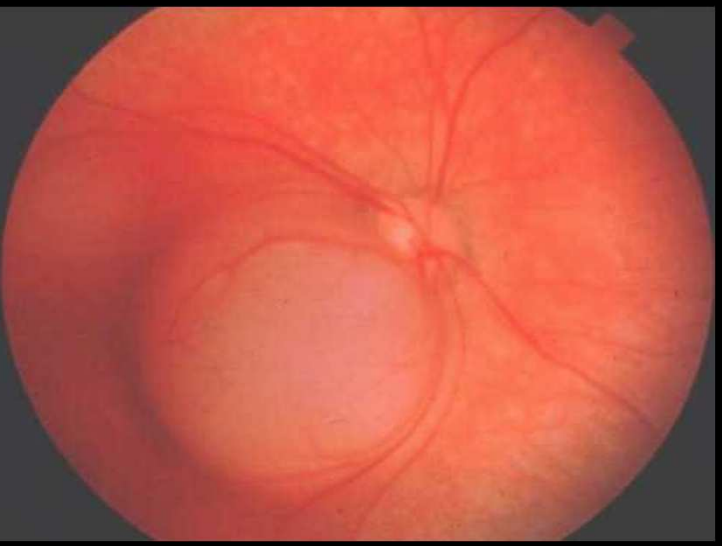


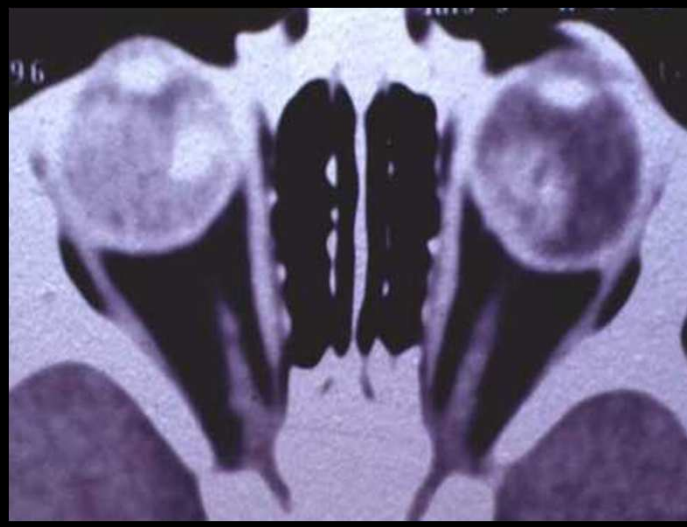
# Retinoblastoma

## Diagnosis



**Indirect Ophthalmoscopy**

**Ultrasonography**



**MRI / CT**

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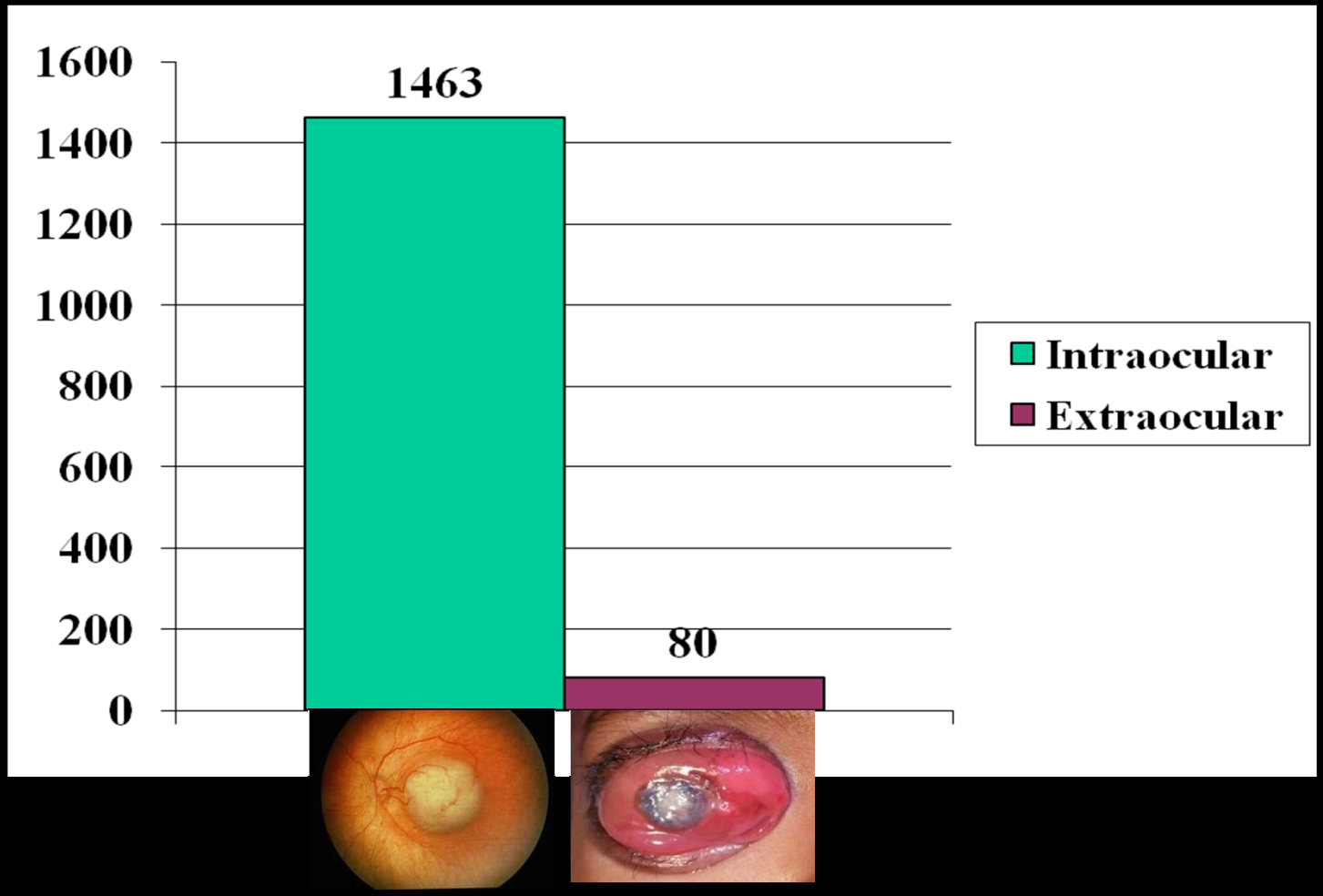
# Tumor Location

N=1543 eyes

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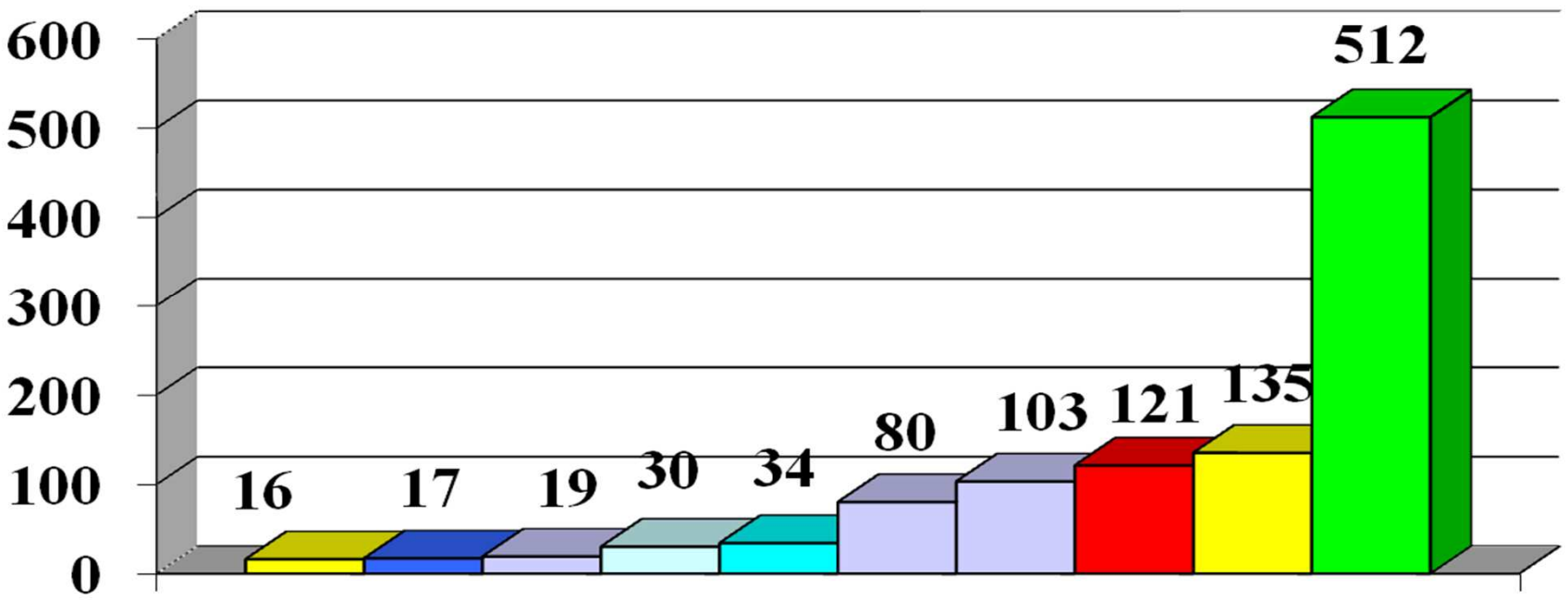
# Initial Clinical Presentation

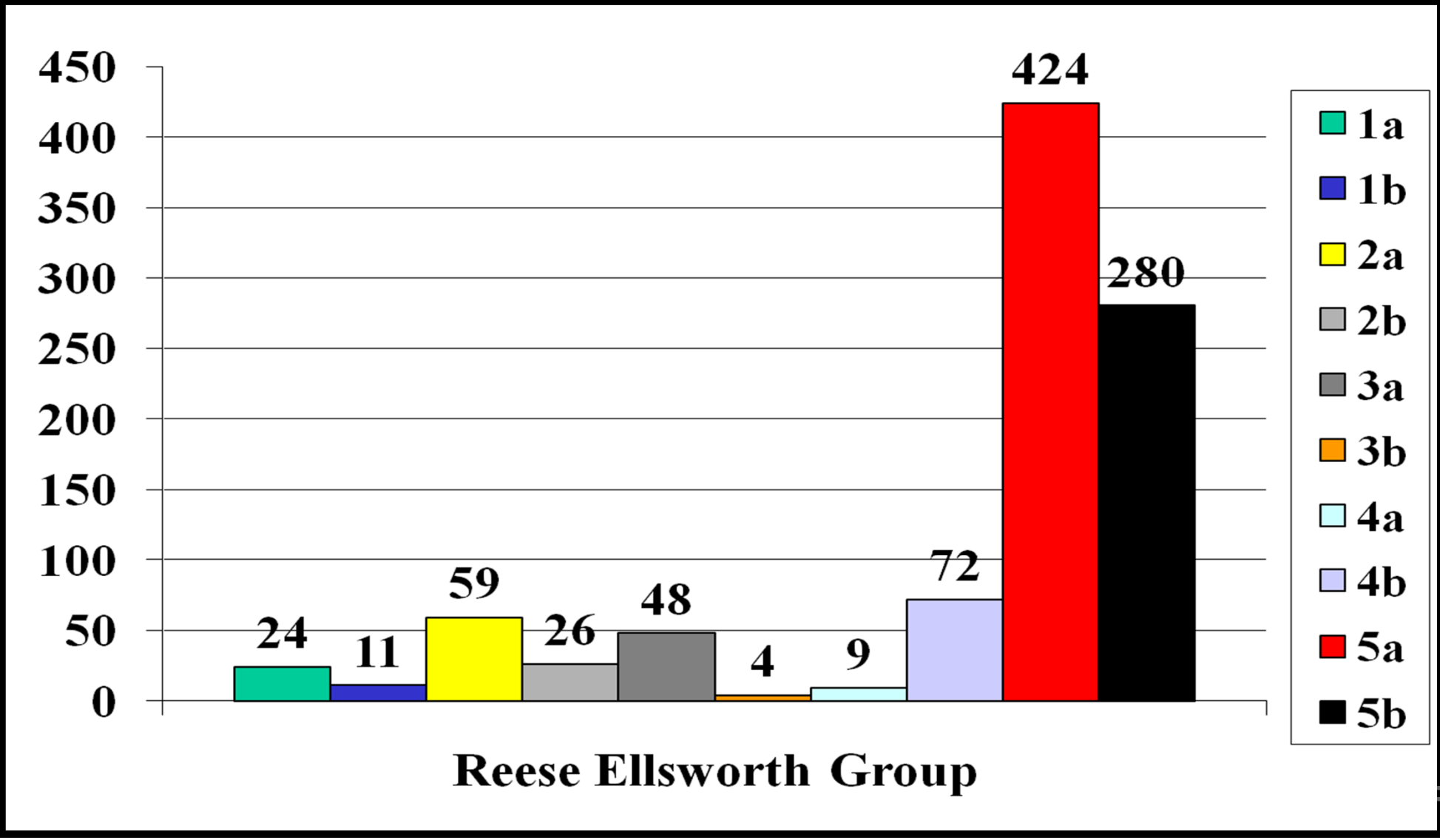
N = 1543 eyes




- Pain
- Pthisis Bulbi
- Enlarged Eyeball
- Eyelid Edema
- Redness
- Proptosis
- Squint
- Asymptomatic
- Visual Loss
- White Reflex

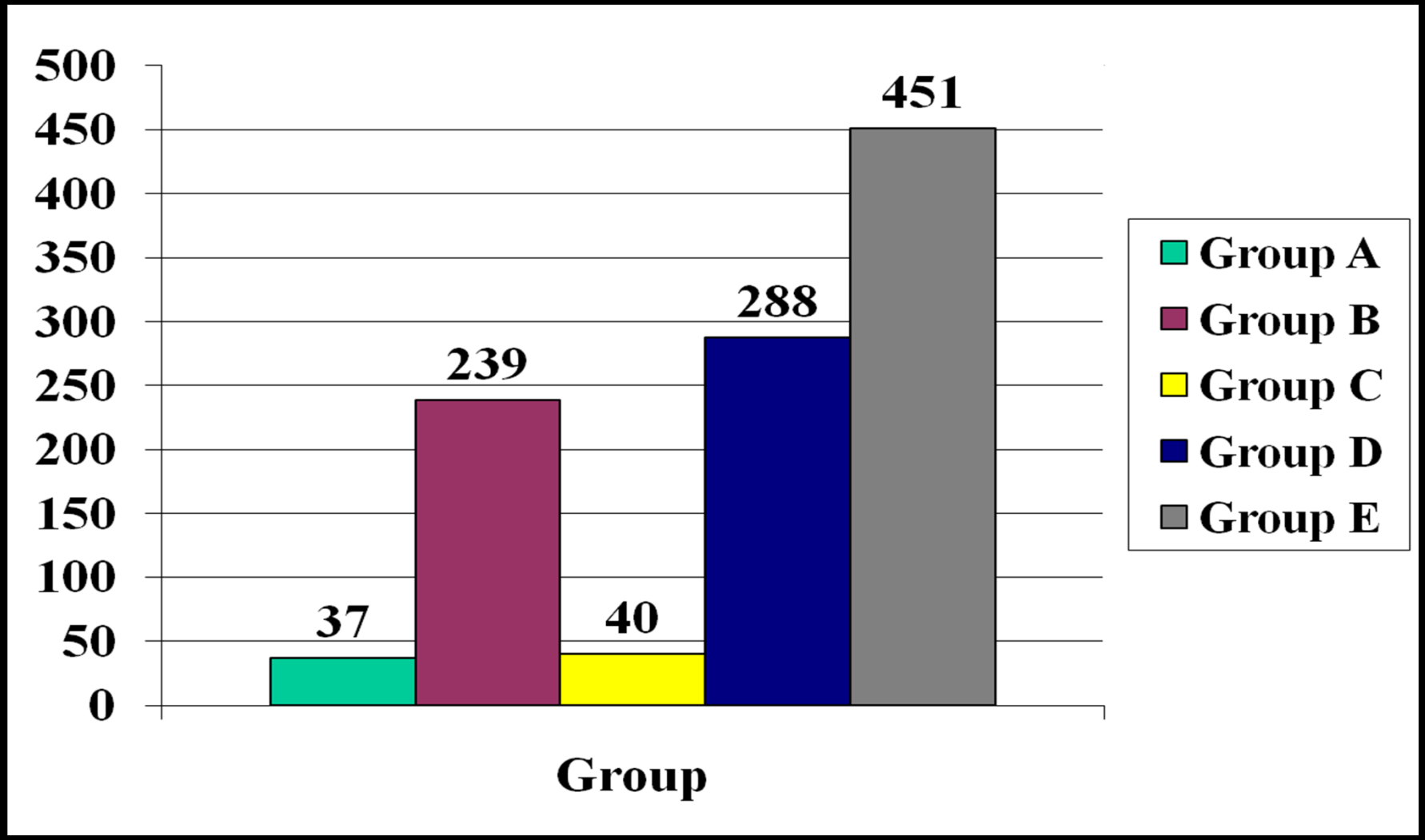
N=1543 eyes

# Reese Ellsworth Group



# Intraocular Retinoblastoma International Classification

N=1543 eyes

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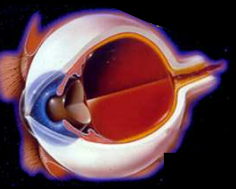
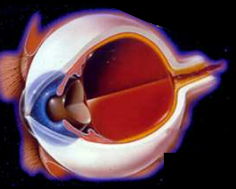


# Decade back…..

## Eye Salvage Rates…

| RE Group | Ellsworth 1977 | Hungerford 1995 |
|---|---|---|
| I | 91% | 100% |
| II | 83% | 84% |
| III | 82% | 82% |
| IV | 62% | 43% |
| V | 29% | 36% |



# Retinoblastoma - Management

## Goals of Treatment

**Salvage Life**

**Salvage Organ**

**Salvage Function**

- **Save life**
- **Preserve the eye**
- **Provide optimal vision**

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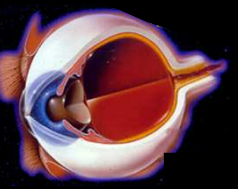


# Intraocular RB

## Treatment Options

**Early**
**Grp I, II**

Focal
Local

- Cryotherapy
- Thermotherapy
- Laser photocoagulation

**Intermediate**
**Grp III, IV**

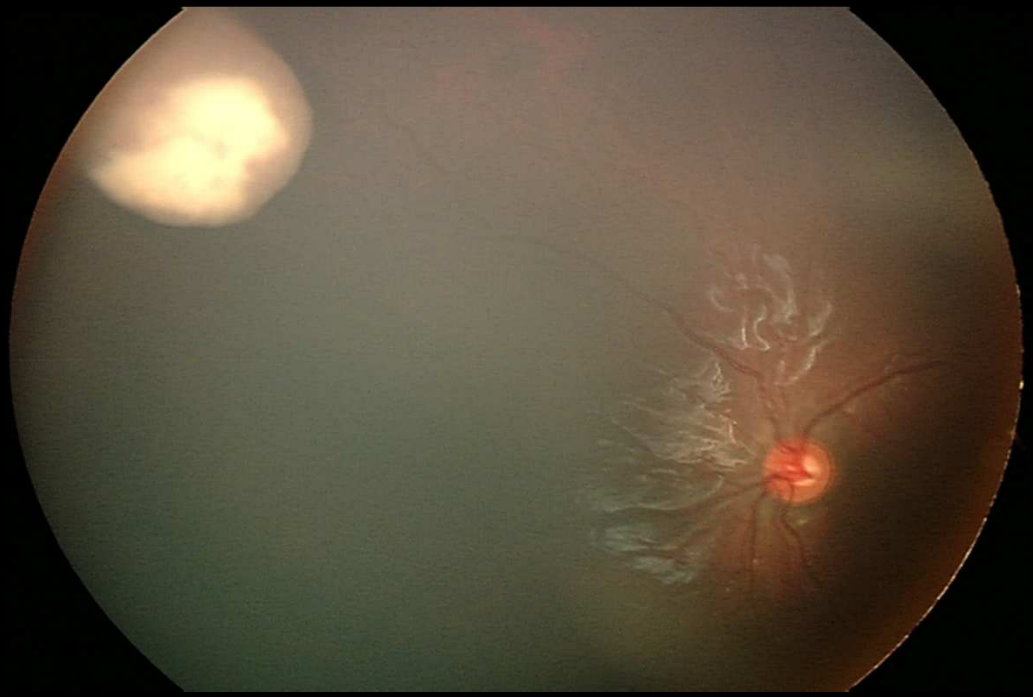
- Chemoreduction + Local Therapy
- Plaque brachytherapy
- External beam radiotherapy

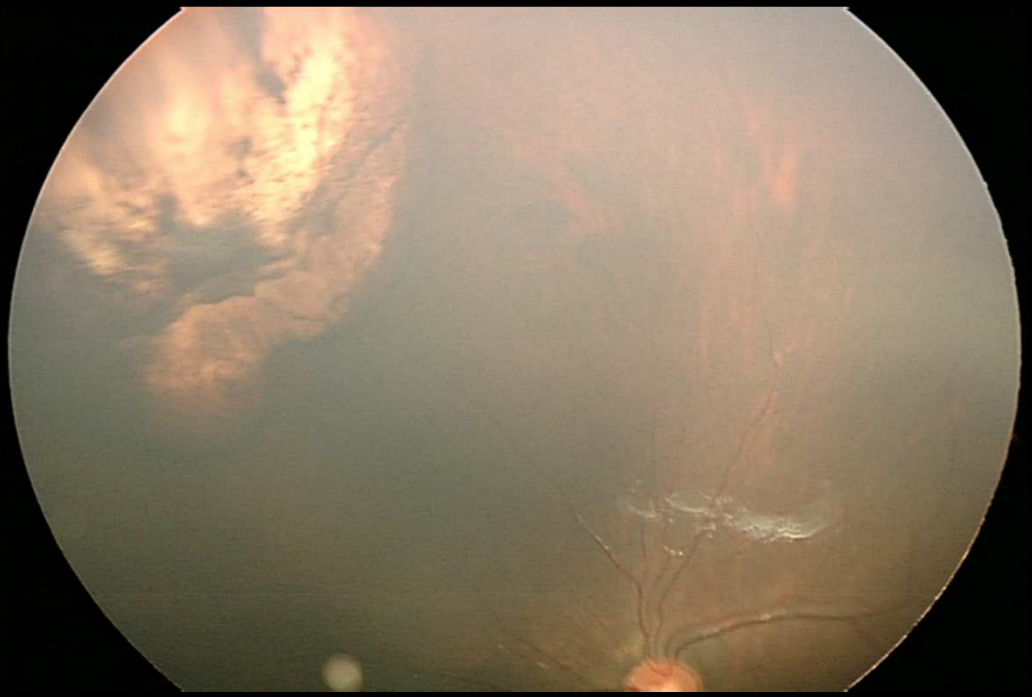
**Late**
**Grp V**

- Enucleation
- Adjuvant therapy – Chemo / EBRT
- Orbital exenteration

VAR

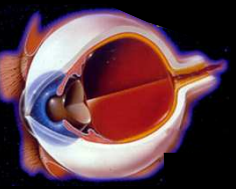
# Cryotherapy



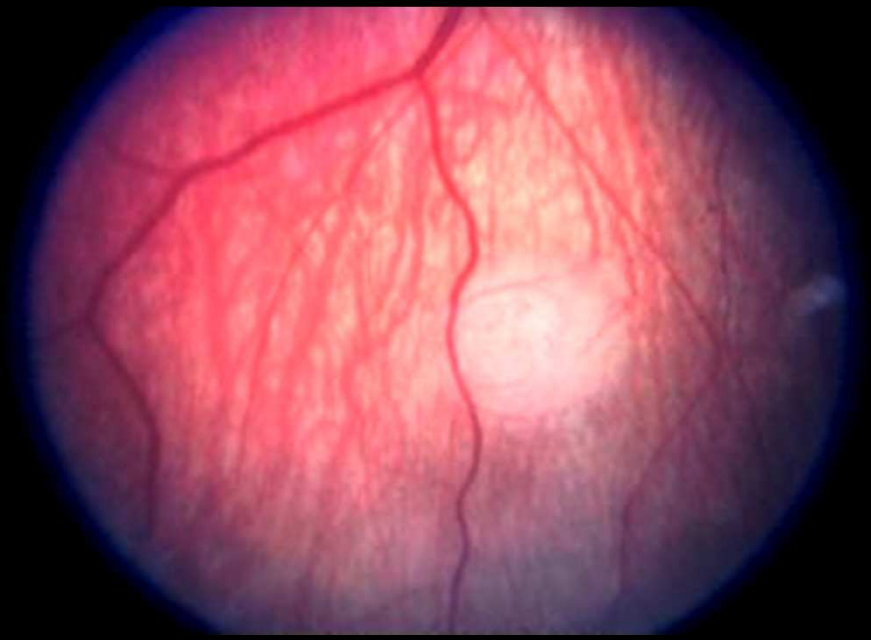


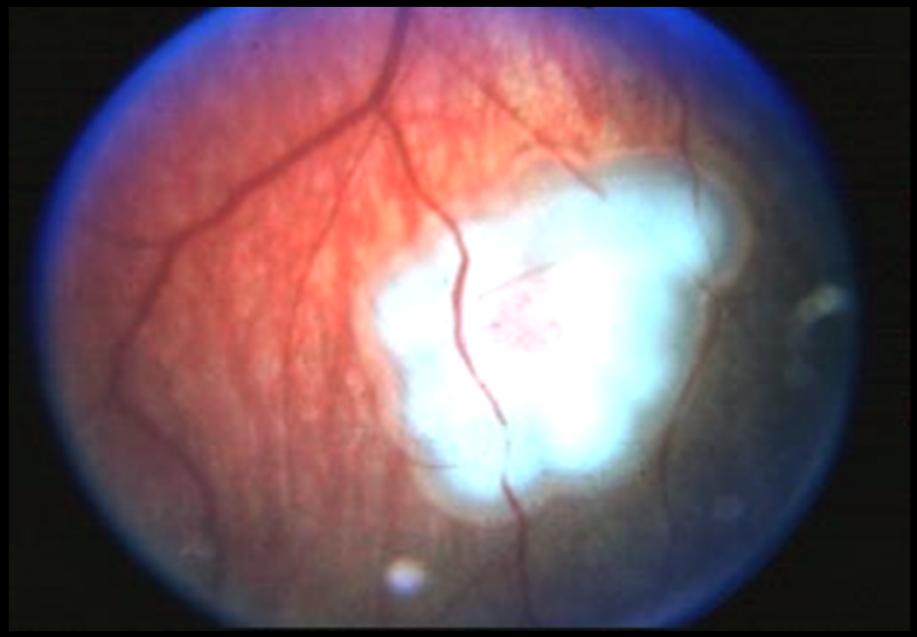
**Good local therapy. Leaves Big scars**

VAR



# Photocoagulation



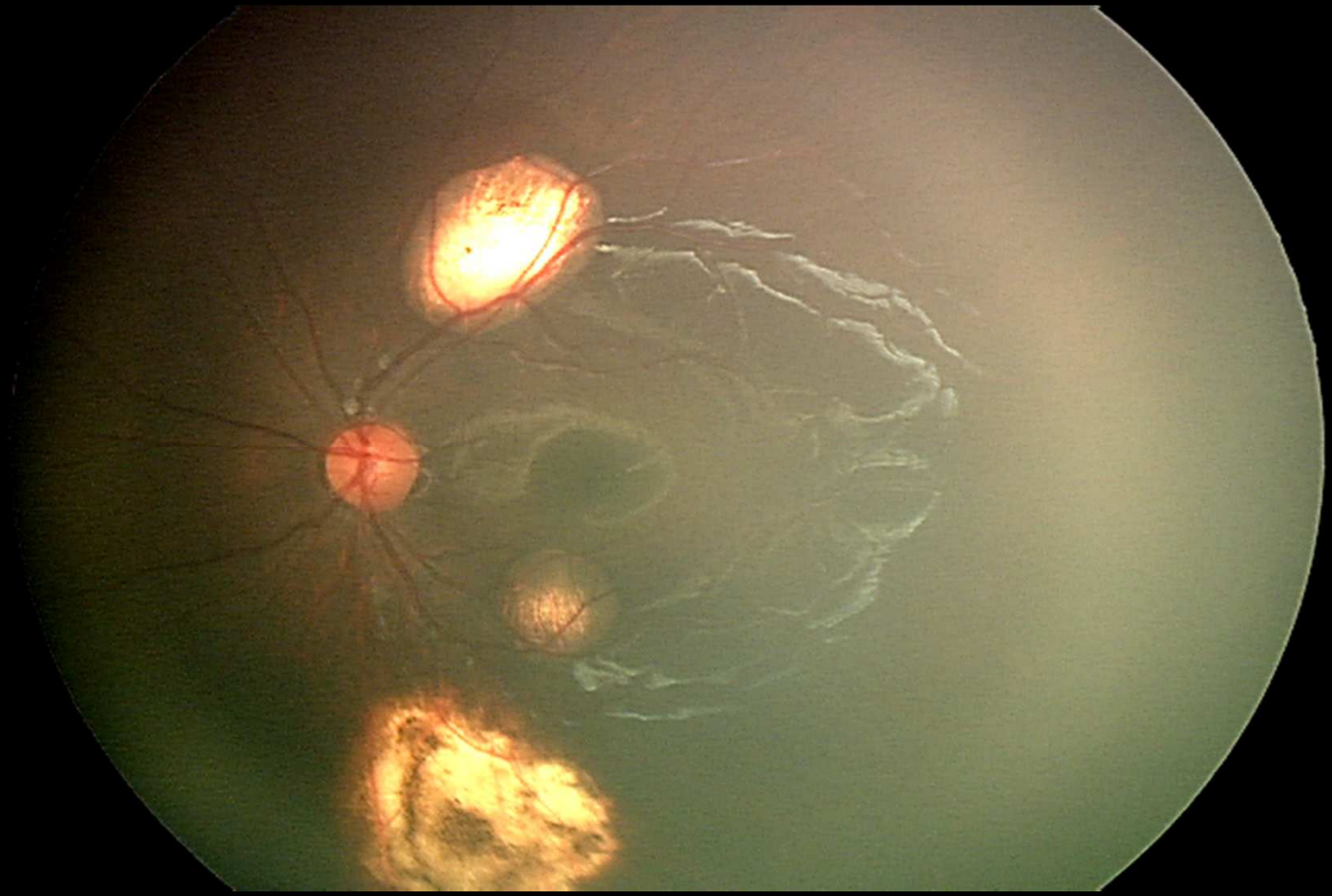


**Good local therapy.**

**Causes big scaring, loses vascularization**

VAR

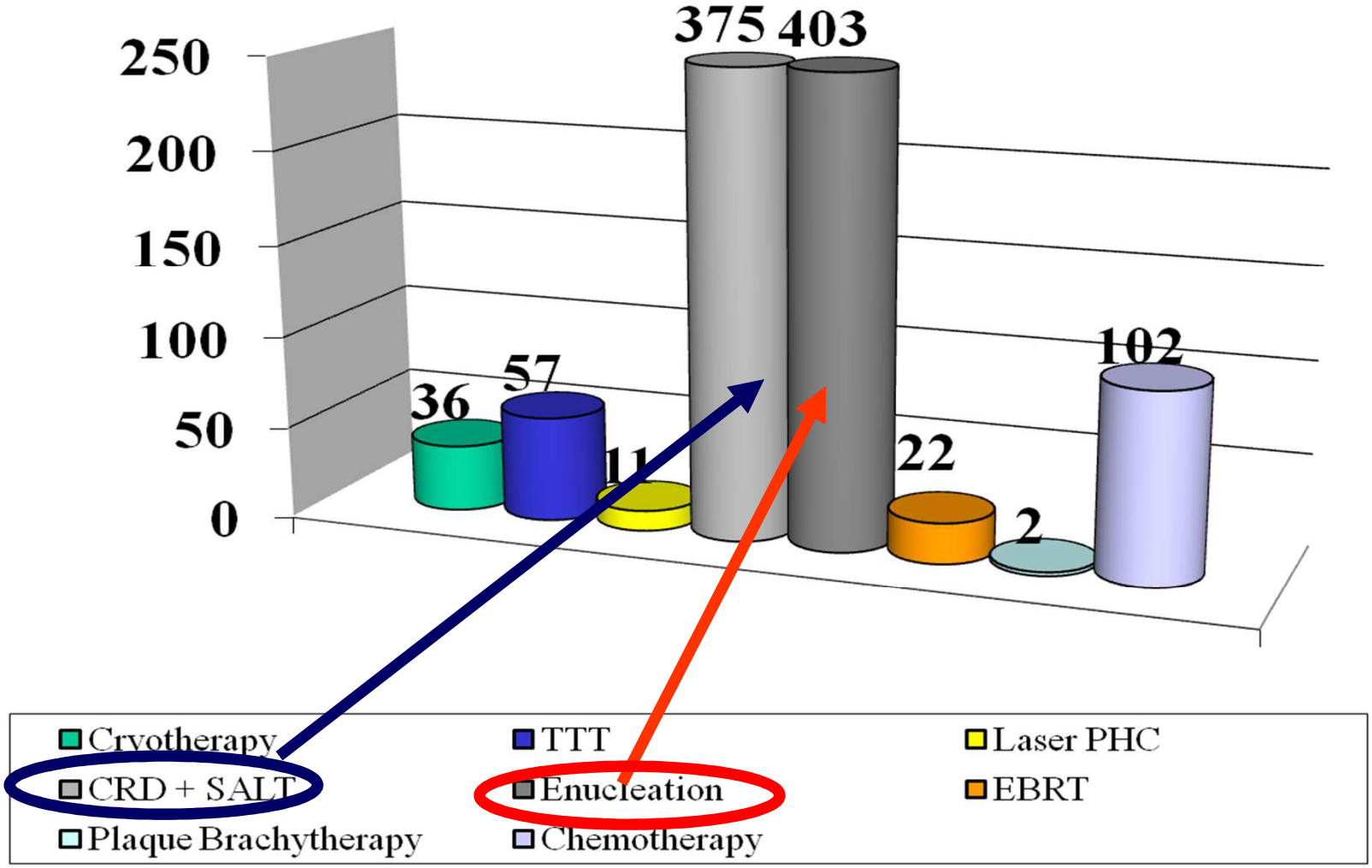
# Thermotherapy TTT

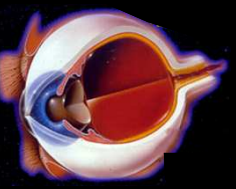


✓Good local therapy. Minimal scaring

VAR

# Primary Treatment for Intraocular Tumors



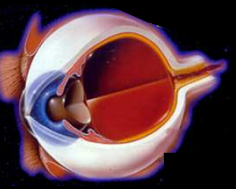


# Chemoreduction

## Group II, III, IV, V

- Reduces tumor volume
- Allows *more focused, less damaging* local measures – TTT, Cryo etc

**Makes your job easy !**

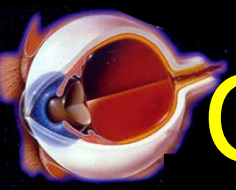


# Chemoreduction VEC Protocol

- Inj. Vincristine 1.5 mg/$m^2$ day 1 (0.05 mg/kg BW <36 months age)
- Inj. Etoposide 150 mg/$m^2$ day 1&2 (5 mg/kg BW <36 months age)
- Inj. Carboplatin 560 mg/$m^2$ day 1 (18.6 mg/kg BW <36 months age)

3 - 4 weekly, 6 cycles, EUA before each cycle

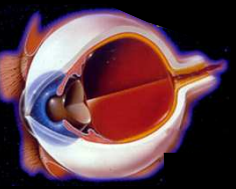
- High dose chemo protocol
  - Vcn 1.5mg/m2; Etop 250mg/m2; Carb 750mg/m2



# Chemoreduction: Shield's Protocol

- Inj. Carboplatin 560 mg/$m^2$ day 1
  - (18.6 mg/kg BW <36 months age)
- Inj. Etoposide 150 mg/$m^2$ day 1 and day 2
  - (5 mg/kg BW <36 months age)
- Inj. Vincristine 1.5 mg/$m^2$ day 1
  - (0.05 mg/kg BW <36 months age)
- High dose protocol
  - Vcn 1.5mg/m2; Etop 250mg/m2; Carb 750mg/m2
- 3 - 4 weekly, 6 cycles
- EUA before each cycle
  - Chemocryotherapy and SALT

VAR

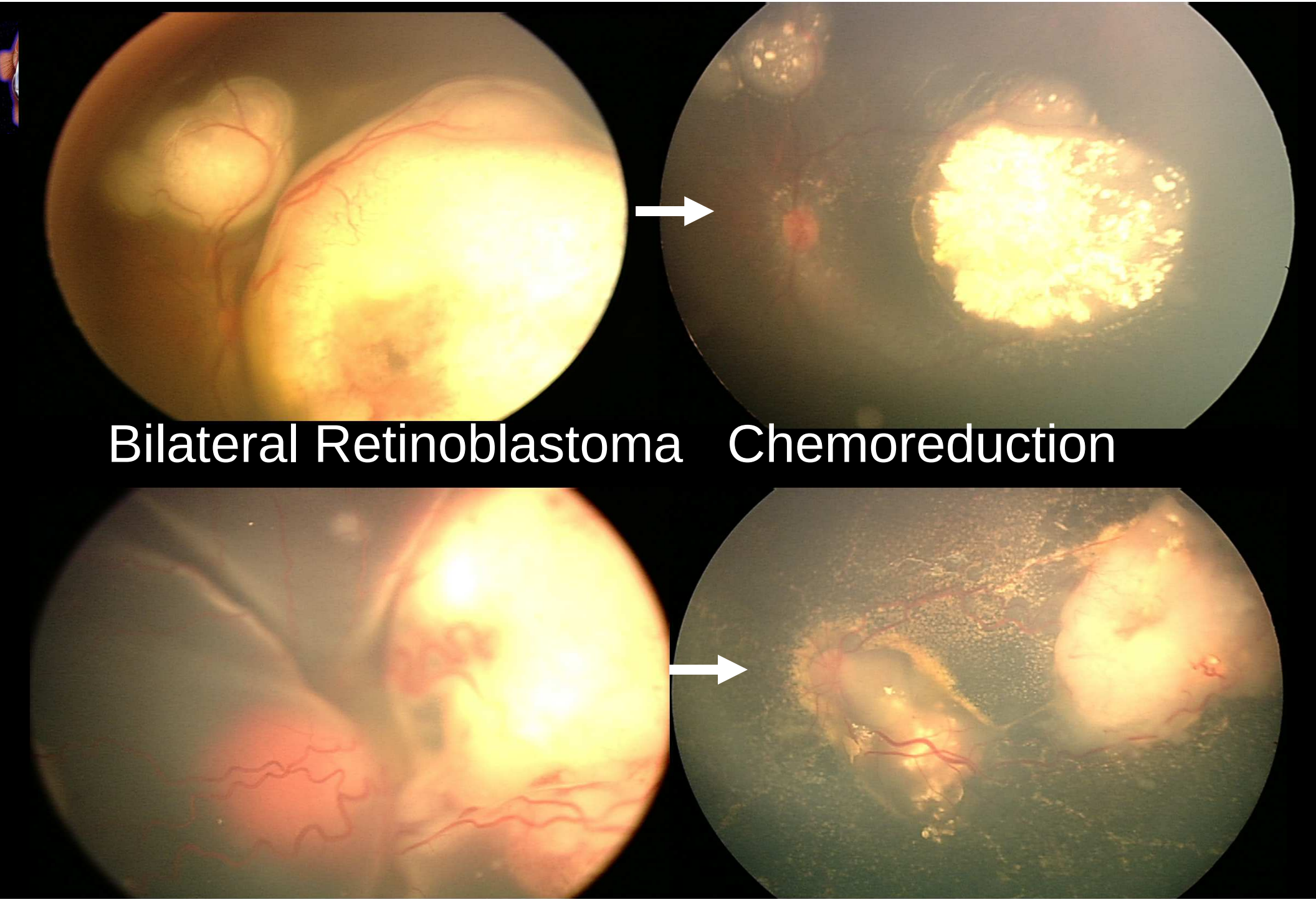


# Retinoblastoma : Chemo Protocol

- Neo adjuvant chemotherapy - Chemo reduction (Grp IV, V)
- Concurrent - SALT - Sequential Aggressive Local Therapy
  - EUA before each cycle
  - Cryo / TTT → Chemotherapy
- Adjuvant Chemo after Enucleation or exenteration

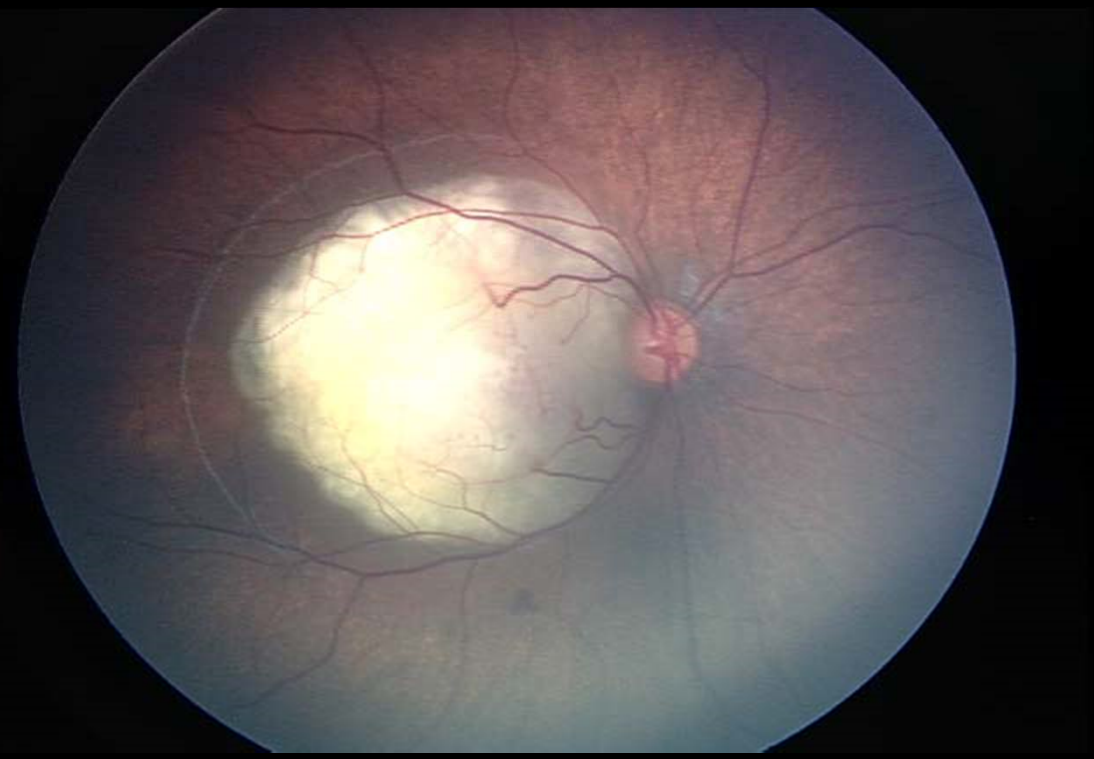
**Chemo Intervals: 3 - 4 weekly, 6 – 12 cycles**

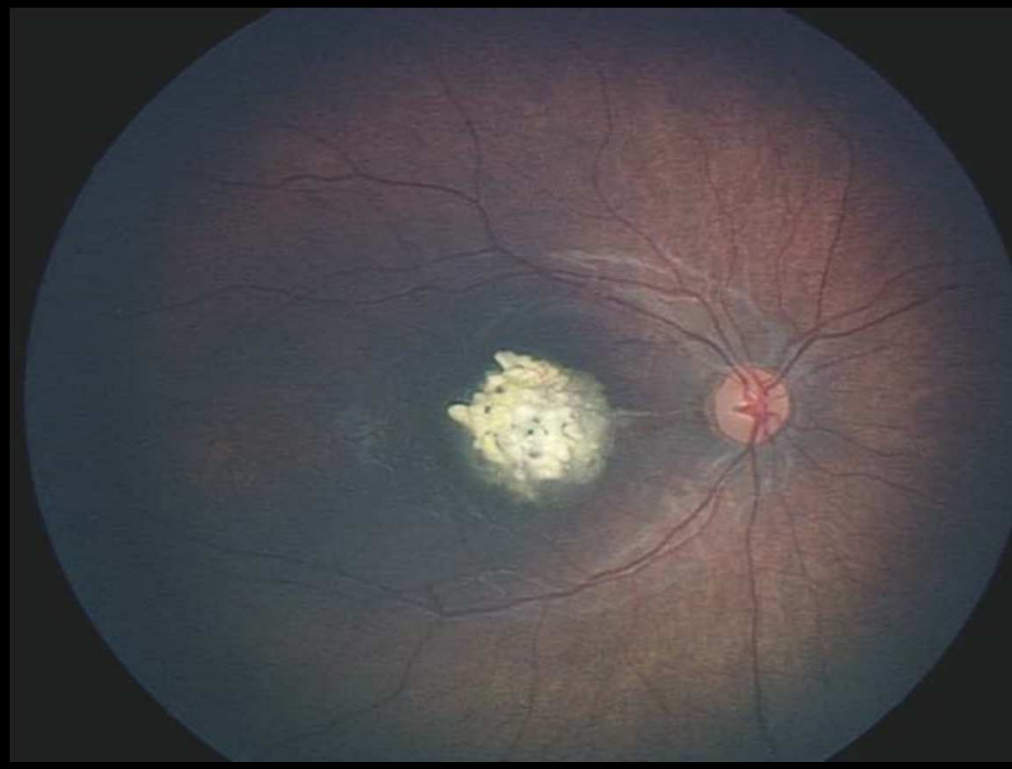
VAR


Bilateral Retinoblastoma
Chemoreduction

# Chemoreduction for retinoblastoma

## Chemoreduction alone



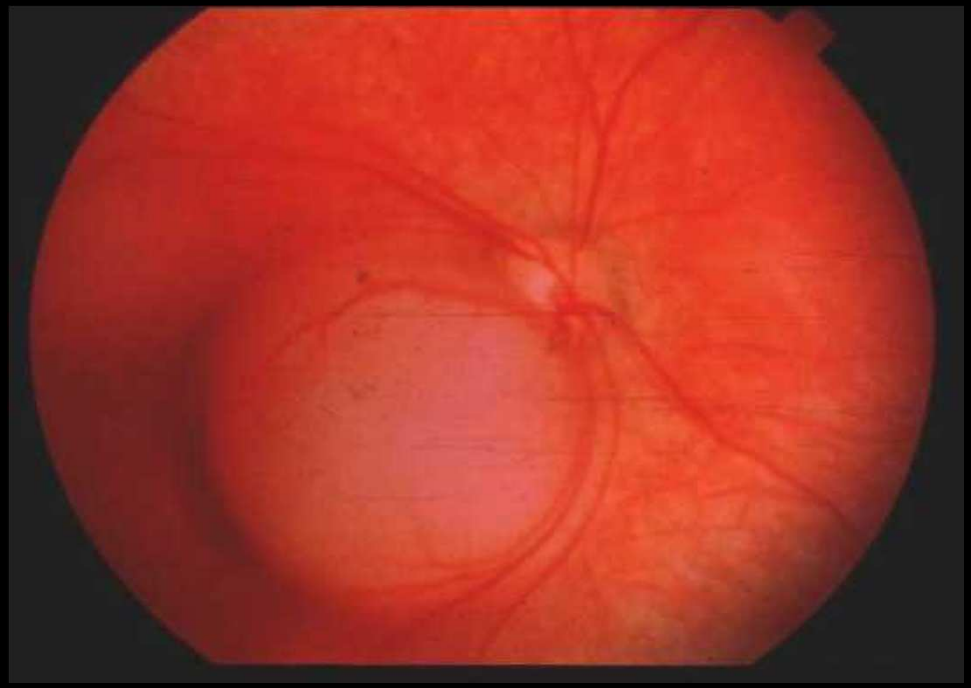


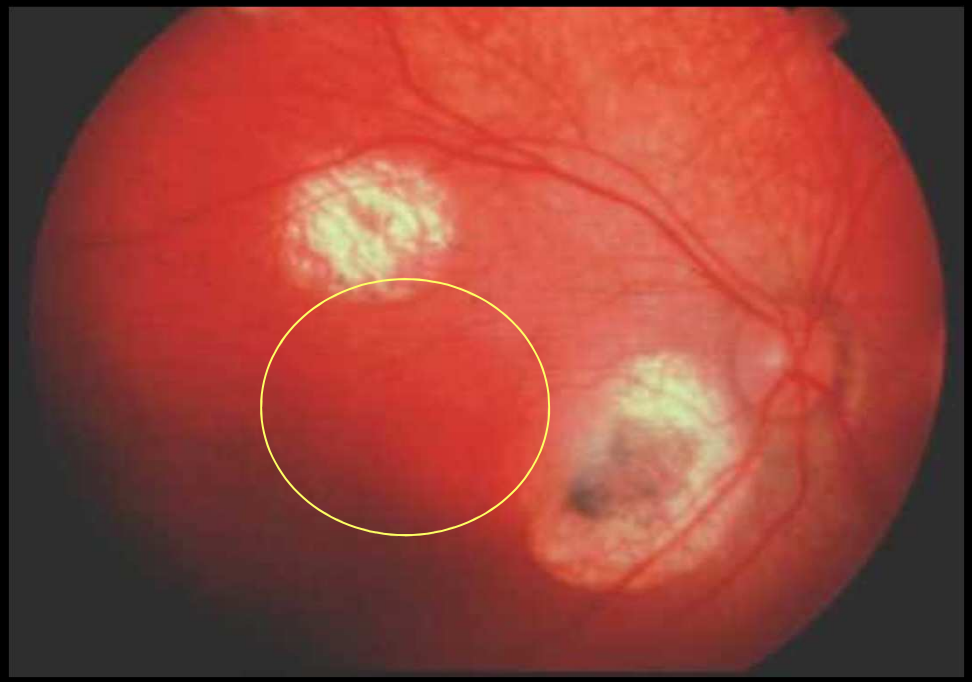
Macular tumor: laser not done to optimize vision

VAR

# Chemoreduction for retinoblastoma

SALT : Chemoreduction + TTT





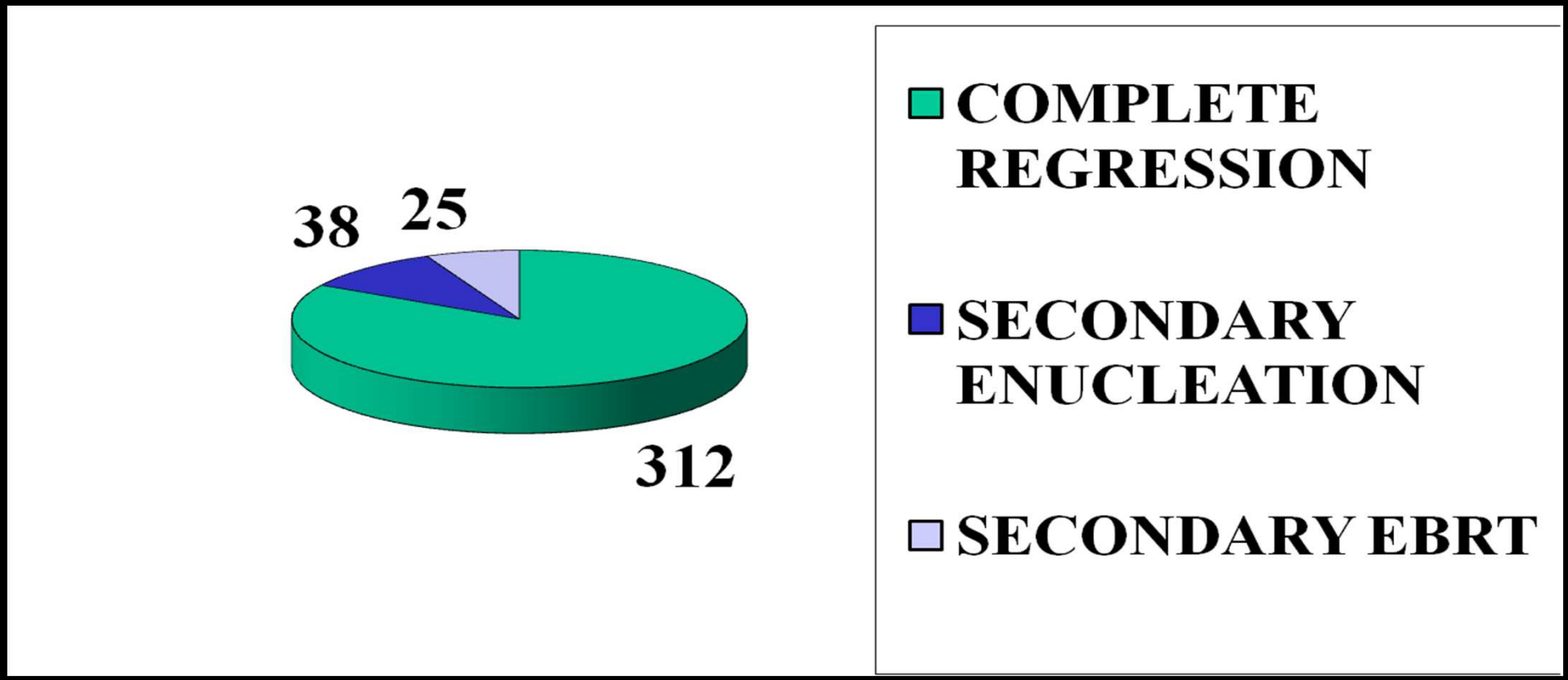
Macular tumors

Two large tumors, scar sizes r much smaller than the tumor

VAR

N = 375 eyes

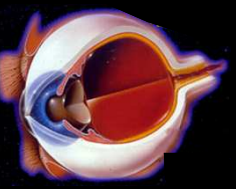
# Chemoreduction + Focal Rx Results




312 of 375 (83%) eyes regressed with CRD + Focal Rx

337 (90% had eye salvage)

VAR

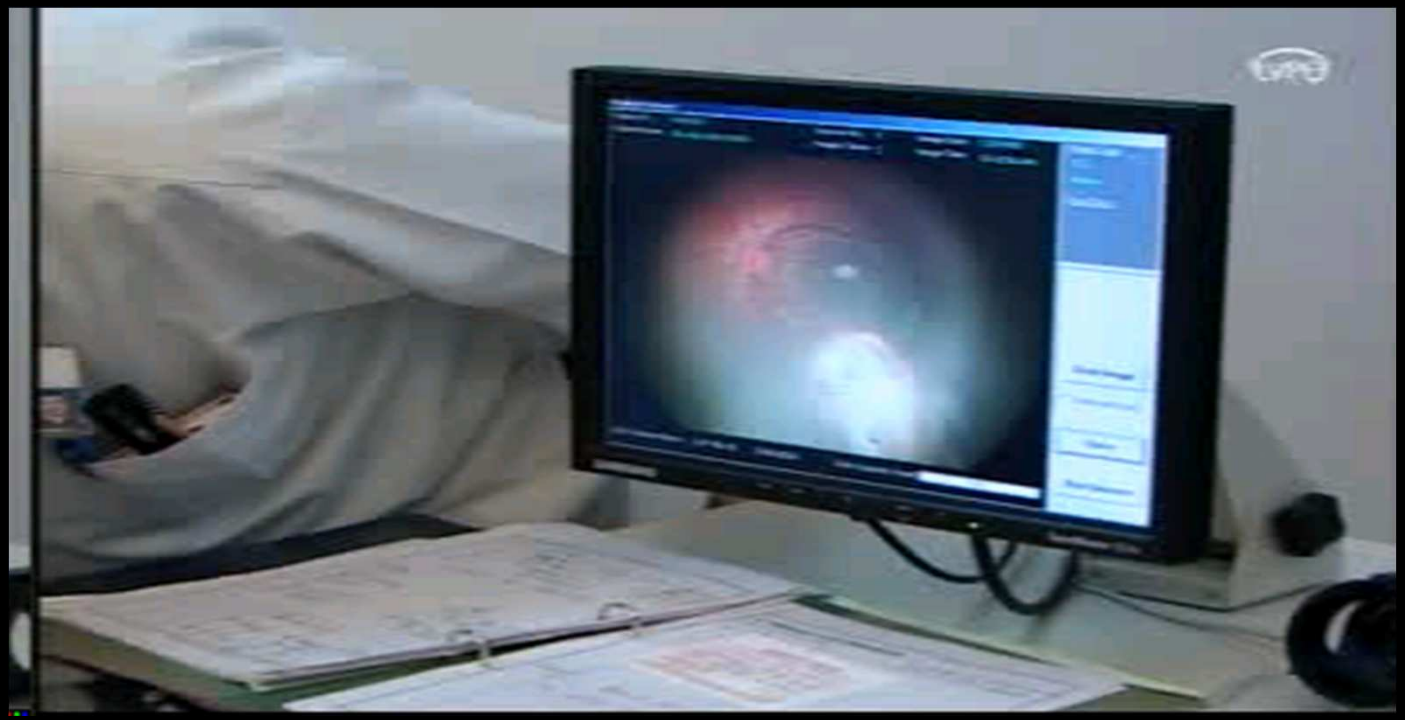


# Chemoreduction
## Advantages

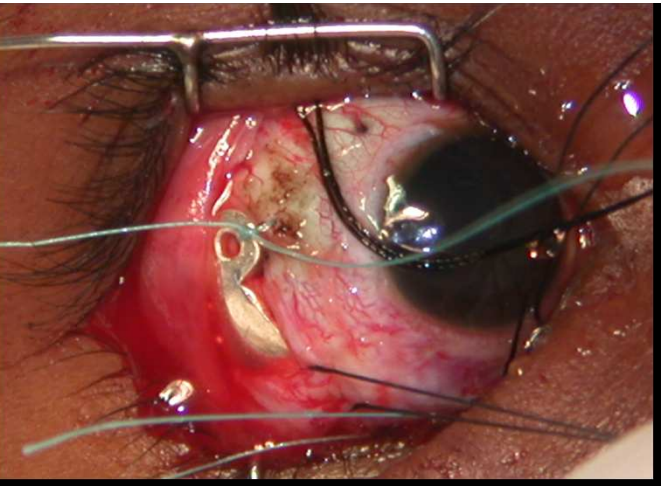
- Allows for salvage of the eye
- Maximizes potential for residual vision
- Possibly prevents systemic mets
- Delays or prevents pinealoblastoma

VAR

# Periocular Chemotherapy



- Deep posterior subtenon Carboplatin injection
- Currently under trial
- Encouraging results in Grp V B
- (70% eye salvage Vs 30%)



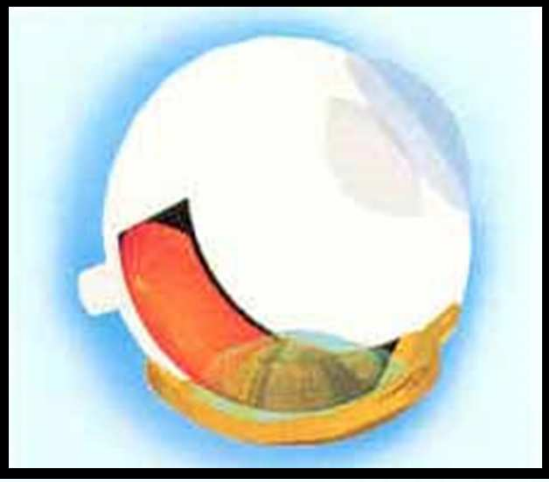
# Plaque Brachytherapy

- 16 mm diameter, 8 mm thickness
- Chemoreduction failure or rec
- Rarely as primary therapy
- Commonly used Iodine$^{125,}$ Ruthenium$^{106}$
- 4500-5000 cGy to tumor apex
- 90% success in tumor control

VAR

# Ruthenium 106

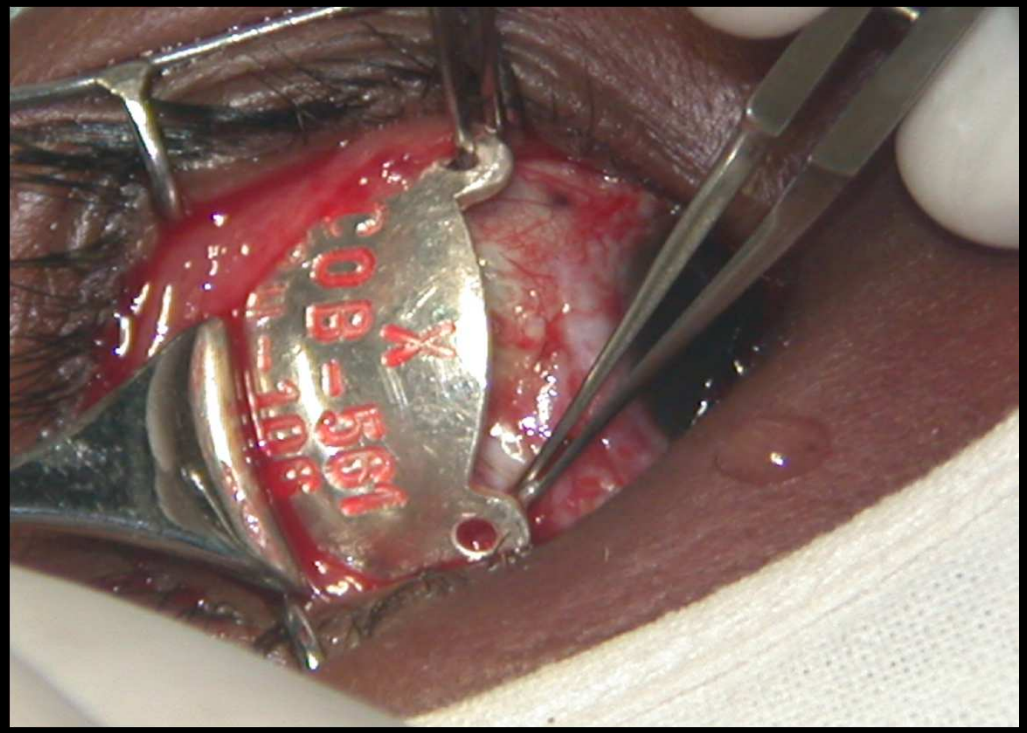
Brachytherapy



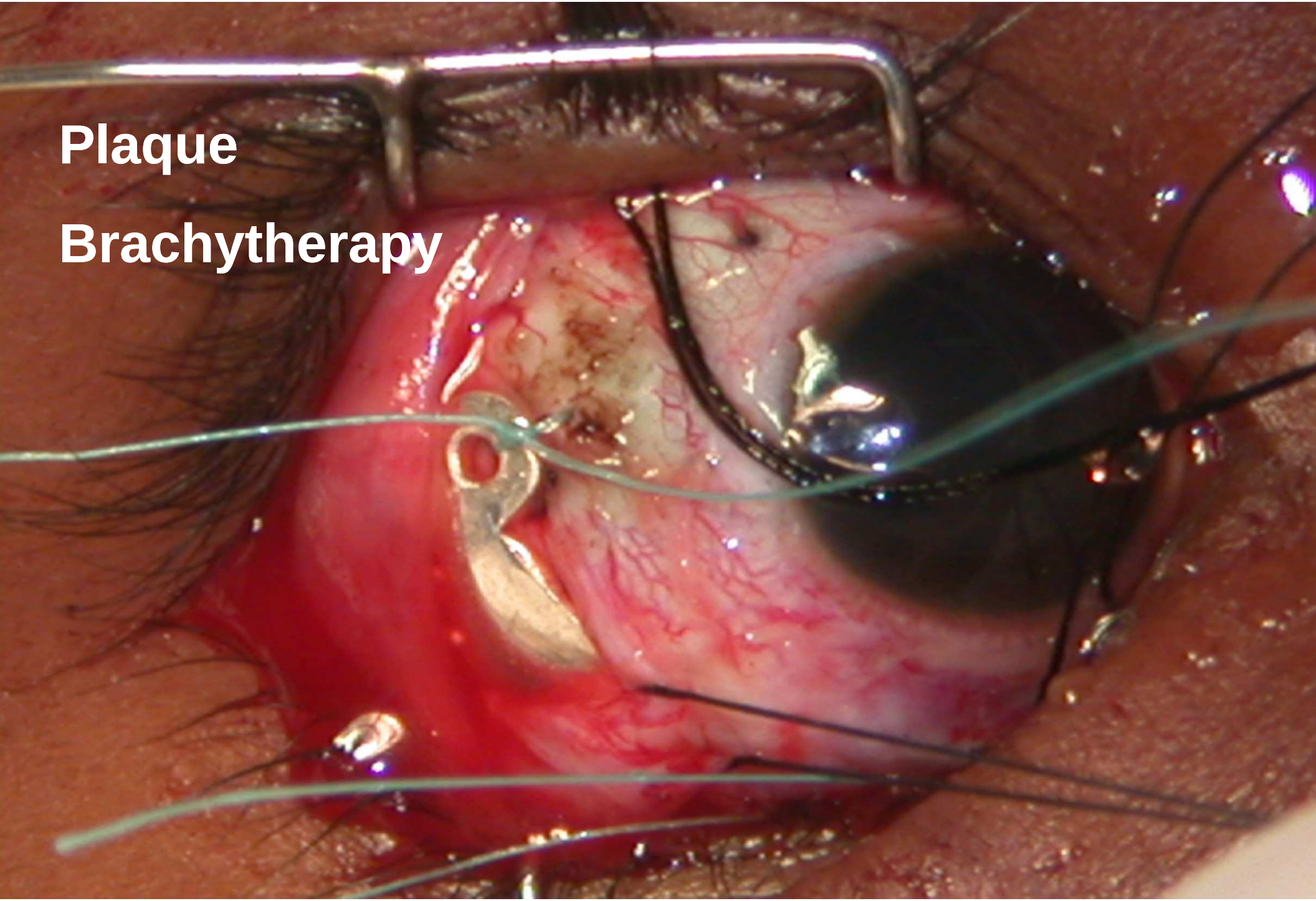
Plaque therapy

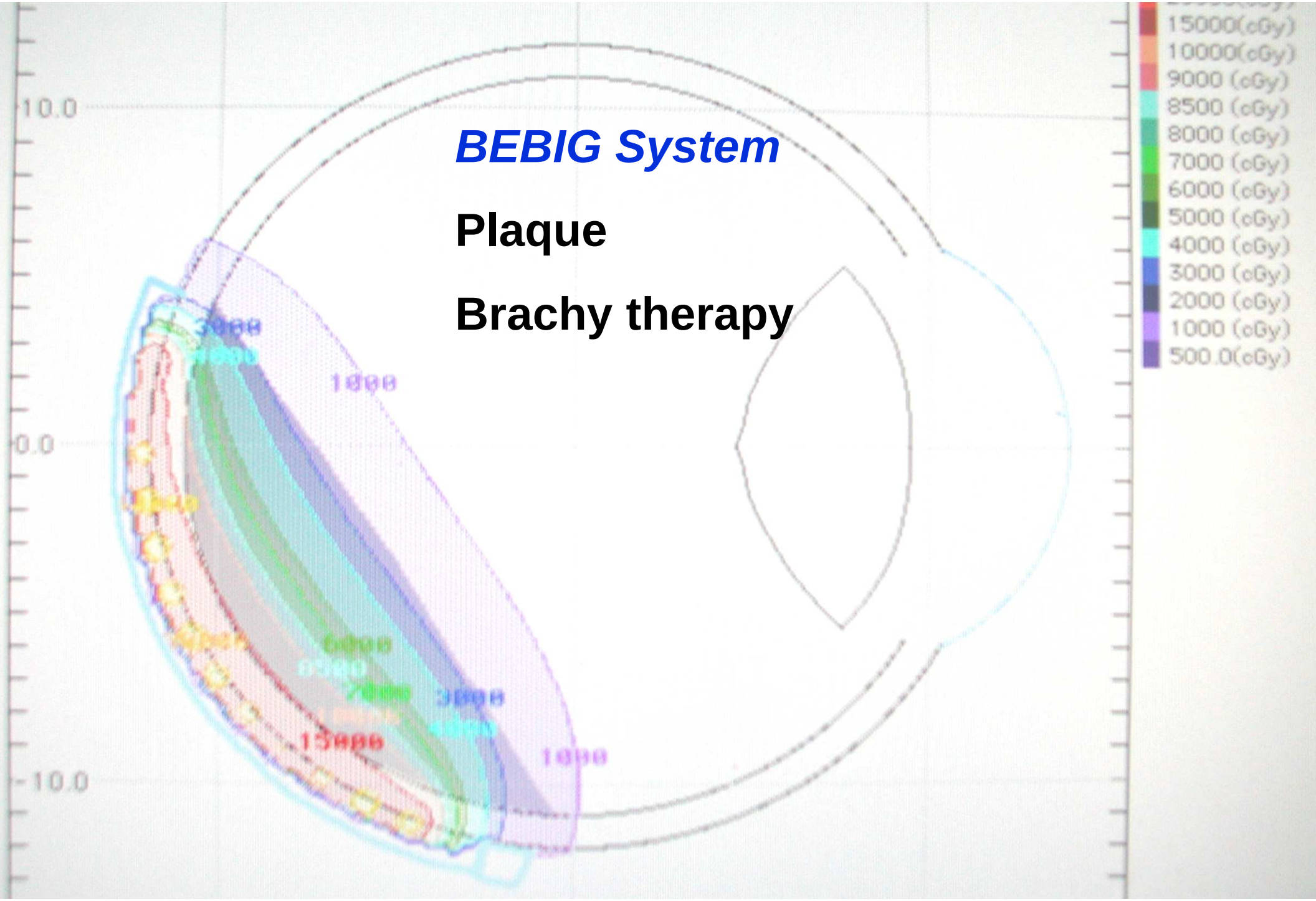
VAR

# Plaque Brachytherapy


VAR

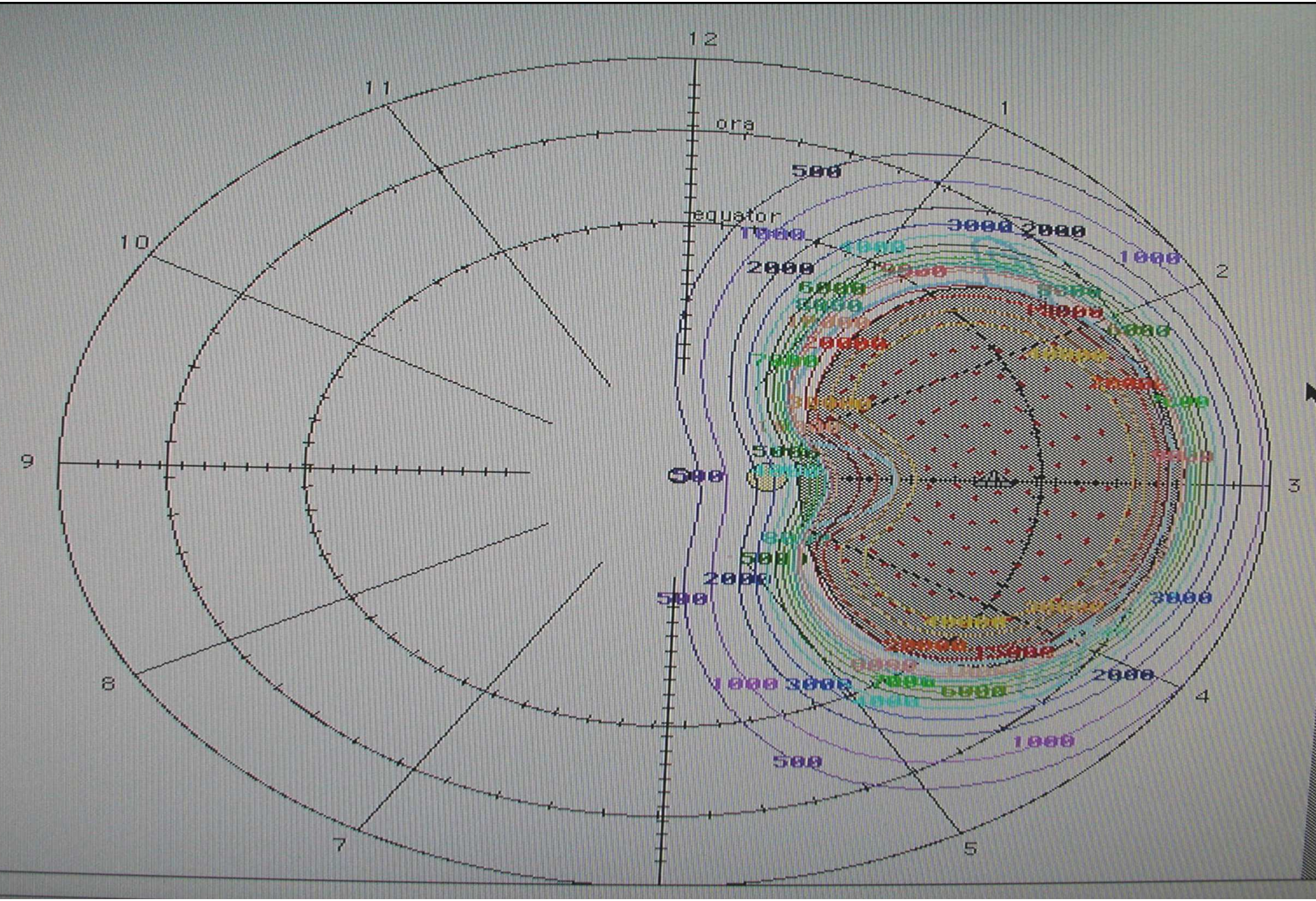

Plaque
Brachytherapy




## *BEBIG System*

**Plaque**

**Brachy therapy**


12
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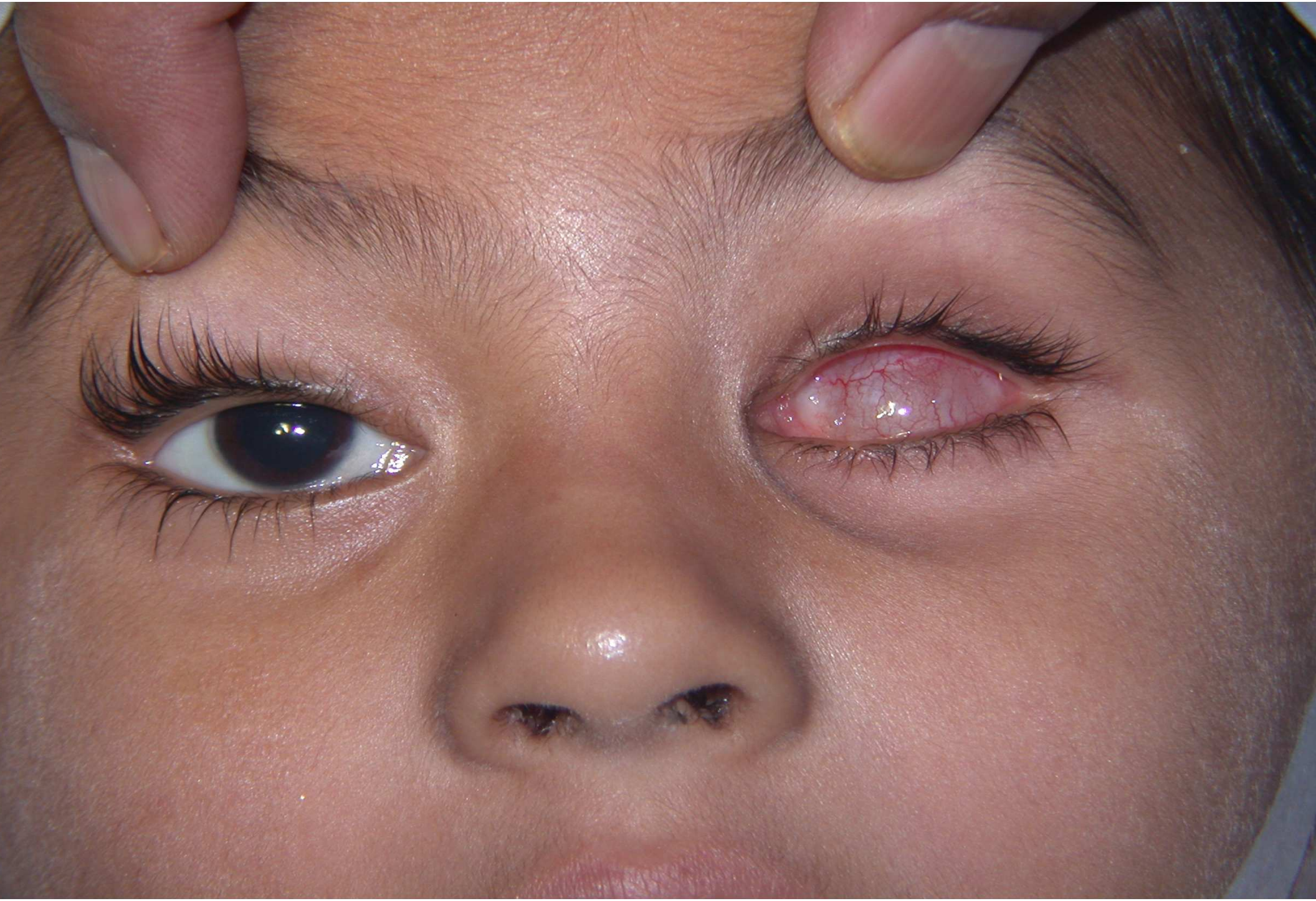
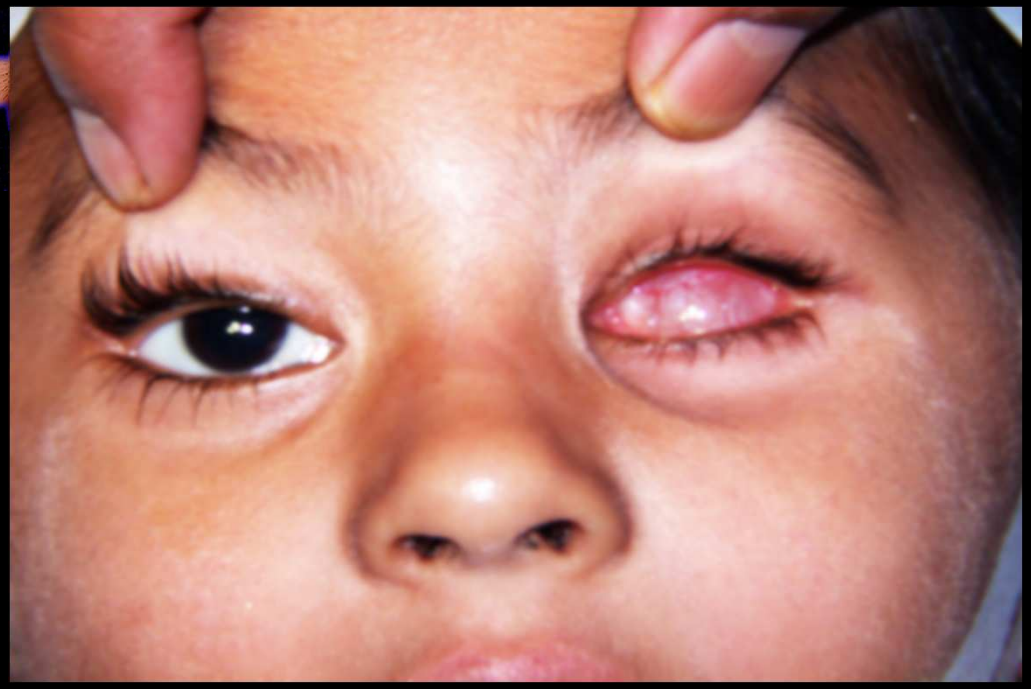
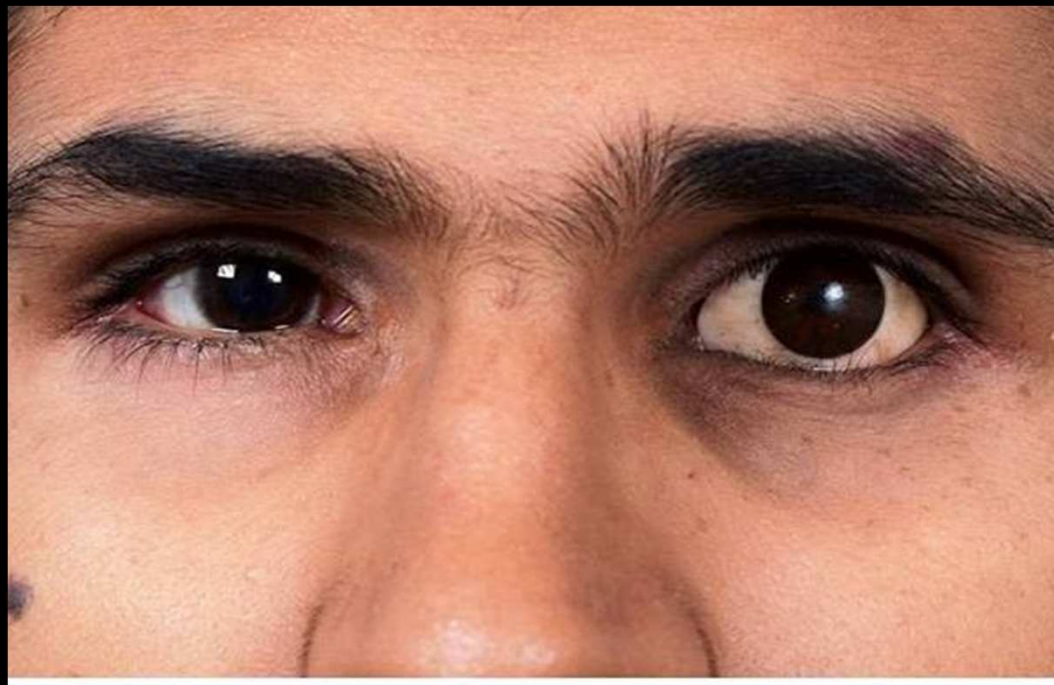
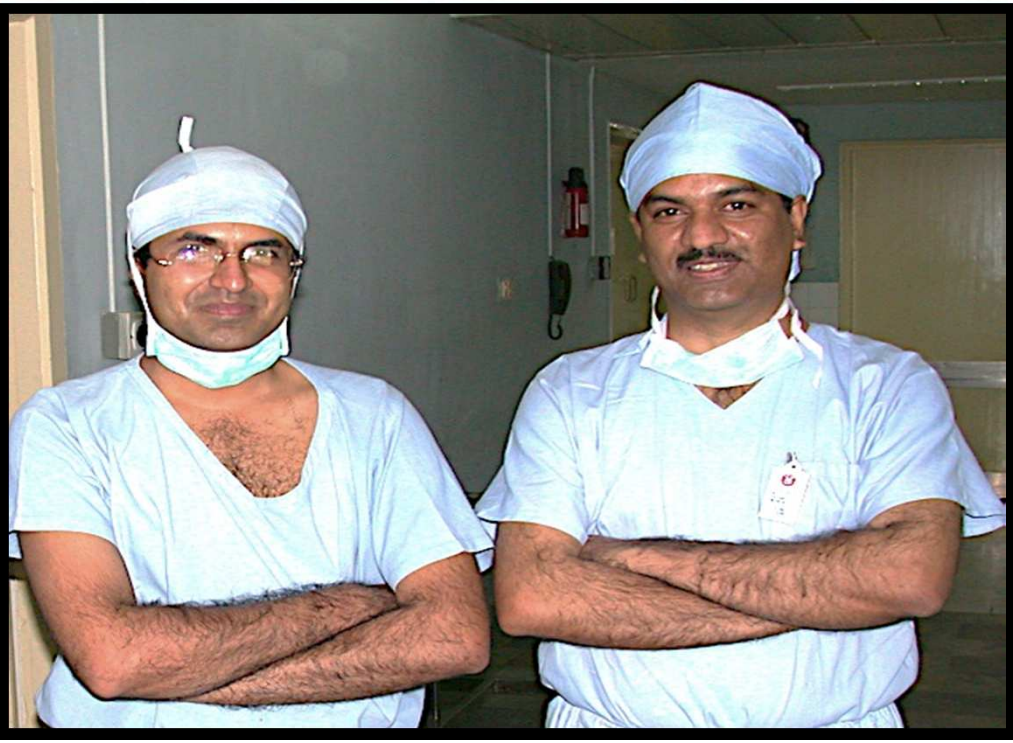
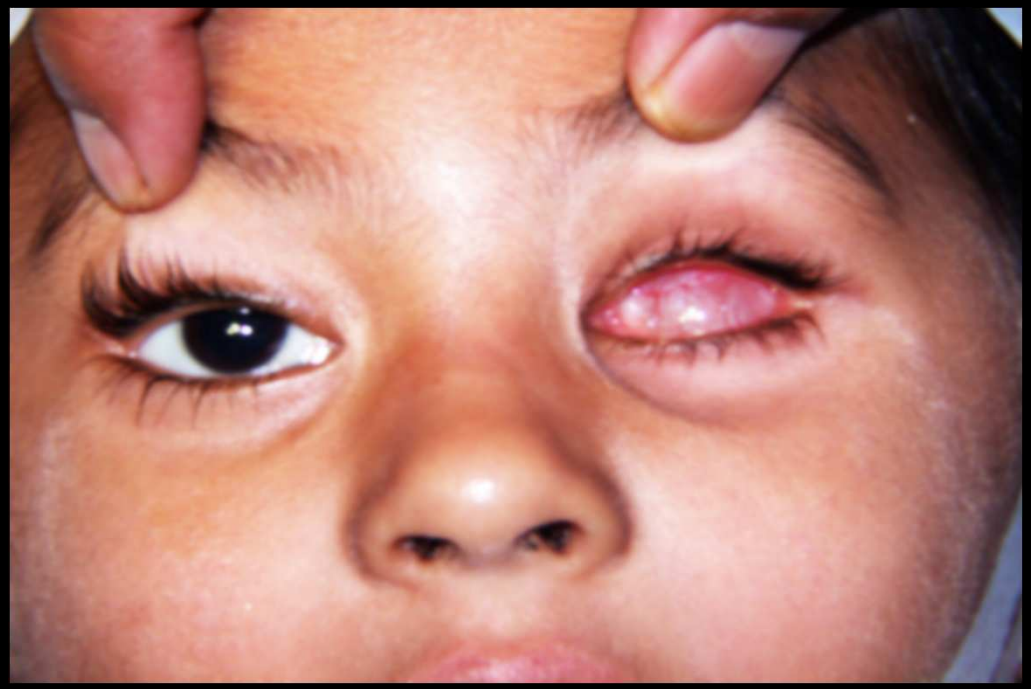


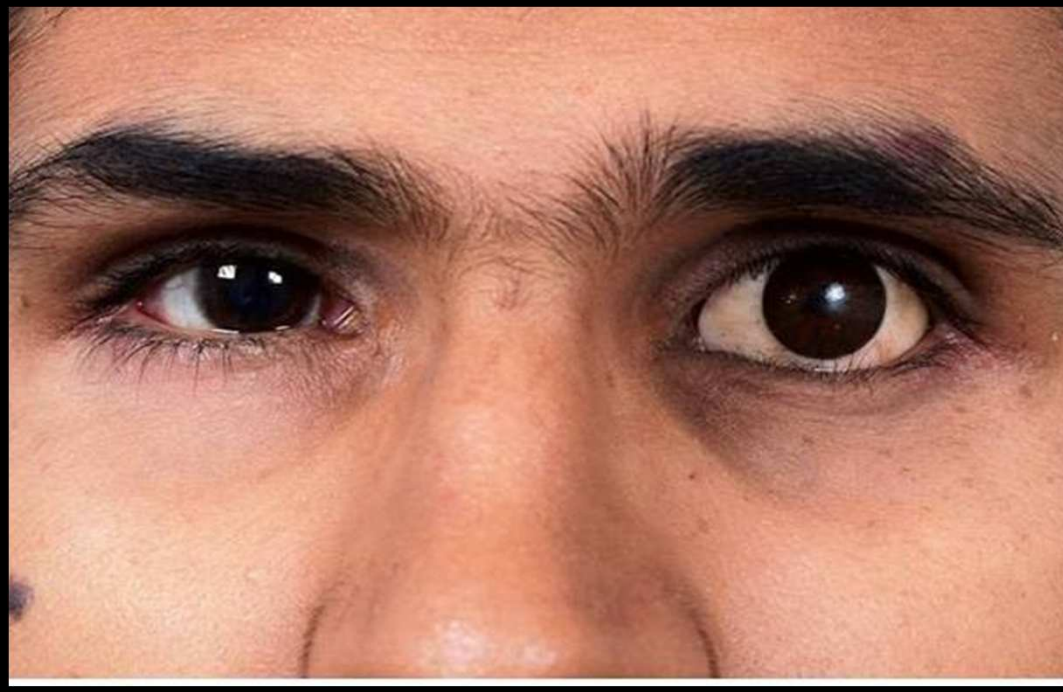






# 3 yr OU RB, Left enucleated, Right recurrent RB Plaque in 2002

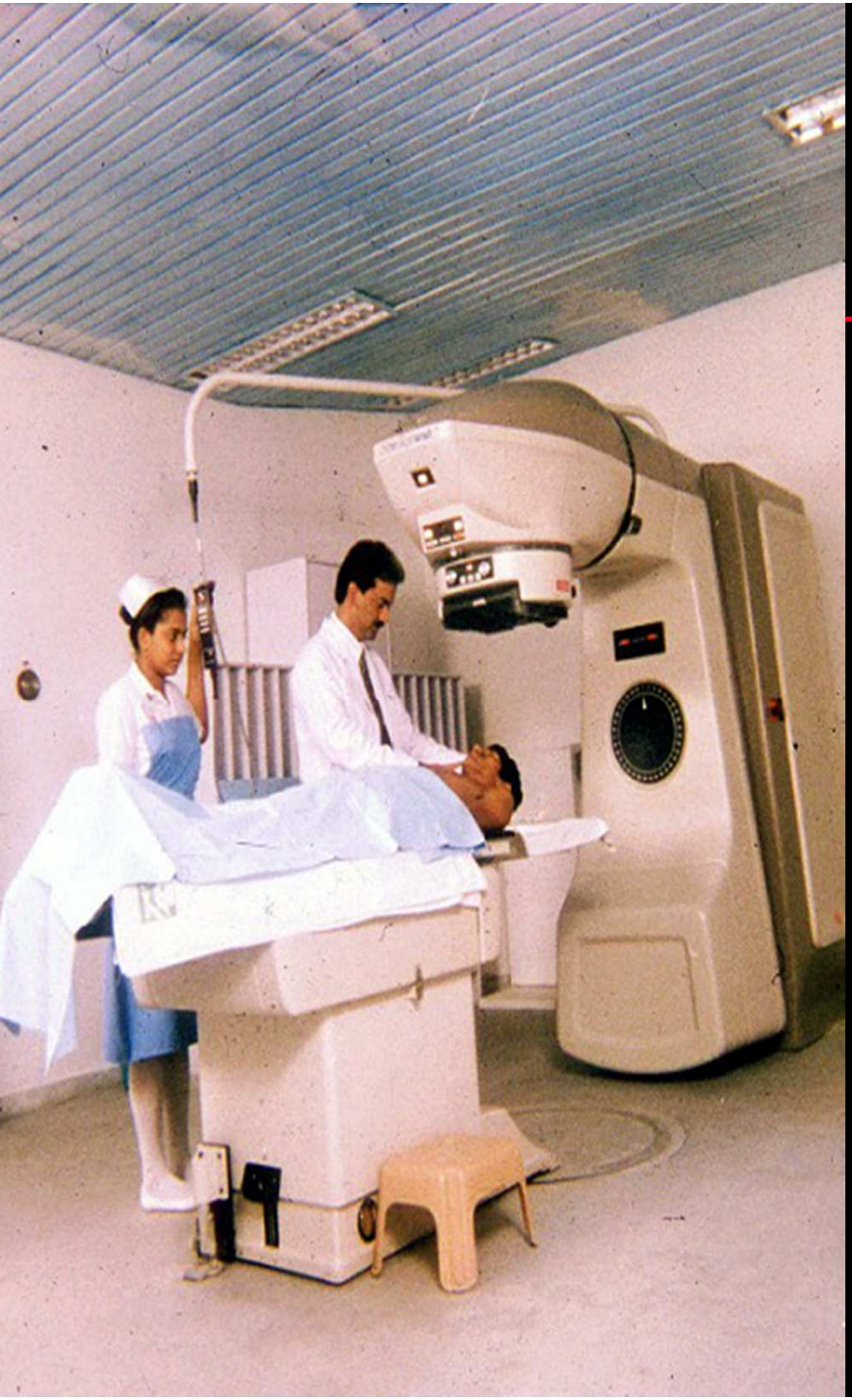




3 yr old from Bihar / Nepal border

now 15 yrs Age

VAR



# Retinoblastoma
# Ext Radiotherapy Indications

## Intra Ocular RB

- Persistent RB
- Rec. Grp V

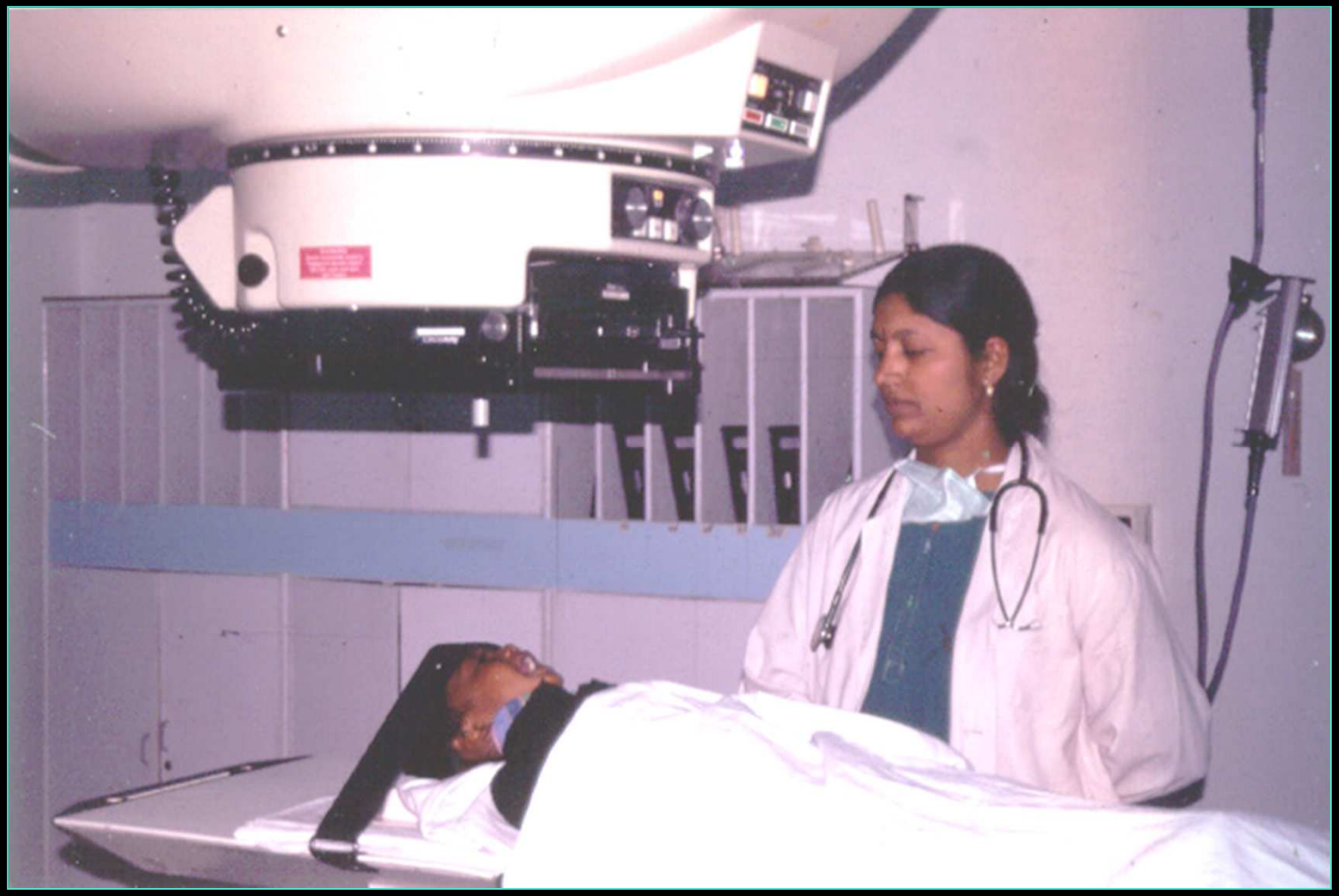
***Minimal Role!***

## Extra ocular RB

- Post enucleation
  - Extra ocular extn
- Orbital RB

VAR

# External Beam Radiotherapy



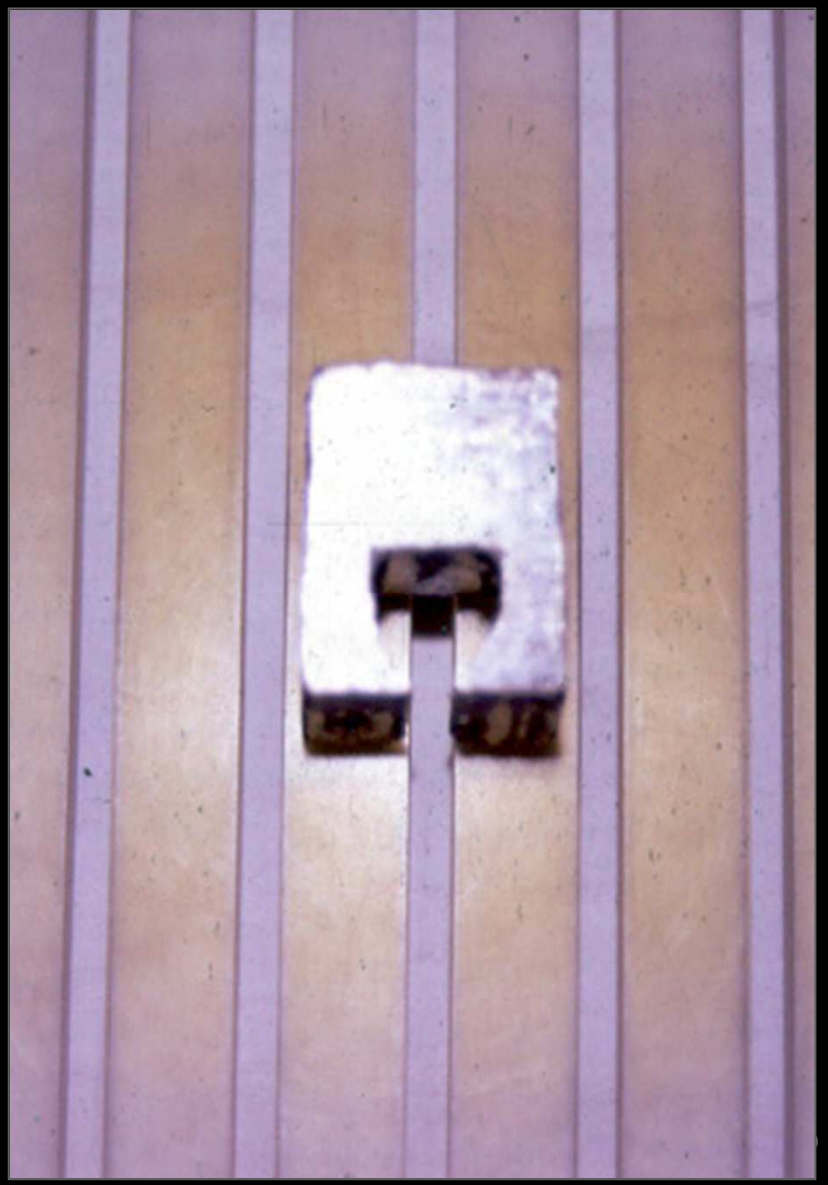
## Under Anesthesia

VAR

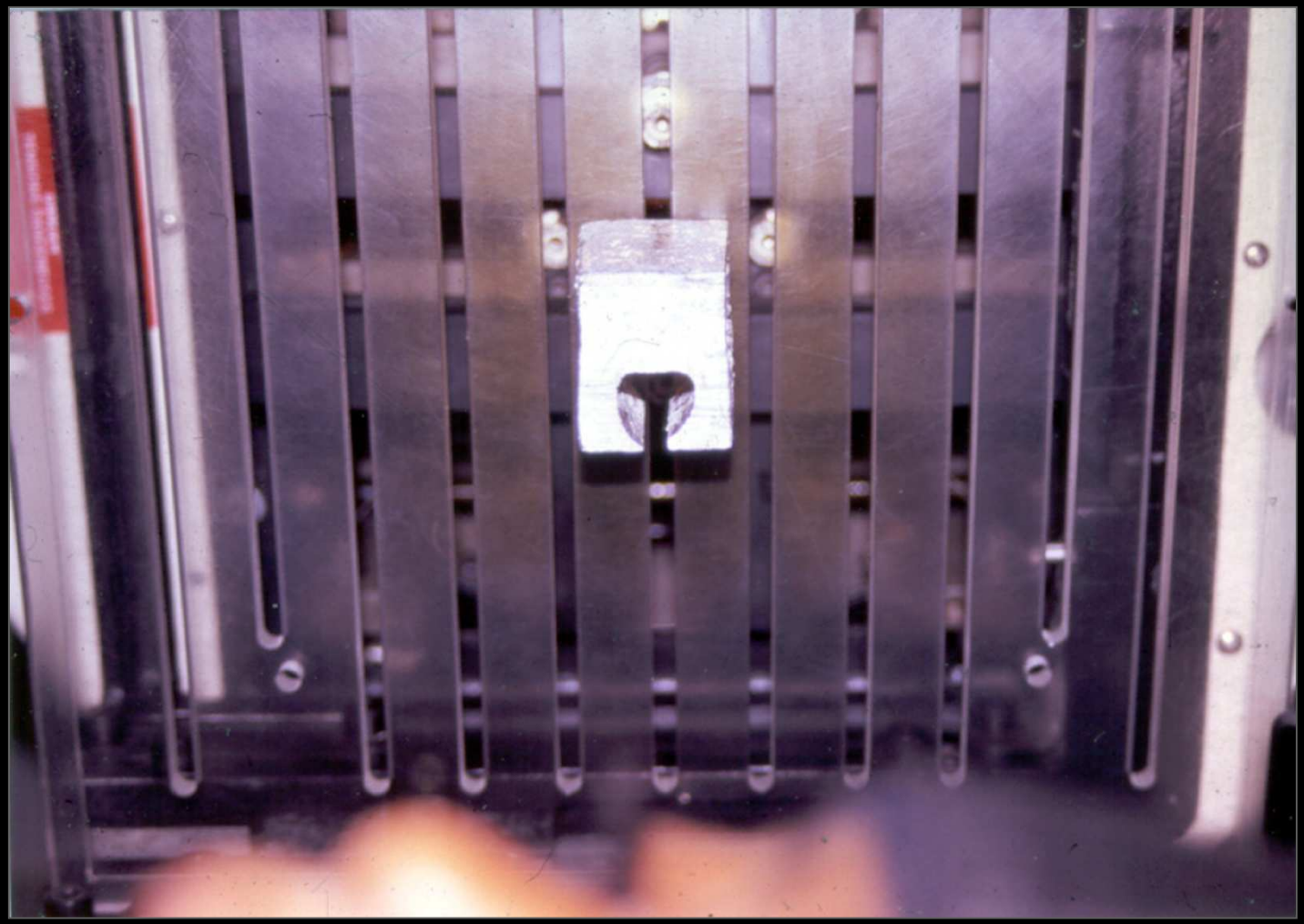
# External Radiotherapy

## Styrofoam Cutter

## Customized Lead block



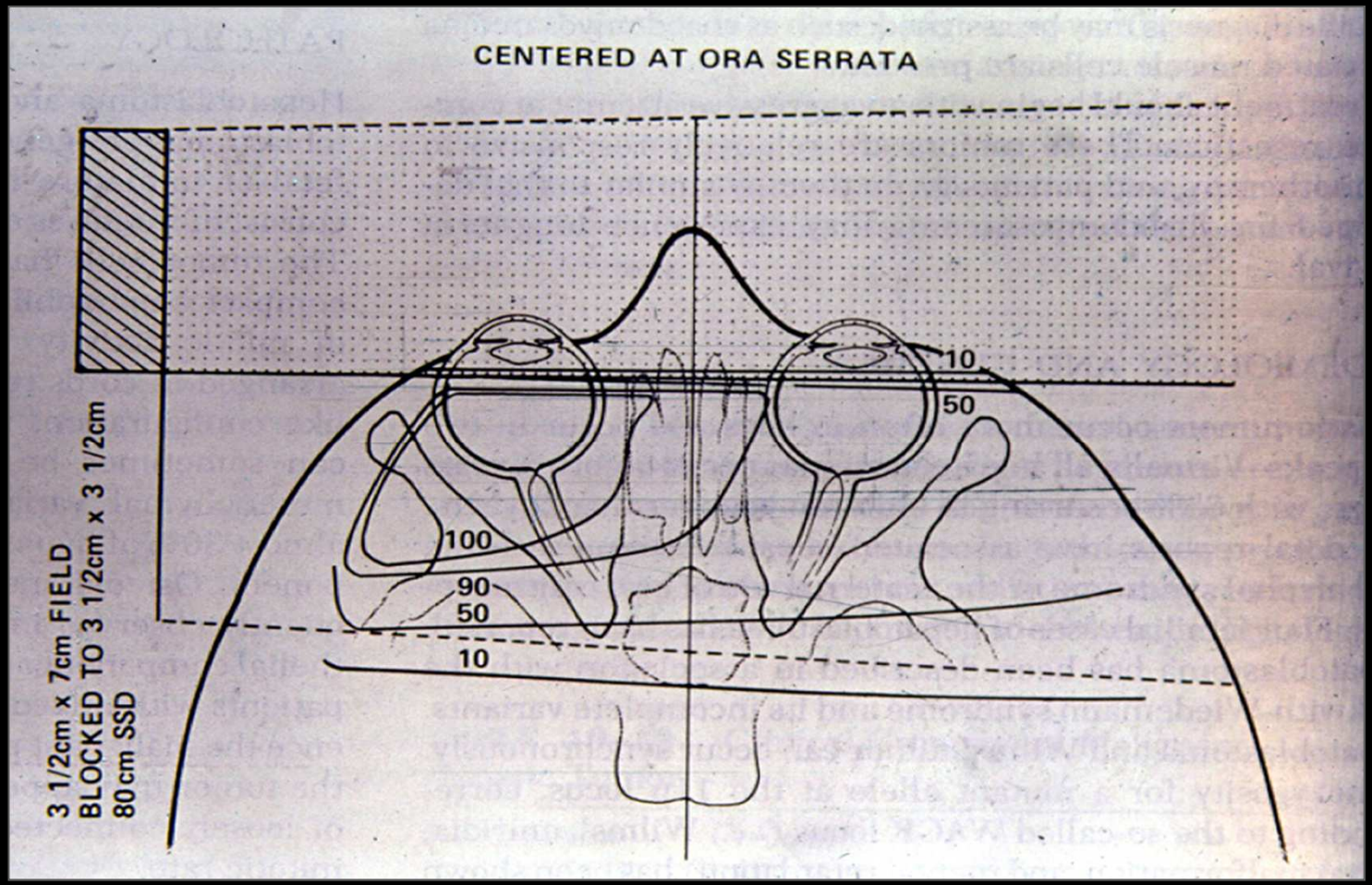
# External Radiotherapy



## Customized Lead Block

VAR

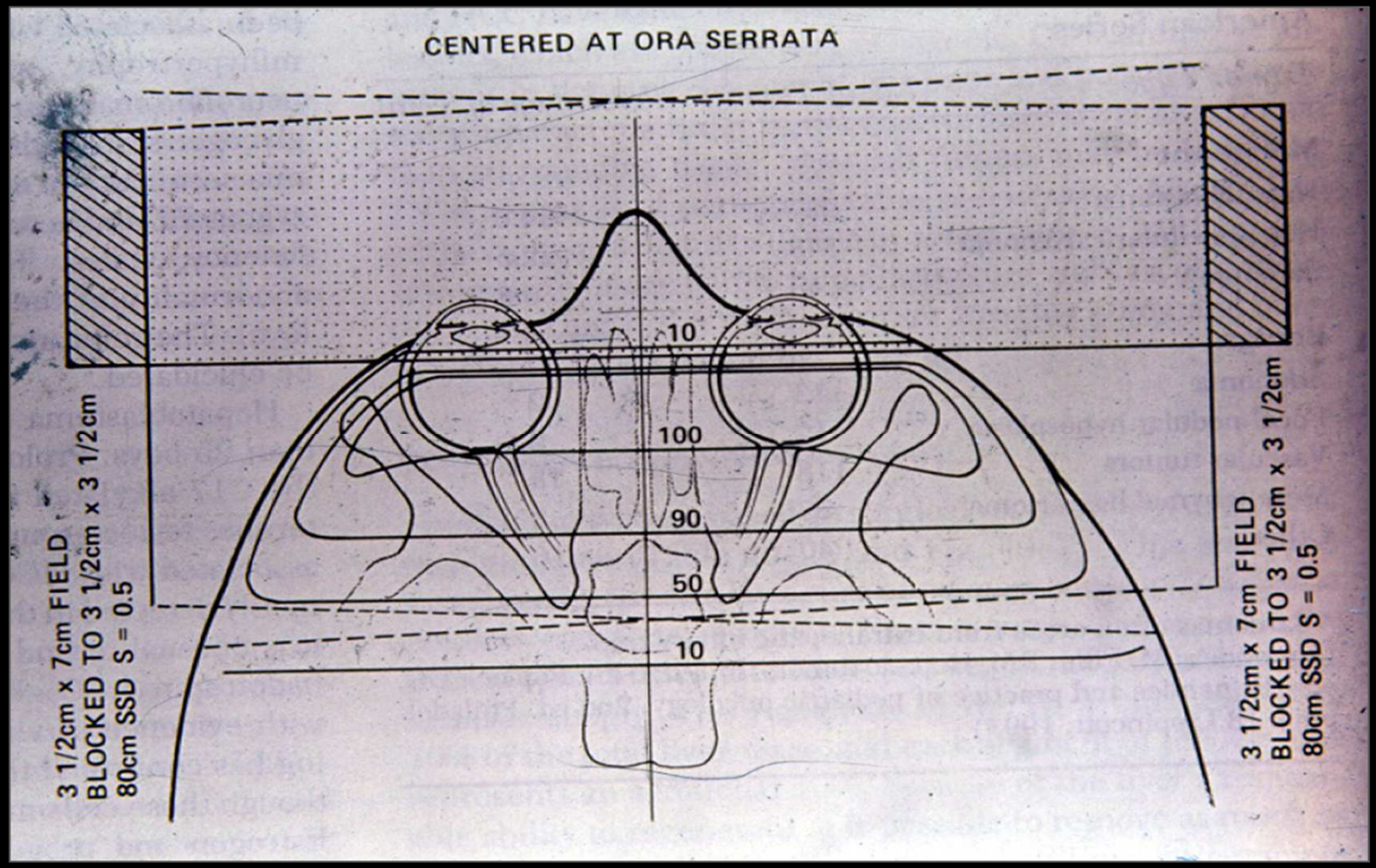
# External Beam Radiotherapy




**Unilateral field with Half Beam Block**

VAR

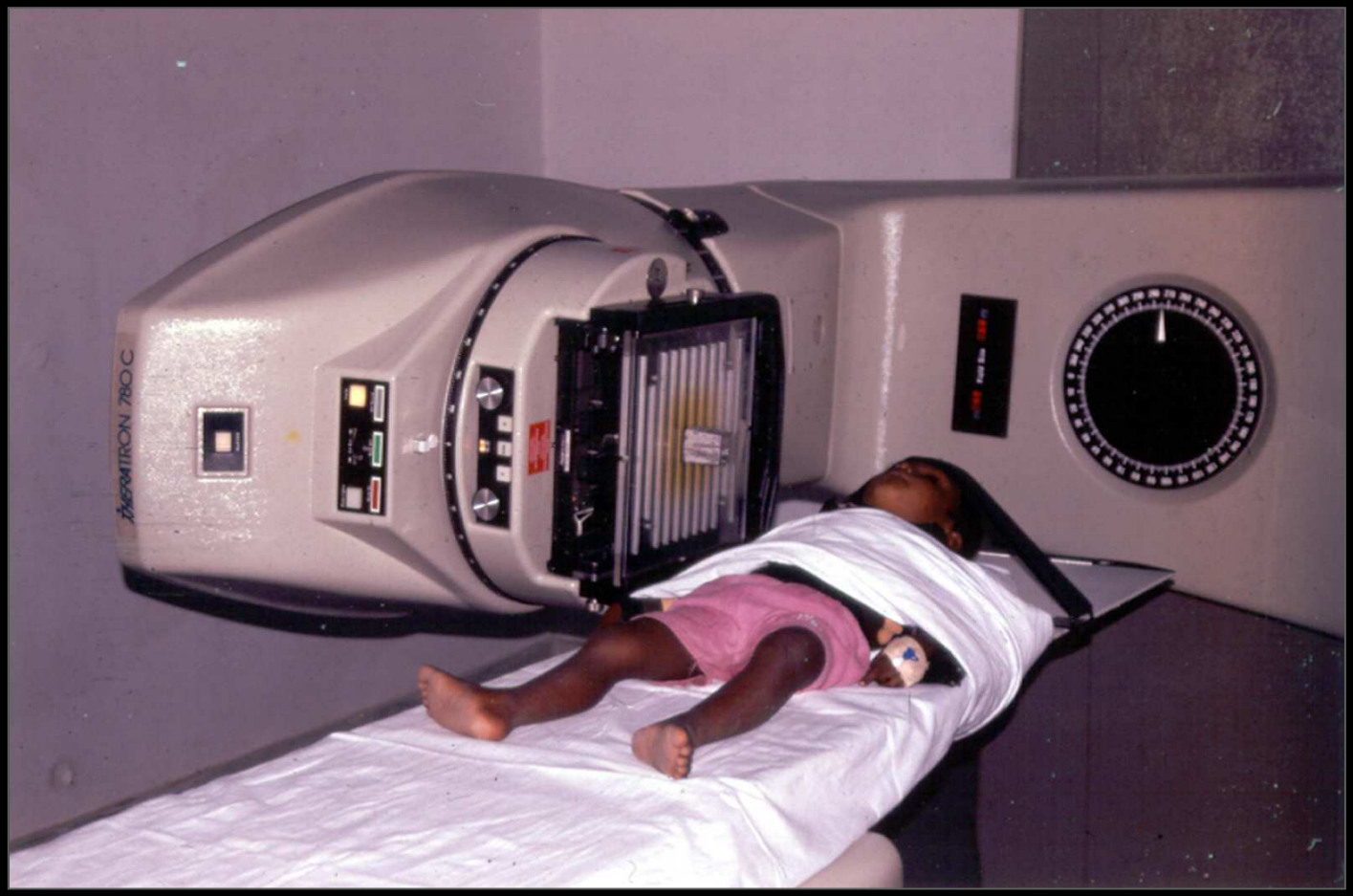
# External Beam Radio Therapy




**Bilateral fields with Half Beam Blocks**

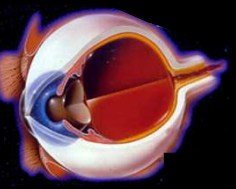
VAR

# External Beam Radiotherapy

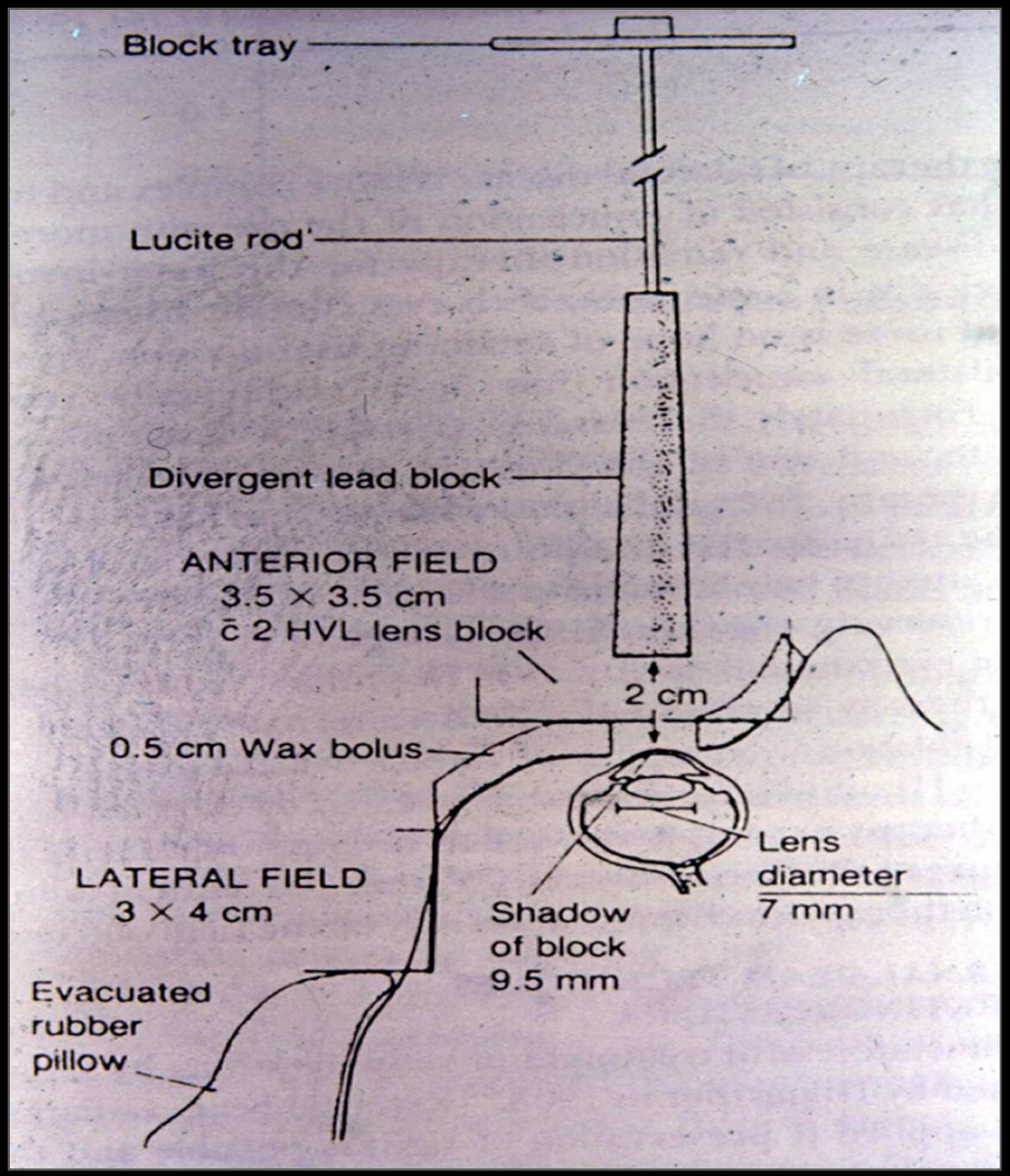



**Lateral beam with customized block**

VAR

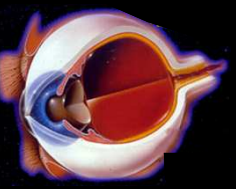


**External beam Radiotherapy**

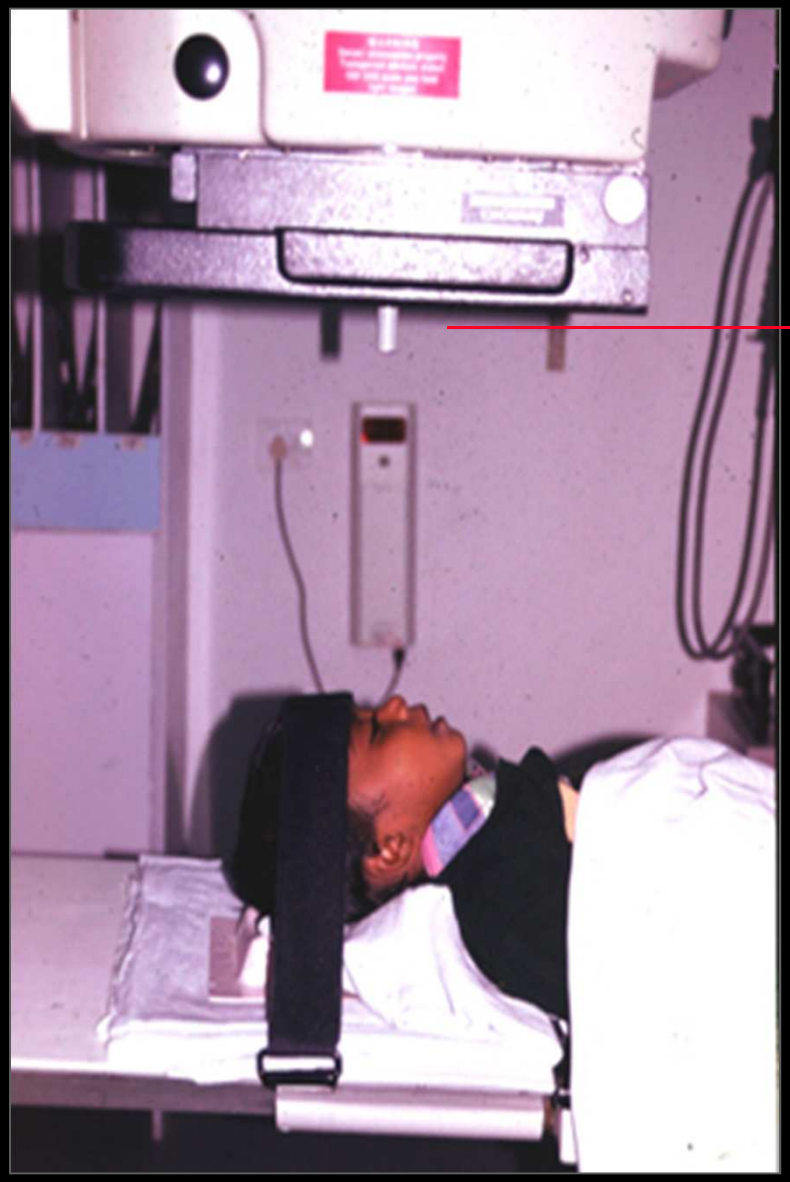



**Pencil beam block for lens**

VAR



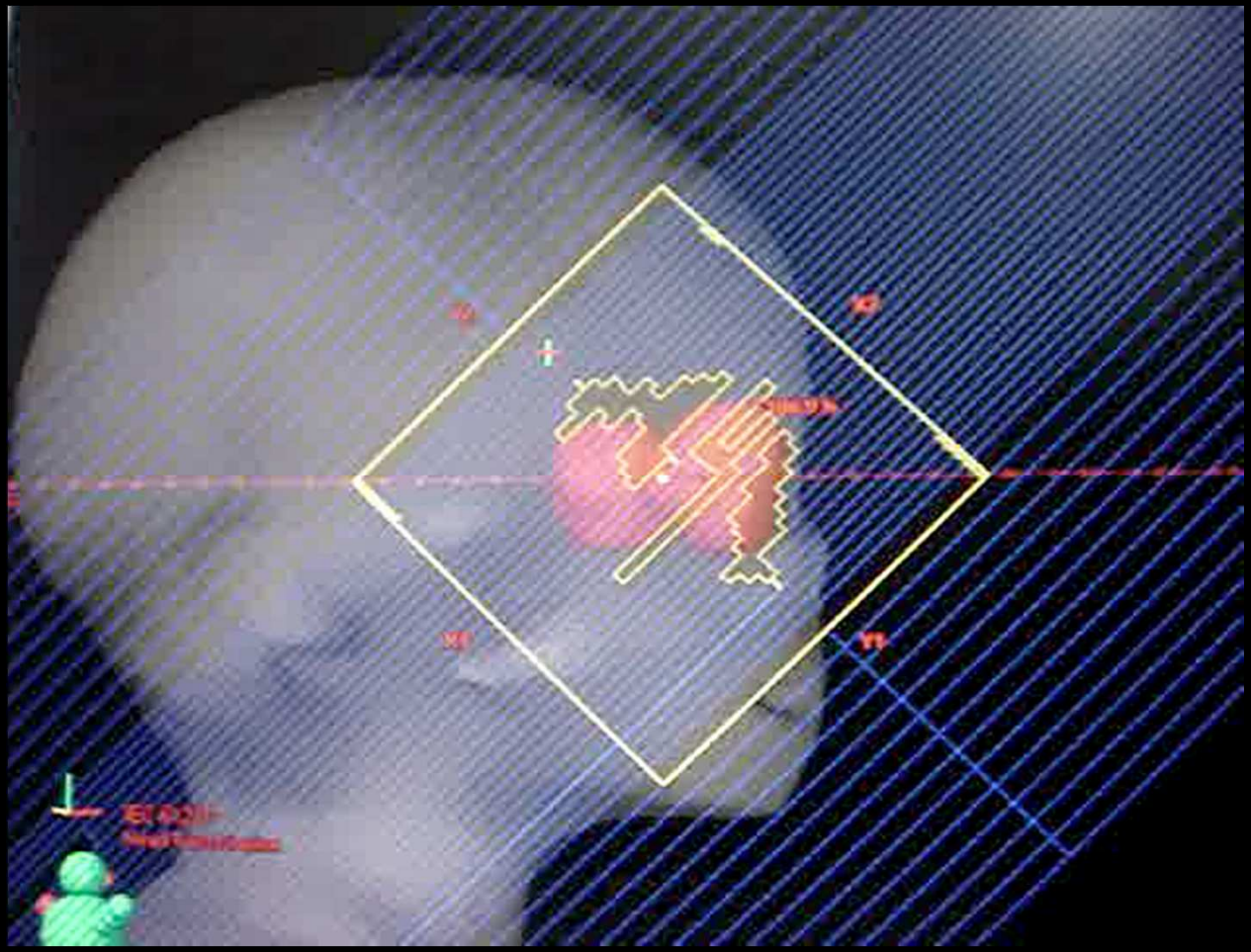
## External Radiotherapy



Pencil Beam Block for Lens Shielding

VAR

# High definition Rapid Arc
# BiL RB



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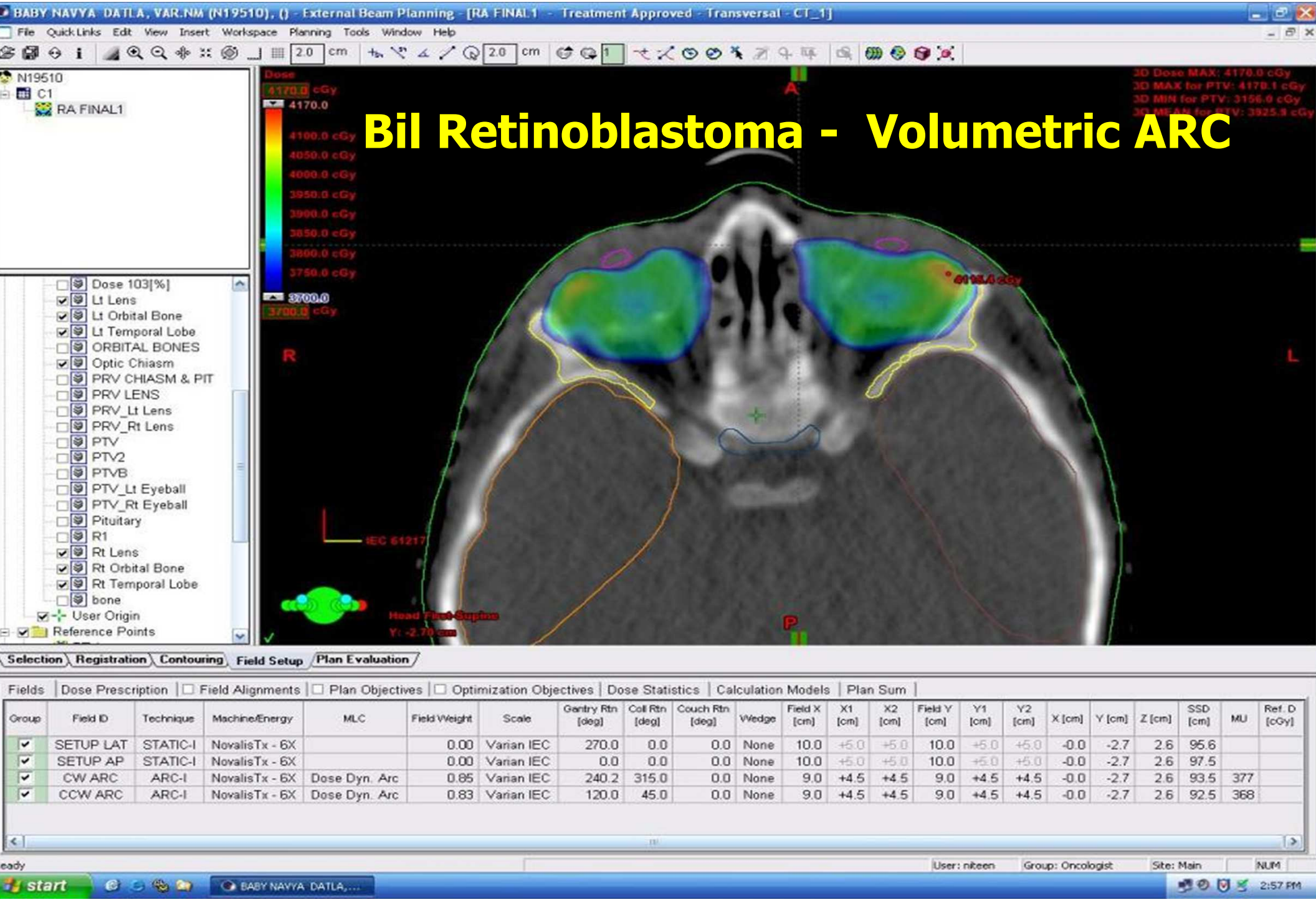
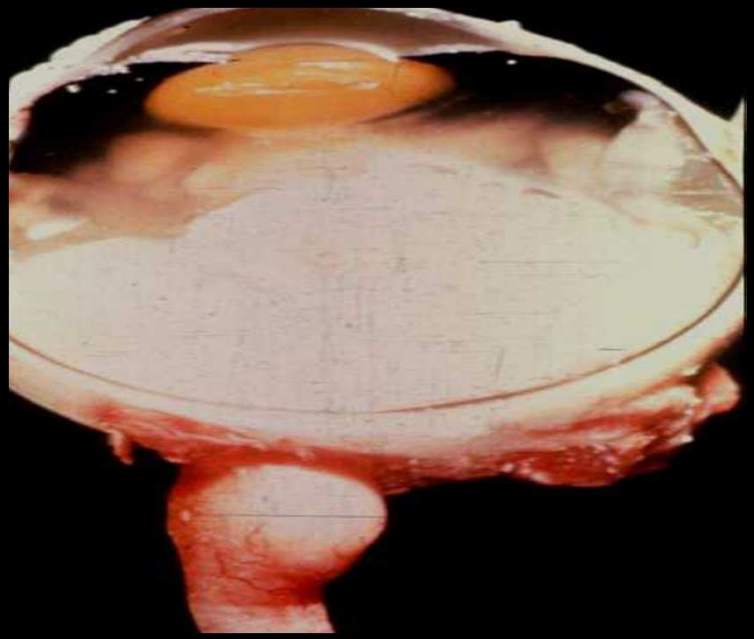



# Bil Retinoblastoma - Volumetric ARC

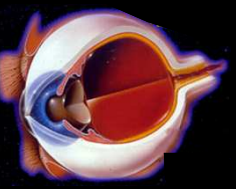
# Locally advanced disease Enucleation



- 1970 : 95%
- 1980 : 75%
- 1990 : 50%
- 2000 : 25%
- 2010 : <10% !

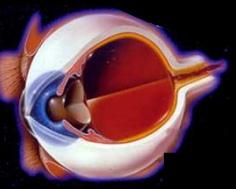
*Changing Trends!*

VAR



# Enucleation

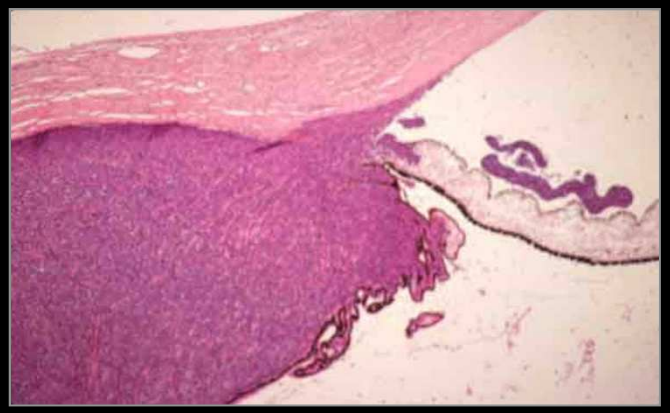
- Advanced unilateral tumor
  - Secondary glaucoma
  - pars plana invasion
  - anterior segment seeding
- Worse eye in advanced bilateral

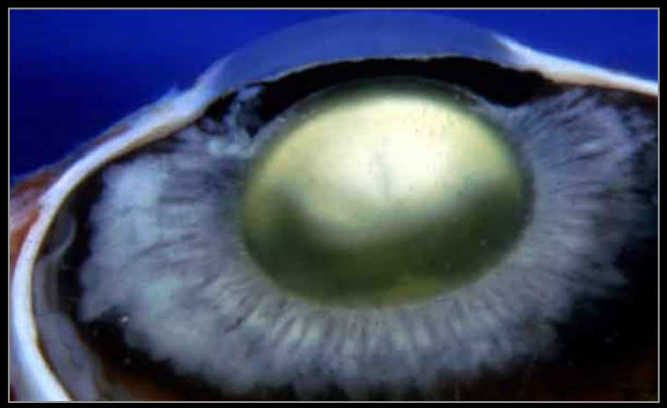


Enucleation is NOT the end!
It is JUST the beginning!!

# Post Enucleation

## Histopath risk factors – for adjuvant Chemo / RT



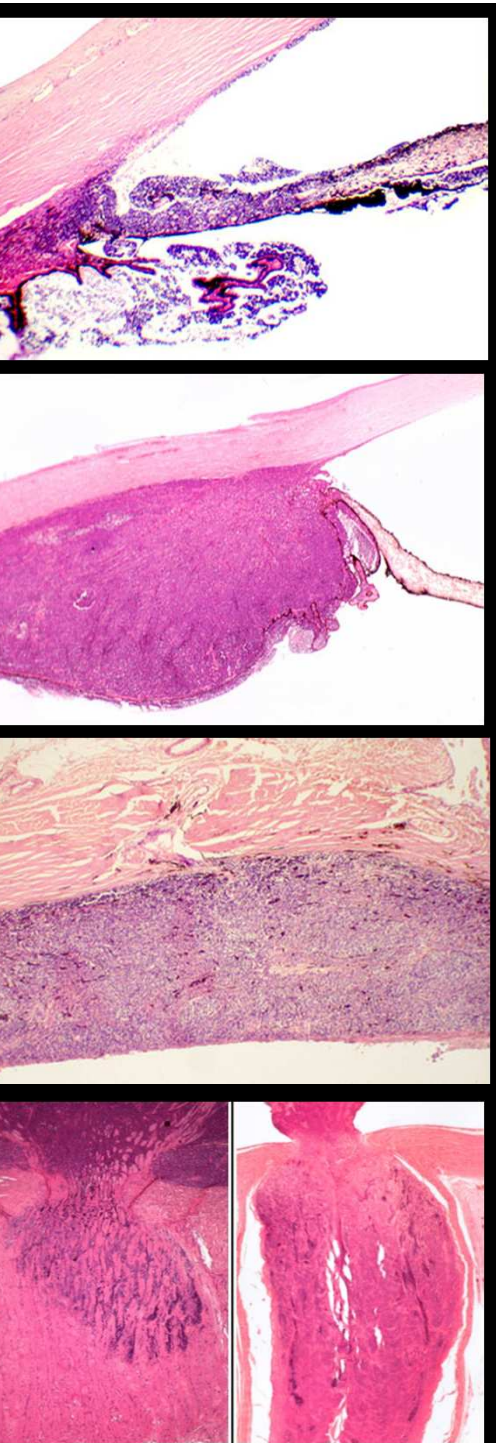


- Anterior chamber infiltr
- Trabecular meshwork infiltr
- Ciliary body infiltration
- Choroid infiltration
- Optic nerve invasion
- Extra Scleral infiltration

⇨ **RT**

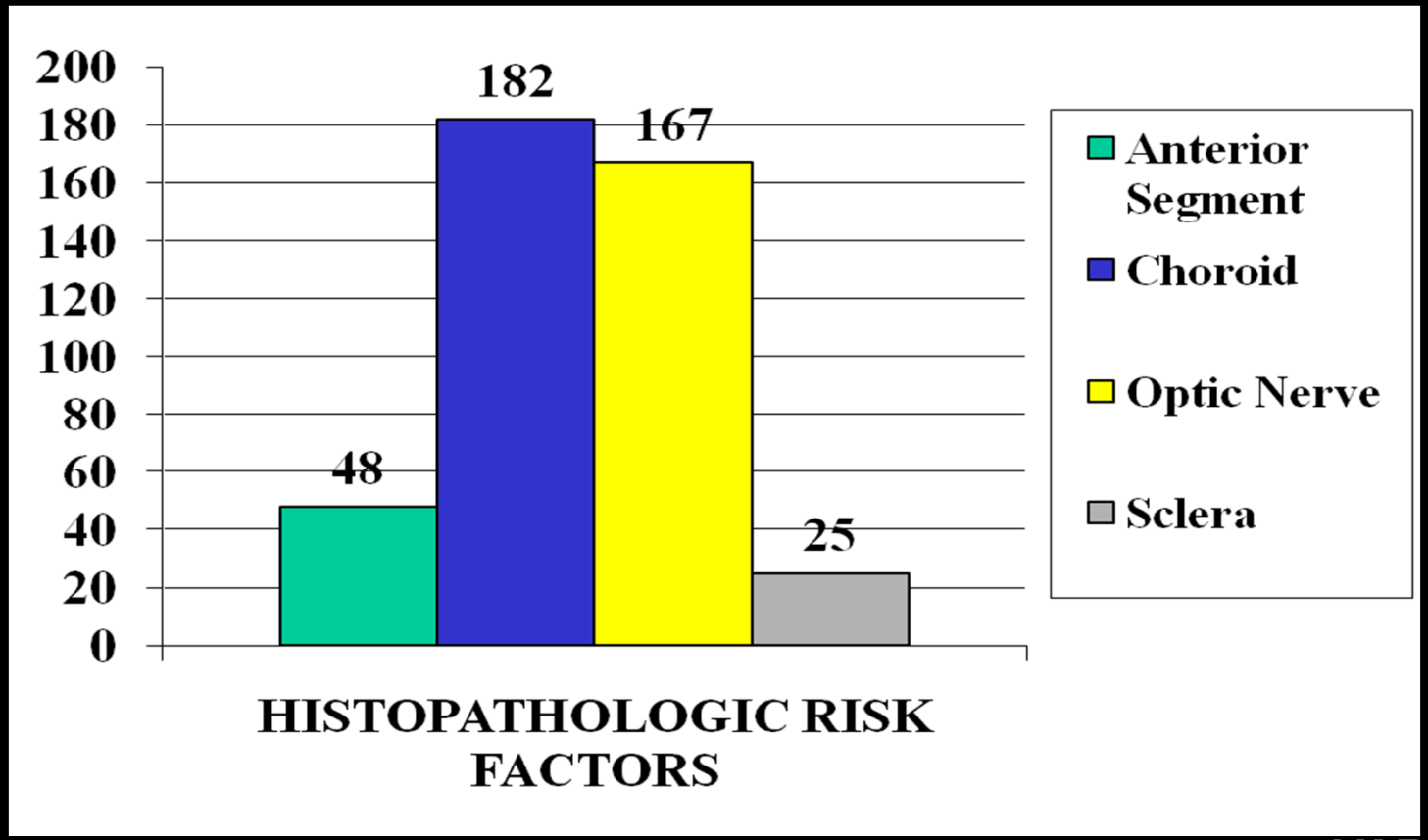
***Bone marrow & CSF involvement***

VAR



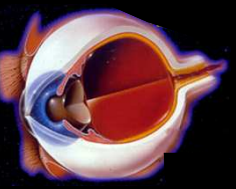
N=547 eyes

# Histopathologic Risk Factors
# 285 of 547 (52%)



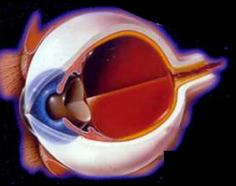

Numbers do not total up tecause multiple HRF were present

VAR

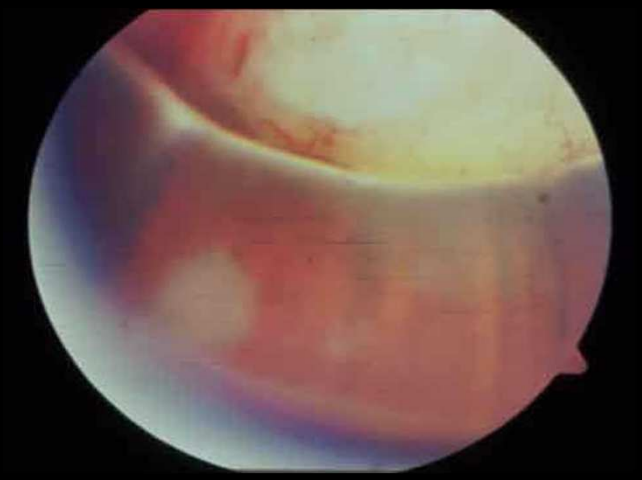


# Adjuvant Chemotherapy

- 6 cycles of VCE - histo risk factors
- 12 cycles of HD Chemo- EOE & ON-TR



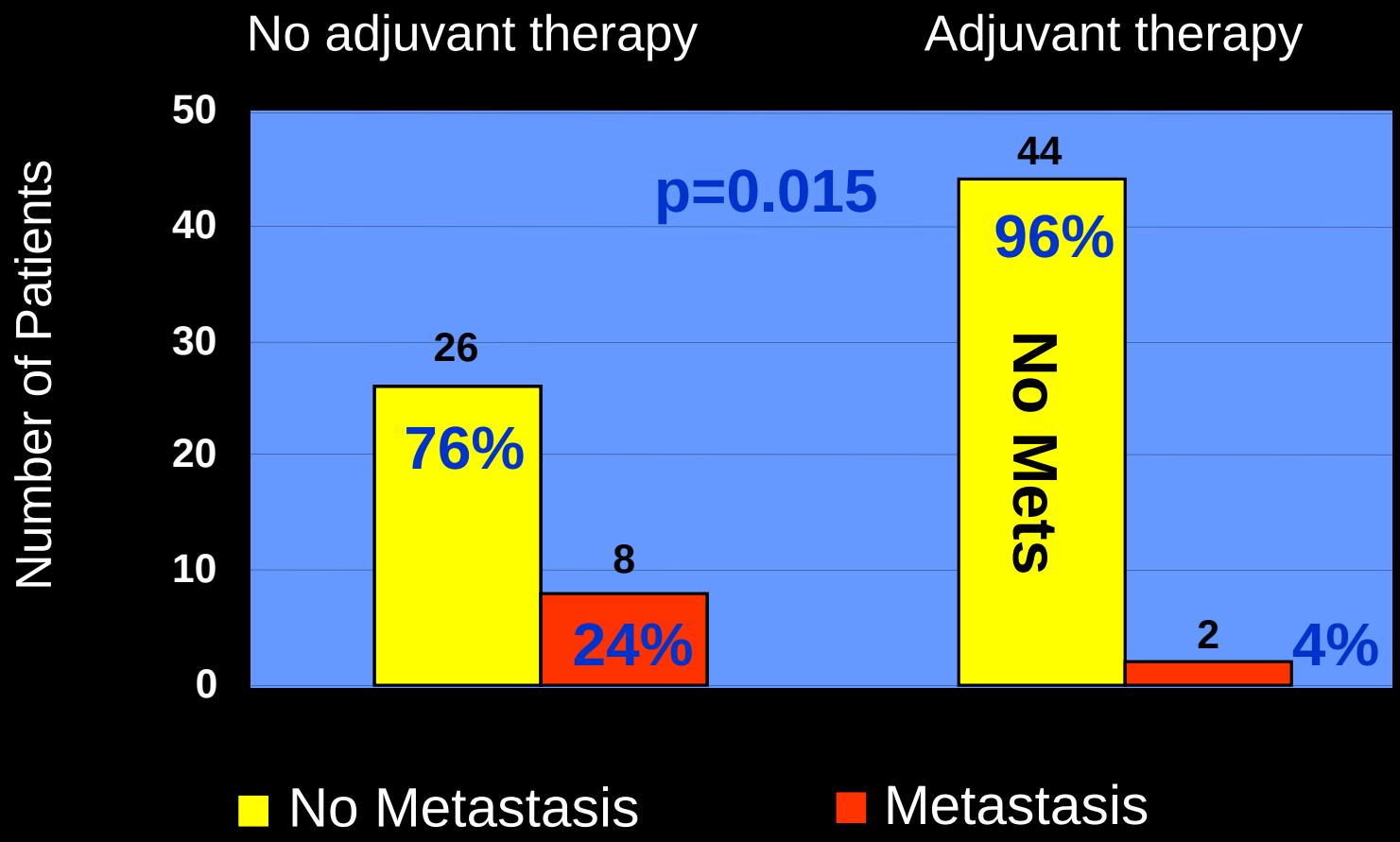
# Post Enucleation
# Adjuvant Orbital EBRT



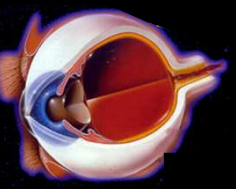
- Optic nerve invasion @ cut end
- Scleral / extraocular extension
- Inadvertent ocular perforation
- Intraocular surgery in unsuspected retinoblastoma

# Does adjuvant therapy help ?

# Incidence of metastasis

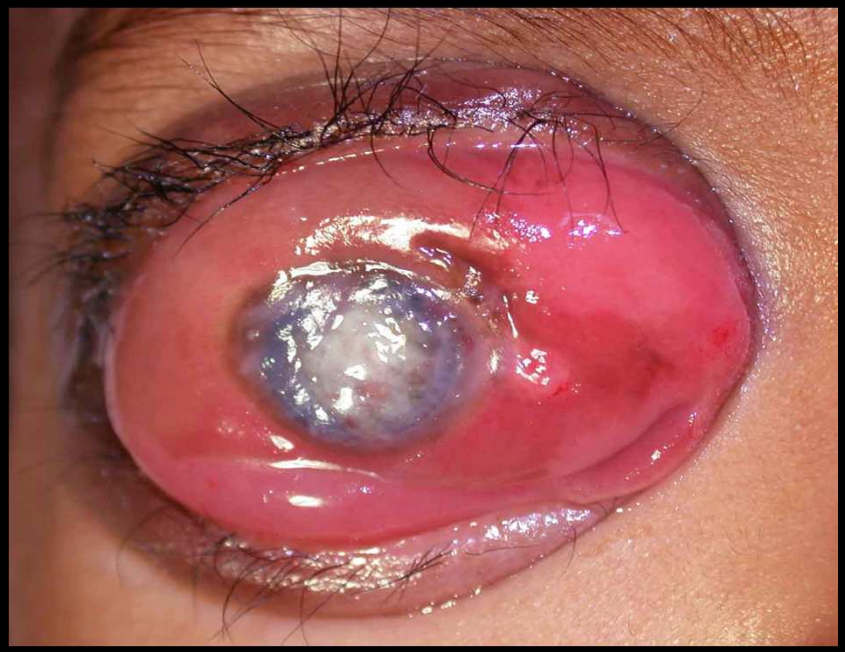



VAR



# Orbital Retinoblastoma

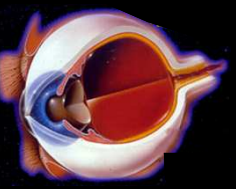
## Management Options



- Orbital exenteration
- External beam radiotherapy
- Systemic chemotherapy

**70% MORTALITY!**

VAR



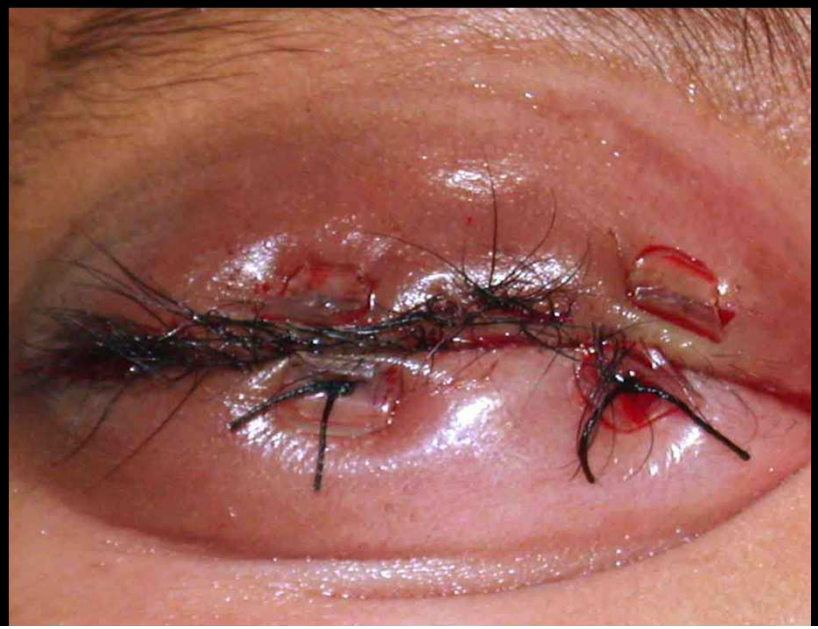
# Orbital Retinoblastoma
## Treatment Protocol

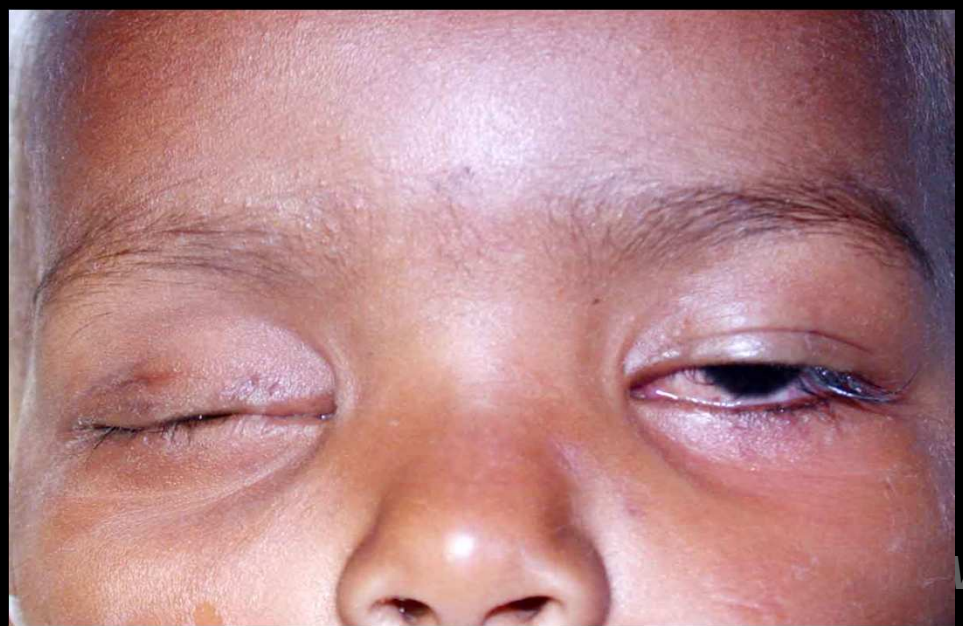
- High-dose chemotherapy
- Enucleation after minimum 3 cycles
- Orbital EBRT
- Continued high-dose chemo for 12 cycles

**70% Survival!**

VAR

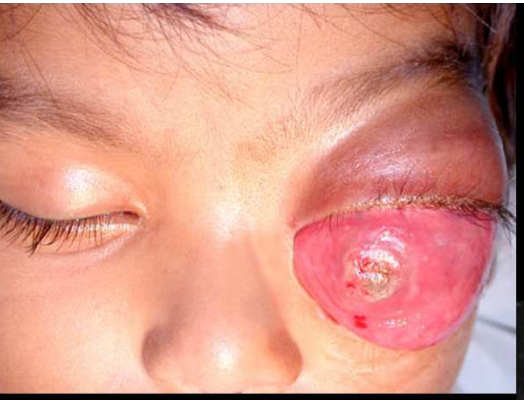
# Neo-adjuvant Chemotherapy

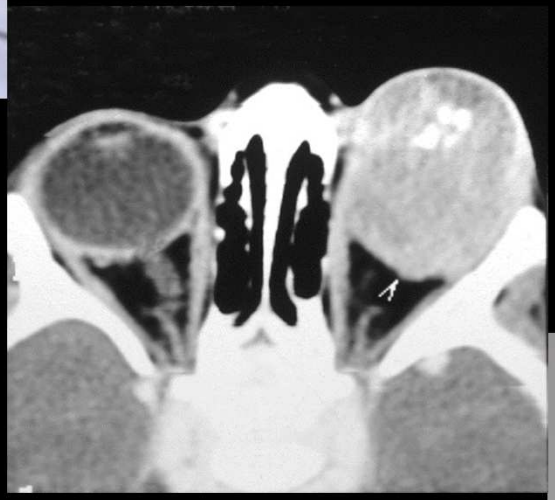


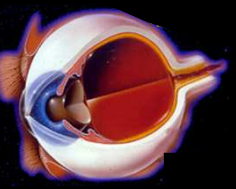


VAR

# Neo-adjuvant Chemotherapy







# Summary
## Chemoreduction Era
### Eye Salvage Rates

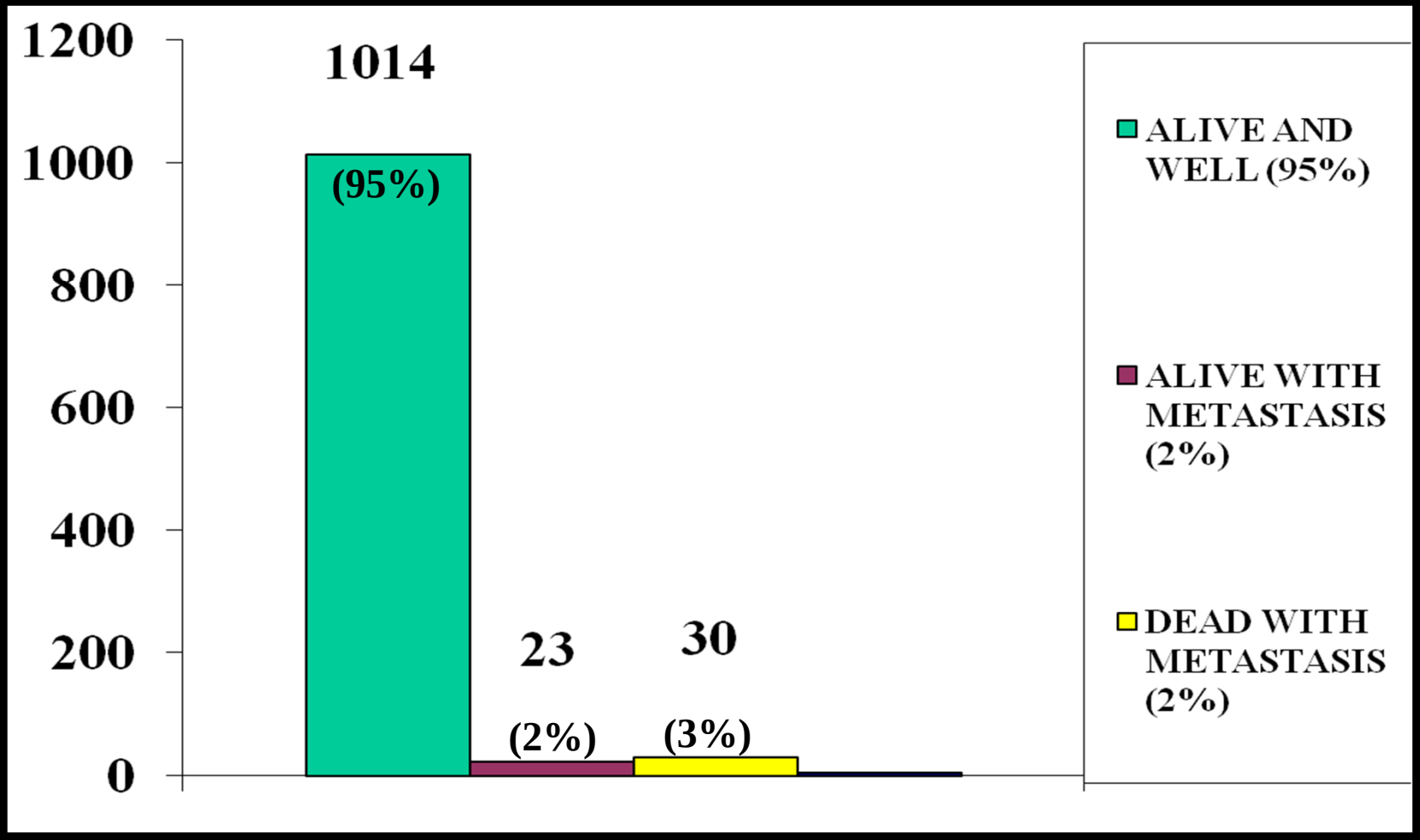
| RE | Ellsworth 1977 EBRT | Hungerford 1995 EBRT | Shields 2003 CRD+SALT | LVPEI 2005 CRD+SALT* |
|---|---|---|---|---|
| I | 91% | 100% | 100% | 100% |
| II | 83% | 84% | 100% | 100% |
| III | 82% | 82% | 100% | 100% |
| IV | 62% | 43% | 75% | 90% |
| V | 29% | 36% | 50% | 75% |

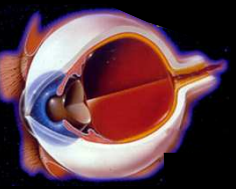
* HD Chemotherapy for group V, Periocular chemotherapy for VB

VAR

# Outcome

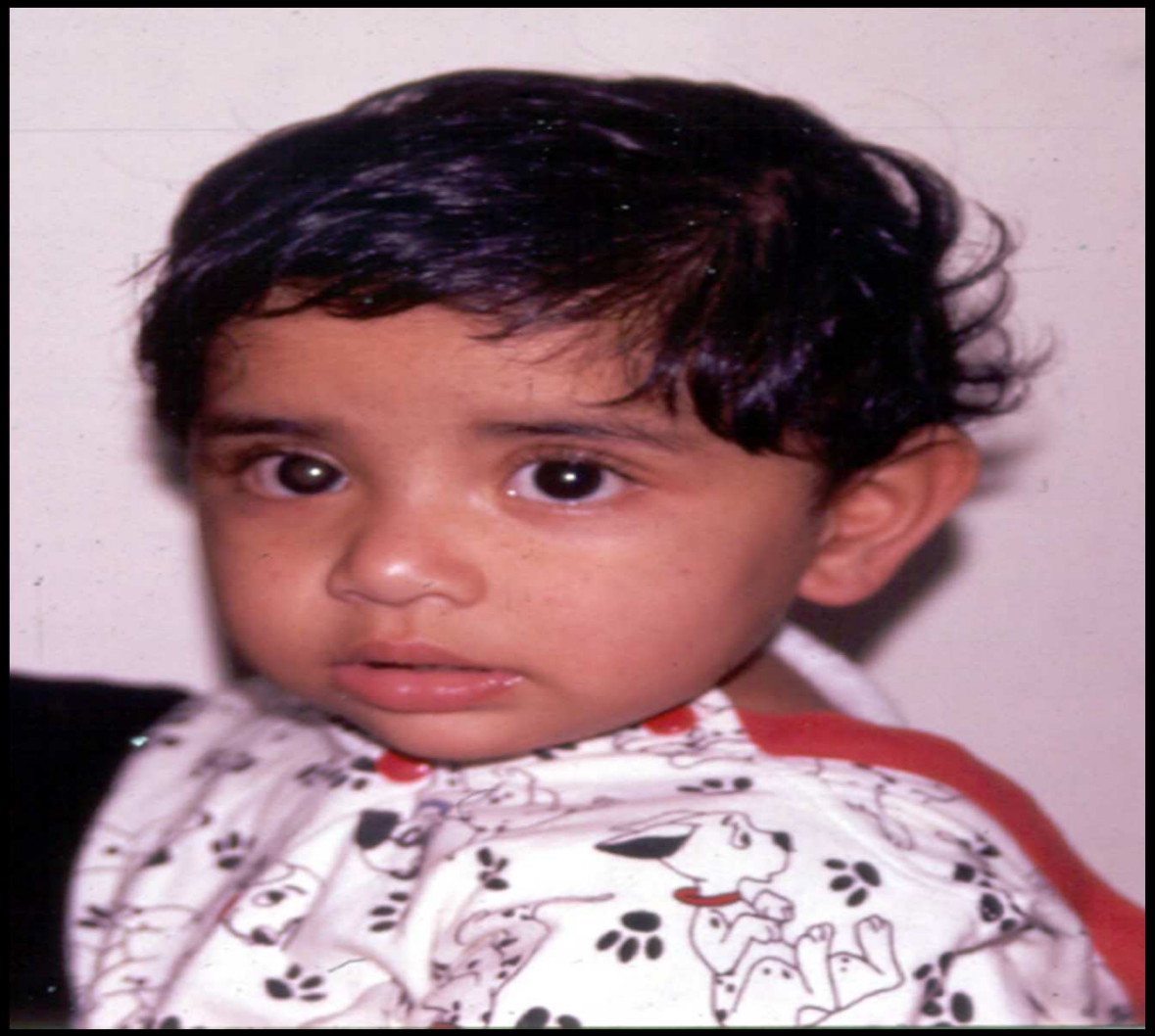
N=1067patients





# Retinoblastoma Overall Outcome

- Overall survival was 95%
- 36% of eyes needed enucleation
- 55% of eyes undergoing enucleation had HP risk factors and needed adjuvant therapy
- Chemoreduction had 90% eye salvage



**Bil. Retinoblastoma - Post Chemo / Radiotherapy**

***Make the Difference !***


EYES make World Beautiful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