Uveal Melanoma

Faisal Ahmed, MD

Department of Radiation Oncology

James M. Slater, MD
Proton Treatment and Research Center

Loma Linda University School of Medicine

Case Presentation

- A 65-year old gentleman presents with acute visual changes in the right eye (OD).

- Ophthalmoscopy was significant for a chorioretinal thickening in the anterior superior nasal quadrant.

Patient History

- Past Medical/Surgical History
  - Hyperlipidemia
- Family History
  - Father with dysokastic nevus syndrome
  - Mother breast cancer
- Social History
  - Retired Arc Welder
  - No EtOH use
  - Non-smoker, no drug use

Physical Examination

Vitals: Ht 68 cm, Wt 147 lbs, BP 135/83, HR 72, Temp 97.9, SpO2 97% on RA
Eyes: Mild conjunctival injection OD
Lungs: Clear with symmetric air movement
Heart: RRR, S1S2 normal
Abd: Soft, non-distended, left-mid tender
Skin: No jaundice
Lymph: No LAD noted

Diagnostic work up

- Ultrasonography is significant for a 6 x 6 mm (base), 4.0 mm height choroidal tumor with moderate internal reflectivity.

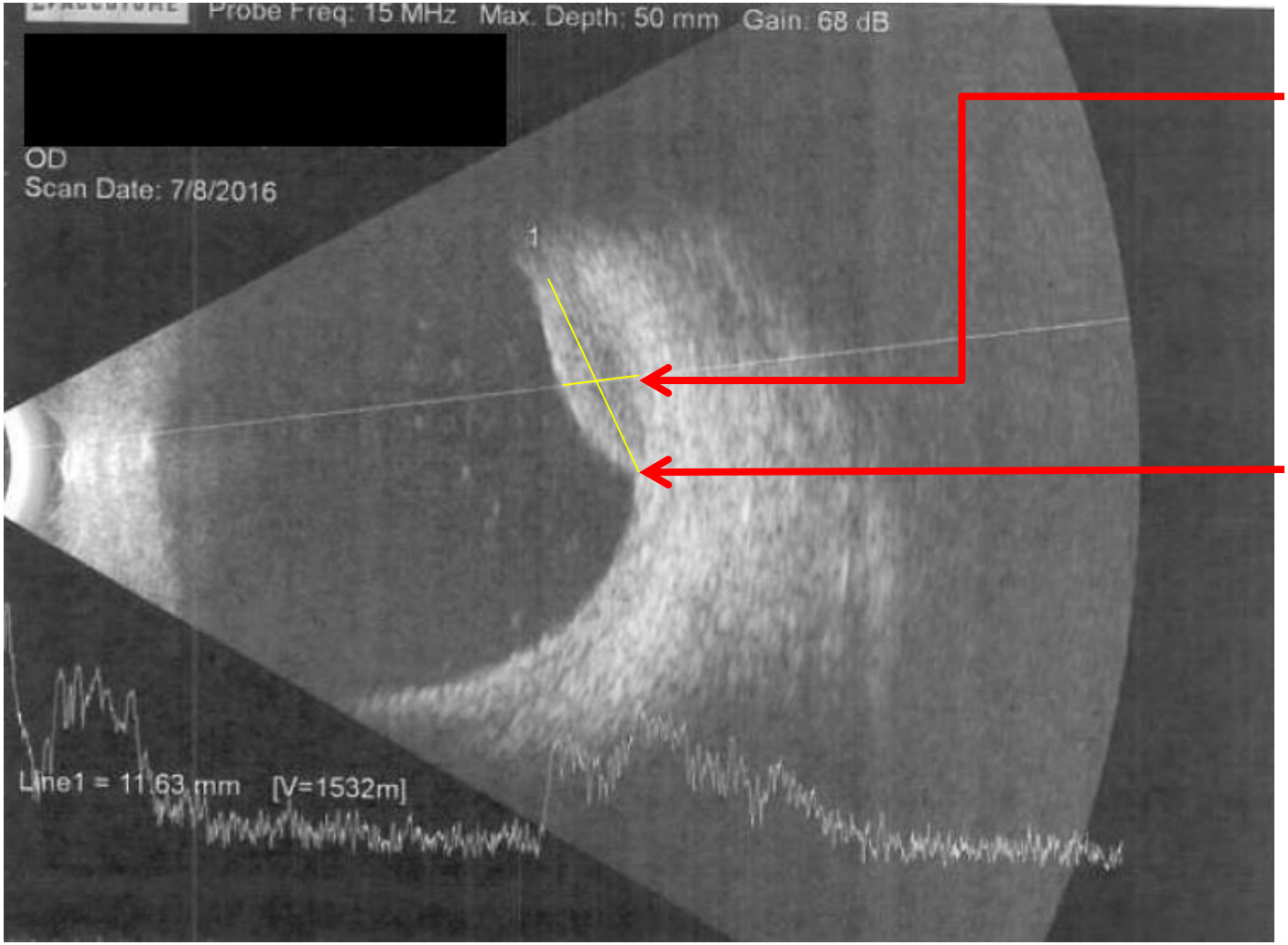
- Fundus photography-pigmented subretinal lesion

- CT chest, abd – negative

Laboratory Studies

- CBC
  - Within normal limits
- Chem Panel within normal limits
  - Cr 0.98
- Liver panel
  - AST 18, ALT 36, AP 111
  - Albumin 4.2

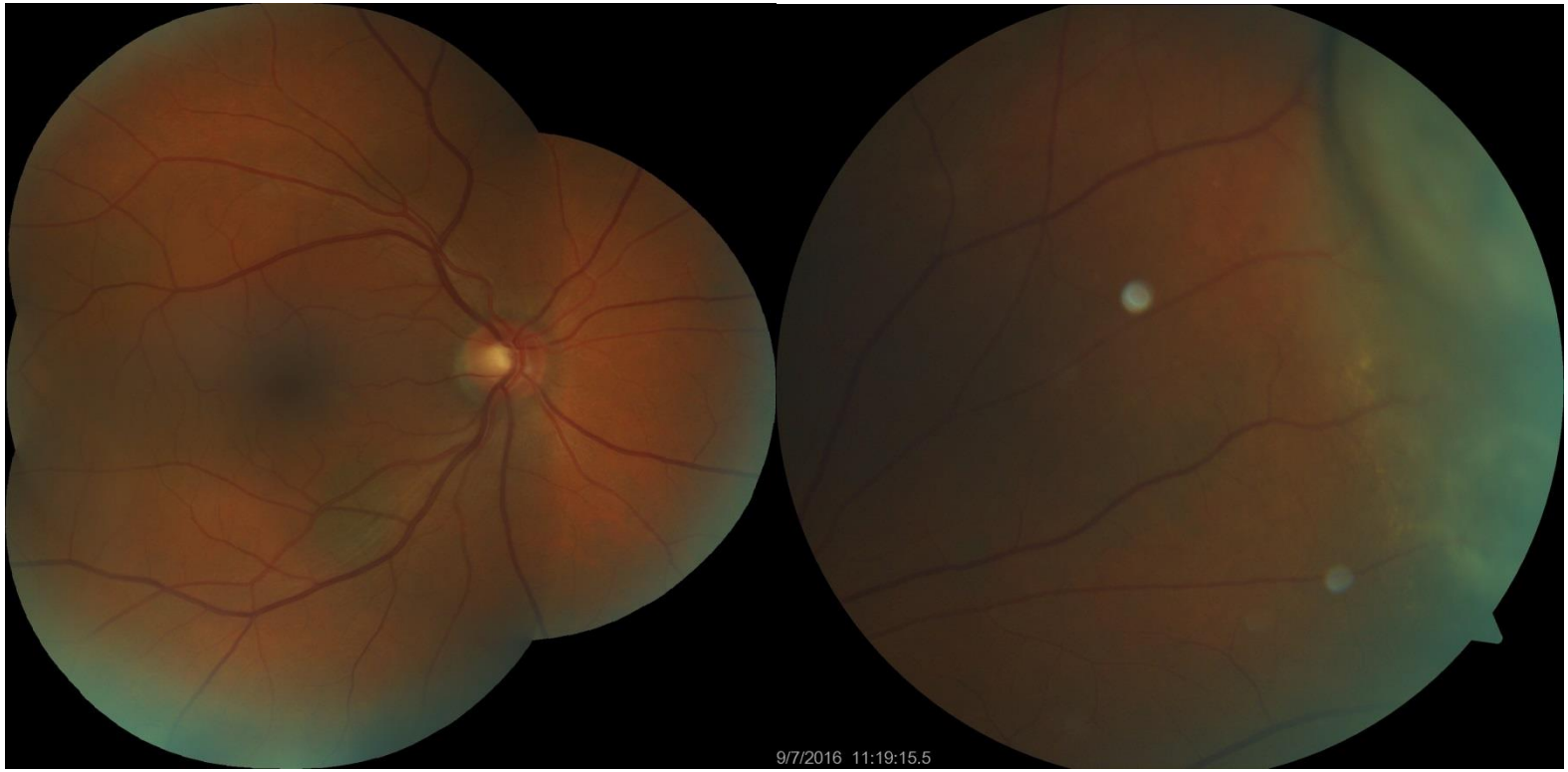
B-scan ultrasonography



3.9 mm mass height

6 mm mass base diameter

Pts Fundus Photo– Right Eye (OD)



Ocular melanoma of the right upper inner quadrant with involvement of the ora serrata. The tumor was anterior and difficult to image on fundus imaging. Left-montage showing right optic disc, central fovea and vascular arcades. Right-darkened tumor on anterior view of fundus.

Background

- Uveal melanoma is the most common malignant tumor of the eye/orbit and accounts for ~70% of all cancers of these tissues
- US Incidence: ~5.1/million patients/year
- Typically occurs in the 5th or 6th decade. Sixty-five percent of melanoma patients are over the age of 50 years.
- Risk Factors: light eye color, fair skin, UV radiation exposure, xeroderma pigmentosum, oculodermal melanocytosis, dyskokastic nevus syndrome
- Rarely bilateral

Anatomy and Patterns of Spread

- 80% located in the choroid (vascular layer between retina and sclera)
- 10-15% in ciliary body (ciliary body tumors have higher DM risk)
- <10% in iris
- Intraocular spread, including vitreous seeding, extrascleral extension, distant mets (liver mostly)

Presentation / Histology

- Asymptomatic, visual field distortion, change in visual acuity, field loss, floaters, flashers, pain, glaucoma

- Histology: Not often biopsied
  - Melanoma
    - Spindle cell (Grade I)
    - Mixed cell (Grade II)
    - Epitheliod (Grade III)

Workup

- H&P
- Ultrasound, Fundus photography, CXR, CT-CA, CBC, LDH, CMP
- Diagnosis is based on primarily on imaging, ophthalmoscopic appearance and ancillary testing only. Biopsy is not routinely done, unless for genetic risk stratification.
- The tumor typically appears as a unilateral, solitary, elevated, dark brown or gray, variably pigmented, dome-shaped mass. Lipofuscin (orange pigment) is often found on the surface of the tumor and can help differentiate these lesions from uveal nevi. Retinal detachment may be present and is more likely in larger tumors.

COMS Classification

- Eye tumors can be classified by these guidelines from the Collaborative Ocular Melanoma Study (COMS):
  - Small: 1-3 mm in height and 5-16 mm in diameter
  - Medium: 3.1-8 mm in height and not >16 mm in diameter
  - Large: >8 mm in height and >16 mm in diameter

3 Major COMS Trials

Collaborative Ocular Melanoma Study Group	Small	Medium	Large
Study Type	Non-randomized, prospective	Randomized, prospective	Randomized, prospective
#N	204	1317	1003
Objective	To describe the time to tumor growth and characteristics associated with growth of small tumors.	I-125 brachytherapy vs. Enucleation for treatment of medium tumors.	Pre-enucleation radiation vs. Enucleation alone for treatment of large tumors.
Notable Findings	❖ 21% grew by 2 years ❖ 31% grew by 5 years ❖ Characteristics associated with growth: initial thickness and diameter, lipofuscin, absence of drusen, absence of RPE changes	❖ No clinically statistically significant difference in survival between the 2 treatments for up to 12 years after treatment	❖ No significant difference in survival between the 2 treatments ❖ Age and largest basal diameter prognostic

Treatment paradigm

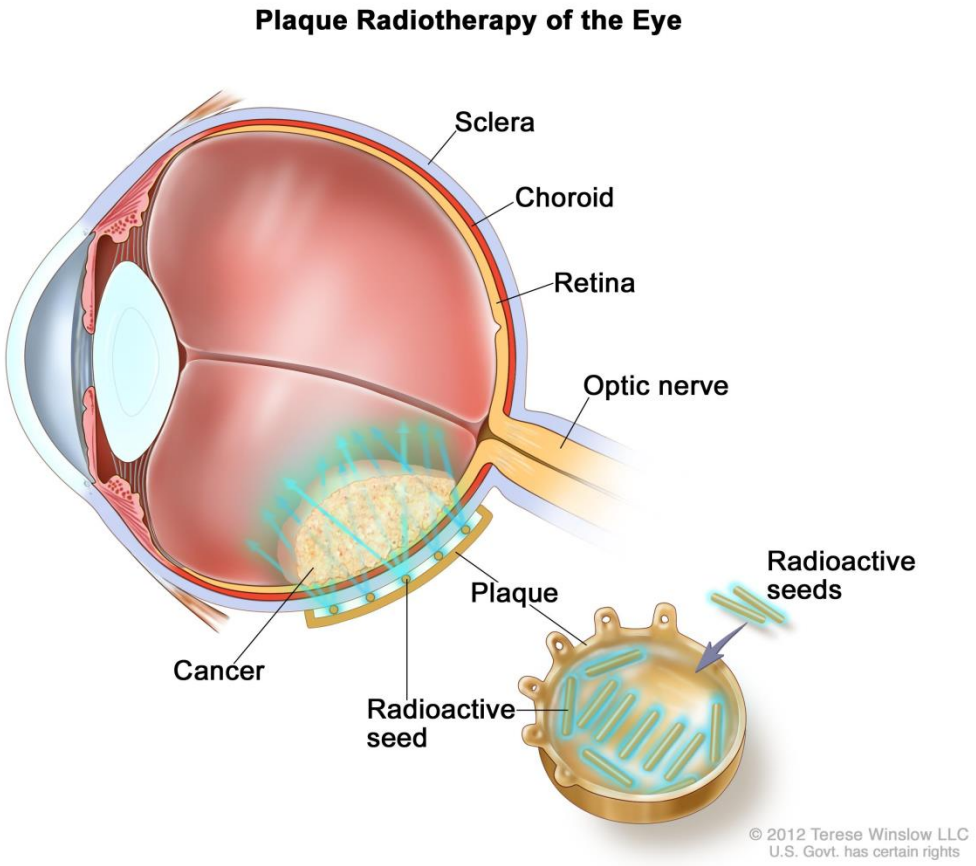
- Small:
  - Observation
  - Evidence of growth: Surgery, Plaque Brachytherapy, Particle RT (protons, carbon ions, helium ions)
- Medium:
  - Surgery (enucleation, orbital exenteration, local resection +RT, or Particle RT
- Large:
  - Enucleation
  - Partical RT

RT Toxicities

- Acute: Dermatitis, eye irritation
- Late: Vision loss, Cataracts, retinopathy, glaucoma, dry eye, loss of lashes, chronic tearing

RT Techniques

- I-125 plaque
  - Field: tumor + 2mm margin
  - Plaque surgically sutured to sclera for 4-7 days
  - Rx: minimum 85 Gy; dose rate 0.6 to 1.05 Gy/hr to apical height of the tumor or 5mm whichever is greater.



RT Techniques

- Proton Beam Therapy
  - 50–70 Gy (RBE) range in 5 Fractions
  - Patient is taken to OR for tantalum fiducials placed around tumor, identified by trans illumination
  - Immobilization with rigid mask and bite block
  - Eye is fixed using stimulus directed light
  - Can treat through lids or with lid retraction

Proton Therapy Vs. Plaque Brachy

- Tumors located in the back of the eye and under orbital muscles are difficult to treat with plaque without significant risk to the muscles or nerves.
- The success of proton treatments is solid with >5,000 patients treated with a 5-year local control of 98% and 95% for small/medium and large ocular melanomas, respectively.
- The overall 5-year metastases-free survival is 80%, smaller lesions (95%) and larger lesions (60%).
- Improvement of vision depends on the original condition of the eye, tumor size and location and whether there is retinal detachment.

PBT Outcomes

Study	Number of patients, median age	Dose and fractionation	Median F/U (months)	Outcomes
Loma Linda, 2001 Treatments 1990–1998	78 Median age 61	Median 70.2 Gy (RBE), 5 fractions	34	3 year OS 87.1%, 3 year LC 92.8%, 3 year MFS 85.7%, 3 year DSS 86.5%5 year OS 70.3%, 5 year LC 90.5%, 5 year MFS 76.2%, 5 year DSS 75.6%
Harvard, 2002 Treatments 1975–1996	1922 Median age 60	70 Gy (RBE), 5 fractions (94%), remainder 50 Gy (RBE)	62	5 year LC 96.7%, 15 year LC 95.1%
Harvard, 2015 Treatments 1975–2005	3088 Median age 61	70 Gy (RBE), 5 fractions (87%), remainder 50 Gy (RBE)	148	15 year ACM 49%, 20 year ACM 58.6%, 25 year ACM 66.8% 15 year melanoma mortality 24.6%, 25 year melanoma mortality 26.4%, 41.6% of all mortality due to melanoma metastasis
UCSF, 2002 Treatments 1978–2000	996 (199 PBT, 348 helium ion, 449 I-125 brachytherapy) No age given	56 Gy (RBE), 4 fractions	54	5 year LC 96.5% LC higher with particle therapy than brachytherapy

Adapted from Verma et al., *Clin Oncol* , 2016

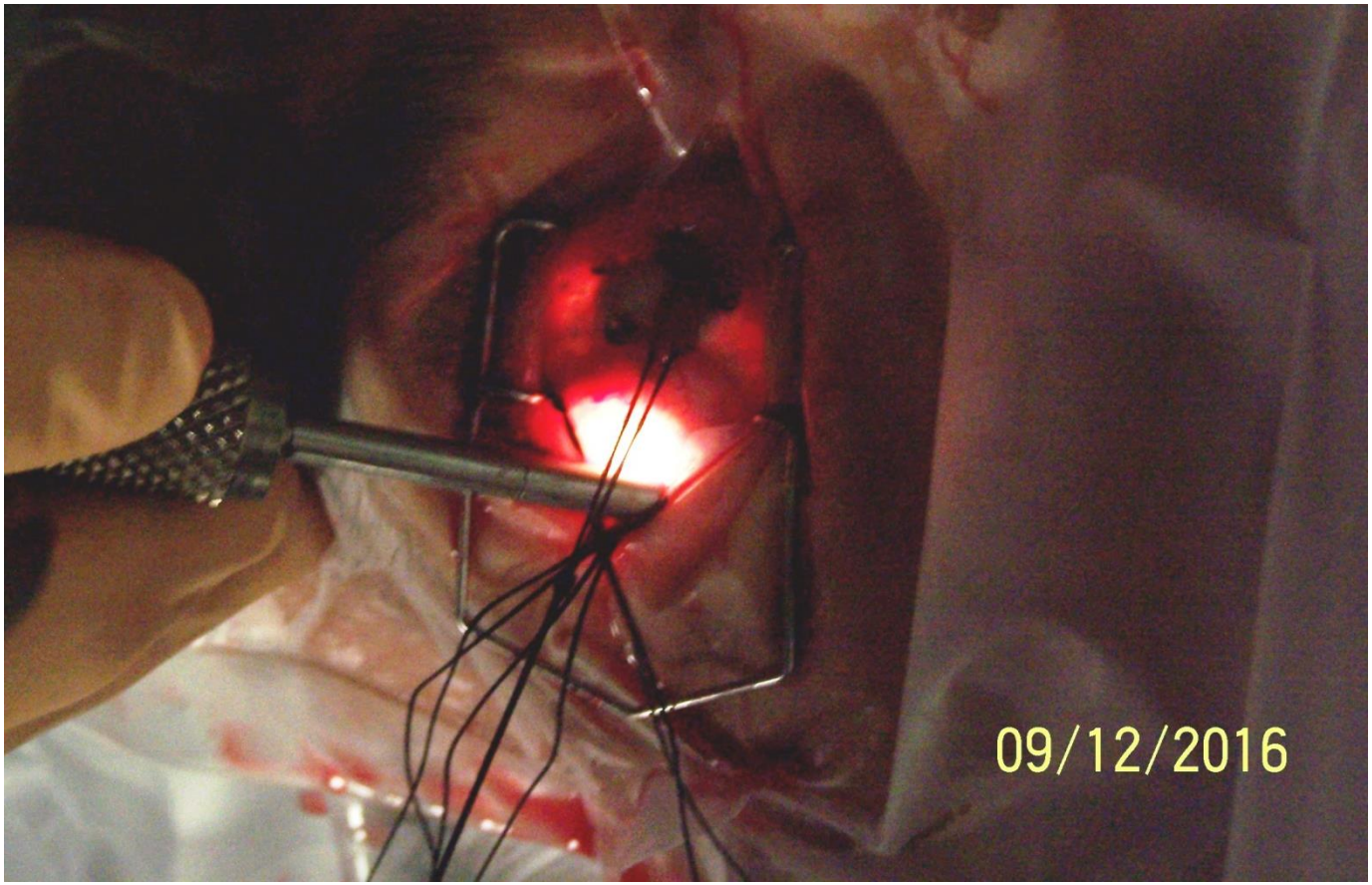
This patient's plan

- The scleral quadrants were inspected back to the optic nerve and there was no evidence of extraocular extension of the tumor invading the orbit.
- The eye was then transilluminated and the tumor's shadow was visualized in the nasal periphery, partially underneath the medial rectus muscle. 4 marks were placed at the margins of the tumor; anterior, posterior, inferior, and superior.
- The tantalum rings were then sutured to the sclera at these sites using 5-0 Mersilene suture.
- **70 Gy in 5 fractions was then delivered with proton beam therapy**

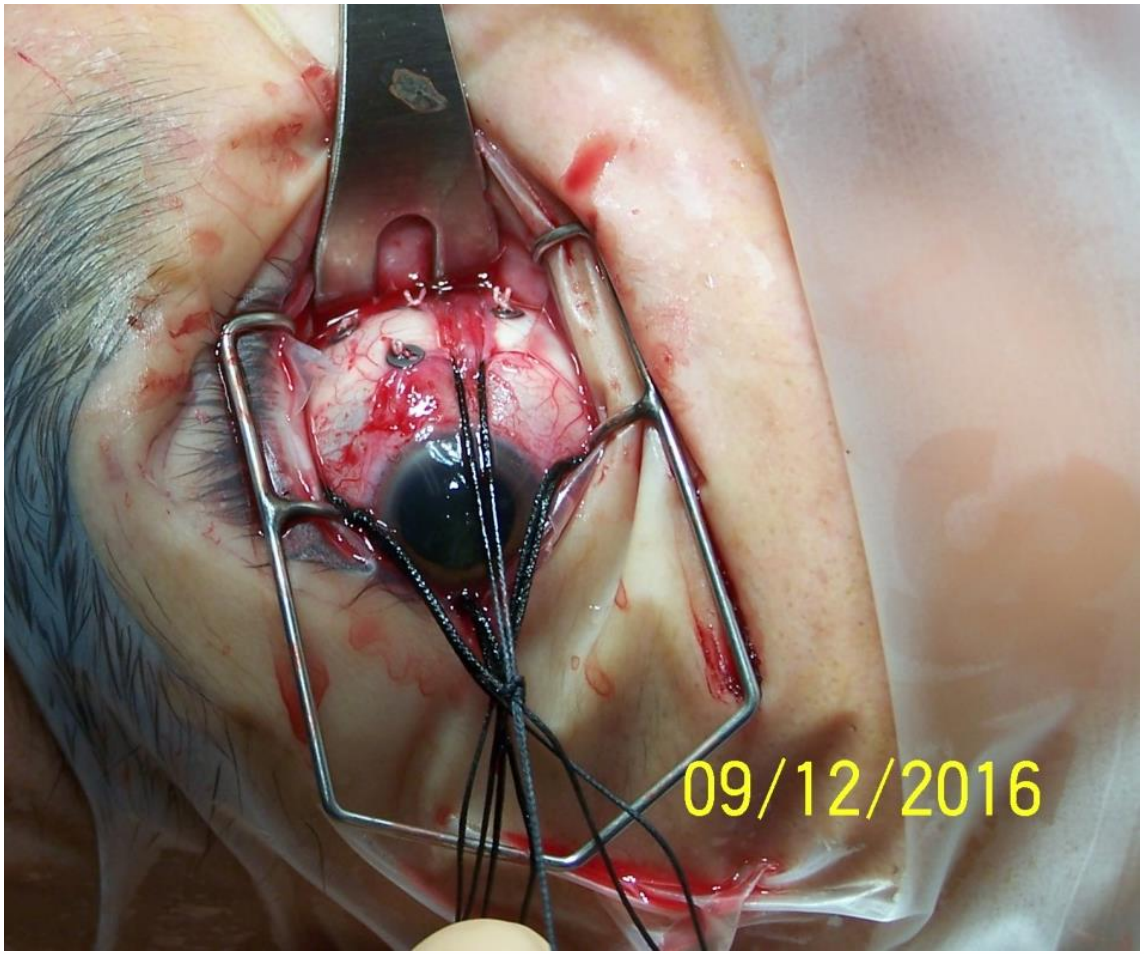
Follow Up

- Small tumors under observation are evaluated q3 months
- Patients who receive radiotherapy are seen in follow up q3 months with ophthalmoscopy exam for the first year, q4 months the following year, and q6 months thereafter
- Patients who are enucleated are usually seen twice a year
- Metastatic evaluation with liver imaging and labs are completed q6 months for large tumors, and q12 months for small/medium tumors

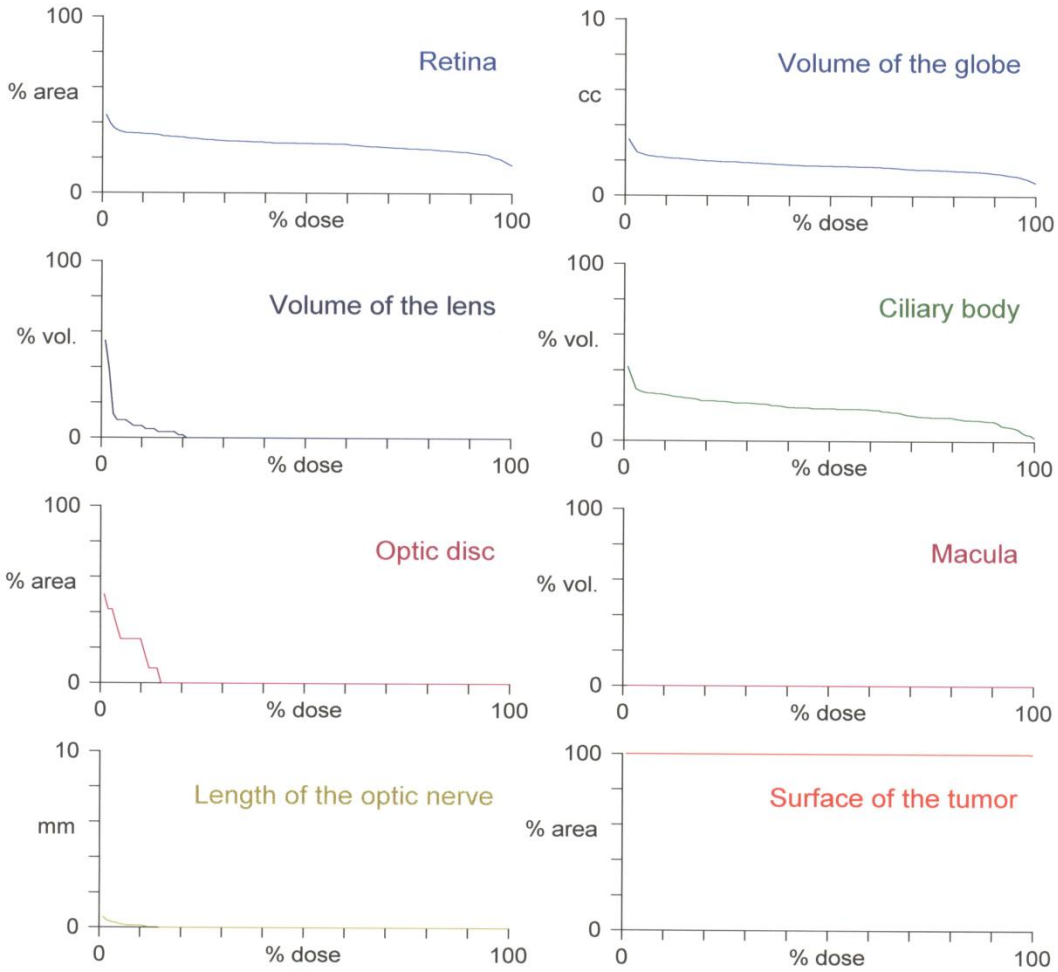
Trans Illumination



Tantalum Clips

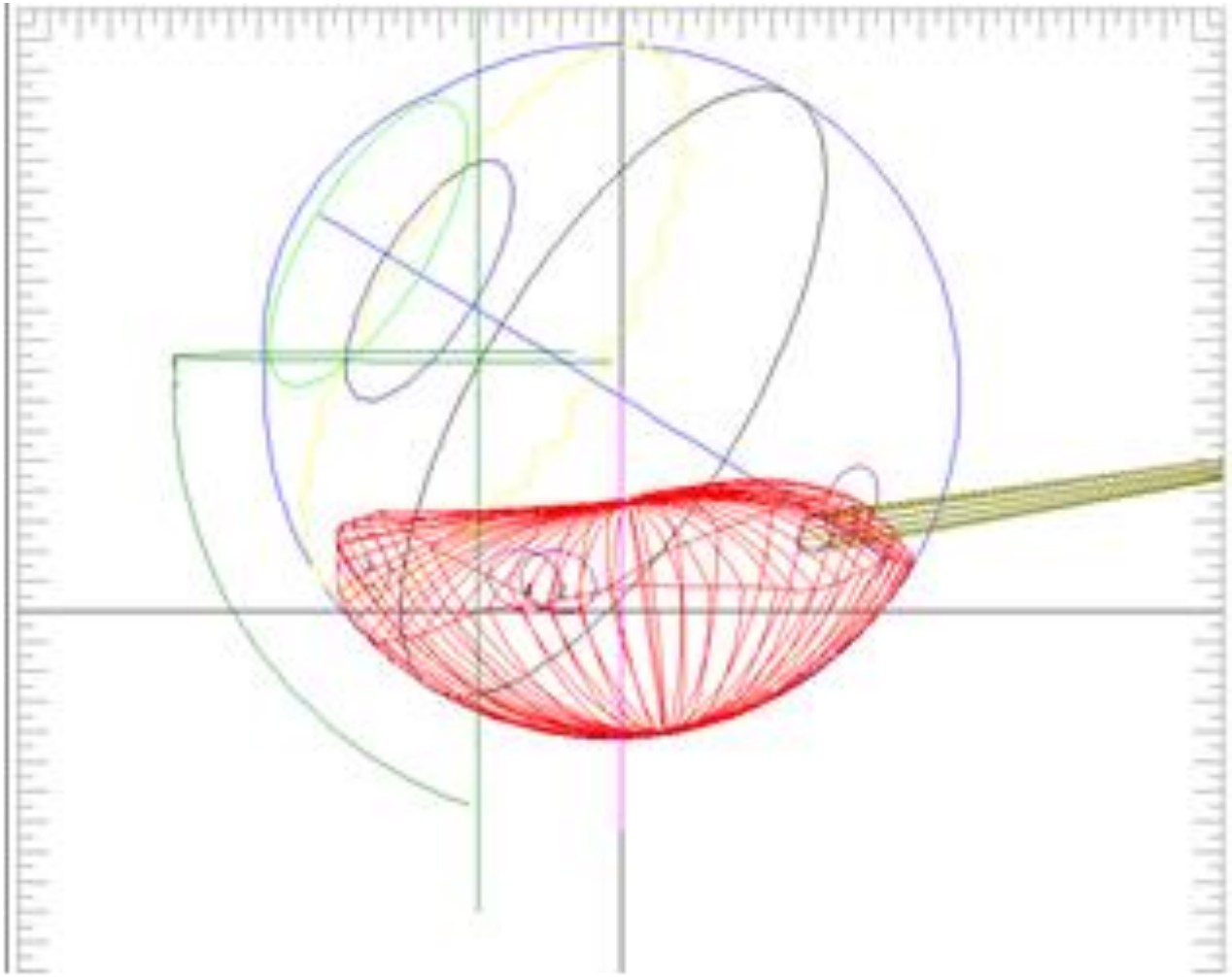


DVH

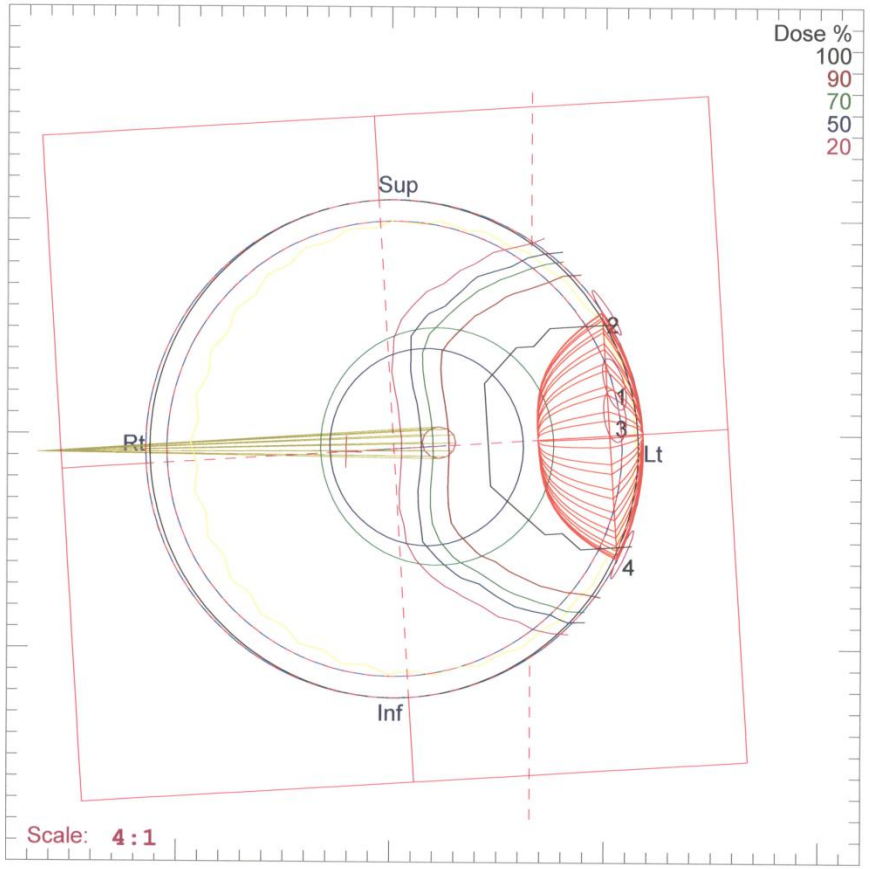


Goal is to minimize dose to structures as maximally possible without dose compromise of the target.

Central tumors will induce vision loss as the macula will be compromised.

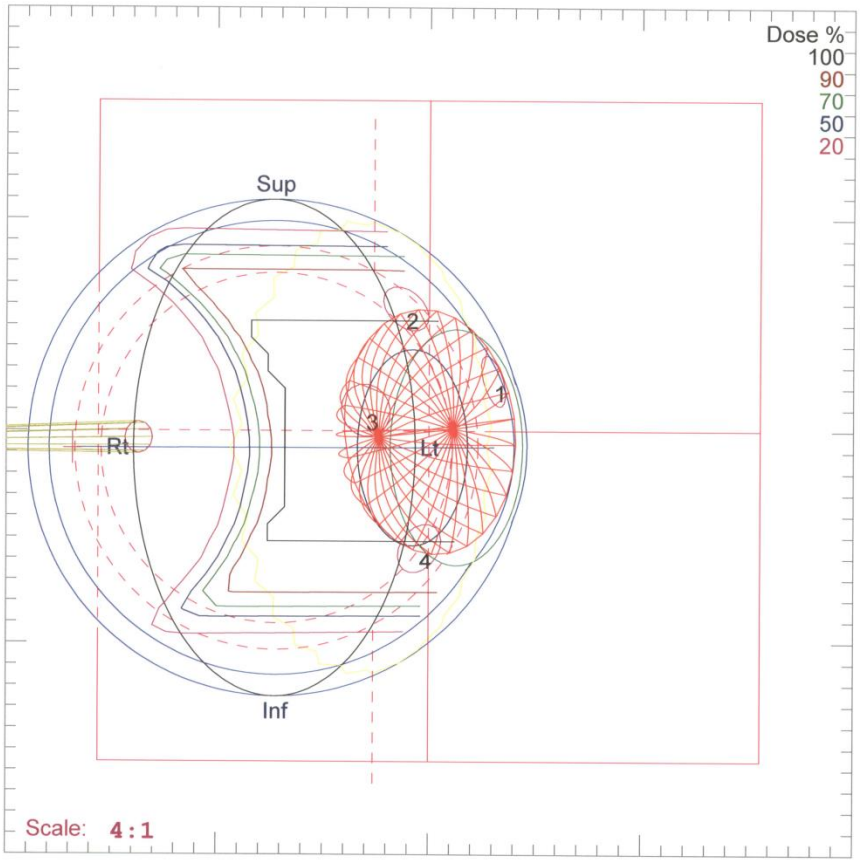


Three dimensional computed model of the eye and tumor constructed using anatomical marks and fiducials, lens (area outlined in black), globe (blue), eye lid (olive), nerve (gold).



Plane: Th= -78 Eps= -4 Psi= 0 (deg.) X= 0.0 Y= 0.0 Z= 0.0 (mm)

Transverse tumor plane



Plane: In beam at 0 deg. X= 0.0 Y= 0.0 Z= 0.0 (mm)

Vertical beam plane