Ocular Melanoma & Proton Therapy

Kavita K. Mishra, MD, MPH
Director & Associate Professor
Ocular Tumor Proton & Plaque Therapy Program
UCSF Comprehensive Cancer Center
January 13, 2020

Objectives

Topics
Overview of ocular melanoma and proton technology: *What do we know from the past 50 years?*
Clinical data & outcomes: *Which factors matter for which outcomes?*
Treatment Planning & Delivery: *Current techniques and what is on the horizon?*

kavita.mishra@ucsf.edu

LBNL-UCSF: Particle Therapy

1939	- Nobel Prize cyclotron
1950s	- Pituitary disease
1975	- Cancer RT
1975	Helium – 1st pts
1977	C
	Ne
1979	Ar
1982	Si

1,463	Cancer pts
347	UM Pts He

kavita.mishra@ucsf.edu

LBNL *1931-1992*

kavita.mishra@ucsf.edu

Helium & Proton Ocular Program

1975: Proton Rx at Harvard

1977: Helium Ion Rx
LBNL 184 inch cyclotron
(Castro and Quivey)

Particle Rx consistently excellent radiotherapy results

Ocular model computer program (Goitein and Miller)

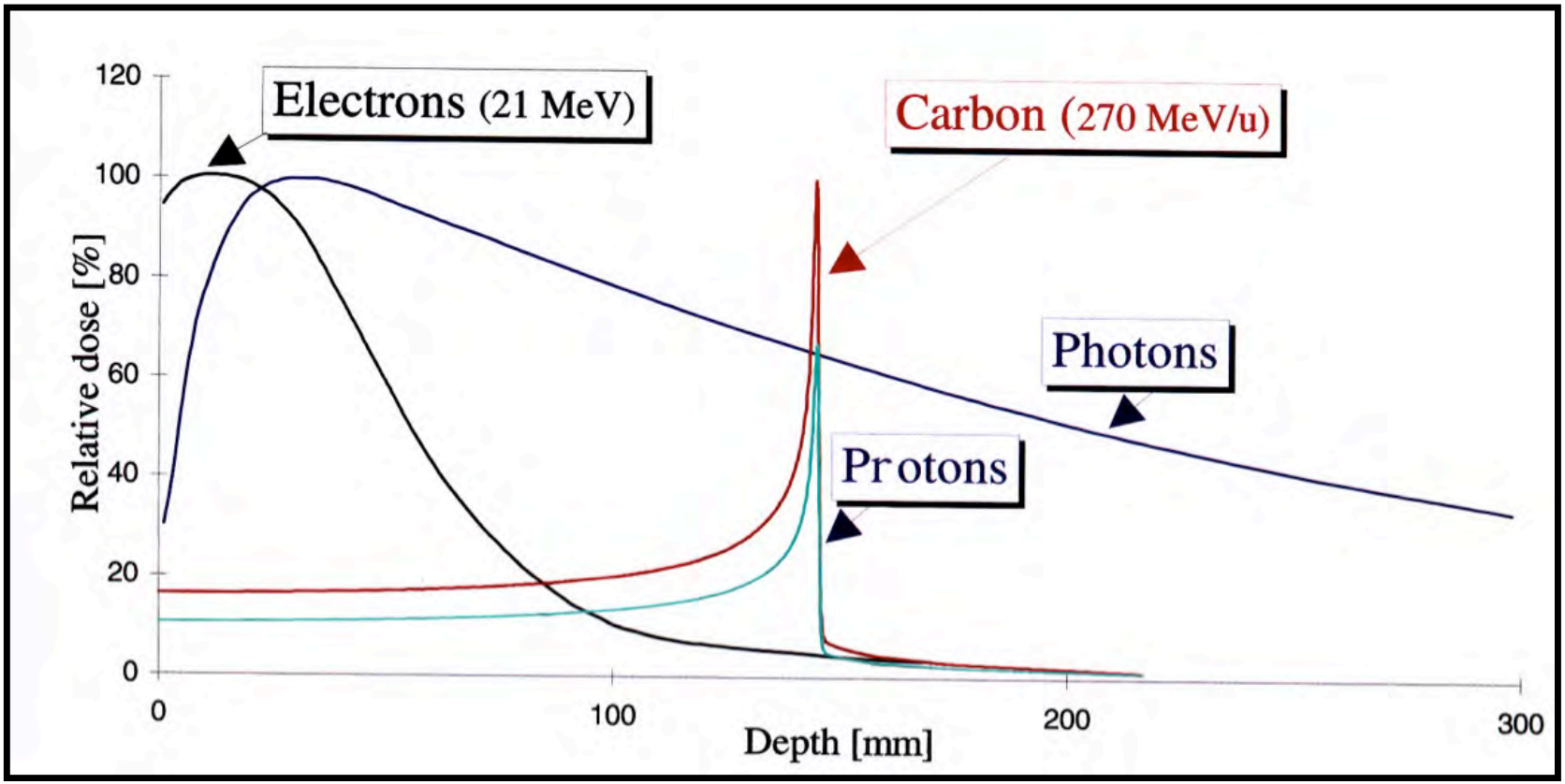
1994: Transfer to Crocker Proton (CNL) 76 inch cyclotron

kavita.mishra@ucsf.edu

UCSF + LBNL + Crocker

kavita.mishra@ucsf.edu

Background: Proton Therapy



kavita.mishra@ucsf.edu

UCSF Department of Radiation Oncology

Background: Question* - Protons

280. What is the accepted RBE value for proton therapy?

(A) 0.96
(B) 1.1
(C) 1.6
(D) 2.0

* American College of Radiology In-Training Examination for Radiation Oncology Residents

Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

kavita.mishra@ucsf.edu

Background: Question* - Protons

280. What is the accepted RBE value for proton therapy?

(A) 0.96
(B) 1.1
(C) 1.6
(D) 2.0

Key: B
Solution: The widely accepted RBE for protons (relative to 250 kVp photons) is 1.1. Currently, there is no agreement on refining this value based on specific tissue, energy or dose values.
References: Paganetti H1, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD. Relative biological effectiveness (RBE) values for proton beam therapy. Int J Radiat Oncol Biol Phys. 2002 Jun 1; 53(2):407-21.

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kavita.mishra@ucsf.edu

Background: Question* - Protons

85. Relative to photons, how will the therapeutic ratio of protons be altered if the RBE value for 1.1 is NOT considered in the treatment plan?

(A) No effect
(B) Reduced, due to low tumor dose
(C) Increased, due to reduced dose to normal structures
(D) Reduced, by increasing the effective dose to normal structures

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kavita.mishra@ucsf.edu

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(C) Increased, due to reduced dose to normal structures
(D) Reduced, by increasing the effective dose to normal structures

Key: D
Solution: In generic terms, the RBE of 1.1 assigned to proton therapy indicates that protons are approximately 10% more effective in inducing cell kill in comparison to MV photons. Failure to account for this during treatment planning would result therefore in higher effective doses and hence an increased risk of normal tissue damage although, tumor control could potentially be improved.
References: Francesco Tommasino and Marco Durante Proton Radiobiology. Cancers (Basel). 2015 Mar; 7(1): 353-381.
Paganetti, et al. Relative biological effectiveness (RBE) values for proton beam therapy. Int J Radiat Oncol Biol Phys. 2002 Jun 1; 53(2):407-21.
Levin, et al. Proton beam therapy. Br J Cancer. 2005 Oct 17; 93(8):849-54.

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kavita.mishra@ucsf.edu

Background: Question* - Protons

174. The rationale for proton therapy versus conventional photon therapy in Hodgkin disease is to:
(A) decrease treatment time.
(B) escalate dose above 45 Gy.
(C) minimize late adverse effects.
(D) minimize acute adverse effects.

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Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

kavita.mishra@ucsf.edu

Background: Question* - Protons

174. The rationale for proton therapy versus conventional photon therapy in Hodgkin disease is to:
(A) decrease treatment time.
(B) escalate dose above 45 Gy.
(C) minimize late adverse effects.
(D) minimize acute adverse effects.

Key: C
Solution: Proton therapy lacks exit dose and therefore delivers less dose to normal tissues than photon therapy, particularly in the low and intermediate dose ranges. Early clinical data demonstrate that proton therapy leads to acute toxicity and disease outcomes similar to those expected from photon therapy. The strongest rationale for using proton therapy in Hodgkin disease patients is the reduction in clinically significant late adverse effects, especially since many Hodgkin disease patients are treated at a young age will live for many decades after being cured.
References: Hoppe BS, et al. (2014) Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. Int J Radiat Oncol Biol Phys. 89(5); 1053-9.

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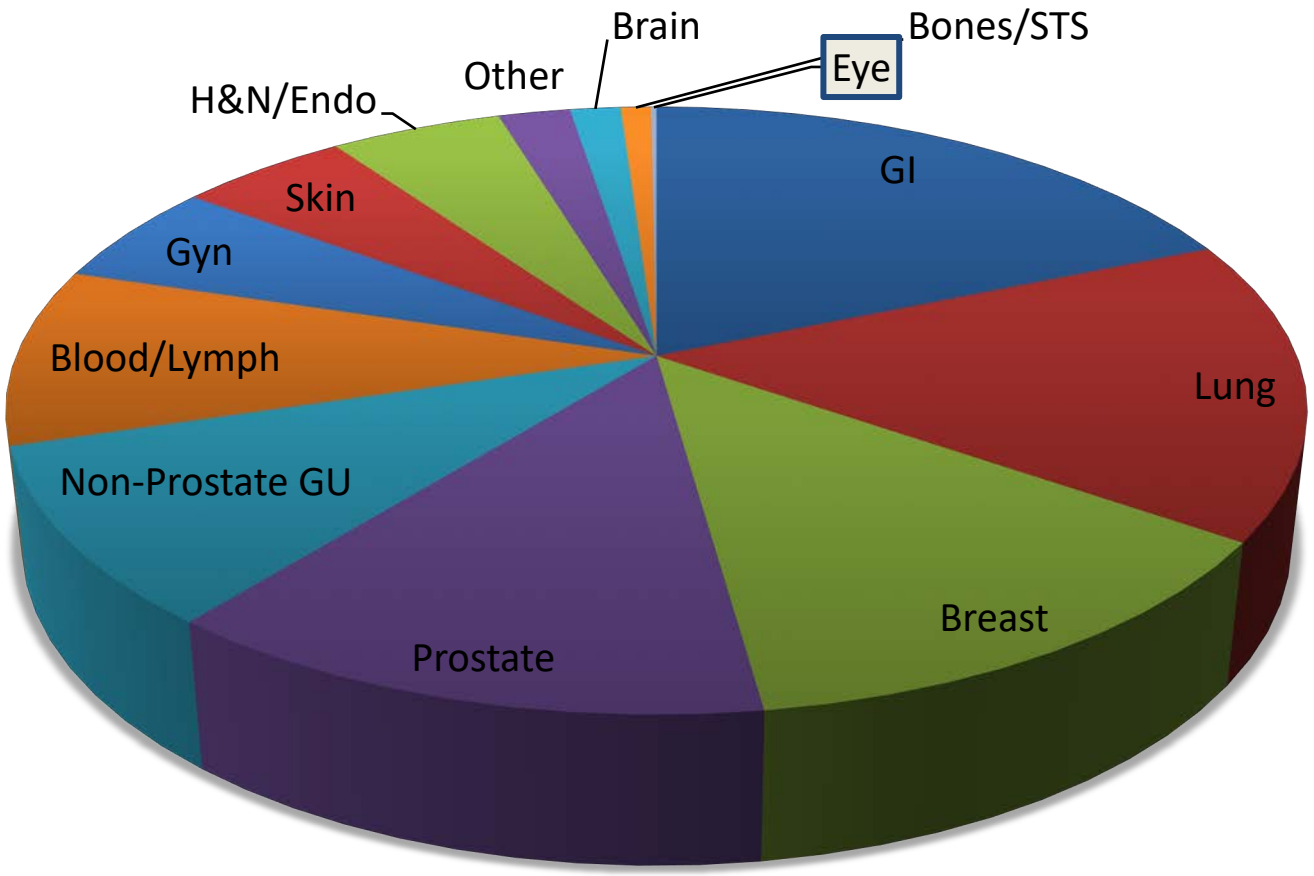
kavita.mishra@ucsf.edu

Background: Eye



Source: American Cancer Society Statistics (http://www.cancer.org/docroot/stt/stt_0.asp?from=fast)

kavita.mishra@ucsf.edu

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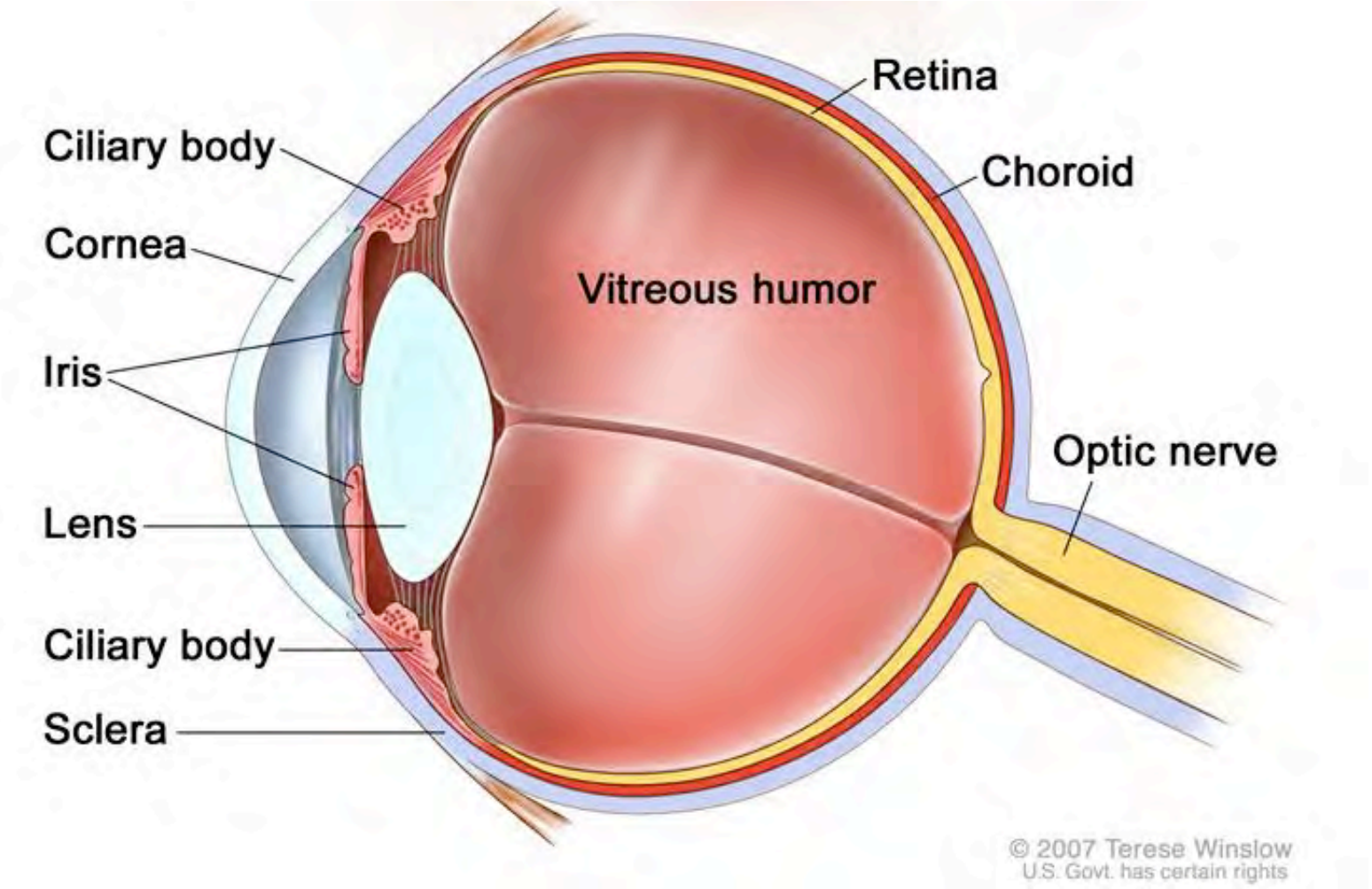
Background: Eye

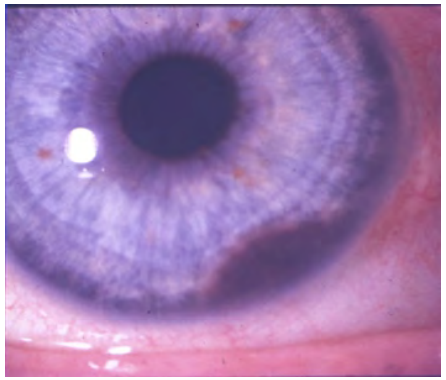


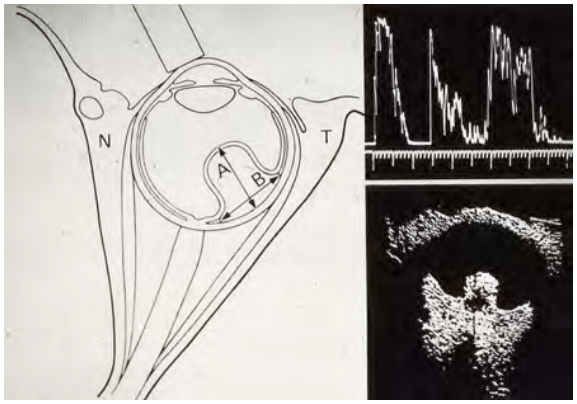
Source: Terese Winslow © Terese Winslow Medical Illustration

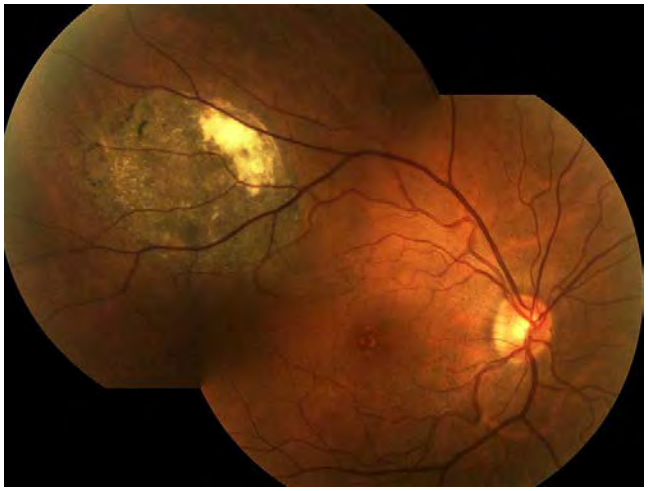
kavita.mishra@ucsf.edu

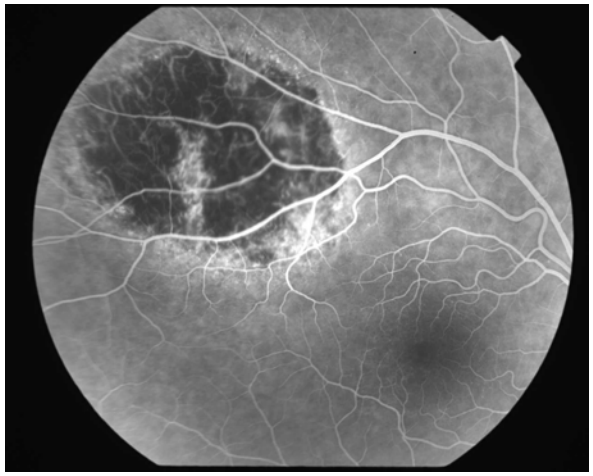
Clinical

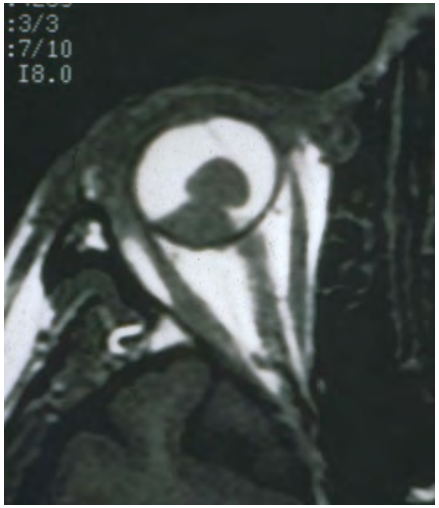
Light colored; Welders; Sun/snow burns
1/3 asx

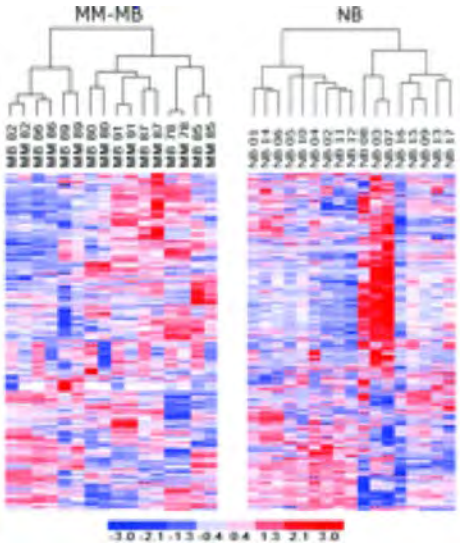












kavita.mishra@ucsf.edu

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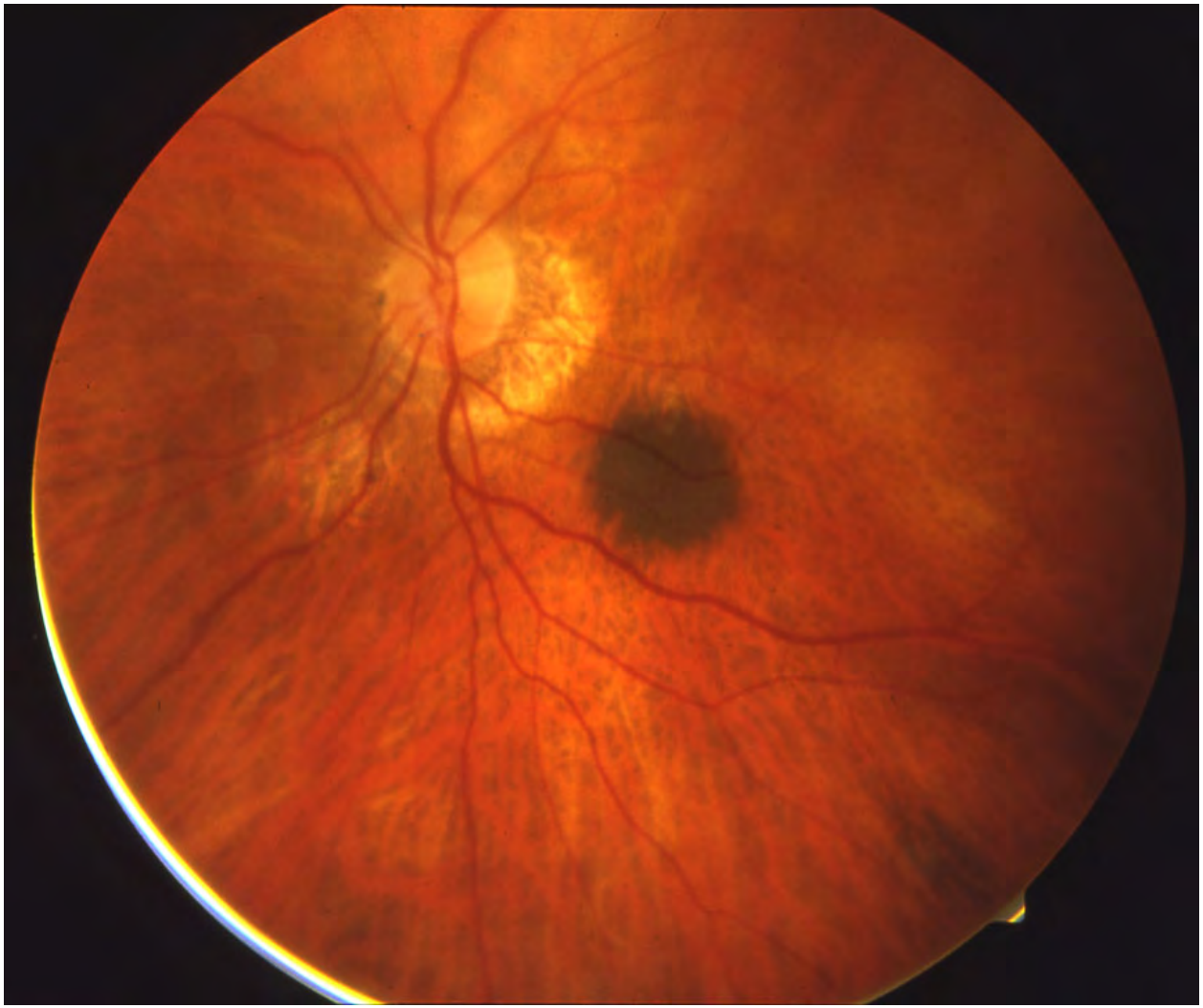
Clinical



- Nevus
- Hemangioma
- Detachment
- Metastasis
- Hemorrhage

kavita.mishra@ucsf.edu

Clinical

Table 64-3 AJCC and COMS Staging[85-92]

AJCC 2010 Staging of Ciliary Body and Choroidal Melanomas*

Thickness (mm)

Largest basal diameter (mm)

FIGURE 51-1 • Classification for ciliary body and choroid uveal melanomabased on thickness and dismeter.

Primary Tumor	
All Uveal Melanomas	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Iris* **	
T1	Tumor limited to the iris
T1a	Tumor limited to the iris not more than 3 clock hours in size
T1b	Tumor limited to the iris more than 3 clock hours in size
T1c	Tumor limited to the iris with secondary glaucoma
T2	Tumor confluent with or extending into the ciliary body choroid or both
T2a	Tumor confluent with or extending into the ciliary body choroid or both with secondary glaucoma
T3	Tumor confluent with or extending into the ciliary body choroid or both with scleral extension
T3a	Tumor confluent with or extending into the ciliary body choroid or both with scleral extension and secondary glaucoma
T4	Tumor with extrascleral extension
T4a	Tumor with extrascleral extension less than or equal to 5 mm in diameter
T4b	Tumor with extrascleral extension more than 5 mm in diameter

*Note: In clinical practice the largest tumor basal diameter may be estimated in optic disc diameters (dd: average: 1 dd = 1.5 mm). Tumor thickness may be estimated in diopters (average: 2.5 diopters = 1 mm). However, techniques such as ultrasonography and fundus photography are used to provide more accurate measurements. Ciliary body involvement can be evaluated by the slit-lamp, ophthalmoscopy, gonioscopy, and transillumination. However, high-frequency ultrasonography (ultrasound biomicroscopy) is used for more accurate assessment. Extension through the sclera is evaluated visually before and during surgery, and with ultrasonography computed tomography or magnetic resonance imaging.
**Note: When histopathologic measurements are recorded after fixation, tumor diameter and thickness may be under-estimated because of tissue shrinkage.
***Note: Iris melanomas originate from, and are predominantly located in, this region of the uvea. If less than half of the tumor volume is located within the iris, the tumor may have originated in the ciliary body and consideration should be given to classifying it accordingly.
Ciliary Body and Choroid
Primary ciliary body and choroidal melanomas, as defined in Figure 51.1 are classified according to the four tumor size categories below:

T1	Tumor size category 1
T1a	Tumor size category 1 without ciliary body involvement and extraocular extension
T1b	Tumor size category 1 with ciliary body involvement
T1c	Tumor size category 1 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T1d	Tumor size category 1 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T2	Tumor size category 2
T2a	Tumor size category 2 without ciliary body involvement and extraocular extension
T2b	Tumor size category 2 with ciliary body involvement
T2c	Tumor size category 2 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T2d	Tumor size category 2 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T3	Tumor size category 3
T3a	Tumor size category 3 without ciliary body involvement and extraocular extension
T3b	Tumor size category 3 with ciliary body involvement
T3c	Tumor size category 3 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T3d	Tumor size category 3 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T4	Tumor size category 4
T4a	Tumor size category 4 without ciliary body involvement and extraocular extension
T4b	Tumor size category 4 with ciliary body involvement
T4c	Tumor size category 4 without ciliary body involvement but with extraocular extension less than or equal to 5 mm in diameter
T4d	Tumor size category 4 without ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T4e	Any tumor size category with extraocular extension more than 5 mm in diameter
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Largest diameter of the largest metastasis 3 cm or less
M1b	Largest diameter of the largest metastasis 3.1-8.0 cm
M1c	Largest diameter of the largest metastasis 8 cm or more

AJCC 2010

- Tumor size – LBD & Thickness
- CBI and/or EOE

COMS*

	Height	Diameter
Small	1 to ≤3 mm &	5 to 16 mm
Medium	≥2.5 to ≤10 mm &	≤16 mm
Large	>10 mm AND/OR	>16 mm

* Collaborative Ocular Melanoma Study

kavita.mishra@ucsf.edu

Clinical

- Liver/Lung
- 5y Met-Free Survival
  - 1A: 98%
  - 1B: 80%
  - 2: 30%

ASSAY DESCRIPTION

DecisionDx-UM® gene expression assay for uveal melanoma is a proprietary assay that uses RT-PCR to determine the expression of a panel of 15 genes (3 control) in the supplied tumor tissue. The **DecisionDx-UM** classification is calculated from the gene expression results and comparing these results to a training set of patients with known outcomes.

RESULTS

DecisionDX-UM Class = 2

Discriminant Value = 0.42

Patients with a Class 2 molecular signature have a high risk of experiencing near term (within 5 years) clinical metastasis. A discriminant value ≥ 0.100 is reported with normal confidence.

Test Results should be interpreted using the Clinical Experience information contained in this report which is derived from clinical studies involving patient populations with specific clinical features as noted in section titled Clinical Experience. These results have not been validated in patients with clinical features different from those described. The discriminant value relates to Class 1 vs 2. See page 2 of initial report for discussion on discriminant value confidence.

CLINICAL EXPERIENCE FOR CLASS 1A, 1B AND 2

The **DecisionDx-UM** assay has been evaluated in over 700 patients with uveal melanoma to date. The majority of these patients participated in a prospective, multi-center study to validate the predictive accuracy of this gene expression-based molecular assay. Outcomes are collected and the ability of the molecular signature to predict metastasis is being evaluated at regular intervals. The most recent censor date (June 9, 2011) of the prospective study included 514 patients with follow-up data available for analysis. The censor date for this addendum is June 9, 2011. The actuarial outcomes for metastasis of the predicted low-risk (Class 1A), intermediate-risk (Class 1B), and the high-risk (Class 2) molecular signatures are shown below.

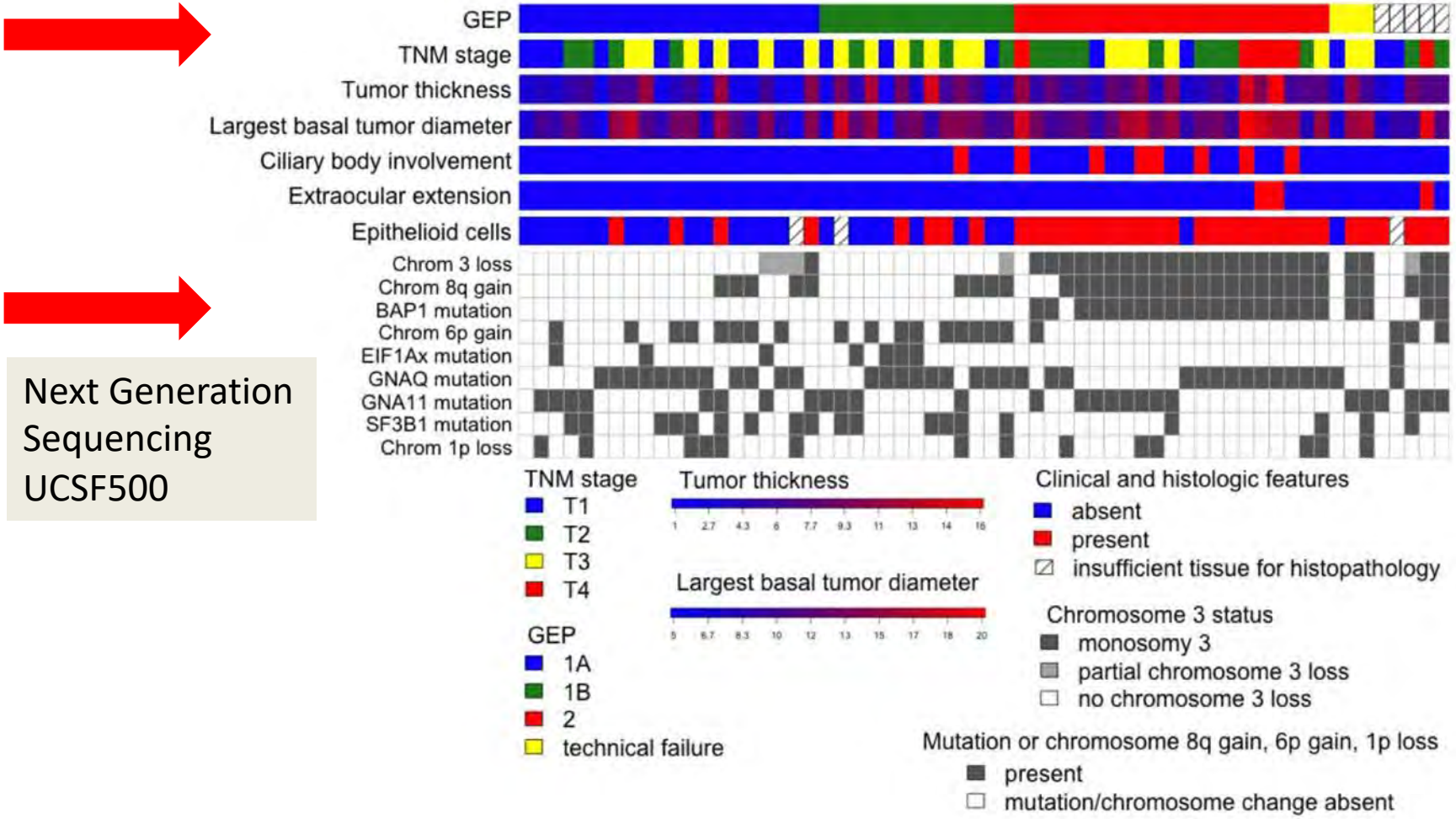
Molecular Signature Class	Percent Metastasis Free at 3 Years	Percent Metastasis Free at 5 Years
Class 1A	98%	98%
Class 1B	93%	79%
Class 2	50%	28%
n=514; Log-rank (Mantel-Cox) test: p<0.0001		

Source: Onken, Harbour et al., Curr Eye Res 2010; 35(9): 857-863; doi: 10.3109/02713683.2010.493265

kavita.mishra@ucsf.edu

Clinical

Gene Expression Profiling



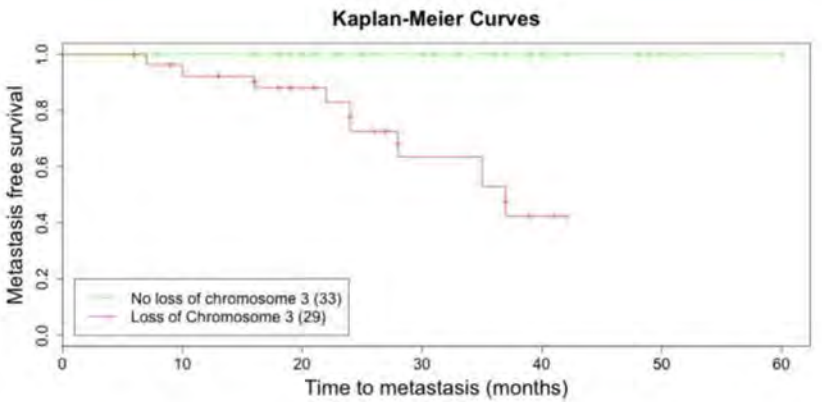
Next Generation Sequencing UCSF500

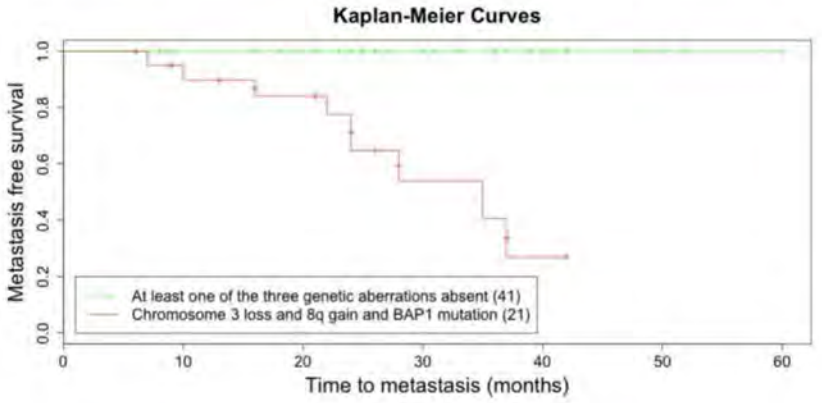
Source: Afshar et al., Trans Vis Sci Tech. 2019; 8(2):18, https://doi.org/10.1167/ tvst.8.2.18

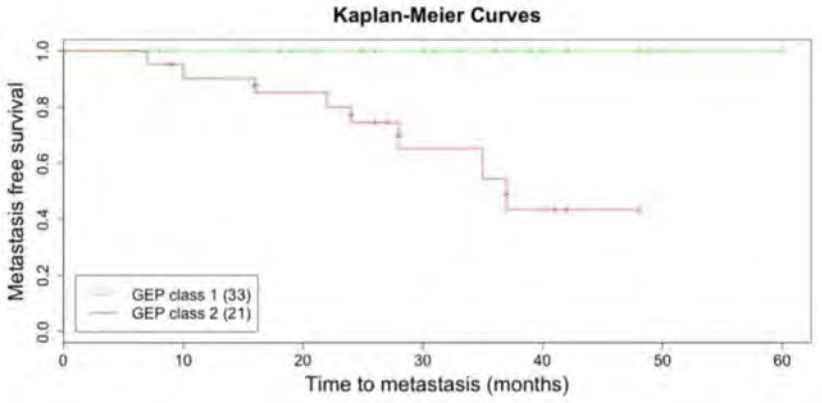
kavita.mishra@ucsf.edu

Clinical

- Chromosome 3 loss
- 8q gain
- BAP1 mutation
- Class 2 GEP







Source: Afshar et al., Trans Vis Sci Tech. 2019; 8(2):18, https://doi.org/10.1167/ tvst.8.2.18

kavita.mishra@ucsf.edu

UM: Local Therapy

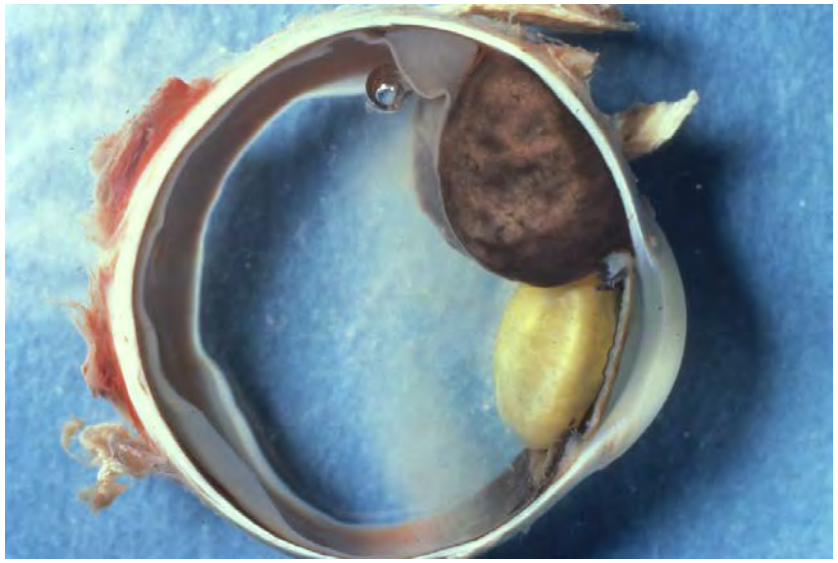
- Small lesions/tumors: serial observation or RT
- Medium tumors: RT
  - Goals of RT include
    (1) tumor control
    (2) eye preservation
    (3) visual preservation
    (4) minimize other side effects
  - Particle RT, Plaque, SRS/SRT
  - Comparable survival rates with surgery
- Large tumors: RT or surgery/enucleation

kavita.mishra@ucsf.edu

UM: Surgical Therapy

- Laser treatment — very small tumors, near macula
- Partial Eyewall resection — select cases, +/- RT

- Enucleation — consider for blind eye, painful eye, very large volume, radiation failure
- Orbital Exenteration — extraocular spread

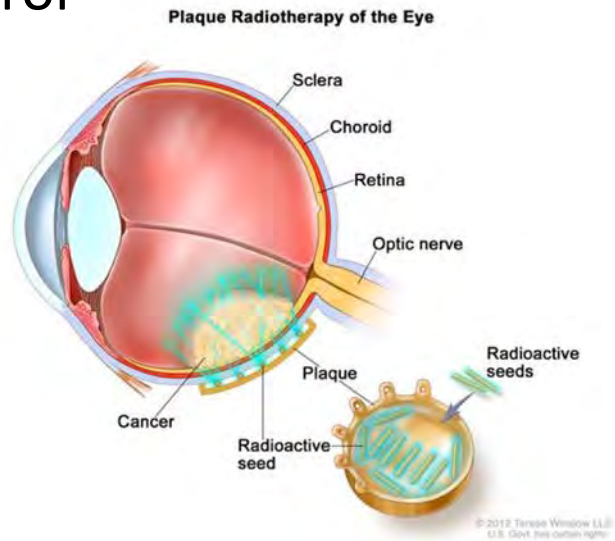


kavita.mishra@ucsf.edu

UM: Plaque Therapy

- Radon, Cobalt-60 — Early experience
- I-125 & Pd-103 plaques — Currently in use North America
- I-125 & Ru-106 — Europe/Asia

- Peripapillary or macular tumors or +exudative retinal detachment have poorer visual outcome and local control
- Not recommended for
  - EOE
  - very large tumors
  - blind painful eyes



Source: ABS-OOTF, Brachytherapy 2014; 13:1-14

kavita.mishra@ucsf.edu

UM: Plaque Therapy

- Procedure:
  - Verify tumor and plaque position in OR
  - Patient discharged with lead eye shield and relevant precautions
  - Returns for plaque removal
- Dose range — 70-100 Gy to apex over ~5-7 days
- Dose rate — 0.60-1.05 Gy/hr
- I-125 common dosing — 85 Gy to tumor apex (base + 2mm margin) over 1 week
- 5-year local control rates averaged ~89.5%

Source: ABS-OOTF, Brachytherapy 2014; 13:1-14

kavita.mishra@ucsf.edu

UM: Question* - Plaques

63. Which tumor feature is suitable for episcleral plaque brachytherapy for uveal melanoma?
    (A) 5 mm height
    (B) Ring melanoma
    (C) Gross extrascleral extension
    (D) Involvement of more than half of the ciliary body

* American College of Radiology In-Training Examination for Radiation Oncology Residents

Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

kavita.mishra@ucsf.edu

UM: Question* - Plaques

63. Which tumor feature is suitable for episcleral plaque brachytherapy for uveal melanoma?

(A) 5 mm height
(B) Ring melanoma
(C) Gross extrascleral extension
(D) Involvement of more than half of the ciliary body

Key: A
Solution: Exclusion criteria based on the 2003 ABS guidelines
References: Nag, The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. IJROBP2003 Jun 1; 56(2):544-55.

* American College of Radiology In-Training Examination for Radiation Oncology Residents

Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

kavita.mishra@ucsf.edu

UM: Question* - Plaques

265. Compared to Iodine-125 brachytherapy seeds, Palladium-103 seeds are characterized by:

(A) longer half-life and lower average energy.
(B) longer half-life and higher average energy.
(C) shorter half-life and lower average energy.
(D) shorter half-life and higher average energy.

Key: C
Rationale: Compared to I-125, Pd-103 has a shorter half-life (17 days vs. 60 days) and a lower average energy (21 keV vs. 28 keV). Pd-103 seeds are used in many of the same applications as I-125, including prostate seed implant and eye plaque therapy.

* American College of Radiology In-Training Examination for Radiation Oncology Residents

Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

Objectives

Topics
Overview of ocular melanoma and proton technology: *What do we know from the past 50 years?*
Clinical data & outcomes: *Which factors matter for which outcomes?*

kavita.mishra@ucsf.edu

UM: Local Therapy Trials

Table 65-4: COMS and UCSF-LBL Trials

Trial	Arm	5y Local control	5y CSS	5y OS
COMS small tumor cohort*	Observation		99%	94%
COMS medium natural history arm*	Deferred/Declined therapy			70%
COMS medium tumor trial	Plaque I-125	89.7%	91%	82%
	Enucleation		89%	81%
COMS large tumor trial	Enucleation alone	95%	72%	57%
	Pre-enucleation RT	100% (p=0.03)	74%	62%

		Local control	Enucleation	CSS
UCSF-LBL trial**	Charged particle***	100% (p<0.001)	9.3%	92%
	Plaque I-125***	87%	17.3%	92%

*Non-randomized natural history arms

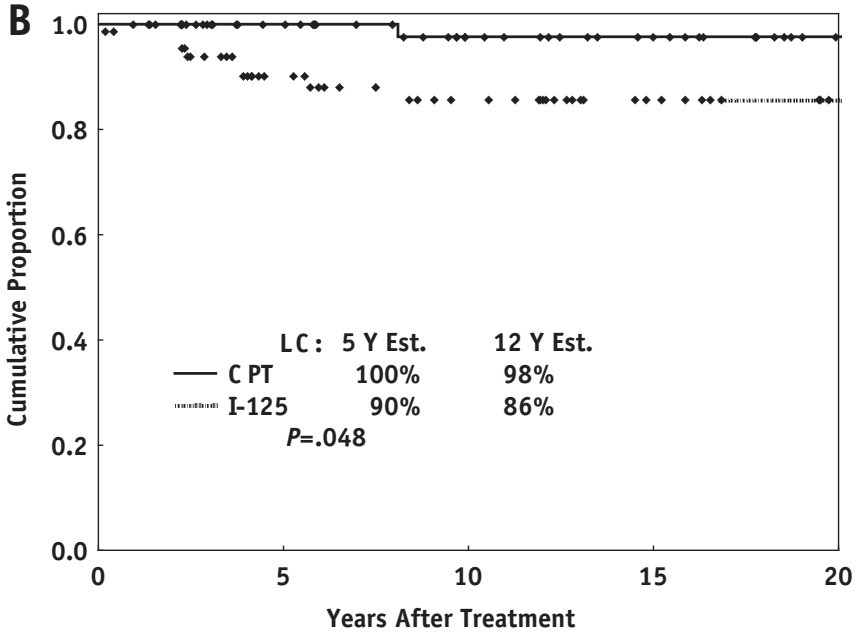
**University of California San Francisco – Lawrence Berkeley Laboratory

***Mean f/u 42 mos (Charged particle - Helium arm); 41 mos (Plaque I-125)

UCSF: Particles v Plaque Update

- Local Control significantly higher with Particles
- LC plaques ~ meta-analyses and COMS data

- LC advantage remains even for tumors ≥2 mm from optic disc
  - ➢ **98 vs 86% LC at 12 years**



Source: Mishra et al., IJROBP (2015) 92: 376-383

kavita.mishra@ucsf.edu

UCSF Department of Radiation Oncology

Meta-Analysis I: Particles v Plaque Therapy

Table 3 Comparison of radiation modalities

Modality	No. of studies included	Weighted mean rate of local failure (%)	Weighted mean tumour LBD (mm)	Weighted mean tumour height (mm)	No. of pts. included
Brachytherapy (n=3868)					
Iodine-125 brachytherapy	13	9.60	11.10	4.80	2104
Ruthenium-106 brachytherapy	7	9.60	10.90	4.10	1653
Palladium-103 brachytherapy	1	4.00	10.30	3.90	100
Cesium-131 brachytherapy	1	9	12.60	5.40	11
Weighted average		9.45	11.00	4.48	
Photon-based external beam radiation therapy (n=524)					
Gamma knife radiosurgery	4	9.50	N/A	7.70	262
Fractionated radiotherapy	2	6.20	11.40	4.60	262
Weighted average		7.85	11.40	6.15	
Charged particle radiation therapy (n=7043)					
Proton beam radiation therapy	7	4.20	14.00	5.50	6825
Helium ion radiation therapy	1	4.60	11.90	6.70	218
Weighted average		4.21	13.93	5.54	

N/A, not available; No., number; pts., patients.

LC higher with Particles despite larger mean tumor size

Source: Chang & McCannel Br J Ophthalmol 2013; 97:804-811

kavita.mishra@ucsf.edu

UCSF Department of Radiation Oncology

Meta-Analysis II: Particles v Plaque Therapy

Critical Review

Charged Particle Radiation Therapy for Uveal Melanoma: A Systematic Review and Meta-Analysis

Zhen Wang, PhD,* Mohammed Nabhan, MD,* Steven E. Schild, MD,† Scott L. Stafford, MD,* Ivy A. Petersen, MD,* Robert L. Foote, MD,* and M. Hassan Murad, MD*

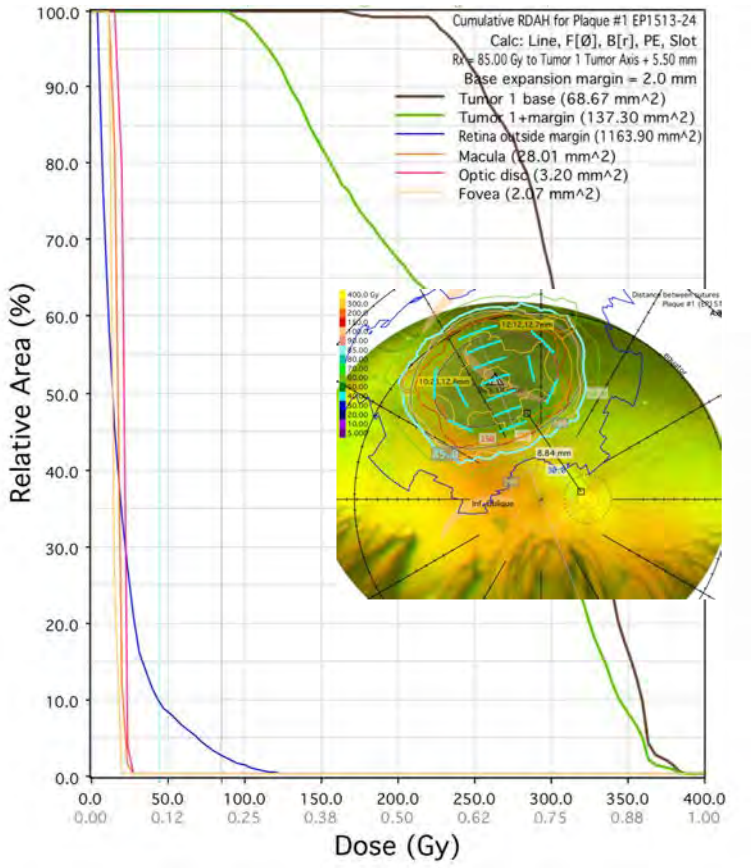
*Mayo Clinic, Rochester, Minnesota; and †Mayo Clinic, Scottsdale, Arizona

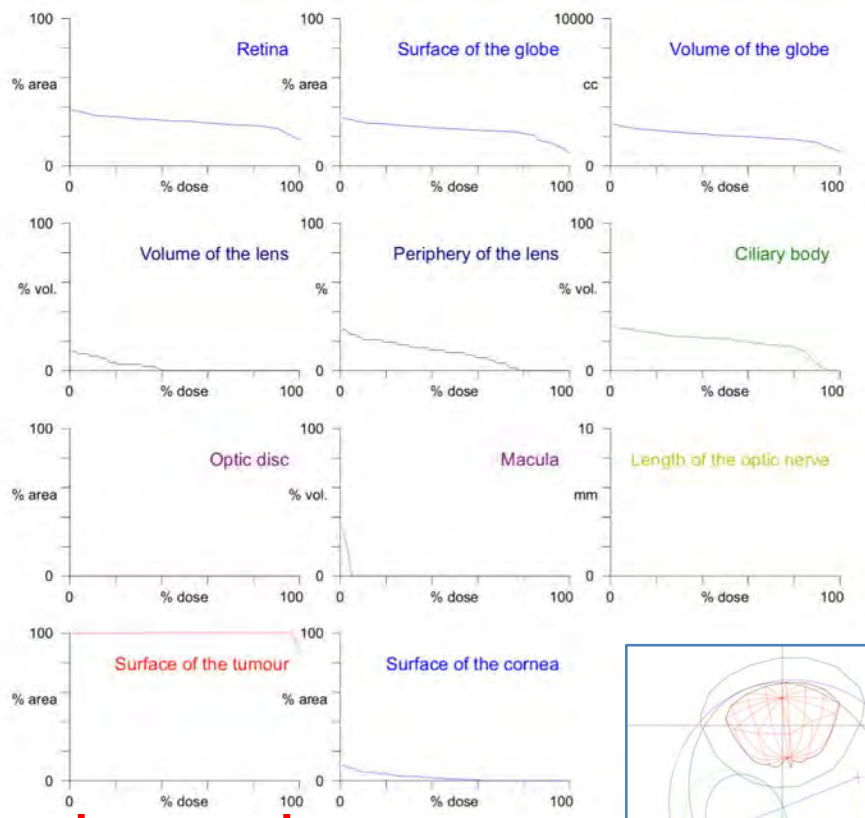
Table 2 Estimated efficacy of CPT versus iodine-125 brachytherapy for uveal melanomas

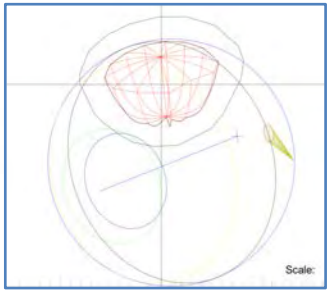
Outcome	No. of patients	No. of included studies	OR	*P* value	95% CI
Death	4127	9	0.13	.10	0.01-1.63
Enucleation	5108	13	0.53	.10	0.23-1.18
Local tumor recurrence	5040	14	0.22	.00	0.21-0.23

"We found a significantly lower incidence of radiation retinopathy with CPT… CPT uses more uniform dose distribution with a lower dose delivered to a smaller volume of retina."

Dosimetry: Particles v Plaque Therapy







kavita.mishra@ucsf.edu

UCSF Department of Radiation Oncology

UM: Local RT Considerations

Particles	Plaques	SRS/SRT
• Excellent LC with long f/u • Uniform dose distribution • Critical structure dosing • 1-2 min rx time • Anterior side effects (eyelids, glaucoma, telangiectasias, dry eye, tear duct stenosis)	• Accessible • LC for large or peripapillary/macular tumors • Penumbra (I-125) • Eye preservation • Radiation exposure • Diplopia, Retinopathy	• Shorter f/u • No surgery • Dose inhomogeneity • Eye fixation/monitoring variable • Longer rx times • Higher body doses • Complications

Source: Chang & McCannel Br J Ophthalmol 2013; 97:804-811; Wang IJROBP 2013; 86:18-26; Mishra et al, Uveal Melanoma, in Textbook for Radiation Oncology, 2nd edition

kavita.mishra@ucsf.edu

UCSF Department of Radiation Oncology

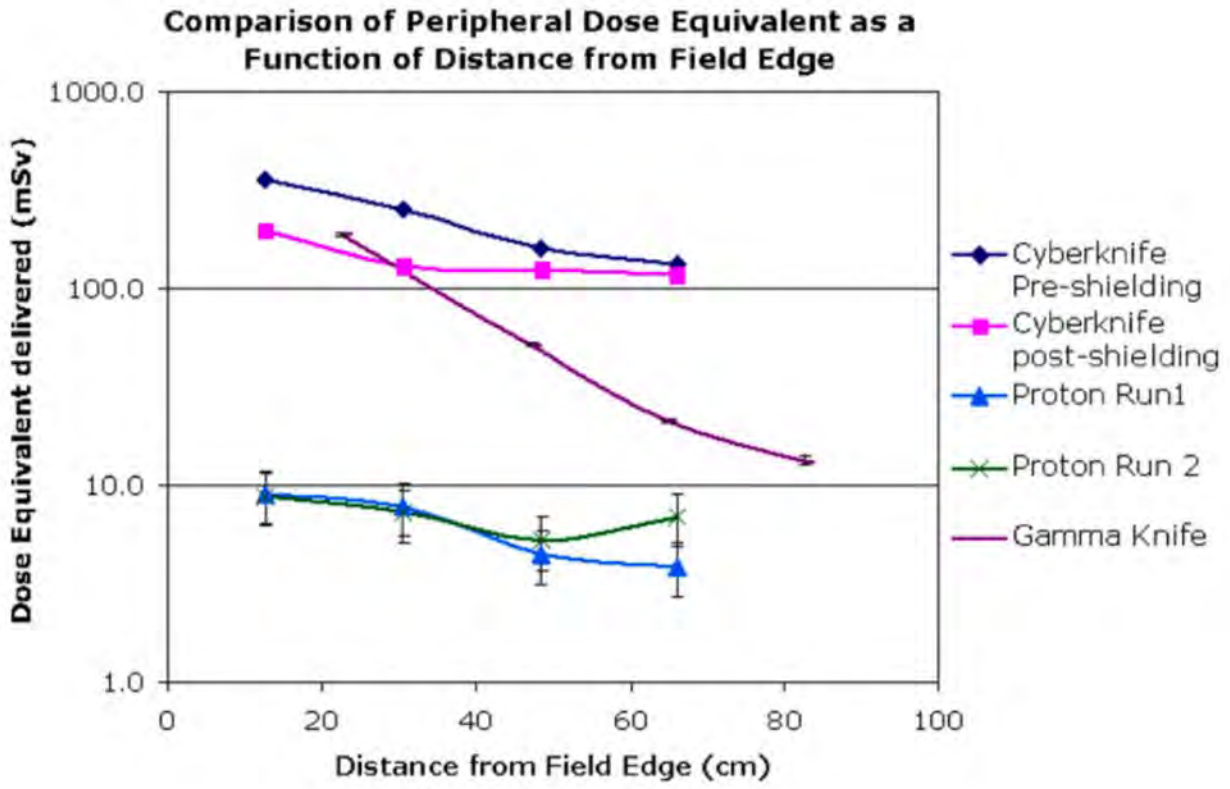
UM: SRS Considerations

Table 1 Visual outcomes following treatment with Stereotactic radiosurgery or proton beam therapy. Significant visual loss defined as a loss of 3 or more lines of Snellen acuity

Visual outcome	*Stereotactic radiosurgery*	*Proton beam therapy*
Visual acuity $\geq 6/60$	33%	55%
Loss of ≥ 3 snellen Lines	65%	45%

3y VA: Protons > SRS

UM: SRS Considerations



- Protons → Lower peripheral doses than GK, CK, SRS/SRT

Source: Zytkovicz, Phys Med Biol 2007; 52:5957-5971

kavita.mishra@ucsf.edu

Cost Effectiveness

Treatment	Medicare reimbursement	Range
Enucleation	$8,678	($6-13K)
Plaque brachy	$19,108	($13-29K)
Proton beam (4-5 fractions)	$12,438	($8-19K)

- Short course cost effectiveness
- Additional costs comparison (retinopathy, clinic, vision)

Source: Moriarty et al., PLoS One (2015) 10(5): e0127814

kavita.mishra@ucsf.edu

UM: Question* - Proton & Plaque

259. Compared to plaque brachytherapy, what is an advantage of proton therapy for the treatment of uveal melanoma?

a. Less expensive
b. Treats larger tumors
c. Mobile radiation field
d. Lower risk of enucleation

* American College of Radiology In-Training Examination for Radiation Oncology Residents

Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

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a. Less expensive
b. Treats larger tumors
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Key: B
Rationale: Proton therapy for treatment of uveal melanoma is more expensive than brachytherapy. Plaque brachytherapy provides a mobile radiation field that moves with the eye; proton therapy is a static treatment. On a meta-analysis of outcomes, there was no difference in the risk of enucleation between charged-particle therapy and brachytherapy. Proton therapy allows for the treatment of larger tumors, including tumors that touch the optic disc.
References: The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy, 13(1) 2014, 1-14.
Wang, et al., Charged particle radiation therapy for uveal melanoma: A systematic review and meta-Analysis, IJROBP, 86(1), 2013, 18-26.

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UM: Question* - Proton & Plaque

199. What is an advantage of proton therapy over plaque brachytherapy for retinoblastoma treatment?

(A) Eye immobilization is unnecessary during radiation treatment
(B) Can treat unilateral tumors
(C) Has fewer anterior segment complications
(D) Can treat tumors that invade the optic nerve

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kavita.mishra@ucsf.edu

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Key: D
Solution: Proton therapy can treat tumors close to or invading the optic nerve. The use of plaque brachytherapy to treat a tumor invading the optic nerve would deliver too much dose to the opticnerve. Both proton therapy and plaque therapy can treat unilateral tumors. Eye immobilization during proton therapy is essential for reproducibility of treatment. With plaque therapy, the radiation source moves with the eye. Plaque therapy has fewer anterior segment complications.
References: Sethi, et al. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma, Brachytherapy. 2014 Jan-Feb; 13(1).
Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy, Cancer. 2014.

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Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

Objectives

Topics
Overview of ocular melanoma and proton technology: *What do we know from the past 50 years?*
Clinical data & outcomes: *Which factors matter for which outcomes?*
Treatment Planning & Delivery: *Current techniques and what is on the horizon?*

kavita.mishra@ucsf.edu

UCSF-CNL Proton Ocular Program

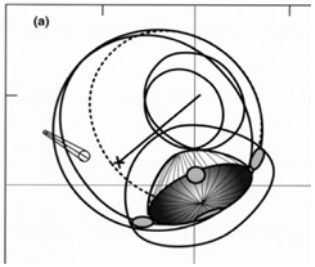
Pt dx and transfer care to ocular/radiation oncologist

Simulation in Rad Onc w/ immobilization device and orthogonals

56 GyE in four daily fx of 14 GyE

Treatment at CNL

Pt decide PBRT; Tantalum ring placement



Planning w/ EYEPLAN; anterior structure sparing technique*

Source: *Daftari et al, IJROBP 1997, 39:997–1010

kavita.mishra@ucsf.edu

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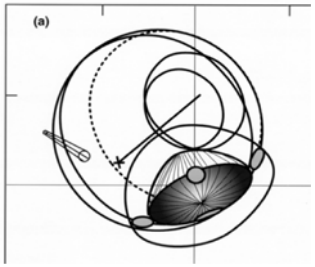

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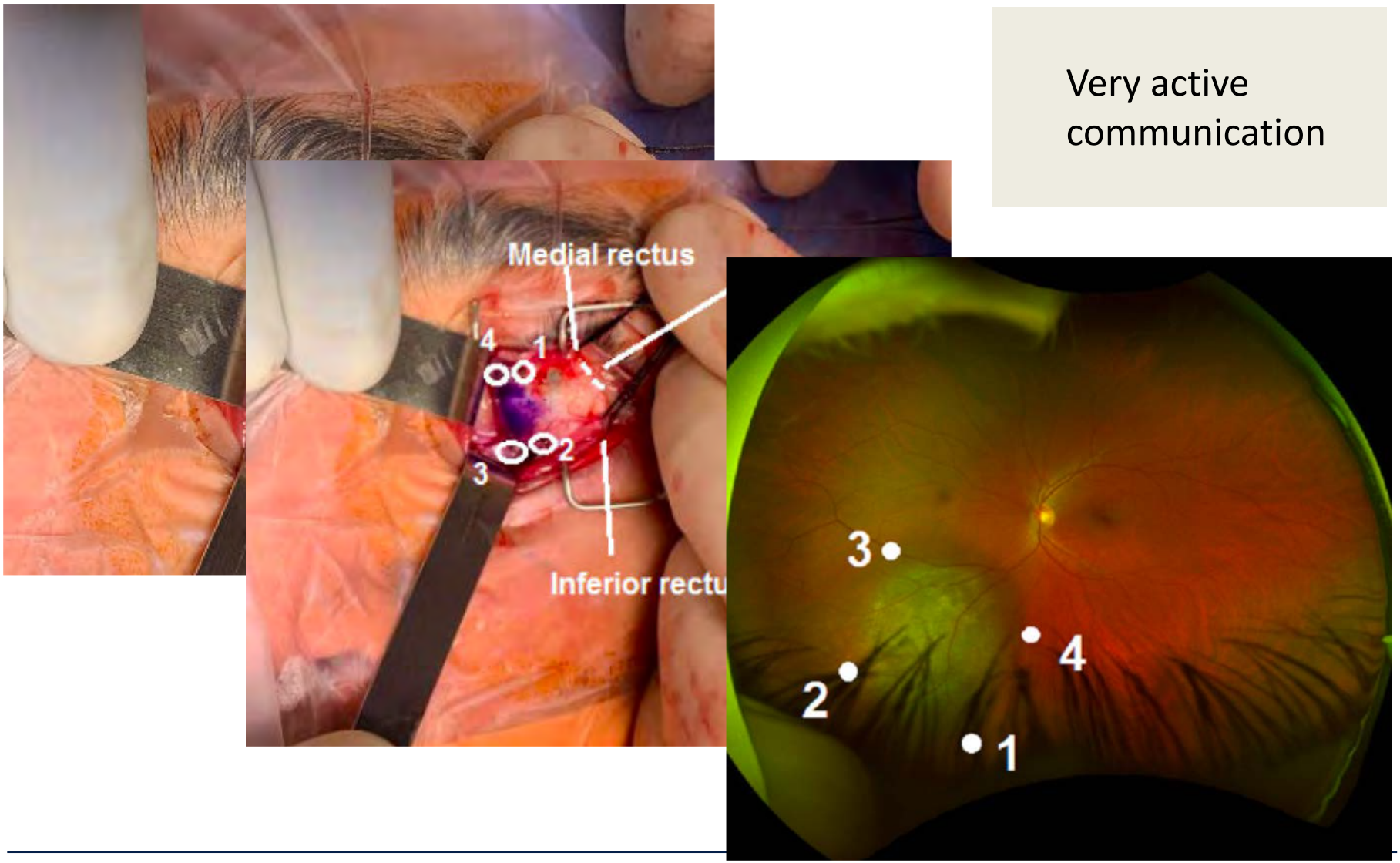
kavita.mishra@ucsf.edu

UCSF-CNL: Surgery



Very active communication

Courtesy of Armin Afshar, MD MBA (UCSF)

kavita.mishra@ucsf.edu

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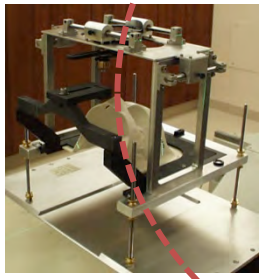

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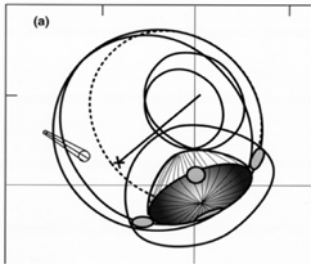

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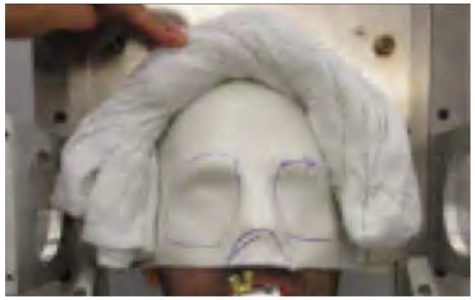
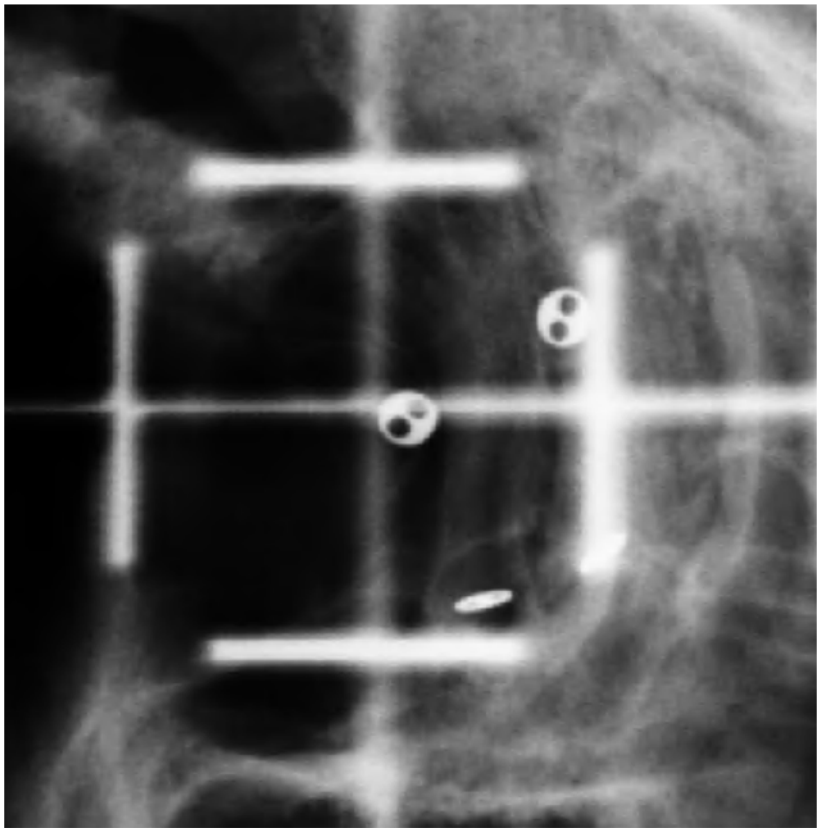
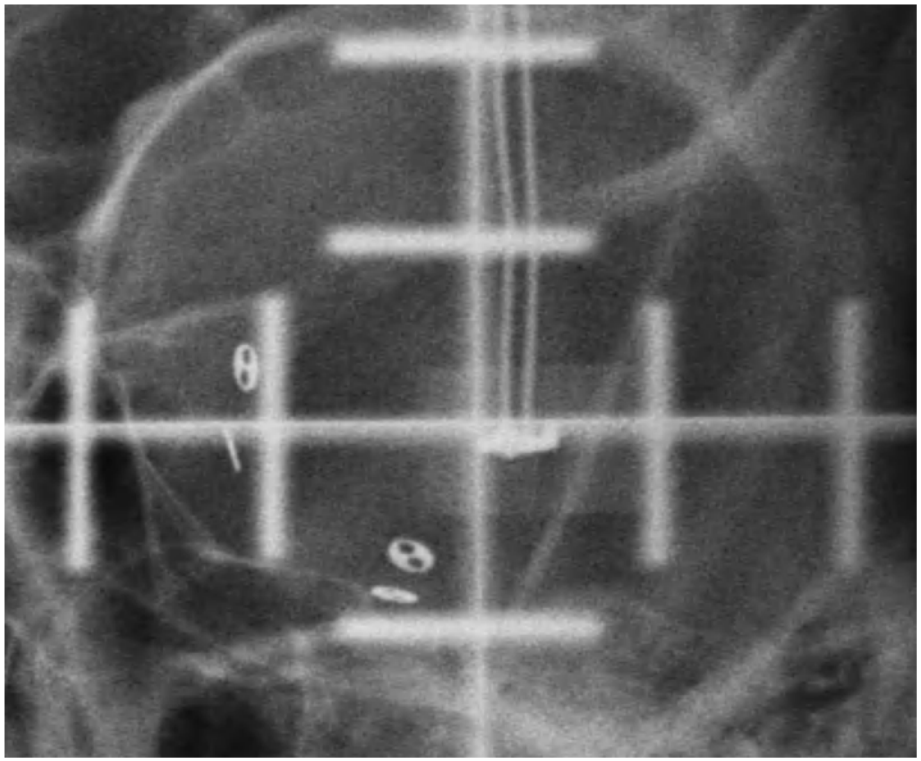
UCSF-CNL: Simulation







kavita.mishra@ucsf.edu

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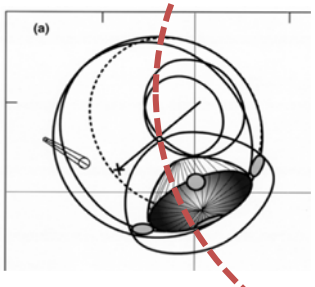


Planning w/ EYEPLAN; anterior structure sparing technique*

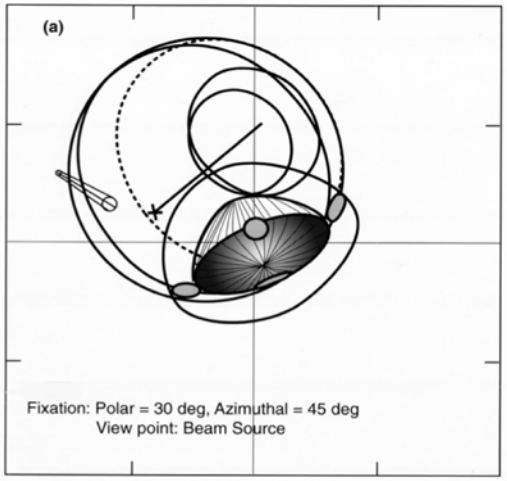
Source: *Daftari et al, IJROBP 1997, 39:997–1010

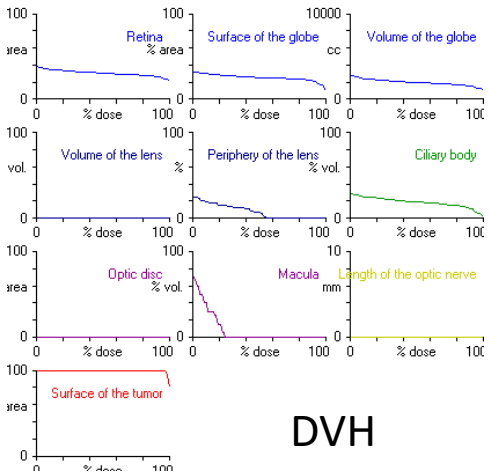
kavita.mishra@ucsf.edu

UCSF-CNL: Treatment Planning

Input:

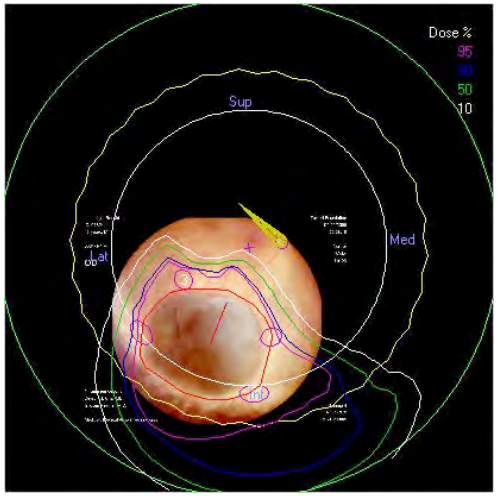
1. Ultrasound tumor and eye measurements
2. Clinical exam and drawings
3. Fundus photograph
4. Surgical T-ring drawing with relation to tumor, limbus, inter-ring distances, etc.
5. Simulation
6. MRI
7. Angiogram
8. Other





DVH

Use eye position, beam parameters, margins, etc. to ensure tumor coverage and minimize dose to critical structures



kavita.mishra@ucsf.edu

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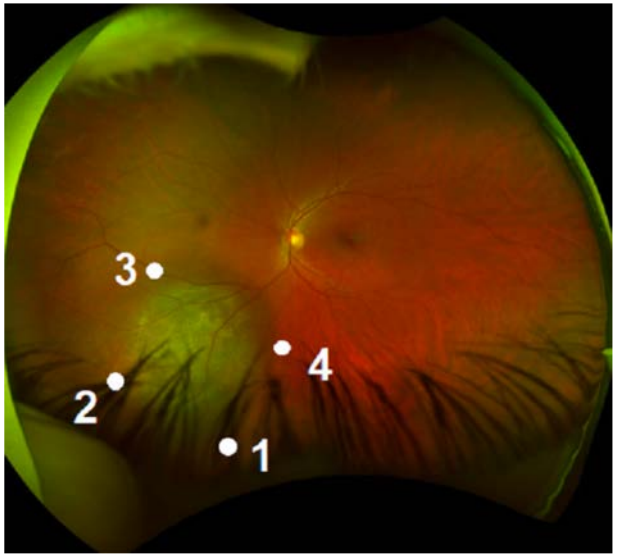

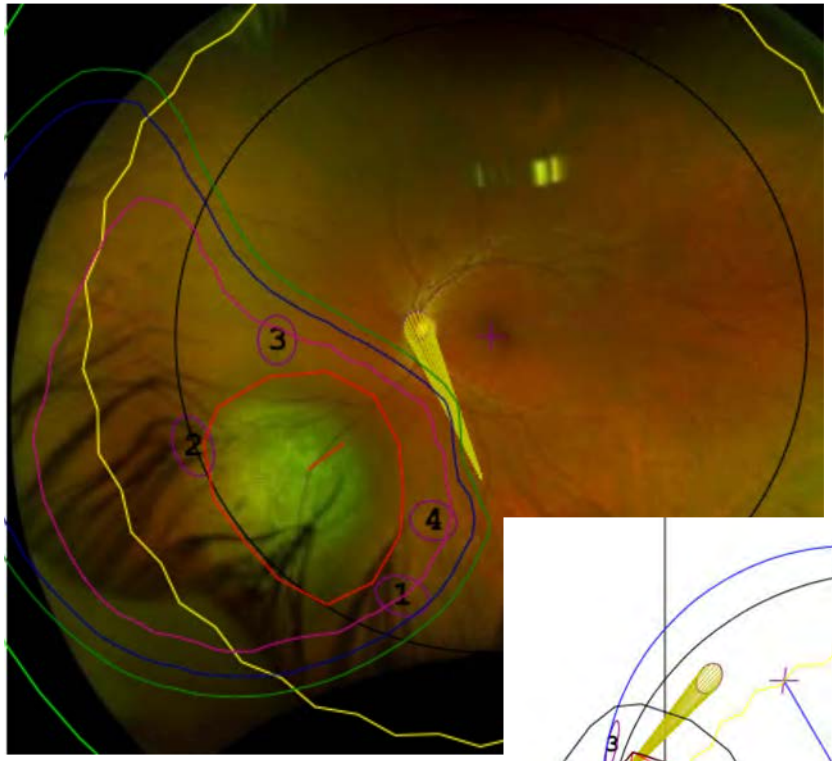

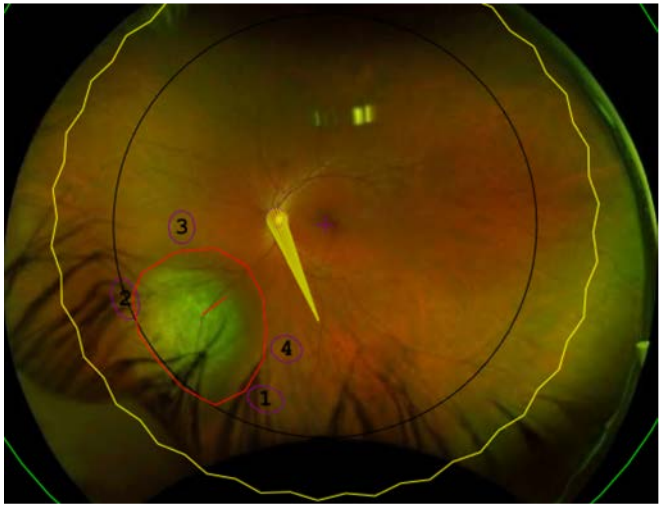

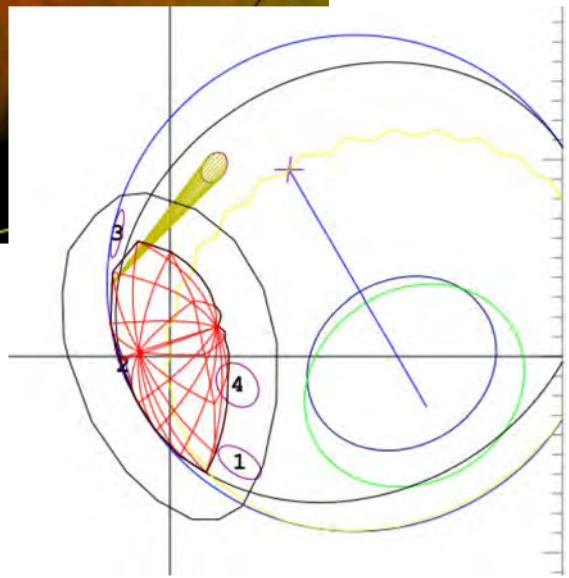

kavita.mishra@ucsf.edu

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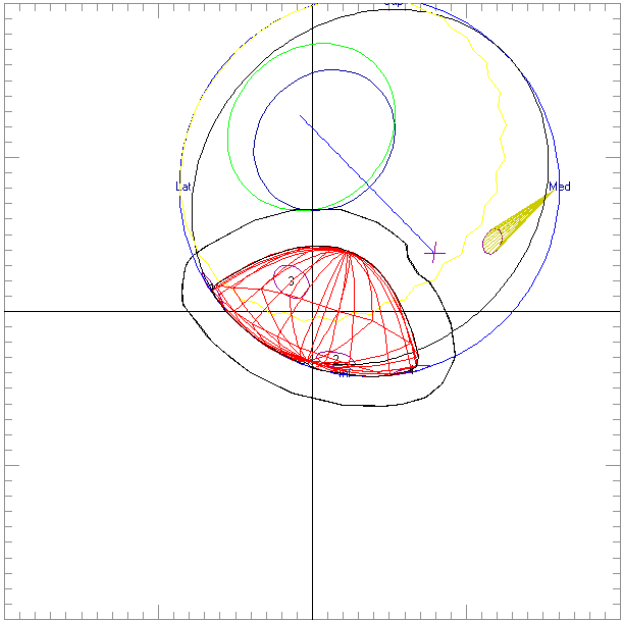
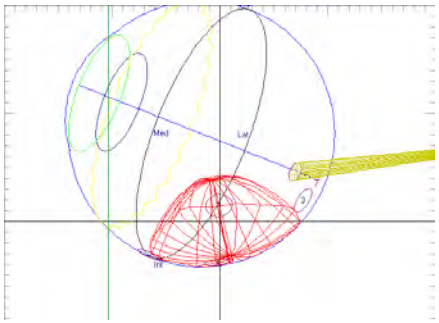
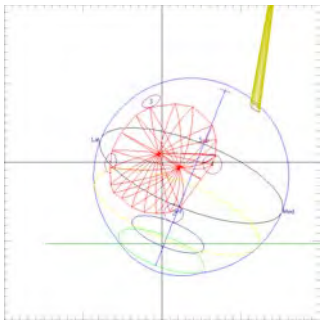
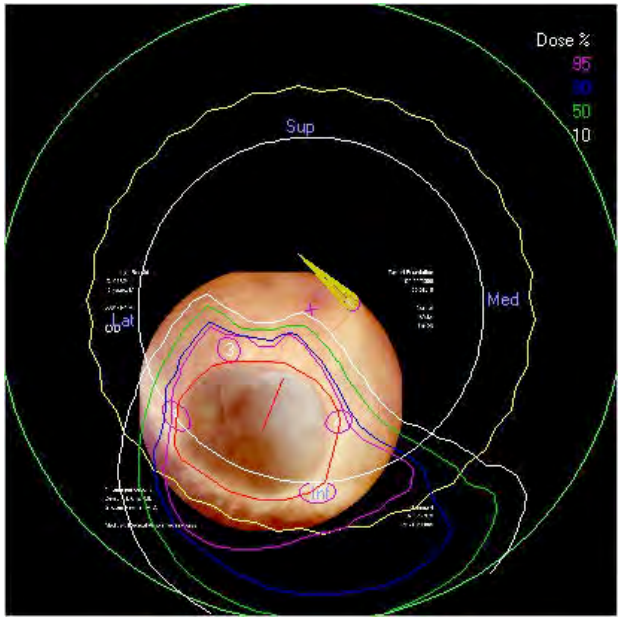






Protect optic disc/ nerve/ macula



kavita.mishra@ucsf.edu

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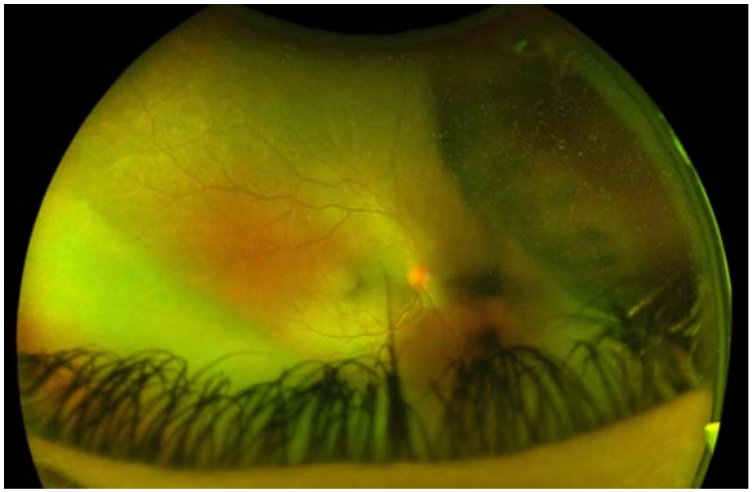

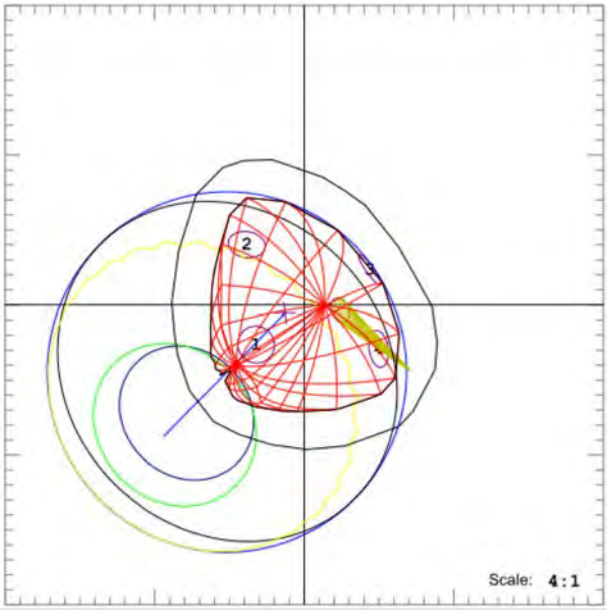

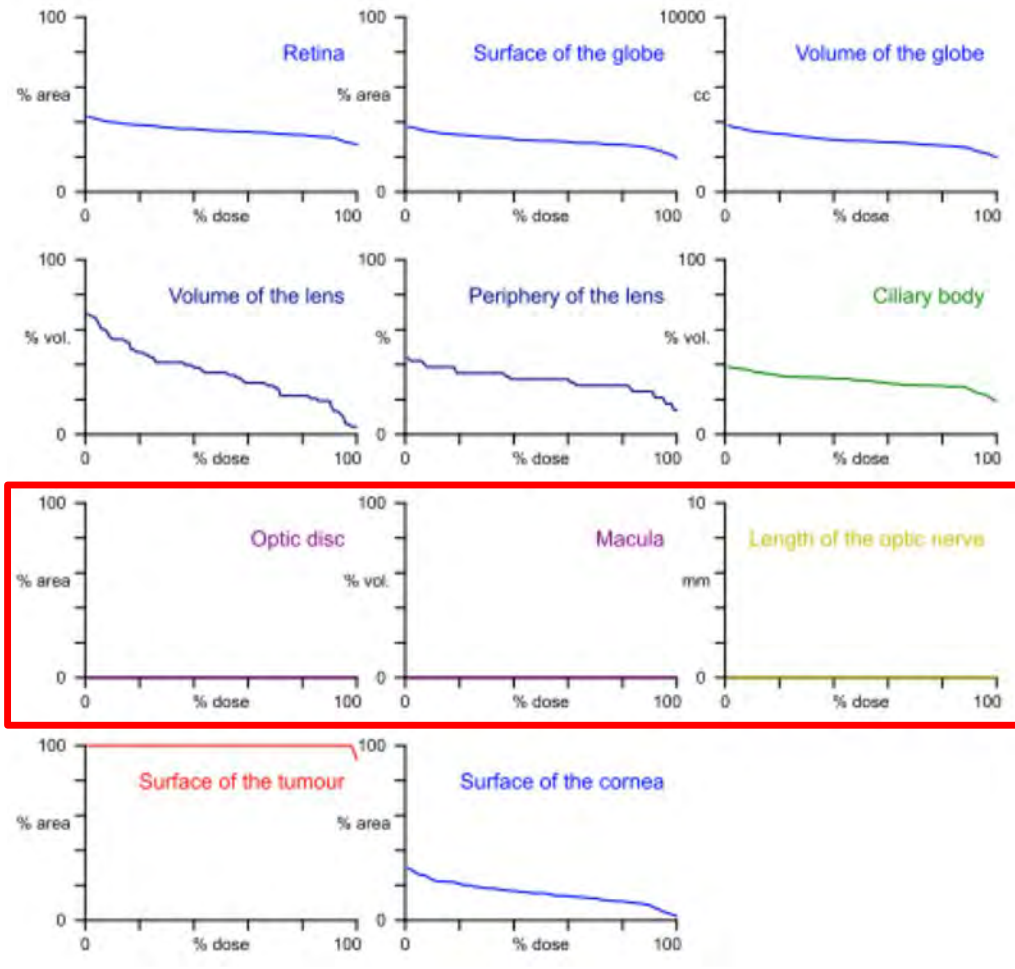

kavita.mishra@ucsf.edu

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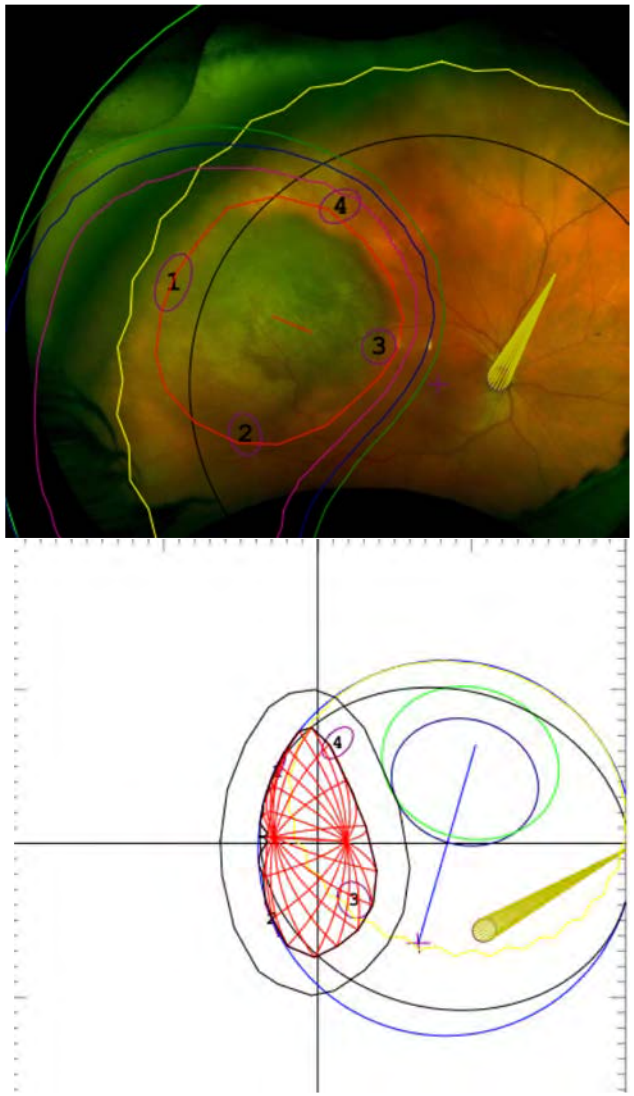
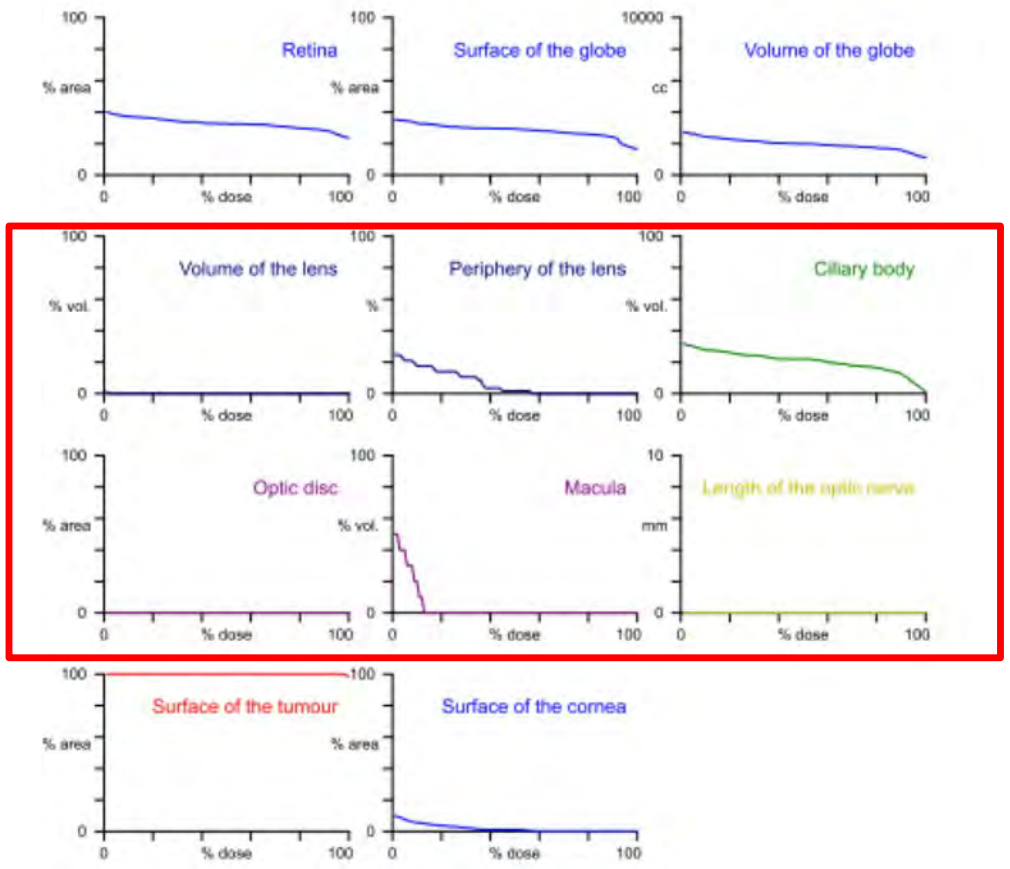
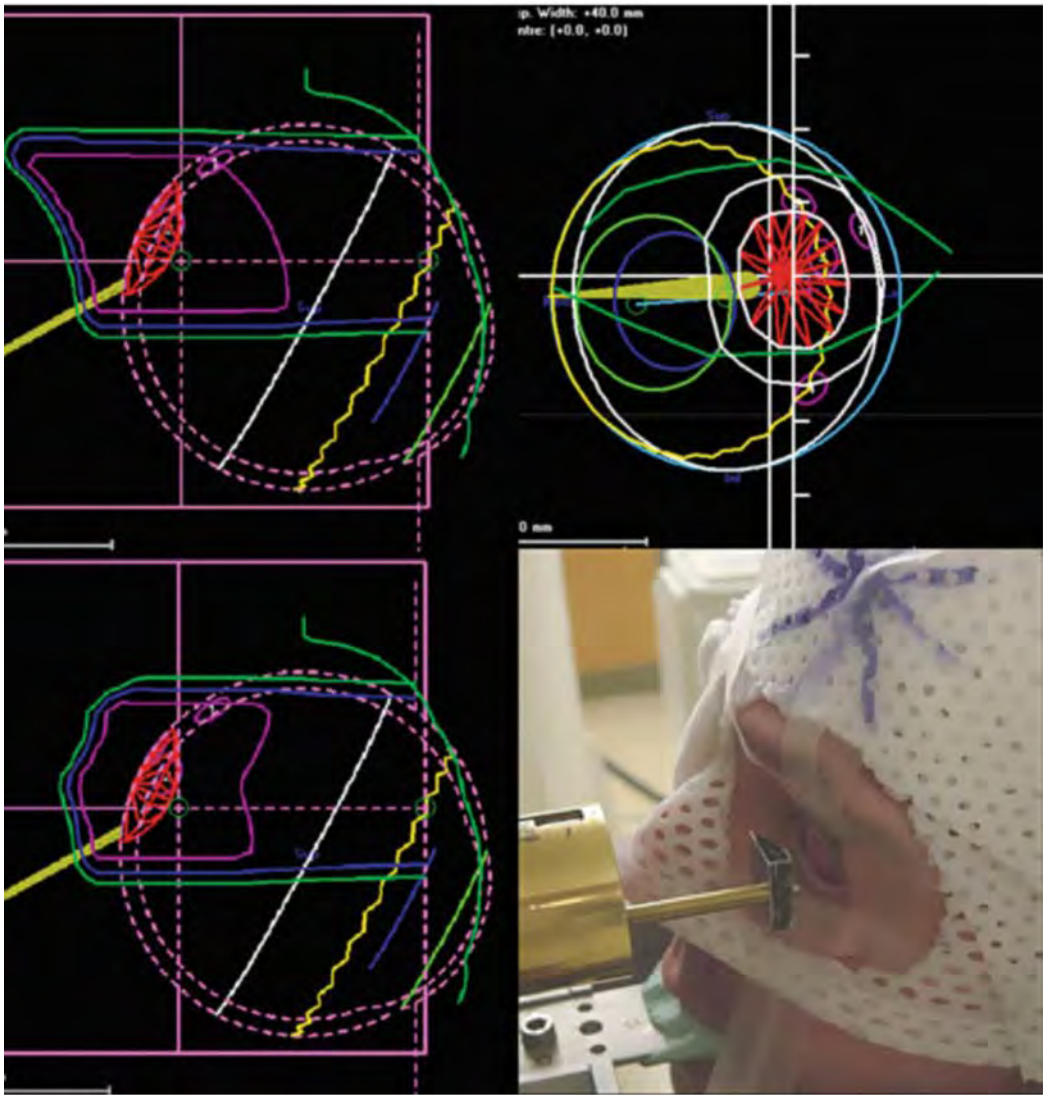




kavita.mishra@ucsf.edu

Proton Eye: Treatment Planning



Courtesy of PTCOG-Ocular OPTIC

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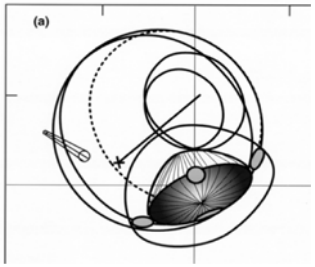

Planning w/ EYEPLAN; anterior structure sparing technique*

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kavita.mishra@ucsf.edu

OM & Protons: Dose

Ocular Tumors

Practice Patterns Analysis of Ocular Proton Therapy Centers: The International OPTIC Survey

Jan Hrbacek, PhD,* Kavita K. Mishra, MD, MPH,†
Andrzej Kacperek, PhD,‡ Remi Dendale, MD,§ Catherine Nauraye, PhD,§
Michel Auger, Eng,§ Joel Herault, PhD,‖ Inder K. Daftari, PhD,†
Alexei V. Trofimov, PhD,¶ Helen A. Shih, MD,¶ Yen-Lin E. Chen, MD,¶
Andrea Denker, PhD,# Jens Heufelder, PhD,**
Tomasz Horwacik, PhD,†† Jan Swakoń, PhD,†† Cornelia Hoehr, PhD,‡‡
Cheryl Duzenli, PhD,‡‡ Alessia Pica, MD,* Farid Goudjil, MSc,§
Alejandro Mazal, PhD,§ Juliette Thariat, MD,‖
and Damien C. Weber, MD*

Consistency of proton UM dose
~60 GyE/4

Table 2 Type of eye tumors treated with proton therapy by 10 centers and fractionation schemes

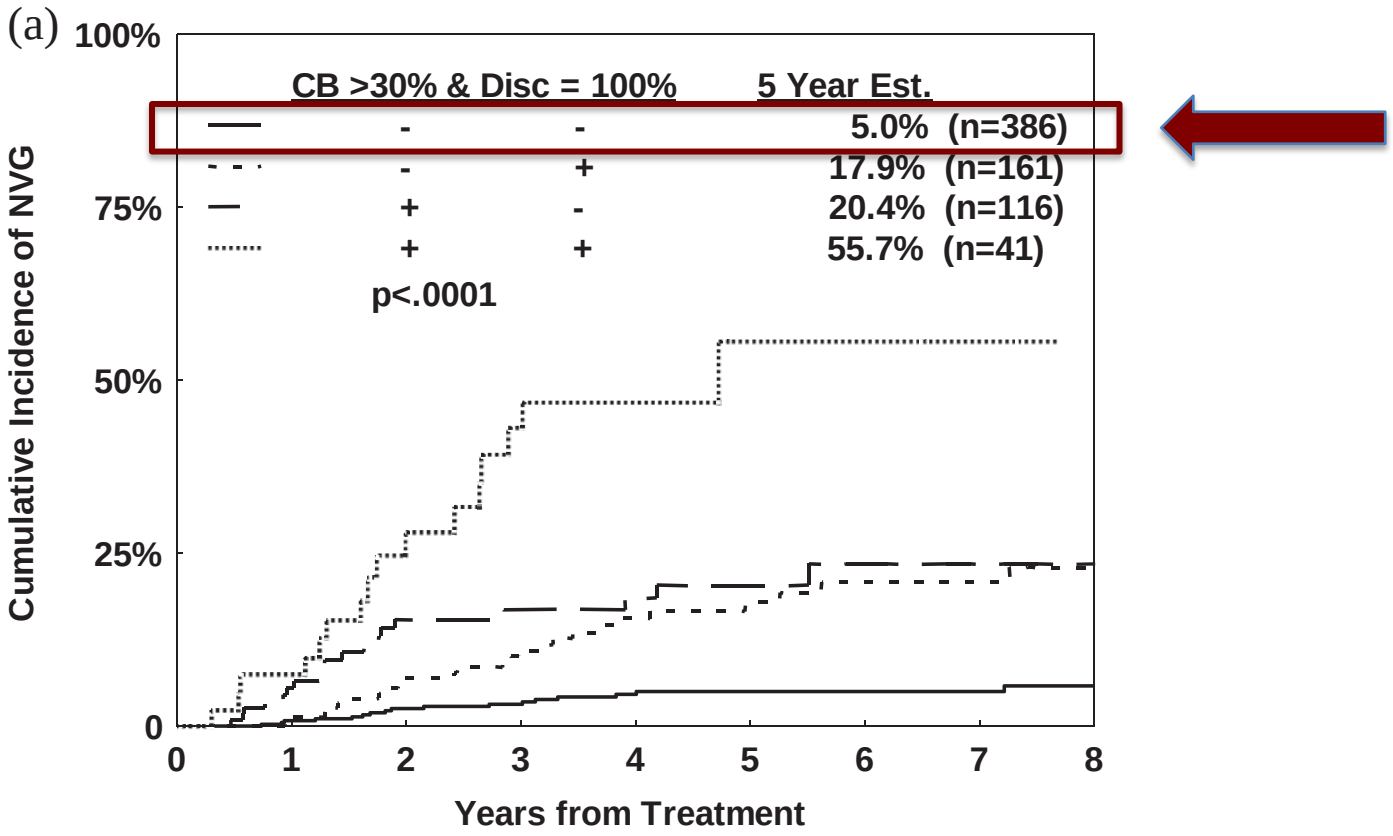
Type eye tumor (no. of centers treating this eye tumor)	Fractionation schemes (no. of centers)
Uveal melanoma (10)	70 GyRBE/5 fx (1)*
	60 GyRBE/4 fx (7)
	58.4 GyRBE/4 fx (1)
	56 GyRBE/4 fx (1)
Iris melanoma (9)	70 GyRBE/5 fx (1)
	60 GyRBE/4 fx (4)
	58.4 GyRBE/4 fx (1)
	56 GyRBE/4 fx (1)
	54-60 GyRBE/4 fx (1)
	50 GyRBE/4 fx (1)
Conjunctival melanoma (9)	70 GyRBE/5 fx (1)
	60 GyRBE/4 fx (2)
	60 GyRBE/8 fx (1)
	58.4 GyRBE/4 fx (1)
	56 GyRBE/4 fx (1)
	50 GyRBE/4 fx or 8 fx (1)
	45 GyRBE/8 fx (1)
	20.4-21.8 GyRBE/4 fx (1)
Ocular hemangioma (8)	20 GyRBE/8 fx (3)
	20 GyRBE/8 fx (1)
	19.8 GyRBE/4 fx (1)
	18-22 GyRBE/4 fx (1)
	18 GyRBE/4 fx (1)
	15 GyRBE/4 fx (1)
Macular degeneration (4)	24 GyRBE/2 fx (2)
	19.8 GyRBE/4 fx (1)
	18 GyRBE/2 fx (1)
Angioma (5)	35 GyRBE/5 fx (1)
	20 GyRBE/4 fx (1)
	20 GyRBE/8 fx (1)
	19.8 GyRBE/4 fx (1)
	18 GyRBE/4 fx (1)
Choroidal metastasis (5)	60 GyRBE/4 fx (1)
	45 GyRBE/4 fx (1)
	40 GyRBE/4 fx (1)
	20-24 GyRBE/2 fx (2)
Retinoblastoma (1)†	31.6 GyRBE/6 fx (1)

Abbreviation: fx = fraction.
* 50 GyRBE/5 fx for small posterior tumors.
† Massachusetts General Hospital treats retinoblastomas on gantries, 45 Gy in 25 fx. These are not counted toward the eye-line totals.

Source: Hrbacek et al., IJROBP (2016) 95: 336-343

UCSF: NVG & Dose

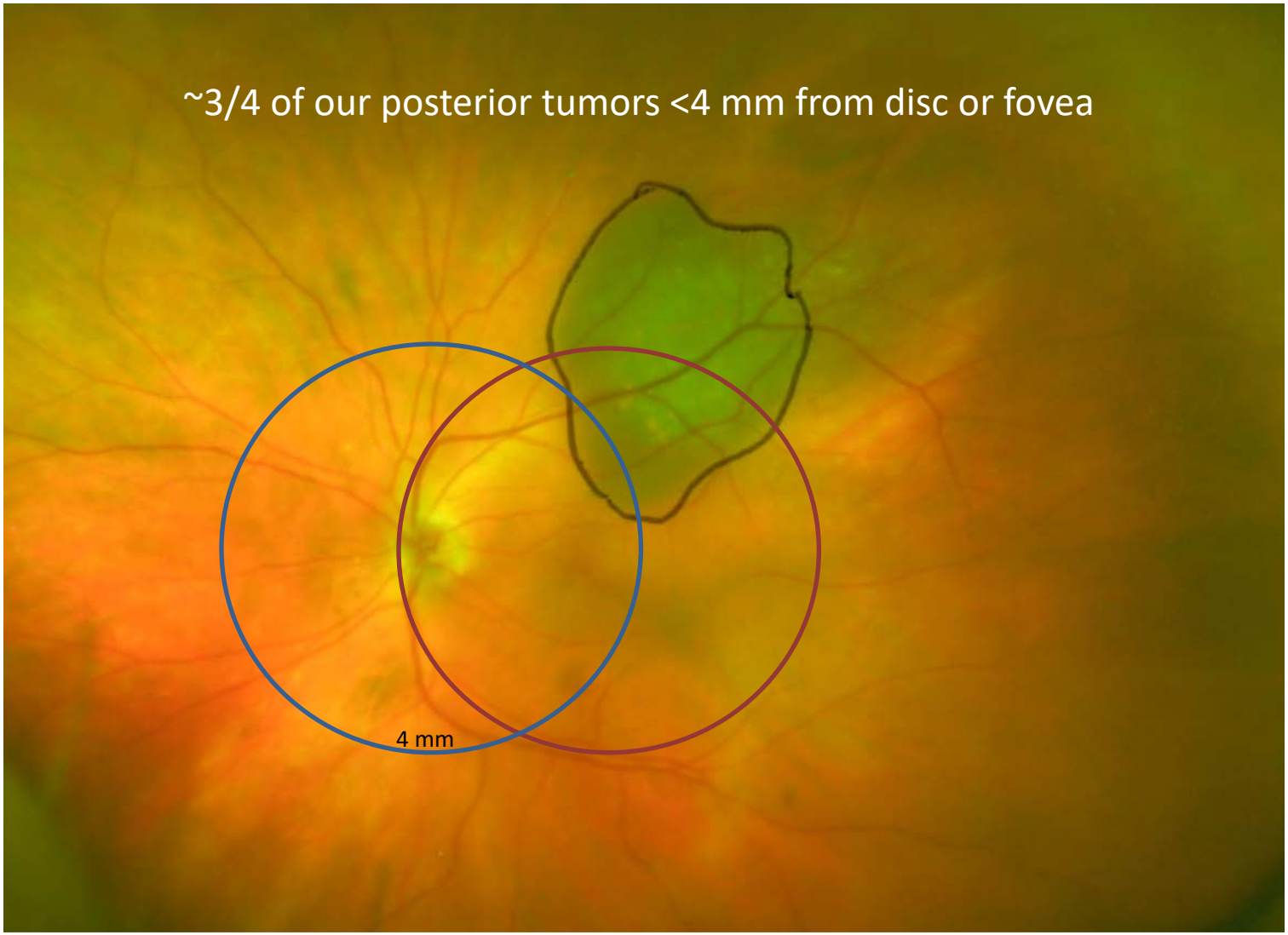
- **Overall 5y NVG risk 12.5%**
- Vol Ciliary Body and Disc dose ≥ 28 GyE



Source: Mishra et al., IJROBP (2013) 92: 330-336

kavita.mishra@ucsf.edu

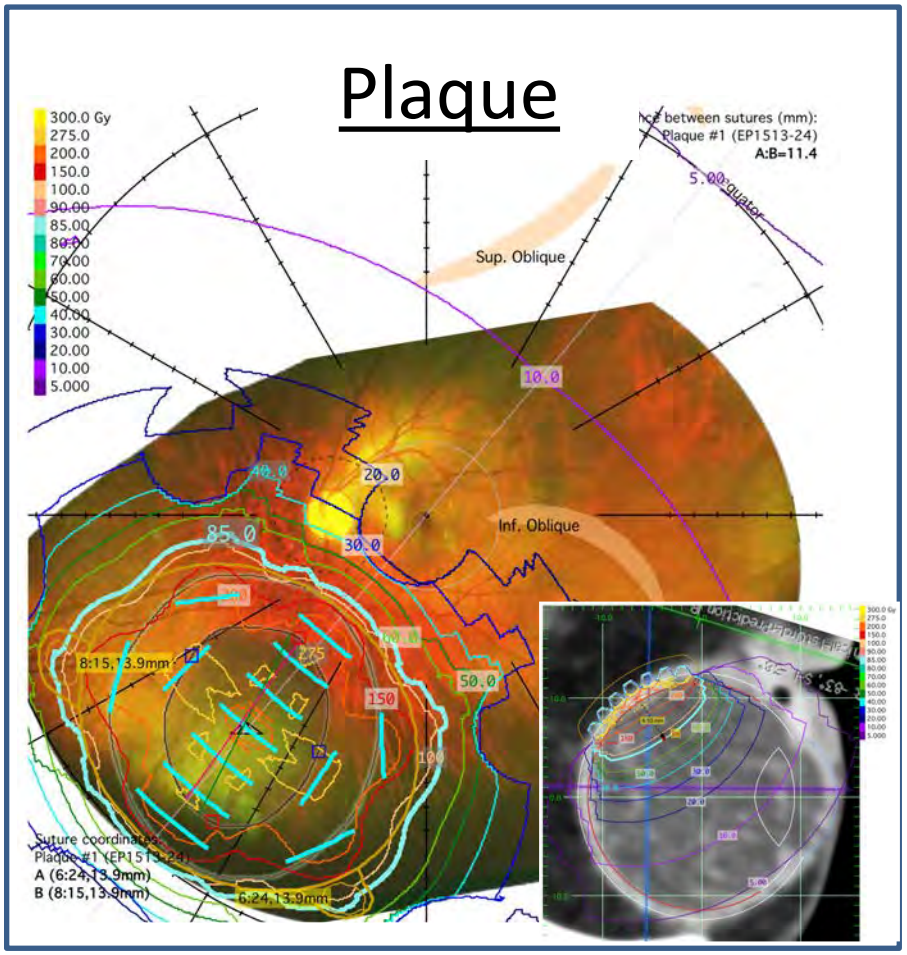
UCSF: Posterior Structures & Dose

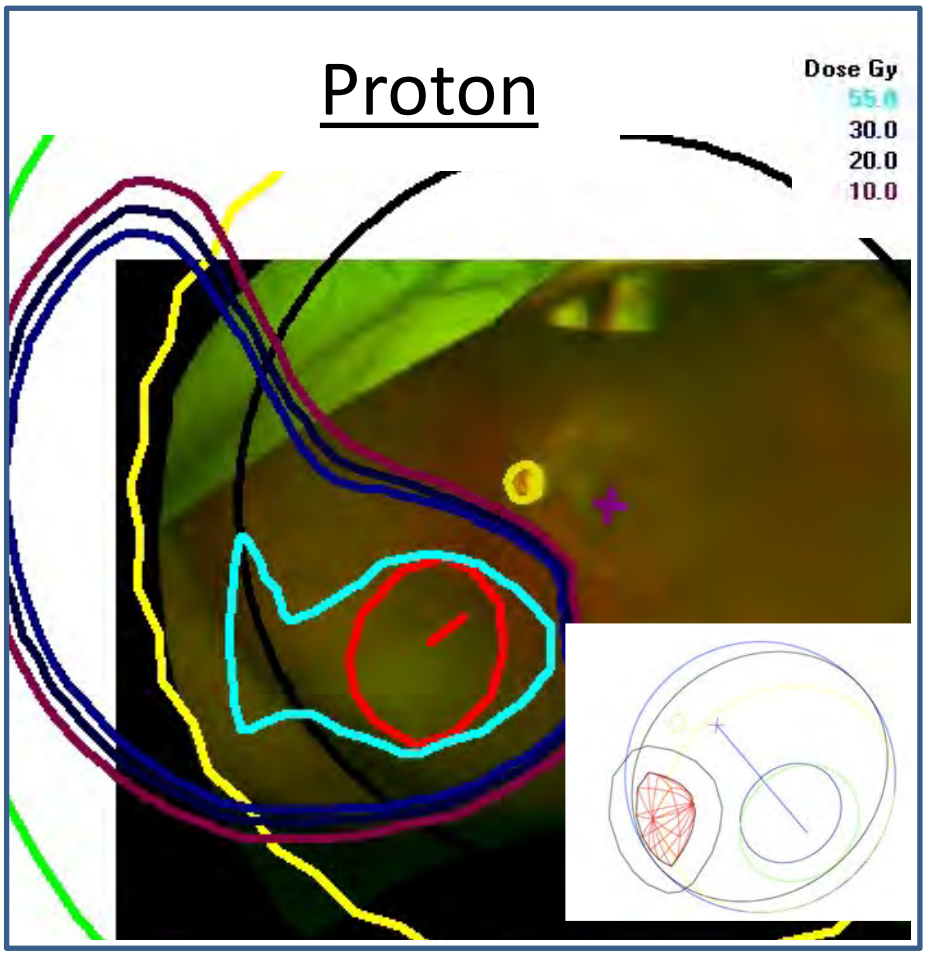


Courtesy: Inder Daftari, PhD

kavita.mishra@ucsf.edu

Eye Tumors: UCSF proton beam vs I-125 plaques





D_{max} 42GyE optic disc, 15GyE macula, 12GyE lens

D_{max} 0GyE to optic disc, macula, & lens

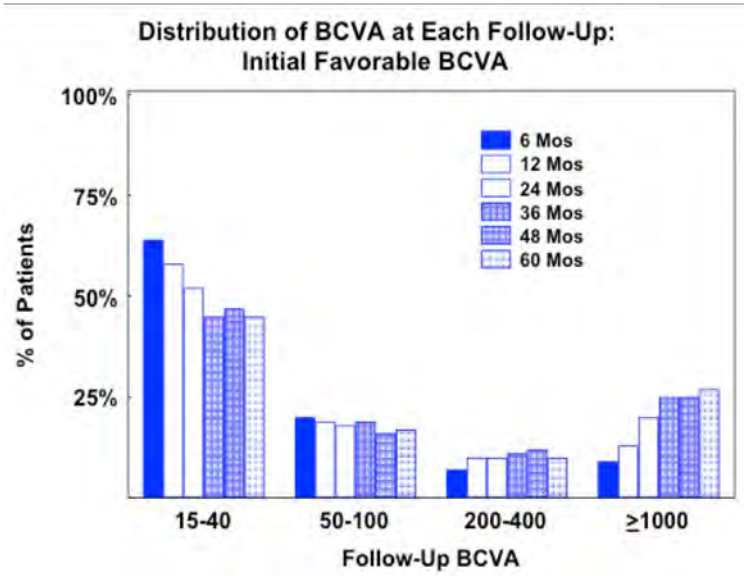
Scholey J, Weinberg V, Daftari I, Mishra K. *Pilot study on critical structure dosing for ocular melanoma radiation techniques: An analysis of I-125 brachytherapy plaque and dedicated proton eye beamline treatment planning dosimetry.* AAPM/PTCOG-NA, 2019.

UCSF: Vision & Dose

- Disc, Macula, Nerve length dose ≥ 28 GyE
- Those with favorable baseline, ~50% maintain excellent vision
- Sparing of each counts – macula or disc/nerve

Table 2. Multivariate Analysis

Favorable Pre-Treatment BCVA Endpoint: (≥20/40 at 48 months)			Unfavorable/Poor Pre-Treatment BCVA Endpoint: (≥20/100 at 24 months)		
Characteristic	LLR p-value	OR (95% CI)	Characteristic	LLR p-value	OR (95% CI)
Macula Receiving 28 GyE (0% vs. >0%)	<0.0001	16.13 (6.97-37.28)	Initial BCVA (≤20/100 vs >20/100)	<0.0001	7.01 (2.81-17.50)
Tumor Height (mm)	<0.0001	1.47 (1.21-1.79)	Age at RT (per yr)	0.0255	0.97 (0.94-1.00)
Optic Nerve Receiving 28GyE (≤1 mm vs >1 mm)	0.0004	0.20 (0.08-0.49)			
Diabetes at Diagnosis	0.01	7.09 (1.30-38.64)			



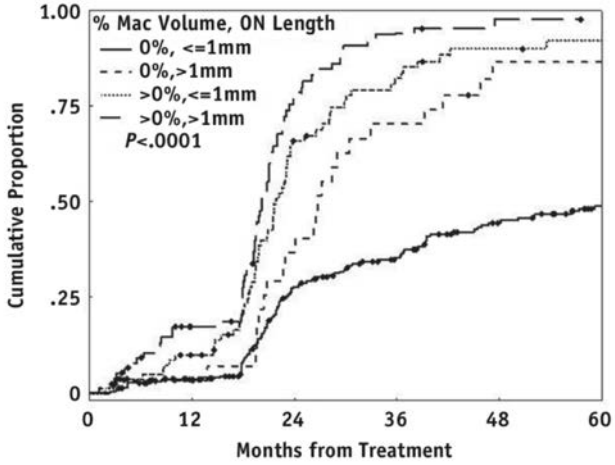


Fig. 4. Time to first best corrected visual acuity (BCVA) decline according to 28GyE volume of the macula and optic nerve.

Source: Polishchuk et al (2016) IJROBP

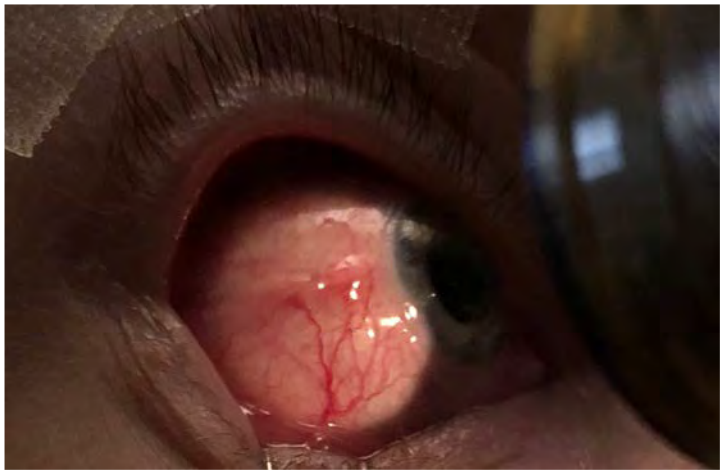
kavita.mishra@ucsf.edu

UCSF: Clinical Methods - Anterior Structure Dose

- Structures to consider: Eyelashes, eyelid, tear duct, lacrimal gland

Methods:

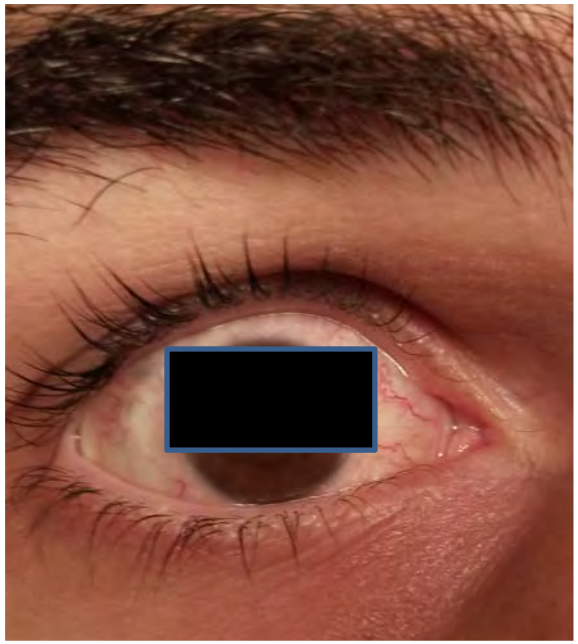
- Retractors with light field; multiple types; 0-3
- Local anesthetics, tape, time frame
- Tilt, rotation
- Upper lid > lower; rim avoidance
- Aesthetics & QOL short and long-term

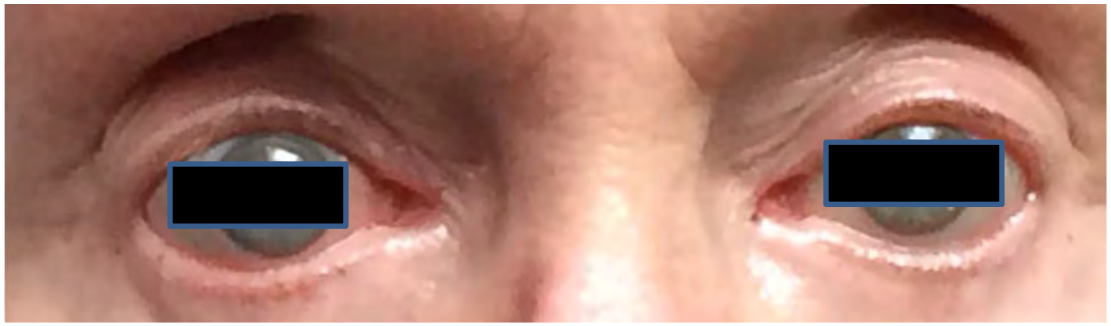


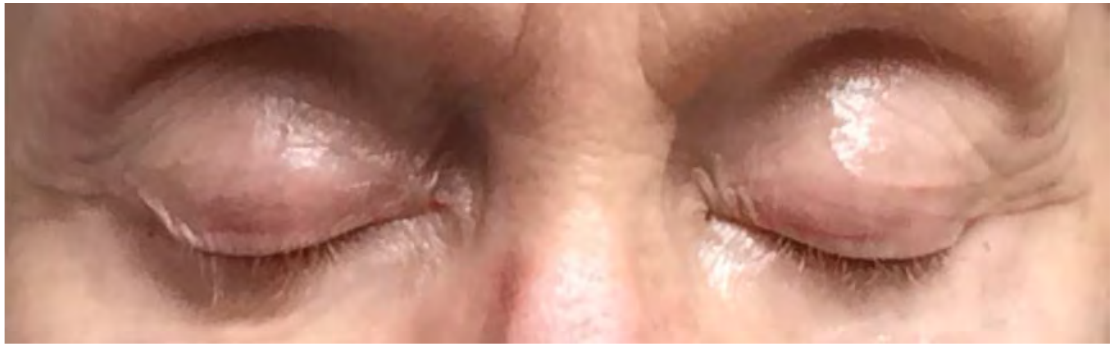
kavita.mishra@ucsf.edu

UCSF: Clinical Methods - Anterior Structure Dose

Improved short and long-term eyelid and aesthetic results with careful retraction methods and treatment planning angle.







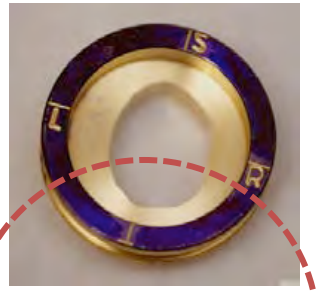
kavita.mishra@ucsf.edu

UCSF-CNL Proton Ocular Program

Pt dx and transfer care to ocular/radiation oncologist

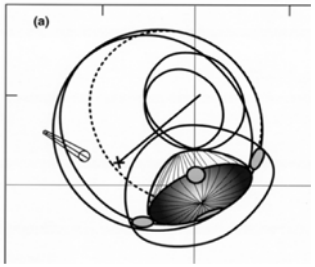
Simulation in Rad Onc w/ immobilization device and orthogonals

56 GyE in four daily fx of 14 GyE



Treatment at CNL

Pt decide PBRT; Tantalum ring placement



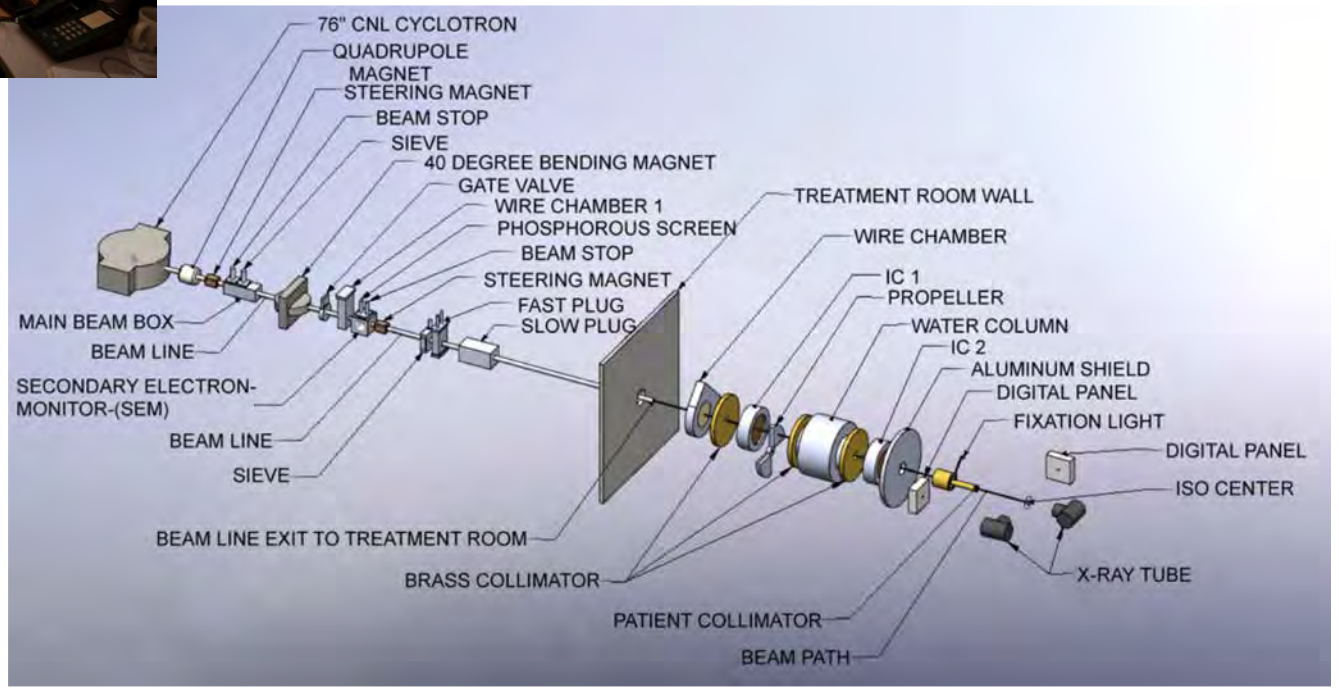
Planning w/ EYEPLAN; anterior structure sparing technique*

Source: *Daftari et al, IJROBP 1997, 39:997–1010

kavita.mishra@ucsf.edu

UCSF Ocular: Dedicated (low energy) fixed eye beamline

- Helium ions (LBNL 77-92) and plaques (UCSF)
- Protons (Crocker): since 1994
  - 76-inch cyclotron
  - 67.5 MeV proton beam

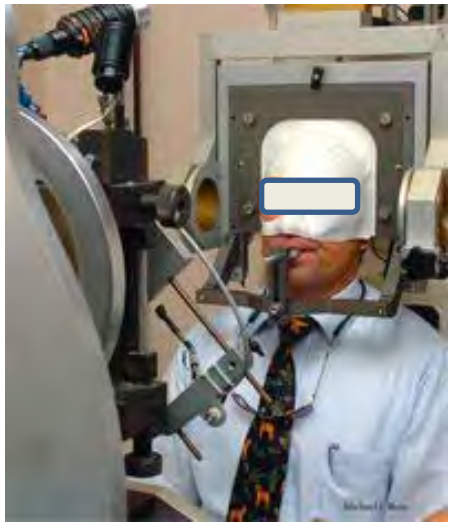


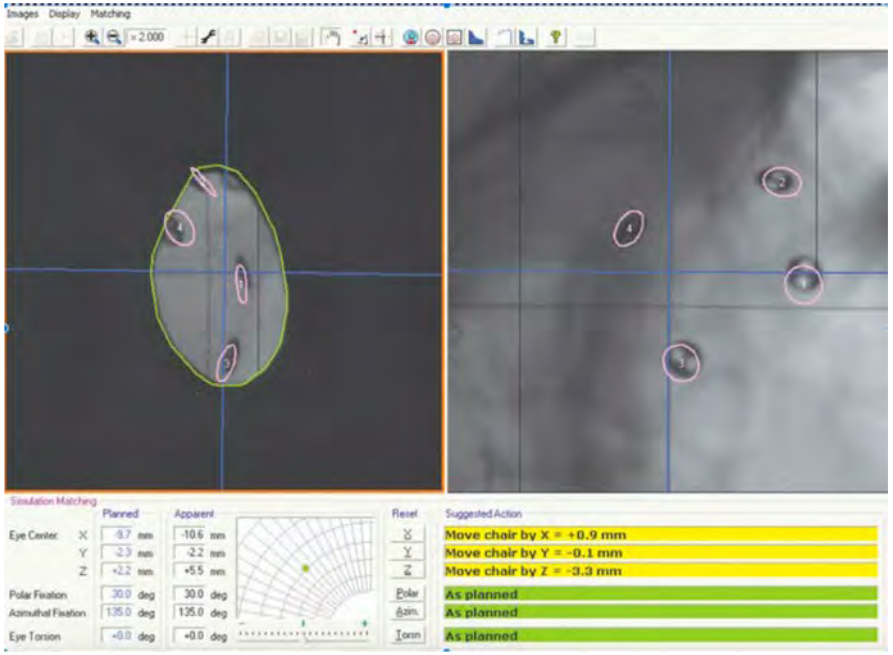
Slide courtesy of Scholey. Daftari et al. *An overview of the control system for dose delivery at the UCSF dedicated ocular proton beam*. International Journal of Medical Physics, Clinical Engineering and Radiation Oncology. 2016. 5. P 242-2.

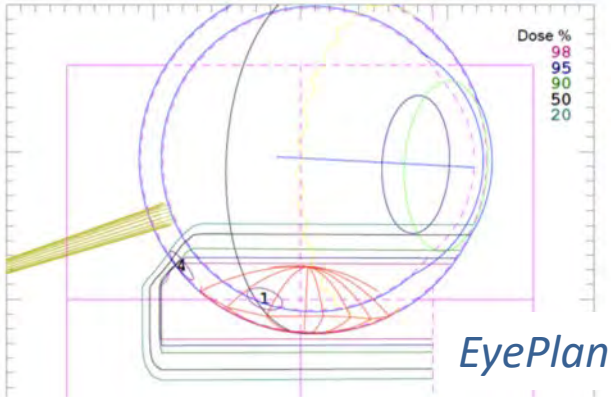
UCSF Ocular: Dedicated (low energy) fixed eye beamline

- Tantalum rings / IGRT
- Gaze fixation (affected >> healthy)
- Eye pupillary tracking

- 56 GyE in 4 daily fx



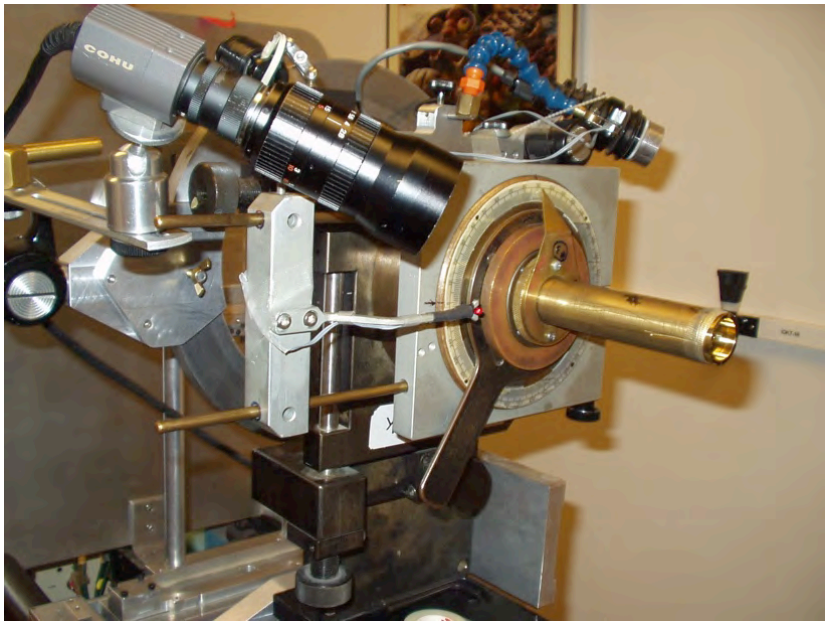


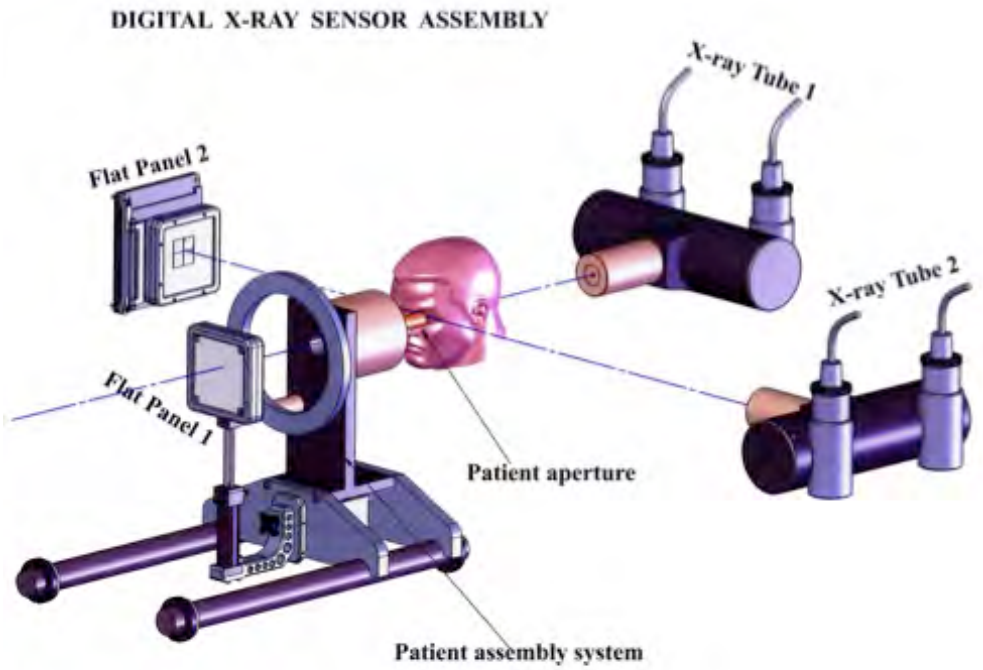


EyePlan TPS

kavita.mishra@ucsf.edu

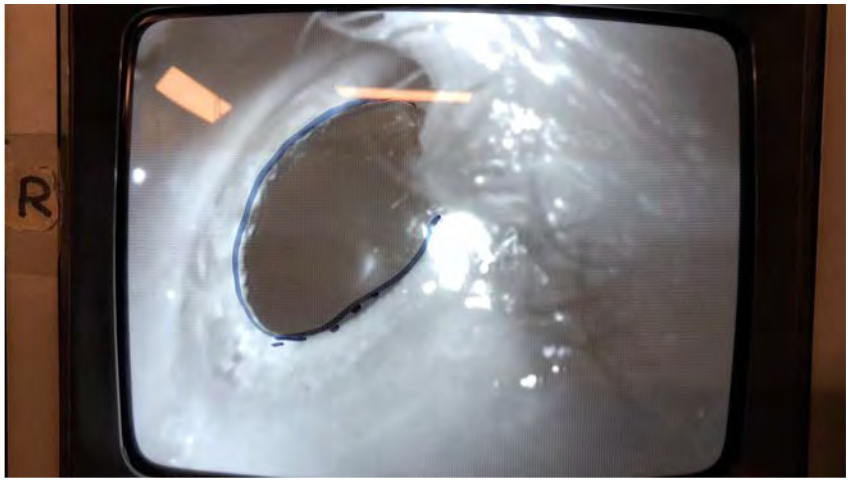
UCSF Ocular: Dedicated (low energy) fixed eye beamline





kavita.mishra@ucsf.edu

UCSF Ocular: Pupillary Magnification & Tracking



Careful IGRT & tracking to ensure dose delivery and critical structure sparing

kavita.mishra@ucsf.edu

Proton Ocular: Clatterbridge Eyeline

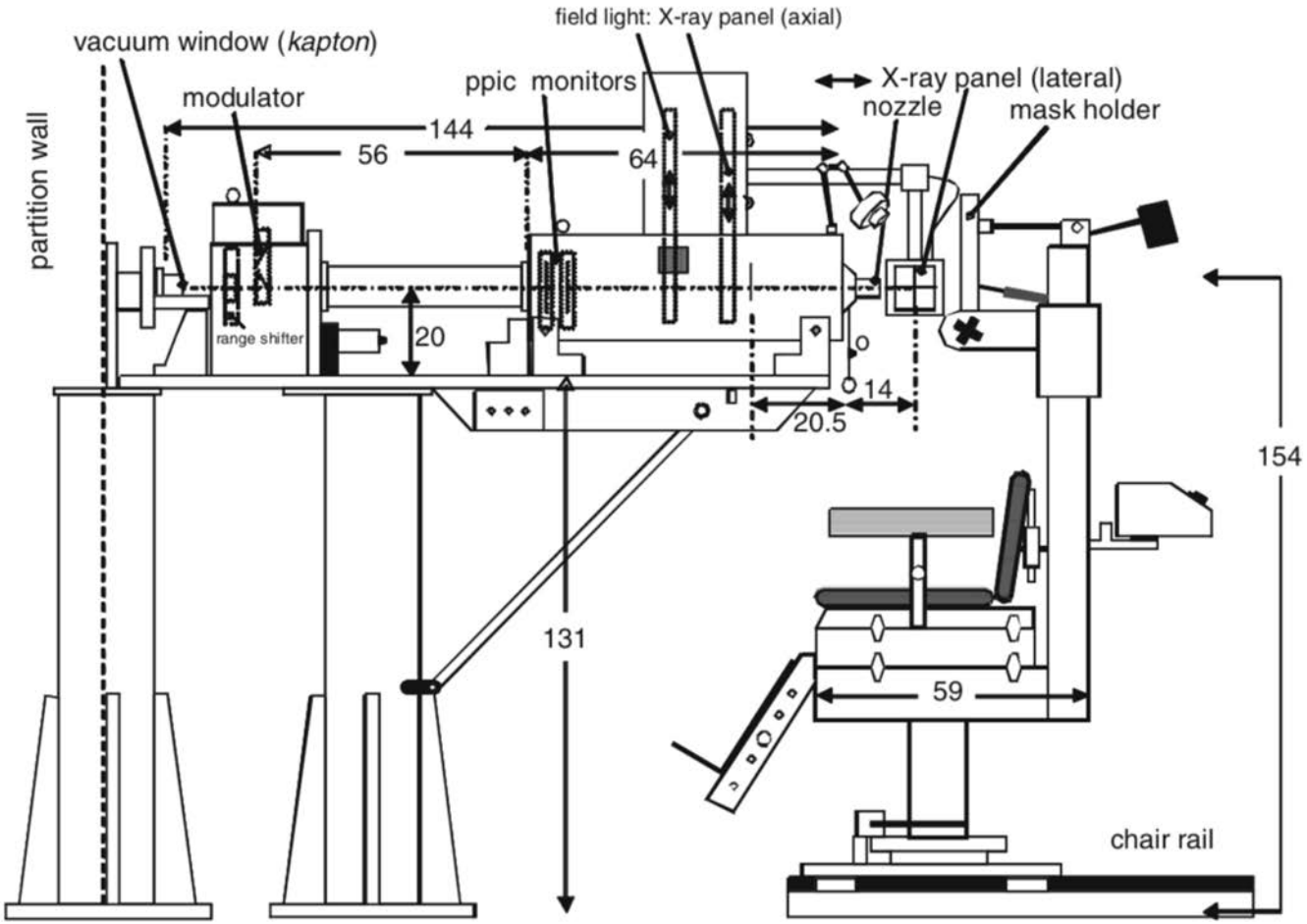


Fig. 10.5 Sketch of the beam line at CCO (in 2009). Measurements are in centimeters. Axial and lateral digital X-ray panels as well as field lights are positioned by pneumatic mechanism

Courtesy: Andrzej Kacperek, PhD (Clatterbridge)

kavita.mishra@ucsf.edu

Proton Ocular: Clatterbridge Eyeline

Courtesy: Andrzej Kacperek, PhD (Clatterbridge)

kavita.mishra@ucsf.edu

Proton Beamlines: Degraded non-dedicated high energy

- More inhomogeneity
- Higher critical structure doses
  - Optic disc dose
  - Retina, nerve dose
  - Anterior dose ciliary body, lens
  - Lacrimal gland

Structure	Volume (cc)	Min Dose (cGy)	Max Dose (cGy)	Mean Dose (cGy)
GTV	0.49	5706.0	6036.0	5876.0
PTV	2.00	5372.0	6061.0	5882.0
OpticNerve_R	0.64	0.0	5911.0	980.0
CiliaryBody_R	0.11	6.0	4174.0	1016.0
Lens_R	0.18	36.0	3712.0	1161.0
Lacrimal_R	0.52	862.0	5336.0	2863.0
Retina_R	4.17	1.0	6061.0	3393.0
OpticDisc_R	0.04	5151.0	5983.0	5793.0
Macula_R	0.02	5898.0	6036.0	5947.0
Brain	1400.13	0.0	4193.0	7.0

Dose Calculation Summary

Eye Structure	20%	50%	90%	of max dose
Retina	38	34	29	% area
Surface of the globe	29	26	18	% area
Volume of the globe	2.3	2.1	1.6	cc
Volume of the lens	0	0	0	% vol.
Periphery of the lens	0	0	0	%
Ciliary body	11	7	1	% vol.
Optic disc	55	30	0	% area
Macula	100	100	100	% vol.
Length of the optic nerve	0.9	0.2	0.0	mm
Surface of the tumour	100	100	100	% area
Surface of the cornea	0	0	0	% area

R&D: Spot-scanning gantry based system

Simulation
- *Immobilization device, mask*
- *Sim process gaze angles, eyelids*
- *CT-based*

- *Aperture production*
- *Collimation accuracy and reproducibility*
- *QA for snout, portable set-up*

Treatment:
- *Dose rate, treatment time*
- *Gaze fixation and eye tracking systems*
- *Light field, work flow*
- *Couch rotation, head tilt, eyelid retraction for surface dose*
- *Displacement of snout on nozzle*
- *Portable set up accuracy*
- *Neutron dose*

- *Ring location – x-ray imager*
- *Resolution flat panels*
- *Onboarding*

Planning:
- *Distal & Lateral fall-off*
- *Range uncertainty*
- *Dose, margins required*
- *Beam/gaze angles*
- *3D and 2D image fusion*
- *Spot scanning optimization*
- *Software-Aperture calcs*
- *Monte Carlo/TOPAS/Eclipse*

kavita.mishra@ucsf.edu

UM: Question* - Proton Spot Scanning

285. What is a greater concern with spot scanning technique versus passive scattering for proton therapy delivery?

(A) Energy selection
(B) Beam shaping
(C) Target motion
(D) Beam line length

* American College of Radiology In-Training Examination for Radiation Oncology Residents

Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

UM: Question* - Proton Spot Scanning

285. What is a greater concern with spot scanning technique versus passive scattering for proton therapy delivery?

(A) Energy selection
(B) Beam shaping
(C) Target motion
(D) Beam line length

Key: C
Solution: Spot scanning involves sequential "painting" of the target with a narrow beam producing dose spots. Target motion is more difficult to deal with under these circumstances.
References: McDermott & Orton. The Physics and Technology of Radiation Therapy. Medical Physics Publishing. (2010).P 20-55.

* American College of Radiology In-Training Examination for Radiation Oncology Residents

Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination

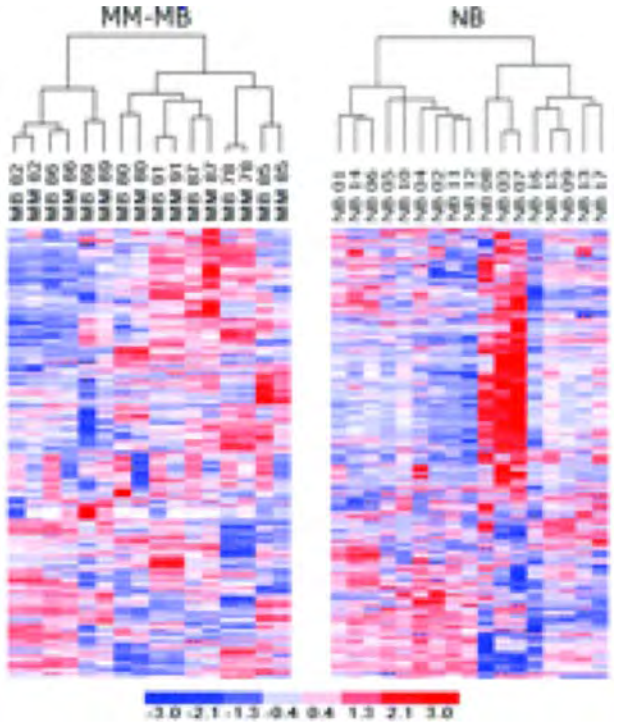
kavita.mishra@ucsf.edu

R&D: Considerations

- Local control
- Eye preservation
- Complications

- Max tumor dose/ homogeneity
- Optic disc and nerve dose
- Retina
- Anterior dose CB/lens
- Lacrimal gland
- Surface/Eyelid, tear duct
- Muscles, brain, orbit

High risk pts

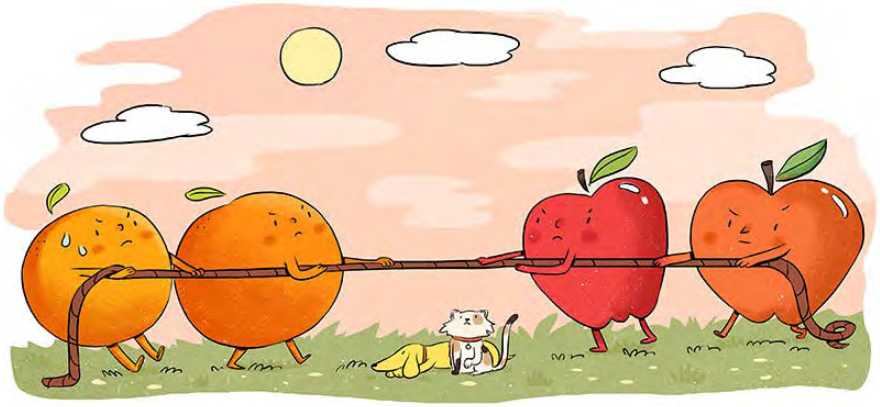


kavita.mishra@ucsf.edu

OM & Protons

Excellent long term LC and eye preservation with proton beam

Rare disease specialty centers with advanced eye proton planning and treatment delivery teams



LC and QOL/Vision outcomes to evaluate RT modalities

kavita.mishra@ucsf.edu

OM & Protons

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kavita.mishra@ucsf.edu