Ocular Melanoma & Proton Therapy

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Ocular Tumor Proton & Plaque Therapy Program
UCSF Comprehensive Cancer Center
January 13, 2020
# Topics

<table>
<thead>
<tr>
<th>Overview of ocular melanoma and proton technology: <em>What do we know from the past 50 years?</em></th>
</tr>
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<tr>
<td>Clinical data &amp; outcomes: <em>Which factors matter for which outcomes?</em></td>
</tr>
<tr>
<td>Treatment Planning &amp; Delivery: <em>Current techniques and what is on the horizon?</em></td>
</tr>
</tbody>
</table>
LBNL-UCSF: Particle Therapy

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

1,463 Cancer pts
347 UM Pts He
LBNL 1931-1992
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

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

Ocular model computer program
(Goitein and Miller)
Background: Proton Therapy

Graph showing the depth dose distribution for different particles: Electrons (21 MeV), Carbon (270 MeV/u), Photons, and Protons.

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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
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.


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

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

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

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(A) No effect
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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.


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

Background: Eye

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

- Ciliary body
- Cornea
- Iris
- Lens
- Ciliary body
- Sclera
- Retina
- Choroid
- Vitreous humor
- Optic nerve

Source: Terese Winslow © Terese Winslow Medical Illustration
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Clinical

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

- Nevus
- Hemangioma
- Detachment
- Metastasis
- Hemorrhage
<table>
<thead>
<tr>
<th>AJCC 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor size – LBD &amp; Thickness</strong></td>
</tr>
<tr>
<td><strong>CBI and/or EOE</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMS*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height</strong></td>
</tr>
<tr>
<td>Small: 1 to ≤3 mm &amp; 5 to 16 mm</td>
</tr>
<tr>
<td>Medium: ≥2.5 to ≤10 mm &amp; ≤16 mm</td>
</tr>
<tr>
<td>Large: &gt;10 mm AND/OR &gt;16 mm</td>
</tr>
</tbody>
</table>

* Collaborative Ocular Melanoma Study
Clinical

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


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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
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Clinical

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

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   (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.
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.
### 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? |
# UM: Local Therapy Trials

Table 65-4: COMS and UCSF-LBL Trials

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

<table>
<thead>
<tr>
<th>UCSF-LBL trial**</th>
<th>Local control</th>
<th>Enucleation</th>
<th>CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Charged particle***</td>
<td>100% (p&lt;0.001)</td>
<td>9.3%</td>
</tr>
<tr>
<td></td>
<td>Plaque I-125***</td>
<td>87%</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

*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)
• 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

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among the lowest treatment failure rates of 0% and 1.7% used routine intraoperative ultrasound for plaque localisation during brachytherapy. These data suggest that intraoperative ultrasound plaque localisation during brachytherapy may reduce the risk of local treatment failure. One can speculate that the optimised plaque placement reduces geographic misses, thereby improving local treatment success rates.

The weighted mean tumour LBD and height among studies using iodine-125 brachytherapy were 11.1 mm and 4.8 mm, respectively. In the Collaborative Ocular Melanoma Study, tumours eligible for iodine-125 brachytherapy were less than 16.0 mm in LBD and 10.0 mm in height. The maximum tumour height was 8.0 mm when the tumour was near the disc. Many studies use these parameters to determine eligibility for globe-sparing therapy. At the Jules Stein Eye Institute, we use the following maximal dimensions for iodine-125 brachytherapy: apical height of 10 mm, and LBD of 16–17 mm, with absolute necessity for ultrasound confirmation of borders.

Ruthenium-106 emits β-particles that only travel a limited distance (4–5 mm); therefore, ruthenium-106 is most appropriate for brachytherapy of tumours less than 5.4 mm in height. The weighted mean local failure rate among studies using ruthenium-106 brachytherapy was 9.6%, identical to the rate calculated for iodine-125. Local recurrence may be reduced when adjuvant transpupillary thermotherapy is used in combination with ruthenium-106 brachytherapy. The two studies that used ruthenium-106 plaques and reported the lowest local failure rates both used adjuvant transpupillary thermotherapy.

Photon-based external beam radiation therapy

The rate of local treatment failure with photon-based external beam radiation therapy (gamma knife radiosurgery or

### Table 3 Comparison of radiation modalities

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

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

LC higher with Particles despite larger mean tumor size
"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."


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Dosimetry: Particles v Plaque Therapy

Cumulative RDPA for Plaque #1 EP1513-24
Calc: Line, F(10), R(7), PE, Slot
Exp. 65.0 Gy to Tumor +5.50 mm
Base expansion margin = 2.0 mm
Tumor 1 base (66.67 mm^2)
Tumor 1 + margin (137.30 mm^2)
Retina outside margin (1163.90 mm^2)
Macula (53.01 mm^2)
Optic disc (3.20 mm^2)
Fovea (2.07 mm^2)

% area Vs. % dose for various structures:
- Retina
- Surface of the globe
- Volume of the globe
- Volume of the lens
- Periphery of the lens
- Ciliary body
- Optic disc
- Macula
- Length of the optic nerve
- Surface of the tumour
- Surface of the cornea
# UM: Local RT Considerations

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

<table>
<thead>
<tr>
<th>Visual outcome</th>
<th>Stereotactic radiosurgery</th>
<th>Proton beam therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity $\geq 6/60$</td>
<td>33%</td>
<td>55%</td>
</tr>
<tr>
<td>Loss of $\geq 3$ snellen Lines</td>
<td>65%</td>
<td>45%</td>
</tr>
</tbody>
</table>

3y VA: Protons > SRS

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UM: SRS Considerations

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

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## Cost Effectiveness

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medicare reimbursement</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enucleation</td>
<td>$8,678</td>
<td>($6-13K)</td>
</tr>
<tr>
<td>Plaque brachy</td>
<td>$19,108</td>
<td>($13-29K)</td>
</tr>
<tr>
<td>Proton beam (4-5 fractions)</td>
<td>$12,438</td>
<td>($8-19K)</td>
</tr>
</tbody>
</table>

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


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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

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Source: https://www.acr.org/Search-Results#q=radiation%20oncology%20in-training%20examination
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   a. Less expensive
   b. Treats larger tumors
   c. Mobile radiation field
   d. Lower risk of enucleation

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.


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

**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 optic nerve. 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.

Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy, Cancer. 2014.

* American College of Radiology In-Training Examination for Radiation Oncology Residents
# UM & Protons Objectives

## Topics

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview of ocular melanoma and proton technology:</td>
<td><em>What do we know from the past 50 years?</em></td>
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<td>Treatment Planning &amp; Delivery:</td>
<td><em>Current techniques and what is on the horizon?</em></td>
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Pt dx and transfer care to ocular/radiation oncologist

Pt decide PBRT; Tantalum ring placement

Simulation in Rad Onc w/ immobilization device and orthogonals

Planning w/ EYEPLAN; anterior structure sparing technique*

56 GyE in four daily fx of 14 GyE

Treatment at CNL


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UCSF-CNL: Surgery

Very active communication
Pt dx and transfer care to ocular/radiation oncologist

Pt decide PBRT; Tantalum ring placement

Simulation in Rad Onc w/ immobilization device and orthogonals

Planning w/ EYEPLAN; anterior structure sparing technique*

56 GyE in four daily fx of 14 GyE

Treatment at CNL

UCSF-CNL: Simulation
Pt dx and transfer care to ocular/radiation oncologist

Pt decide PBRT; Tantalum ring placement

Simulation in Rad Onc w/ immobilization device and orthogonals

56 GyE in four daily fx of 14 GyE

Planning w/ EYEPLAN; anterior structure sparing technique*

Treatment at CNL

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

Use eye position, beam parameters, margins, etc. to ensure tumor coverage and minimize dose to critical structures.
UCSF-CNL: Treatment Planning
UCSF-CNL: Treatment Planning

Protect optic disc/ nerve/ macula
UCSF-CNL: Treatment Planning
UCSF-CNL: Treatment Planning
Proton Eye: Treatment Planning
Pt dx and transfer care to ocular/radiation oncologist

Pt decide PBRT; Tantalum ring placement

Simulation in Rad Onc w/ immobilization device and orthogonals

Planning w/ EYEPLAN; anterior structure sparing technique*

56 GyE in four daily fx of 14 GyE

Treatment at CNL
OM & Protons: Dose

Ocular Tumors

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

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Consistency of proton UM dose
~60 GyE/4

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

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

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
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**UCSF: NVG & Dose**

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

![Cumulative Incidence of NVG](image)

- CB >30% & Disc = 100%
- 5 Year Est.
- 5.0% (n=386)
- 17.9% (n=161)
- 20.4% (n=116)
- 55.7% (n=41)

*p<.0001*


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~3/4 of our posterior tumors <4 mm from disc or fovea
**Plaque**

- $D_{\text{max}}$ 42GyE optic disc, 15GyE macula, 12GyE lens

**Proton**

- $D_{\text{max}}$ 0GyE to optic disc, macula, & lens

• 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LLR p-value</th>
<th>OR (95% CI)</th>
<th>Characteristic</th>
<th>LLR p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macula Receiving 28 GyE (0% vs. &gt;0%)</td>
<td>&lt;0.0001</td>
<td>16.13 (6.97-37.28)</td>
<td>Initial BCVA (≤20/100 vs &gt;20/100)</td>
<td>&lt;0.0001</td>
<td>7.01 (2.81-17.50)</td>
</tr>
<tr>
<td>Tumor Height (mm)</td>
<td>&lt;0.0001</td>
<td>1.47 (1.21-1.79)</td>
<td>Age at RT (per yr)</td>
<td>0.0255</td>
<td>0.97 (0.94-1.00)</td>
</tr>
<tr>
<td>Optic Nerve Receiving 28 GyE (≤1 mm vs &gt;1 mm)</td>
<td>0.0004</td>
<td>0.20 (0.08-0.49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes at Diagnosis</td>
<td>0.01</td>
<td>7.09 (1.30-38.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Polishchuk et al (2016) IJROBP

Fig. 4. Time to first best corrected visual acuity (BCVA) decline according to 28GyE volume of the macula and optic nerve.
• 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
Improved short and long-term eyelid and aesthetic results with careful retraction methods and treatment planning angle.
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

Pt decide PBRT; Tantalum ring placement

Planning w/ EYEPLAN; anterior structure sparing technique*


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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

UCSF Ocular: Dedicated (low energy) fixed eye beamline

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

- 56 GyE in 4 daily fx
UCSF Ocular: Dedicated (low energy) fixed eye beamline
Careful IGRT & tracking to ensure dose delivery and critical structure sparing
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.
Proton Ocular: Clatterbridge Eyeline

Courtesy: Andrzej Kacperek, PhD (Clatterbridge)
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**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

---

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

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**Dose Calculation Summary**

<table>
<thead>
<tr>
<th>Eye Structure</th>
<th>20%</th>
<th>50%</th>
<th>90%</th>
<th>of max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retina</td>
<td>38</td>
<td>34</td>
<td>29</td>
<td>% area</td>
</tr>
<tr>
<td>Surface of the globe</td>
<td>29</td>
<td>26</td>
<td>18</td>
<td>% area</td>
</tr>
<tr>
<td>Volume of the globe</td>
<td>2.3</td>
<td>2.1</td>
<td>1.6</td>
<td>cc</td>
</tr>
<tr>
<td>Volume of the lens</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>% vol.</td>
</tr>
<tr>
<td>Periphery of the lens</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>%</td>
</tr>
<tr>
<td>Ciliary body</td>
<td>11</td>
<td>7</td>
<td>1</td>
<td>% vol.</td>
</tr>
<tr>
<td>Optic disc</td>
<td>55</td>
<td>30</td>
<td>0</td>
<td>% area</td>
</tr>
<tr>
<td>Macula</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>% vol.</td>
</tr>
<tr>
<td>Length of the optic nerve</td>
<td>0.9</td>
<td>0.2</td>
<td>0.0</td>
<td>mm</td>
</tr>
<tr>
<td>Surface of the tumour</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>% area</td>
</tr>
<tr>
<td>Surface of the cornea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>% area</td>
</tr>
</tbody>
</table>
**R&D: Spot-scanning gantry based system**

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

**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

**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
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
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.
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
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
OM & Protons

UCSF Uveal Melanoma Team
- Jessica Scholey
- Inder K. Daftari, PhD
- Sara St James, PhD
- D. Sevier, G. Balianz, L. Jang
- Charlie Pascal, Engineer
- R.P. Singh, PhD
- Dan Shadoan, PhD
- Jeff Gallup, PhD
- Paula Petti, PhD
- Vivian K. Weinberg, PhD
- Krishna Munoz
- Lindsay Williams
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- Jeannine M. Quivey, MD
- Theodore L. Phillips, MD
- Catherine Park, MD, Chair

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- Devron H. Char, MD
- Tony Tsai, MD, Carlos Medina, MD
- Robert Johnson, MD
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- Joan O’Brien, MD/Paul Stewart, MD

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