Controversial Issues in Practice:
Are protons the universally better option for OM?

- Physics
- Clinical Outcomes
- UCSF Proton Therapy Program
- Conclusions

Proton Physics: Is it better?

RANGE: Physical depth dose curves
Is there better normal tissue sparing?

Macula/Disc sparing with protons

Tissue sparing in the eye with protons

Planning/Delivery advances for protons

Imaging superimposition:
Fundus photo, MRI?

Image guided delivery:
Electronic portal daily alignment with fiducials
Physics: Protons vs Plaque/SRT/Other

- Tight Depth and Lateral dose distribution
- Uniform dose through tumor volume
- 1-2 min rx time (eye fixation, monitoring)
- Risk for SE can be reduced with certain planning techniques
- Lower body doses
- Can be used for peripillary or macular tumors


UCSF 2014

Does Theory = Reality?

Do the theoretical benefits of protons translate to real clinical outcomes in practice?

UCSF-LBNL Particle vs Plaque Study

- Only prospective randomized trial comparing two radiation modalities for the treatment of uveal melanoma to date
- Long-term outcomes
- Trial 1985 to 1991. Tumors close to optic disc were included.

184 uveal melanoma patients randomized

Charged Particle RT Helium Arm (n=86)

I-125 Brachytherapy Plaque Arm (n=98)

UCSF-LBNL trial (n=184)

Charged Particle (f/u 14.6 yrs)

Plaque I-125 (f/u 12.3 yrs)

Local Control

<table>
<thead>
<tr>
<th>Arm</th>
<th>5y</th>
<th>12y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charged</td>
<td>100% (p=0.0006)</td>
<td>98%</td>
</tr>
<tr>
<td>Plaque</td>
<td>84%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Enucleation

<table>
<thead>
<tr>
<th>Arm</th>
<th>5y</th>
<th>12y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charged</td>
<td>11% (p=0.01)</td>
<td>17%</td>
</tr>
<tr>
<td>Plaque</td>
<td>22%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Mishra, Quivey, Daftari et al. ASTRO 2012 Presentation. Median f/u for Particle = 14.6 yrs and for I-125 = 12.3 yrs (p=0.22), and for those alive, 18.3 and 16.8 yrs (p=0.81).

UCSF 2014

Particle vs Plaque: 12 year Update

- Local Control significantly higher with Particles
- Eye Preservation significantly higher with Particles

UCSF-LBNL Particle vs Plaque Study

184 uveal melanoma patients randomized

Charged Particle RT Helium Arm (n=86)

I-125 Brachytherapy Plaque Arm (n=98)
### Particle vs Plaque: 12 year Update

**Local Control**

<table>
<thead>
<tr>
<th></th>
<th>Particle (blue)</th>
<th>I-125 (red)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y</td>
<td>100%</td>
<td>84%</td>
</tr>
<tr>
<td>12 y</td>
<td>98%</td>
<td>79%</td>
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</table>

**Eye Preservation**

<table>
<thead>
<tr>
<th></th>
<th>Particle (blue)</th>
<th>I-125 (red)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y</td>
<td>89%</td>
<td>78%</td>
</tr>
<tr>
<td>12 y</td>
<td>83%</td>
<td>63%</td>
</tr>
</tbody>
</table>

- Treatment with particles is the most important predictor of LC ($p<0.0002$) and eye preservation ($p=0.01$)
- Plaque patients with tumors close to disc did worse ($p=0.03$):
  - < 2 mm: 5 y LC 72% and 12 y LC 64%
  - ≥ 2 mm: 5 y LC 90% and 12 y LC 86%

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### Is the clinical outcomes data consistent?

<table>
<thead>
<tr>
<th></th>
<th>Particles</th>
<th>Plaques</th>
<th>SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC 5y</td>
<td>95% (90-99%)</td>
<td>89.7% (81-96%)</td>
<td>Shorter f/u, 1 to 3 y, 83-98%</td>
</tr>
<tr>
<td>Enuc 5y</td>
<td>10% (0-25%)</td>
<td>12% (4-20%)</td>
<td>[1 to 3 y, 7.7-17%]</td>
</tr>
<tr>
<td>5y Useful vision (&lt;20/200)</td>
<td>40-65%</td>
<td>37% (23-73%)</td>
<td>[shorter f/u, 21-50%]</td>
</tr>
</tbody>
</table>

**Relevant Issues:**
- Follow-up
- Dose distribution
- Eye fixation
- Treatment times
- Side effects

**Modified from Mishra et al, Uveal Melanoma, in Textbook for Radiation Oncology, 3rd edition; 2010:1400-21.**

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### Does Theory = Reality?

Appears consistent...

So how does it all work?
### Local Therapy: Key Points

- **Small tumors:** observation vs treatment
  - Two-thirds appear stable long term
- **Medium and Large tumors:** RT vs surgery (enucleation or local resection ± RT)
  - Comparable CSS and OS rates (COMS trials, etc.)
  - RT allows for excellent LC & preservation of eye/vision
- **RT first line**
- **Certain tumors respond well to all RT modalities (size, loc, etc.)**
- **Particle RT gives consistently best LC with long follow-up**

### Molecular Classification

- **FNA Bx**
- 5 year Metastasis-Free Survival by Class
  - 1A: 98%
  - 1B: 80%
  - 2: 30%

*Draken et al., JMD 2006;8:567-573.*

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### UCSF Ocular PBRT Program

#### Number of Patients Treated 1978-2012

- **Plaque**: 1,413
- **Helium**: 20
- **Proton**: 29
- **Choroidal/ Iris-CB Melanoma**: 1,413
- **Conjunctival tumors**: 20
- **Macular Degeneration**: 29
- **Benign (hemangioma, etc.)**: 31
- **Metastatic disease/ Other misc.**: 21

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### UCSF Ocular PBRT Program

- **Pt dx and transfer care to ocular/radiation oncologist**
- **Simulation in Rad Onc w/ immobilization device and orthogonals**
- **Treatment at CNL**
  - 56 GyE in four daily fx of 14 GyE
- **Pt decide PBRT:** Tantalum ring placement in OR
- **Treatment planning w/ EYEPLAN software**
What do other smart people say?

Systematic review
An evidence based review of proton beam therapy: The report of ASTRO’s emerging technology committee

<table>
<thead>
<tr>
<th>Site</th>
<th>ASTRO Report:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung, H&amp;N, GI, pedi non-CNS</td>
<td>Insufficient evidence to rec PBT</td>
</tr>
<tr>
<td>HCC, Prostate</td>
<td>Evidence for efficacy of PBT but no suggestion that it is superior to photons</td>
</tr>
<tr>
<td>Pedi CNS</td>
<td>PBT appears superior to photons but more data needed</td>
</tr>
<tr>
<td>Large ocular melanomas and chordomas</td>
<td>There is evidence for a benefit of PBT over photons</td>
</tr>
</tbody>
</table>

Allen AM et al, Radiother and Oncology 2012;103:8-1 1. UCSF 2014

UCSF Ocular PBRT Program

- Important advances in planning and treatment protocol
- Excellent local control rates
- Clinical development has lowered SE rates (Enucleation & NVG)
- Particle therapy is considered a gold standard for UM

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