Proton Radiation Therapy for Uveal Melanoma

Pre-Meeting Teaching Course, PTCOG 46

Wanjie, Zibo, China, May 18th, 2007

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Center for Proton Radiation Therapy

Paul Scherrer Institute (PSI), 5232 Villigen PSI, Switzerland
Uveal Melanoma: Treatments at PSI

- Uveal melanoma is a rare and highly malignant eye tumor
- Incidence rates vary greatly between different ethnic groups and geographic locations
- UV damage likely involved in the pathogenesis of uveal melanoma
- Until the 1970’s, enucleation was the treatment of choice
- Eye-preserving proton treatment was pioneered at Harvard Cyclotron by E. Gragoudas (MEEI), H. Suit, J. Munzenrider and M. Goitein (MGH)
- The PSI adopted the MGH/MEEI approach, starting eye treatments in 1984
- Between 1984 and Nov 2006, 4604 eyes were treated, mostly for uveal melanoma
- A new facility, OPTIS2 is under construction.
PT for Uveal Melanoma: Physical Principles

- Range of protons depends on the proton’s initial energy
- Protons are ~2000 times heavier than electrons and consequently travel in a ‘straight line’
- Protons gradually lose energy colliding with electrons until they interact with a nucleus, resulting in a sudden loss of all of their remaining energy (the Bragg-Peak)
- Protons of the energy required for eye treatments (~70 MeV) are stopped by a couple of mm’s of copper: fields can be arbitrarily shaped using individual collimators
- Intelligently ‘mixing’ proton beams of various energies flat dose distributions can be created
Why Protons are so Suitable for Uveal Melanomas

• The maximum range (=energy) of protons in eye tissue can be determined with a 0.1 mm accuracy
• The lack of scattering (especially over the short ranges used in ocular treatments) limits the dose to the normal tissue
• The sharp distal fall off (Bragg-Peak) further limits the dose to the normal tissue
• There is no dose deposited after the Bragg-Peak (i.e. no dose entering the brain)
• The straight forward trajectories and finite range of protons are easily modeled (early 70’s!)
The Challenges Treating Uveal Melanomas with Protons

Challenges:

• Tumor location must be accurately known
• Keep treatment margins as small as possible
• Patient must actively cooperate (to obtain optimal treatment position), but eye needs to be kept still during treatment

Solutions:

→ Tantalum Clips
→ Determine optimal treatment angle (TPS)
→ Head fixation + eye gazing angle
Tumor base is delineated with tantalum clips

Tumor position assessed using stereo-tactic x-ray imaging
Optimal Treatment Position Found in TPS (EyePlan)

EyePlan uses a geometrical (ellipsoidal) model of the eye
Head Fixation Achieved with Mask & Bite-block

Gazing angle determined with LED on disk with polar coordinate system
Suturing the clips to the sclera

The conjunctiva receives a cut to provide access to the eye itself
The eye is positioned by pulling at wires around eye muscles
Professor Zografos

Importance of the TEAM!
The base of the tumor is made accessible for clip suturing.
With trans-illumination the tumor throws a shadow on the sclera: the tumor base
Clips are sutured around the tumor base (determined by trans-illumination)
Treatment planning: Identifying the Clips on X-ray Images
Next: Draw Tumor Base based on Clinical Data
Model Tumor and Determine Optimal Treatment Position

2mm lateral margin for collimator; macula and optic-disc maximally spared

2.5 mm distal margin
TPS determines should-be clip positions (printed on sheet)
Eye Position Adjusted until Clips are Matched (<0.2 mm)
Proton Therapy for Ocular Melanomas

Overall Results
Paul Scherrer Institute and OPTIS Program

- Since 1984 more than 4700 patients treated
- Approx. 200-250 patients treated per year during 10-12 blocks of „OPTIS Weeks“
- Tx Regimen: 4 fractions in one week; 15 CGE dose/fraction
- 60 CGE Total prescribed Dose
- Capacity: +/- 30 patients/OPTIS week

- Local Control: 98%@10 years (> 2000 patients analyzed)
The MGH / MEEI Experience:

Cumulative probability of local recurrence after proton irradiation
The MGH / MEEI Experience:

1,922 patients
Proton-RT between 1975 – 1996
Median F/U 5.2 years
Local Failure: 45 pts., plus 17 eyes enucleated for suspicion but unconfirmed
Local Recurrences: 2 months – 11 years after Proton RT

Actuarial 5 year Local Control: 96.8%
Actuarial 10 year Local Control: 95.7% (includes unconfirmed suspected cases)

Local failures: 21/45 at margin (=1/2 planning errors)
Proton Therapy for Ocular Melanomas

The „Learning Curve“
Ocular Melanoma Proton Therapy at Hahn-Meitner Institute / Charité:
The „Learning Curve“ (courtesy J. Heufelder)

- Green line: patients treated during first 3 years of operation
- Blue line: patients treated thereafter

Tumour control vs. time [months]
Ocular Melanoma Proton Therapy at Hahn-Meitner Institute / Charité: The „Learning Curve“ *(courtesy J. Heufelder)*

- Better definition of the target volume by the ophthalmologists (from smaller to larger)
- Forego reduction of margins or prescription dose due to “organs at risk” constraints (tumor control paramount)
- More realistic construction of the eye model in EYEPLAN integrating CTs
- Better understanding of the influence of a wedge on the dose distribution
- Learning by experience

⇒ Improved tumor control
Proton Therapy for Ocular Melanomas

Results for
Small Size Tumors
Proton Therapy at Paul Scherrer Institute for Small Posterior Uveal Melanoma: Subgroup Analysis. Rutz, Zografos, Verwey et al. (to be published)

- 336 of 2837 patients treated between 1984 and 2000 had small posterior uveal melanomas
- largest diameter ≤ 12.0 mm
- maximal thickness ≤ 4.0 mm
- anterior border posterior to the equator

Results:
- with median FU of 5 yrs, 95% overall survival, 97% disease-specific survival, 98% local control, 99% eye retention
- in the 282 patients with standard safety margins, local control was 100%
Proton Therapy for Ocular Melanomas

Results for
Medium to Large Size Tumors
Proton Radiation Therapy for Medium and Large Choroidal Melanoma: Preservation of the Eye and its Function


78 patients, treated 1990-98. 70.2 CGE in 5 fractions, tumor plus 3 mm

<table>
<thead>
<tr>
<th>Statistical analysis</th>
<th>Local control</th>
<th>Metastases-free survival</th>
<th>Overall survival</th>
<th>Disease-specific survival</th>
<th>Enucleation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year actuarial data</td>
<td>92.8%</td>
<td>85.7%</td>
<td>87.1%</td>
<td>86.5%</td>
<td>24.7%</td>
</tr>
<tr>
<td>5-year actuarial data</td>
<td>90.5%</td>
<td>76.2%</td>
<td>70.3%</td>
<td>75.6%</td>
<td>24.7%</td>
</tr>
<tr>
<td>Tumor base &gt; 16 mm</td>
<td>NS</td>
<td>p = 0.020</td>
<td>p = 0.033</td>
<td>p = 0.017</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor apex &gt; 10 mm</td>
<td>NS</td>
<td>p = 0.089</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior tumor margin post-equator</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior tumor margin pre-equator</td>
<td>NS</td>
<td>NS</td>
<td>p = 0.095</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ciliary body involvement</td>
<td>NS</td>
<td>NS</td>
<td>p = 0.084</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ciliary body + base &gt; 16 mm</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 3 mm from optic disc</td>
<td>p = 0.063</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 3 mm from fovea</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Penetrates Bruch’s membrane</td>
<td>NS</td>
<td>p &lt; 0.001</td>
<td>p = 0.038</td>
<td>p = 0.017</td>
<td>NS</td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
<td>NS</td>
<td>NS</td>
<td>p = 0.004</td>
<td>p = 0.038</td>
<td>NS</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>NS</td>
<td>p = 0.091</td>
<td>p = 0.016</td>
<td>p = 0.033</td>
<td>NS</td>
</tr>
<tr>
<td>Local control</td>
<td>p = 0.026</td>
<td>NS</td>
<td>p = 0.057</td>
<td>p = 0.038</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Secondary metastases</td>
<td>p = 0.026</td>
<td>NS</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.012</td>
</tr>
</tbody>
</table>
Proton Therapy for Ocular Melanomas

Visual Outcome

- Risks of Papillopathy and Maculopathy
Proton Radiation Therapy for Medium and Large Choroidal Melanoma: Preservation of the Eye and its Function


Factors predictive of post-PRT Visual Acuity (VA):

<table>
<thead>
<tr>
<th></th>
<th>VA postradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA preradiation</td>
<td><em>p</em> = 0.001</td>
</tr>
<tr>
<td>Dose &gt; 35 CGE to optic disc</td>
<td><em>p</em> = 0.001</td>
</tr>
<tr>
<td>Dose &gt; 35 CGE to fovea</td>
<td><em>p</em> = 0.022</td>
</tr>
<tr>
<td>Dose to 50% of lens</td>
<td><em>p</em> = 0.083</td>
</tr>
<tr>
<td>Retinal detachment (preradiation)</td>
<td><em>p</em> = 0.017</td>
</tr>
<tr>
<td>Retinal detachment (postradiation)</td>
<td><em>p</em> &lt; 0.001</td>
</tr>
<tr>
<td>Tumor base &gt; 16 mm</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor apex &gt; 10 mm</td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 3 mm from optic disc</td>
<td><em>p</em> = 0.034</td>
</tr>
<tr>
<td>Local control</td>
<td><em>p</em> = 0.067</td>
</tr>
</tbody>
</table>
Proton Therapy at Paul Scherrer Institute for Small Posterior Uveal Melanoma: Subgroup Analysis. *Rutz, Zografos, Verwey et al. (to be published)*

- 236 of 2837 patients treated between 1984 and 2000 had small posterior uveal melanomas.
- Analysis according to infiltration and/or irradiation of Macula
Proton Therapy for Ocular Melanomas

Improved Visual Acuity Outcome and lower Enucleation Rate by Dose Reduction?

- The MGH / MEEI Phase III randomized trial
A randomized trial of varying radiation doses in the treatment of choroidal melanomas.


70 CGE versus 5 CGE in 5 fractions

188 pts., small to medium-sized tumors (> 15 mm base, >5 mm height)
Near optic disc or macula (< 4 disc diameters distance to either)

P-RT 1989 – 1994

RESULTS:

Similar visual acuity retention (55% at 5 years 20/200 or better)

Similar rate of maculopathy and papillopathy

Similar Local Control (2 LF at 50 CGE, 3 LF at 70 CGE)

Similar Rate of Metastasis

Only signif. Difference: Less Visual Field Loss in 50 CGE group
Proton Therapy for Ocular Melanomas

Reirradiation for Local Failure
–
a Second Course of Proton-RT
Conservation treatment of the eye: Conformal proton reirradiation for recurrent uveal melanoma

L. Marucci, E. Gragoudas, J. Munzenrider et al., Massachusetts General Hospital, and Massachusetts Eye and Ear Infirmary, Boston, MA. IJROBP 2006, 64(4):1018

- Thirty-one patients received a second course of PBRT.

- The mean interval between the first and the second PBRT course was 50.2 months (range, 8–165 months).

- Most patients (87%) received 70 cobalt Gray equivalent (CGE) for both courses.

- Visual acuity was 20/200 or better in 30 patients initially and in 22 patients at the second treatment.

- The mean follow-up time after the second treatment was 50 months (range, 6–164 months).
**Marucci et al:** Patient and tumor characteristics at the time of the first treatment and reirradiation

<table>
<thead>
<tr>
<th>Overlap %</th>
<th>Total dose cobalt Gray equivalent</th>
<th>( n ) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–60</td>
<td>120 ( (70 + 50) )</td>
<td>2</td>
</tr>
<tr>
<td>40–60</td>
<td>140 ( (70 + 70) )</td>
<td>10</td>
</tr>
<tr>
<td>70–90</td>
<td>140 ( (70 + 70) )</td>
<td>5</td>
</tr>
<tr>
<td>100</td>
<td>118 ( (70 + 48) )</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>120 ( (70 + 50) )</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>140 ( (70 + 70) )</td>
<td>12</td>
</tr>
</tbody>
</table>
**Marucci et al:** Patient and tumor characteristics at the time of the first treatment and reirradiation

<table>
<thead>
<tr>
<th></th>
<th>Primary tumor</th>
<th>Recurrent tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Useful vision</strong></td>
<td>39–67 at 3 yrs</td>
<td>27% at 5 yrs</td>
</tr>
<tr>
<td><strong>Local control</strong></td>
<td>96% at 5 yrs</td>
<td>69% at 5 yrs</td>
</tr>
<tr>
<td><strong>Eye retention</strong></td>
<td>≥76–99% at 5 yrs</td>
<td>55% at 5 yrs</td>
</tr>
<tr>
<td><strong>Metastasis-free survival</strong></td>
<td>≥58–97 at 4 yrs</td>
<td>73% at 5 yrs</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td>80% at 5 yrs</td>
<td>64% at 5 yrs</td>
</tr>
</tbody>
</table>

“…A second course to total doses between 118 and 140 CGE was associated with a relatively good probability of local control and a low enucleation rate. Although most patients lost vision, the majority were able to retain the reirradiated eye.”
Marucci et al: Patient and tumor characteristics at the time of the first treatment and reirradiation

Circles = Local recurrences free survival, Squares = Metastases free survival
Center for Proton Radiation Therapy, Paul Scherrer Institute

<table>
<thead>
<tr>
<th>To develop first class technology</th>
<th>To provide first class clinical care</th>
</tr>
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<tbody>
<tr>
<td>• COMET</td>
<td>• Pediatric oncology</td>
</tr>
<tr>
<td>• Gantry2</td>
<td>• Adult oncology</td>
</tr>
<tr>
<td>• OPTIS2</td>
<td>• Clinical trials</td>
</tr>
<tr>
<td>• Gating (Gantry2)</td>
<td>• Chordomas and chondrosarcomas</td>
</tr>
<tr>
<td>• Fast re-scanning (Gantry2)</td>
<td>• Loads of other histologies</td>
</tr>
<tr>
<td>• Robotchair (OPTIS2)</td>
<td>• Uveal melanoma</td>
</tr>
<tr>
<td>• Computer aided patient positioning (OPTIS2)</td>
<td></td>
</tr>
</tbody>
</table>
PROSCAN @ PSI

COMET

Exp.

OPTIS2

Gantry2

Gantry1
COMET: patient treatments started Feb. 2007


The real thing at PSI (2006)
Gantry2

Computer generated

The real thing (late 2006)
OPTIS2 Nozzle with robotchair

Robotchair positioning
< 0.1 mm

Robotchair shown without mask-holder
The OPTIS2 Project

OPTIS2 is a completely new design, bringing together the latest techniques already tested and/or in operation at other institutes in Europe (HMI, CPO). Primary aim, however, is to match the clinical outcome of OPTIS, and as such the treatment philosophy remains unchanged.
Digital Imaging using remotely operated Flat Panels

Conventional Polaroid Film

Flat Panel Image
Semi-Automated Computer-Aided Clip Positioning

- Operator identifies clips on digital images
- Software calculates transformation matrix
- Determines new LED position and patient translation
- Patient translation performed by robotchair
Thank you!
Possible Future Developments for OPTIS2

- p-delimited retinoblastoma mounted
- digital images of clips
- on to position eye of anesthetized patient
  - dose/fractionation still to be determined

• Improvement of visual acuity

  - other fractionation scheme
  - less steep distal dose fall-off when touching optic disc (reducing RBE effect)
Carbon ions for locally advanced or unfavorably located choroidal melanoma: A phase I/II dose escalation study

- Three-year overall survival, disease-free survival, and local control rates were 88.2%, 84.8%, and 97.4%, respectively
- No apparent dose–response relationship was observed in either tumor control or normal tissue morbidity at the dose range applied
- Doses varied from 60.0 to 80.0 GyE
- Interesting concept
- More patients, longer FU needed
- Tsujii et al, IJROBP (2007)
Topics of the Presentation

1. The Disease „Uveal Melanoma“
2. Proton Radiation Therapy for Uveal Melanoma at PSI, since 1984
3. Carbon Ion Therapy for Uveal Melanoma (NIRS, Chiba)
4. Proton Radiation Therapy for Small Posterior Uveal Melanomas
5. Alternative Treatments for Small Posterior Uveal Melanomas
6. Need for Research, Questions to answer
7. Innovations at Paul Scherrer Institute in the years to come (Optis2)