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

alignant eye tumor

ent ethnic groups and geographic locations

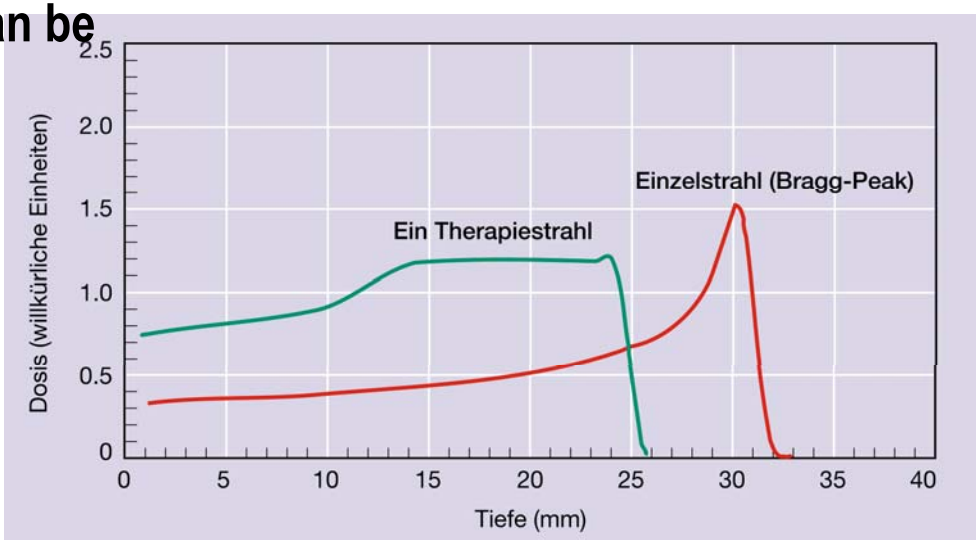
esis of uveal melanoma

atment 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:

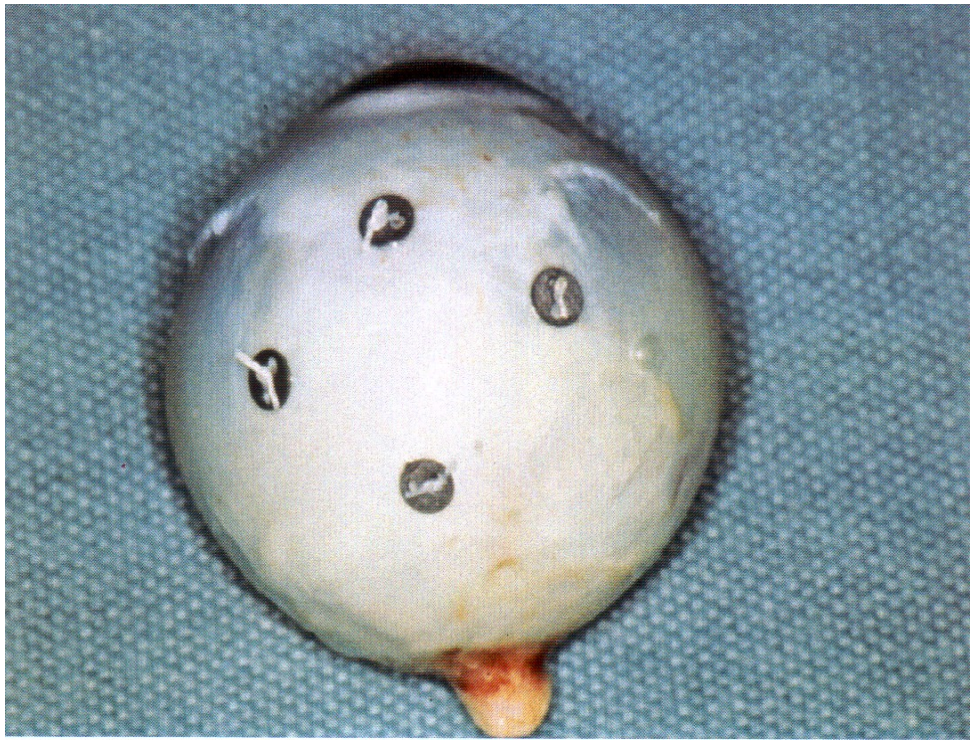
- Tumor location must be accurately known
- Keep treatment margins as small as possible
- Patient must actively cooperate (to obtain optimal treatment position), but eye needs to be kept still during treatment

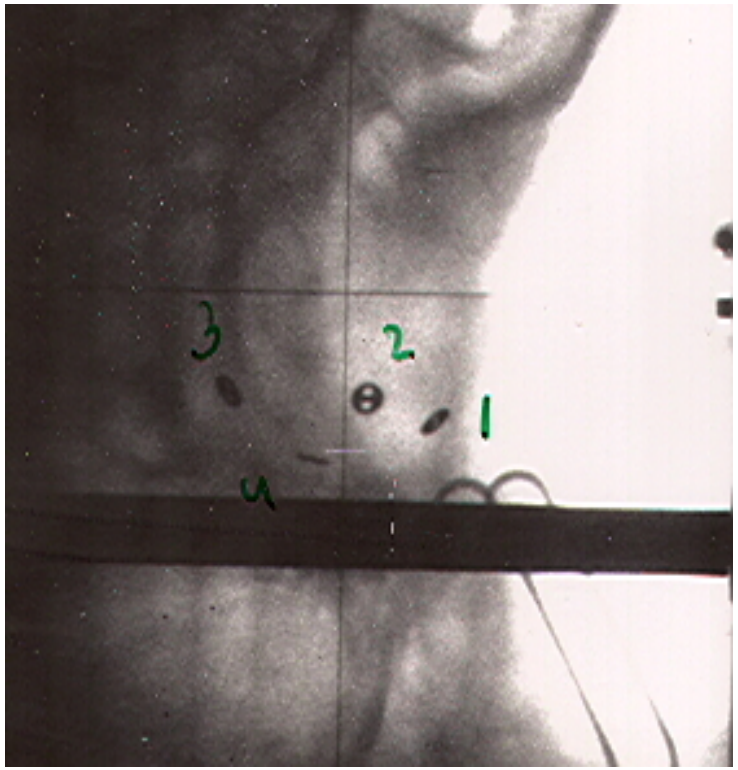
Solutions:

→ Tantalum Clips
→ Determine optimal treatment angle (TPS)
→ Head fixation + eye gazing angle

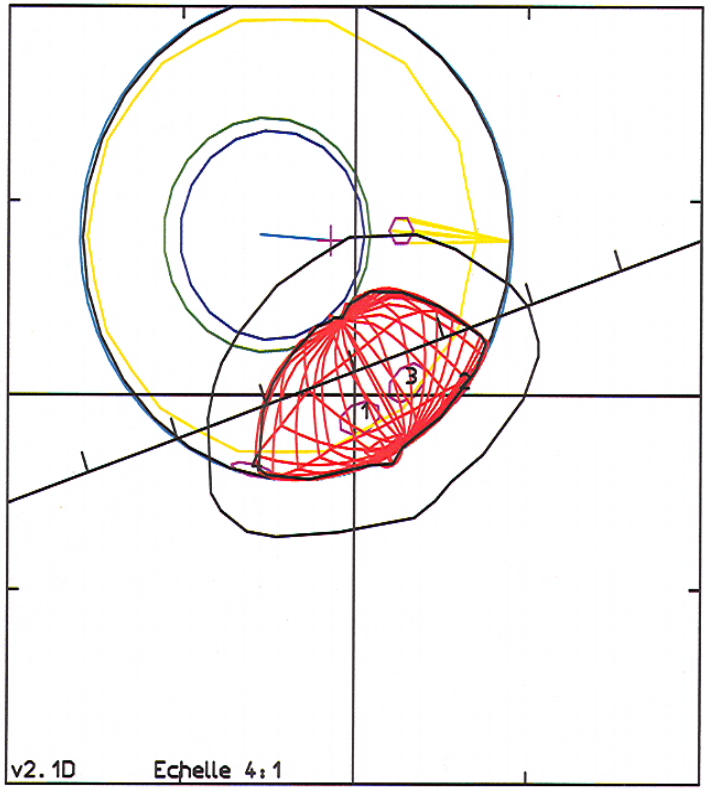
Tumor base is delineated with tantalum clips

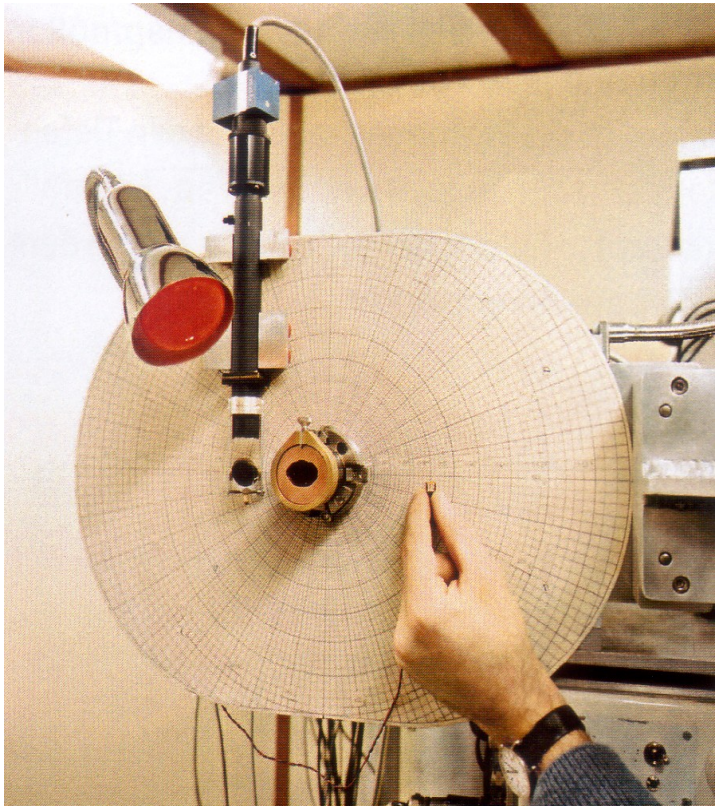
Tumor position assessed using stereo-tactic x-ray imaging





Optimal Treatment Position Found in TPS (EyePlan)

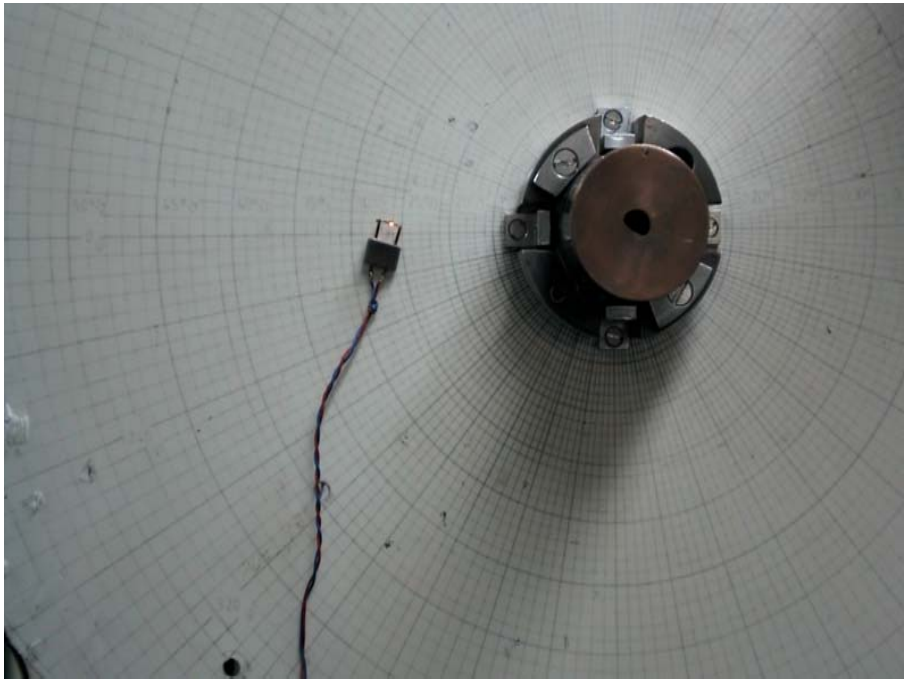




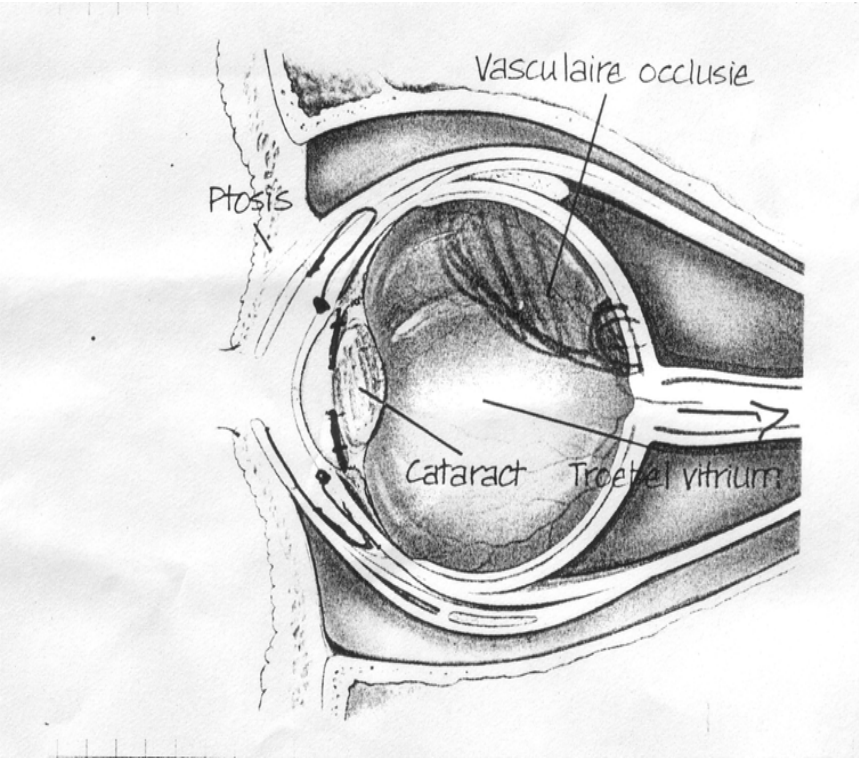
EyePlan uses a geometrical (ellipsoidal) model of the eye

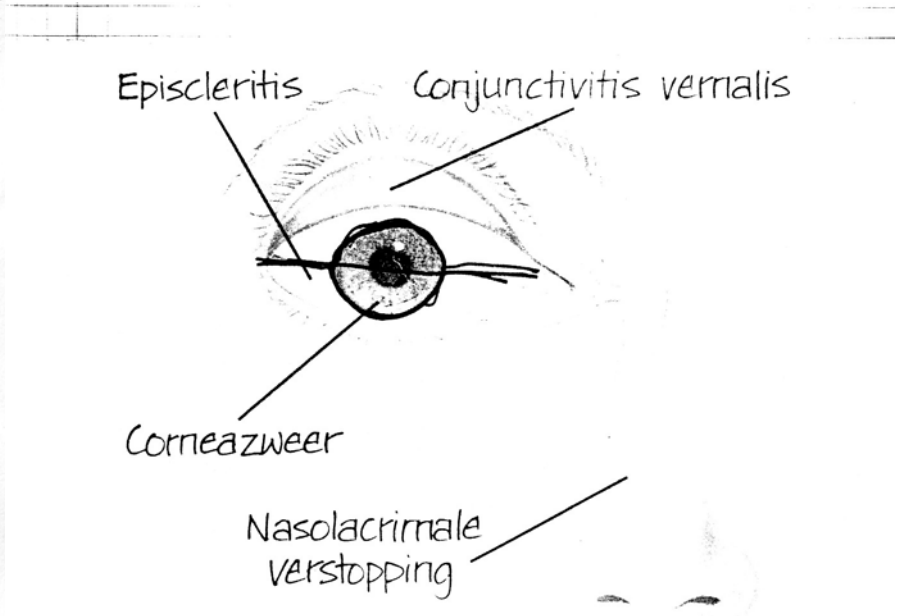
Head Fixation Achieved with Mask & Bite-block

Gazing angle determined with LED on disk with polar coordinate system



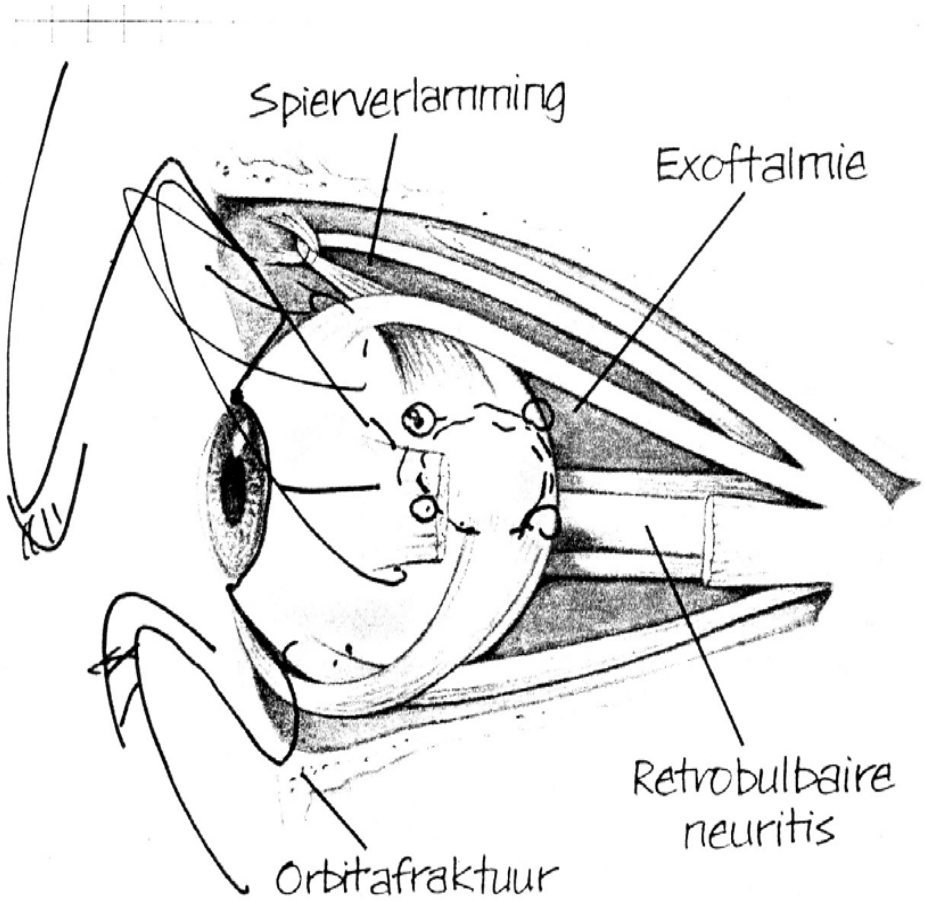
Suturing the clips to the sclera





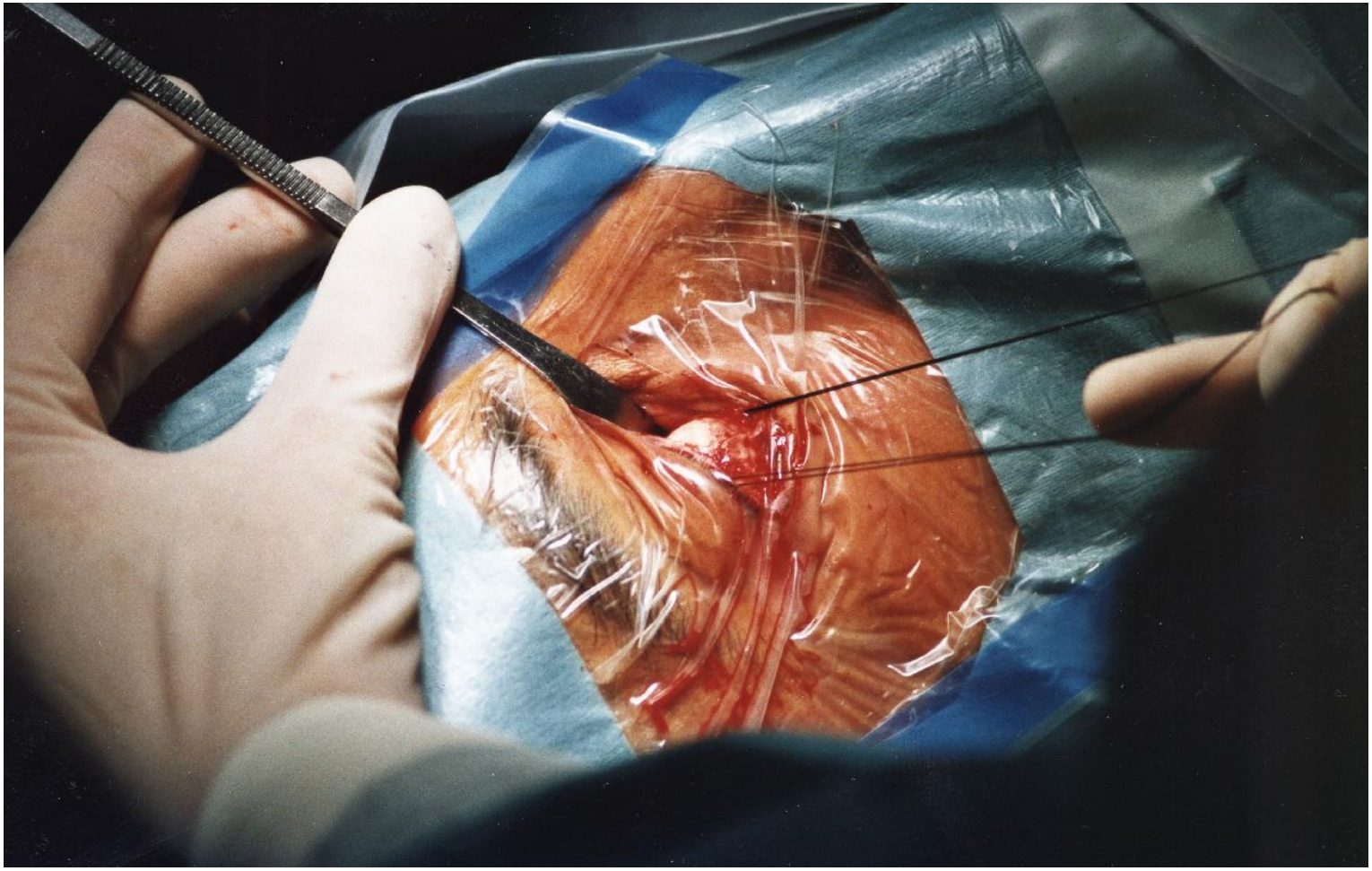
The conjunctiva receives a cut to provide access to the eye itself

The eye is positioned by pulling at wires around eye muscles

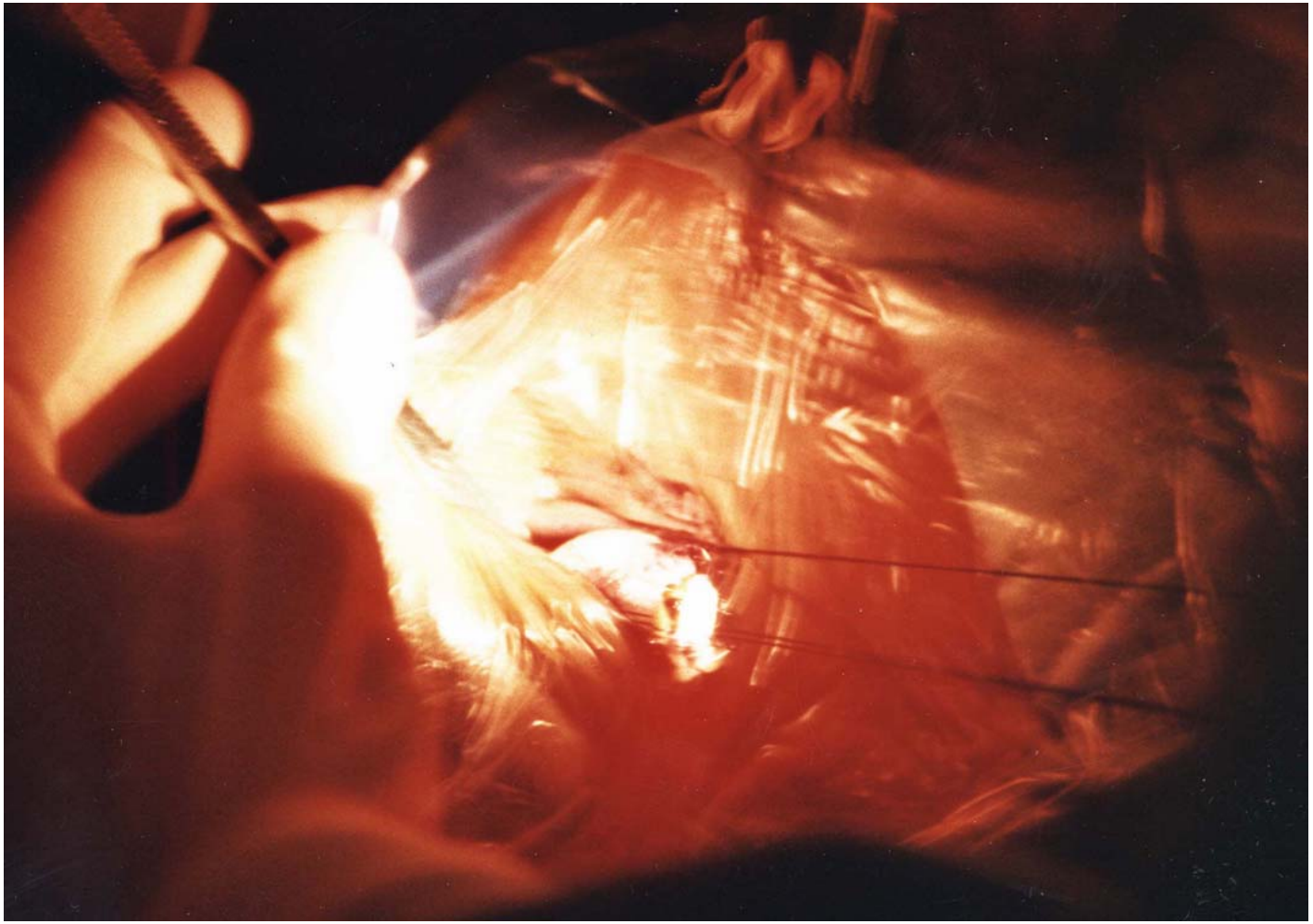


Professor Zografos Importance of the TEAM!

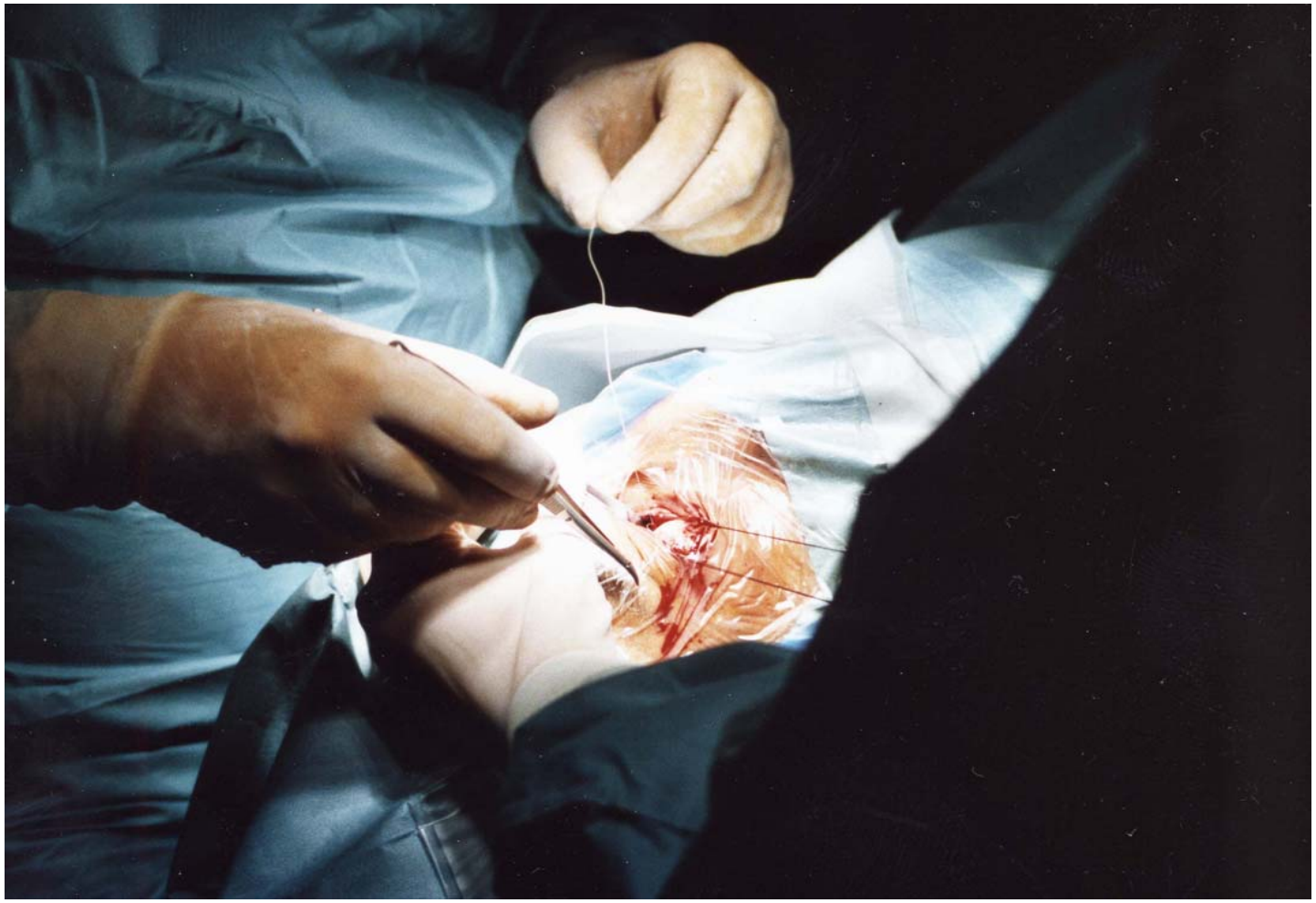
The base of the tumor is made accessible for clip suturing



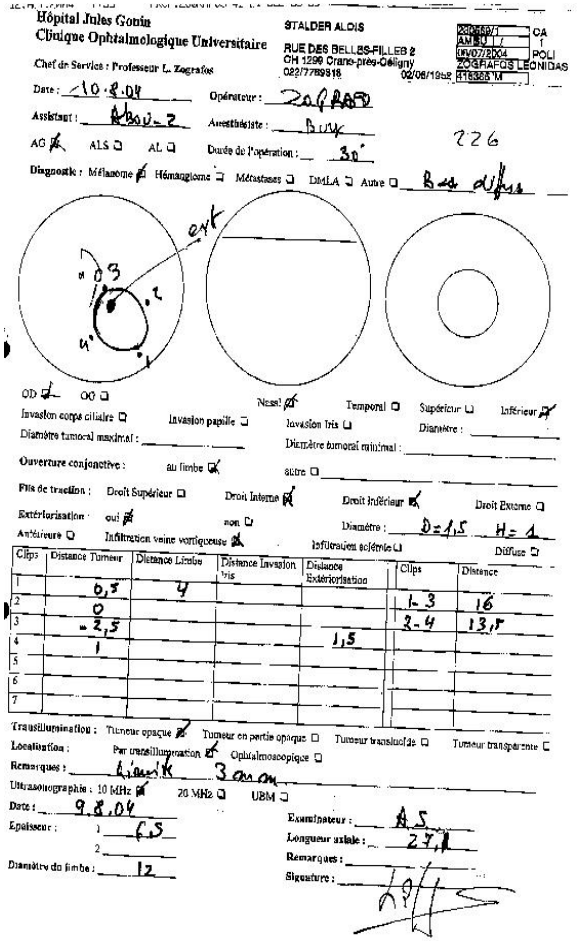
With trans-illumination the tumor throws a shadow on the sclera: the tumor base



Clips are sutured around the tumor base (determined by trans-illumination)



Treatment planning: Identifying the Clips on X-ray Images



Hôpital Jules Gonin
Clinique Ophtalmologique Universitaire
Chef de Service : Professeur L. Zografos

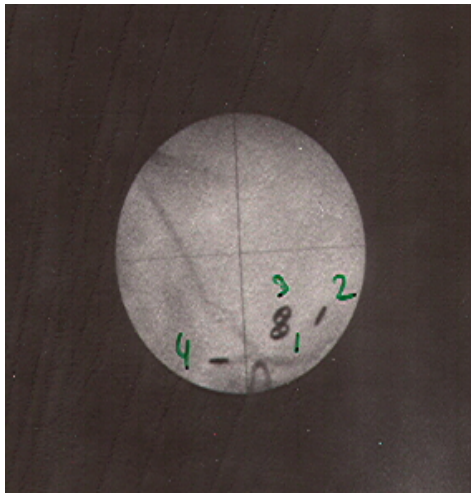
STALDER ALOIS
RUE DES BELLES-FILLES 2
CH 1290 Crans-près-Céligny
022/7789919
02/06/1948

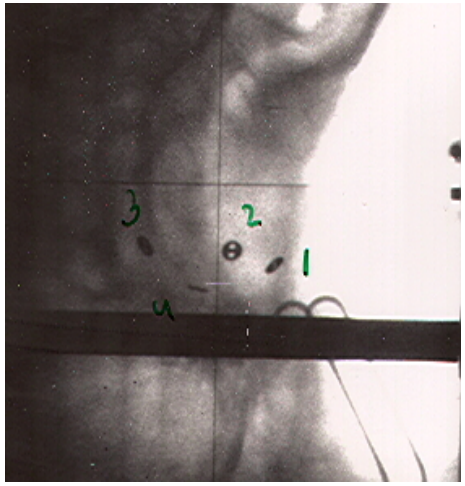
Date : 10.8.04
Opérateur : ZOGRAFOS
Assistant : Rhou-Z
Anesthésiste : Bink
AG ☒ ALS ☐ AL ☐
Durée de l'opération : 30'
Diagnostic : Mélanome ☒ Hémangiome ☐ Métastases ☐ DMLA ☐ Autre ☐ B-a diffus

OD ☒ OG ☐
Nasal ☒ Temporal ☐ Supérieur ☐ Inférieur ☒
Invasion corps ciliaire ☐ Invasion papille ☐ Invasion Iris ☐
Diamètre : Diamètre tumoral maximal : Diamètre tumoral minimal :
Ouverture conjonctive : au limbe ☒ autre ☐
Fils de traction : Droit Supérieur ☐ Droit Interne ☒ Droit Inférieur ☒ Droit Externe ☐
Extériorisation : oui ☒ non ☐ Diamètre : D=1,5 H=1
Antérieure ☐ Infiltration veine vortiqueuse ☒ Infiltration sclérale ☐ Diffuse ☐

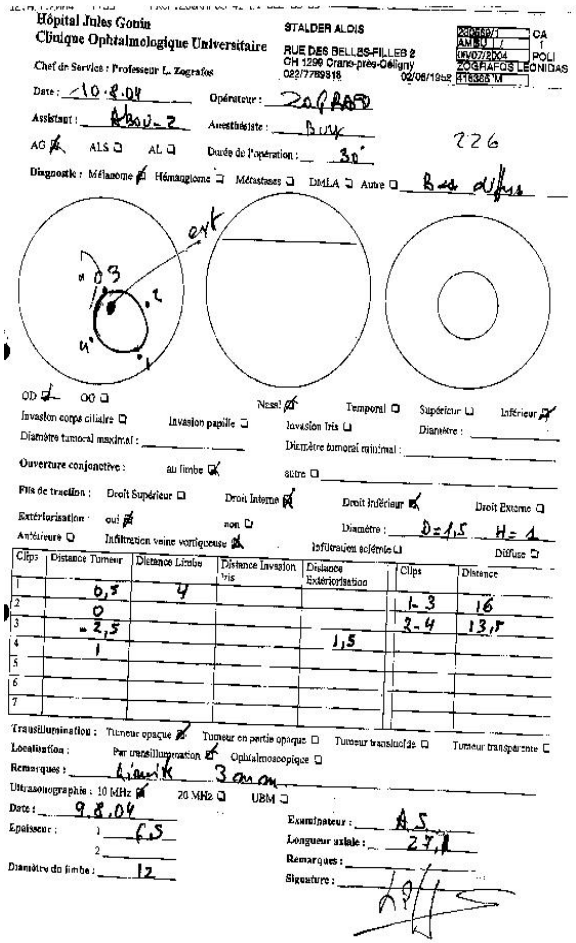
Clips	Distance Tumeur	Distance Limbe	Distance Invasion Iris	Distance Extériorisation	Clips	Distance
1	0,5	4				
2	0				1-3	16
3	2,5				3-4	13,5
4	1			1,5		
5						
6						
7						

Transillumination : Tumeur opaque ☒ Tumeur en partie opaque ☐ Tumeur translucide ☐ Tumeur transparente ☐
Localisation : Par transillumination ☒ Ophtalmoscopique ☐
Remarques : Limite 3 mm
Ultrasonographie : 10 MHz ☒ 20 MHz ☐ UBM ☐
Date : 9.8.04
Epaisseur : 1 6,5 2
Diamètre du limbe : 12
Examinateur : AS
Longueur axiale : 27,1
Remarques :
Signature :





Next: Draw Tumor Base based on Clinical Data



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Extériorisation : oui non
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Antérieure Infiltration veine vorticieuse Infiltration sclérale Diffuse

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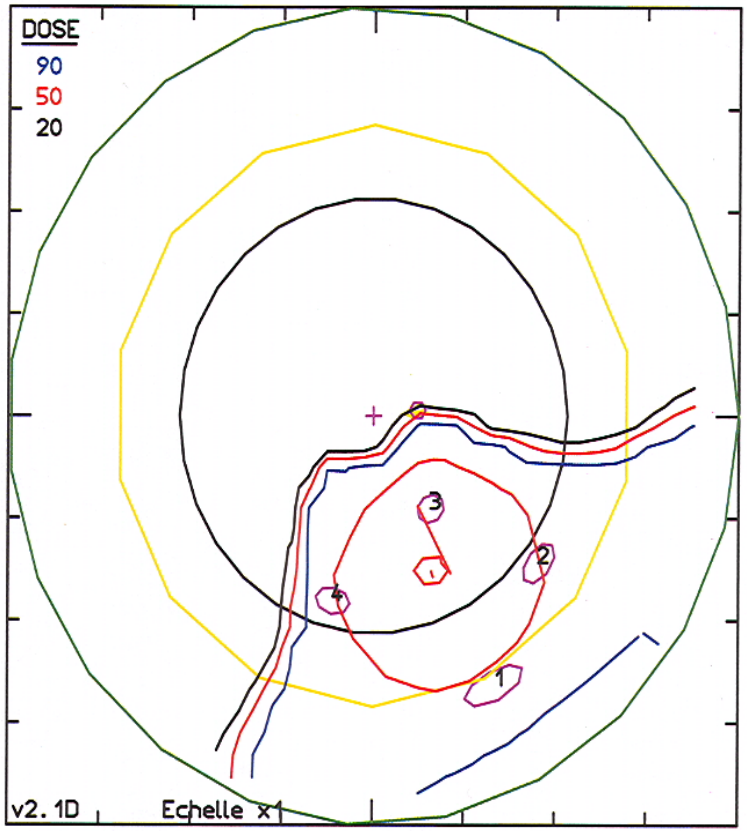
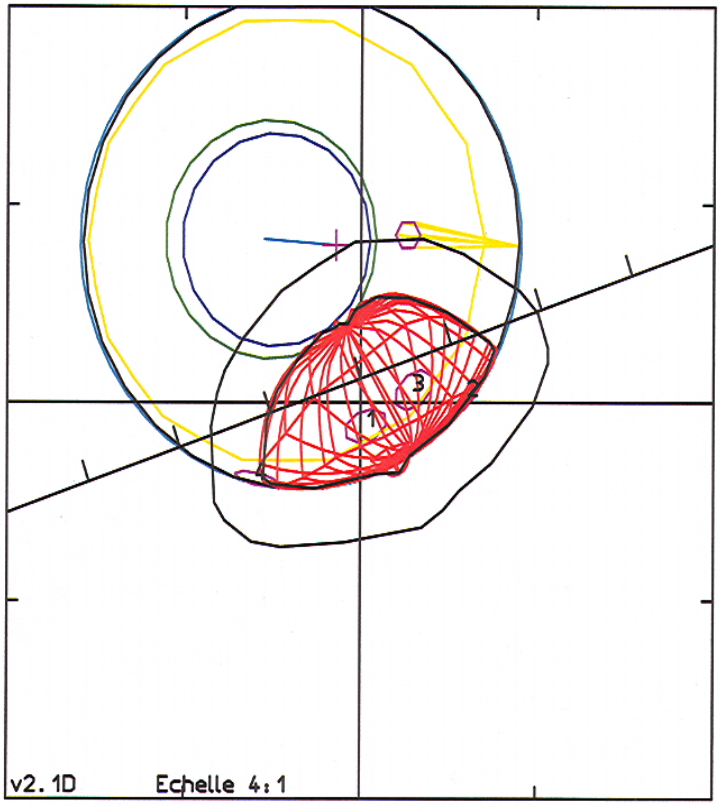


PARCOURS MAX. : 27.5 mm MODULATION : 24.7 mm
Isodoses sur la surface externe de la sclere

Model Tumor and Determine Optimal Treatment Position

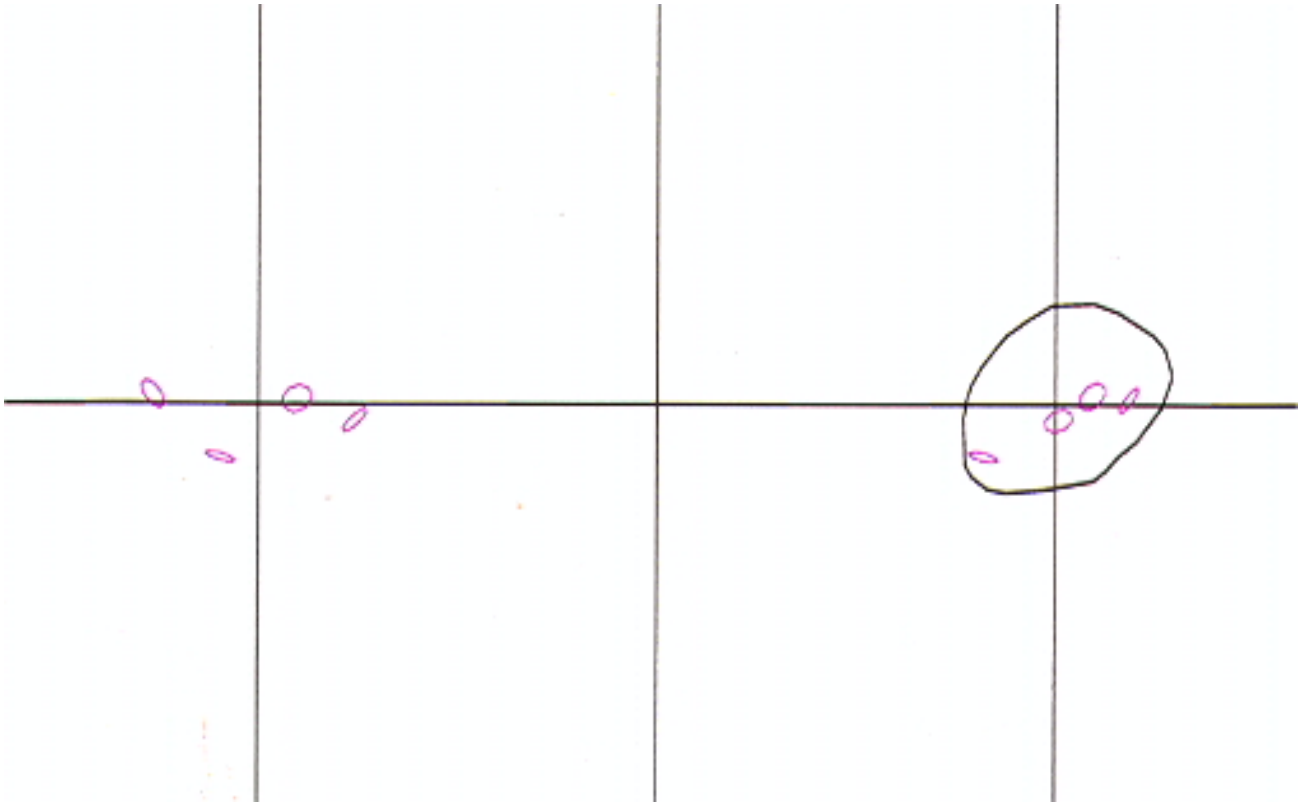


PARCOURS MAX. : 27.5 mm MODULATION : 24.7 mm
PLAN : TH=0,EPS=-29,PSI=0 X=0.0,Y=0.0,Z=0.0
Plan tumoral longitudinal

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

2.5 mm distal margin

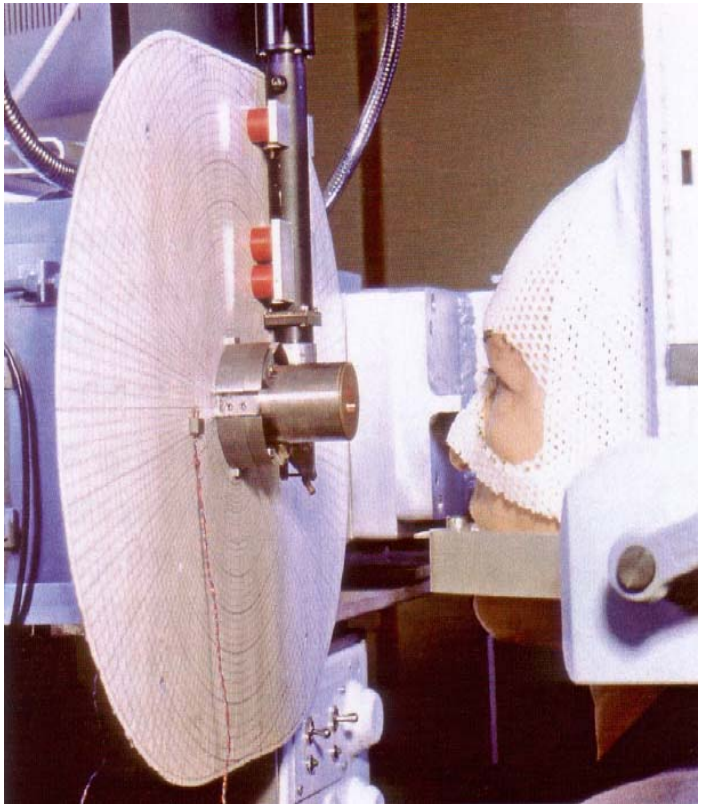
TPS determines should-be clip positions (printed on sheet)

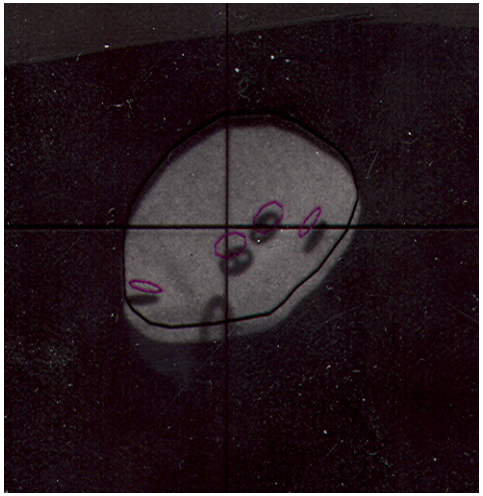


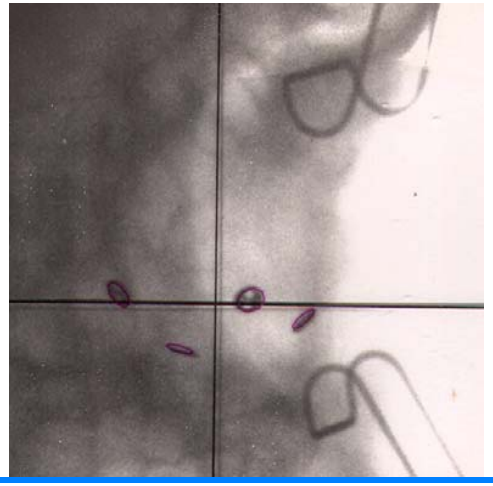
Lateral view

Axial (beam-s eye) view

Eye Position Adjusted until Clips are Matched (<0.2 mm)







Proton Therapy for Ocular Melanomas

Overall Results

Paul Scherrer Institute and OPTIS Program

ated

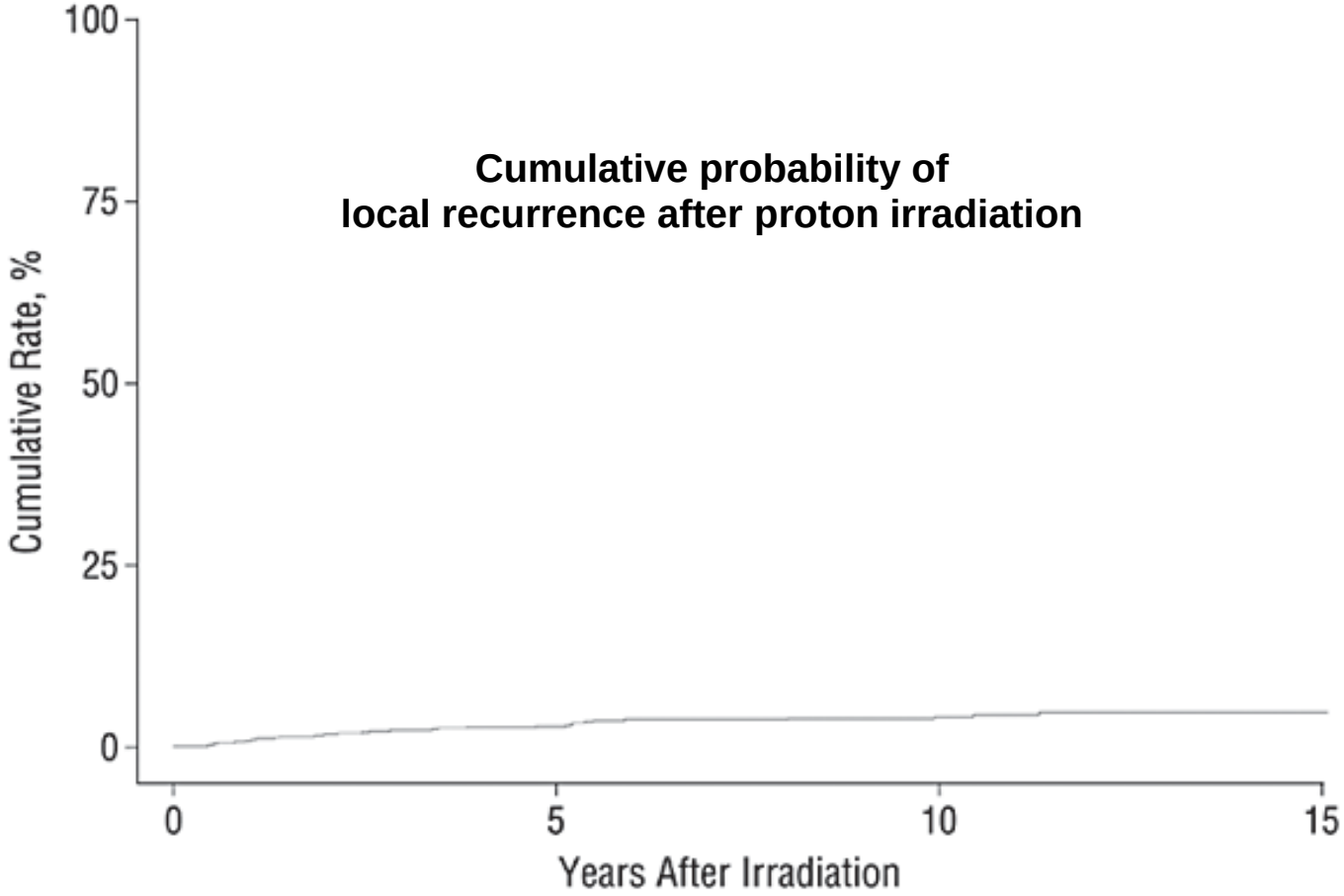
ear during 10-12 blocks of „OPTIS Weeks“

5 CGE dose/fraction

- Capacity: +/- 30 patients/OPTIS week

- **Local Control: 98%@10 years (> 2000 patients analyzed)**

The MGH / MEEI Experience:
Gragoudas, E. et al. Arch Ophthalmol 2002;120:1665-1671.



The MGH / MEEI Experience:
E. Gragoudas, J. Munzenrider et al. Trans Am Ophthalmol Soc 2002, 100:41

1,922 patients

Proton-RT between1975 – 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

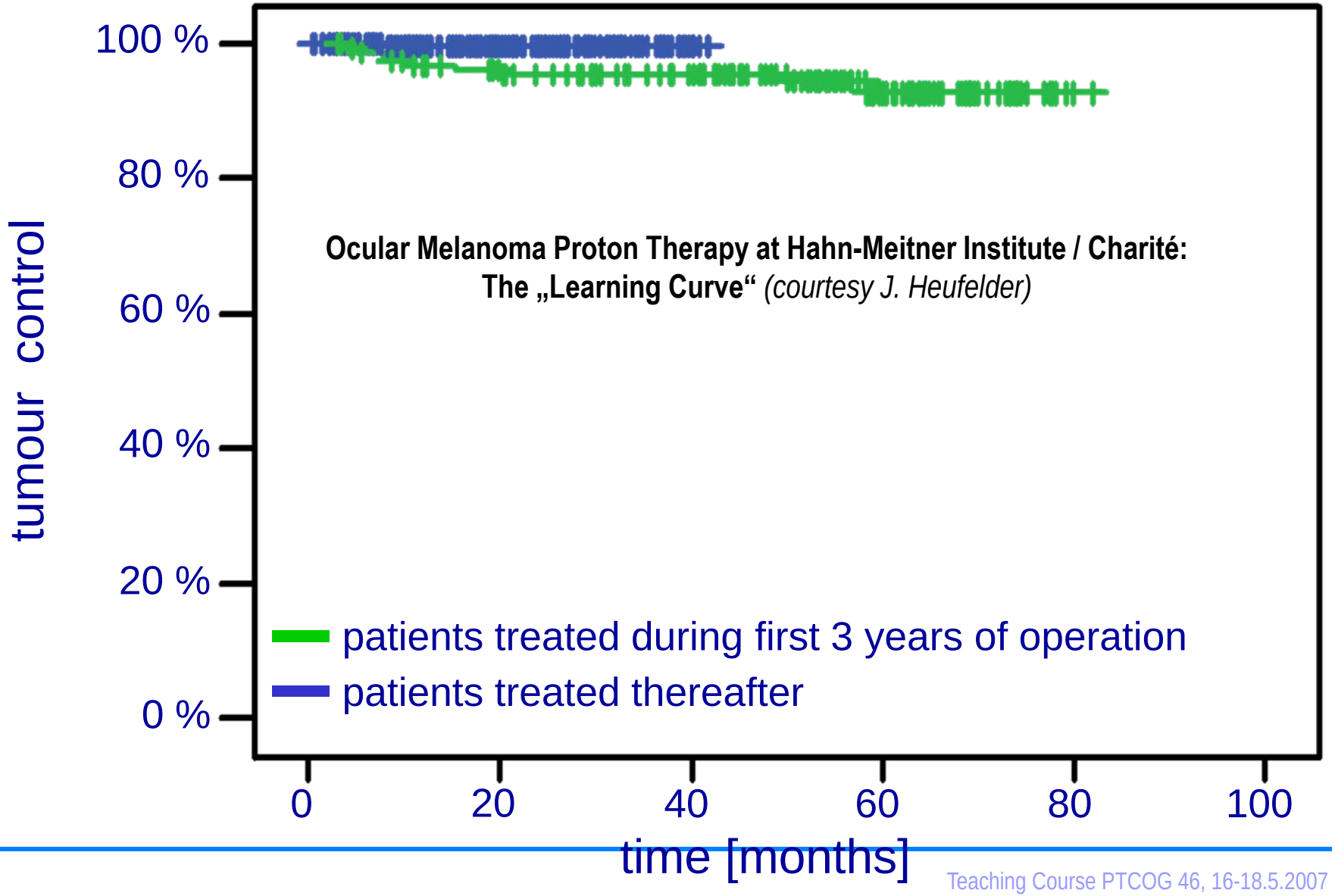
Actuarial 5 year Local Control: 96.8%

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)
tumour control
100 %
80 %
60 %
40 %
20 %
0 %
0
20
40
60
80
100
time [months]
patients treated during first 3 years of operation
patients treated thereafter

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**

$\Rightarrow$ 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

Fuss, Slater et al. IJROBP 49(4):1057, 2001. **Loma Linda Univ. Med. Center**

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

	Local control	Metastases-free survival	Overall survival	Disease-specific survival	Enucleation
3-year actuarial data	92.8%	85.7%	87.1%	86.5%	24.7%
5-year actuarial data	90.5%	76.2%	70.3%	75.6%	24.7%
Statistical analysis:					
Tumor base > 16 mm	NS	$p = 0.020$	$p = 0.033$	$p = 0.017$	NS
Tumor apex > 10 mm	NS	$p = 0.089$	NS	NS	NS
Anterior tumor margin post-equator	NS	NS	NS	NS	NS
Anterior tumor margin pre-equator	NS	NS	$p = 0.095$	NS	NS
Ciliary body involvement	NS	NS	$p = 0.084$	NS	NS
Ciliary body + base > 16 mm	NS	NS	NS	NS	$p = 0.041$
< 3 mm from optic disc	$p = 0.063$	NS	NS	NS	$p = 0.003$
< 3 mm from fovea	NS	NS	NS	NS	NS
Penetrates Bruch's membrane	NS	$p < 0.001$	$p = 0.038$	$p = 0.017$	NS
Age > 70 years	NS	NS	$p = 0.004$	$p = 0.038$	NS
Age > 60 years	NS	$p = 0.091$	$p = 0.016$	$p = 0.033$	NS
Local control	–	$p = 0.026$	$p = 0.057$	$p = 0.038$	$p = 0.001$
Secondary metastases	$p = 0.026$	–	$p < 0.001$	$p < 0.001$	$p = 0.012$

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

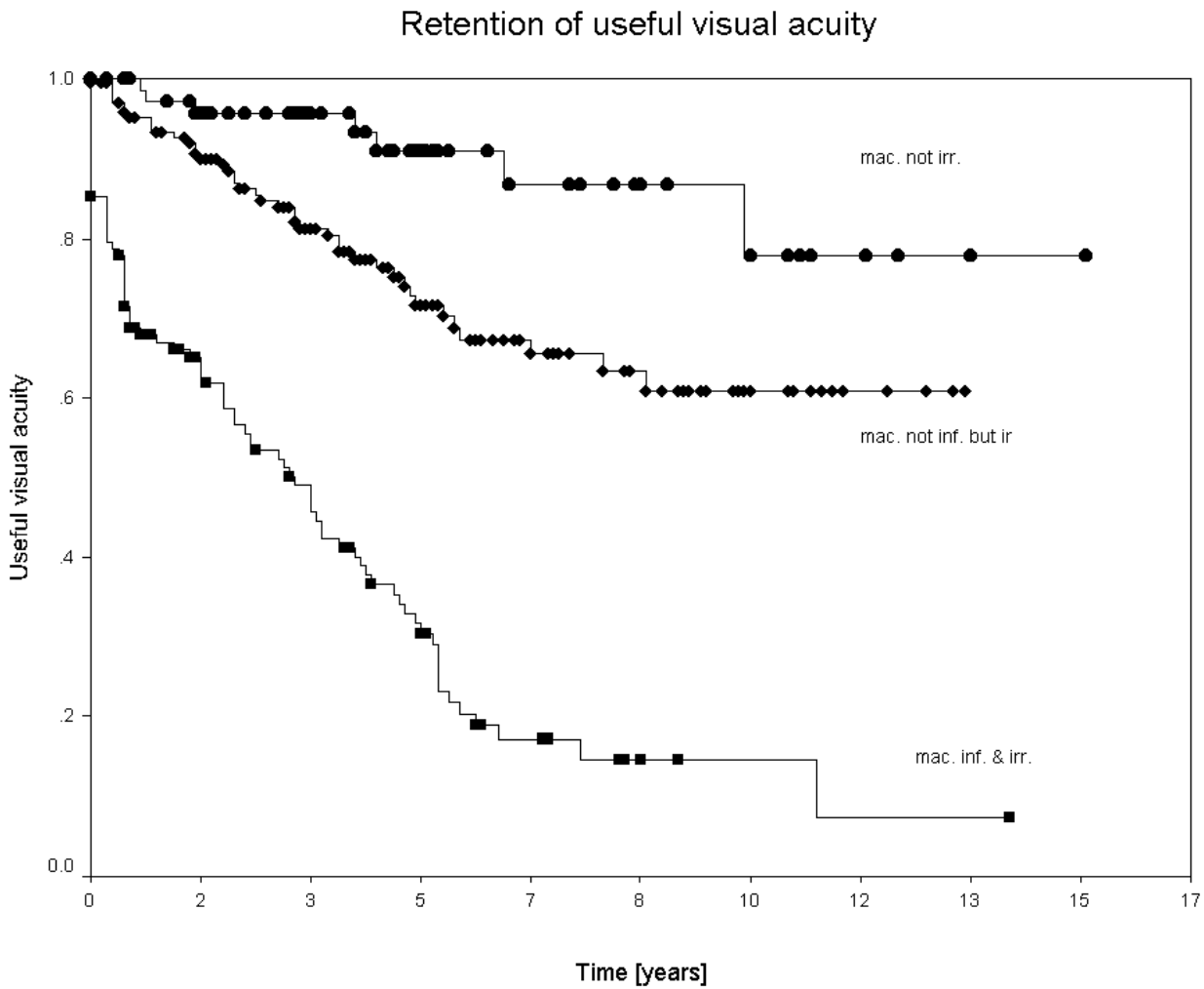
Fuss, Slater et al. IJROBP 49(4):1057, 2001. **Loma Linda Univ. Med. Center**

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

	VA postradiation
VA preradiation	$p = 0.001$
Dose > 35 CGE to optic disc	$p = 0.001$
Dose > 35 CGE to fovea	$p = 0.022$
Dose to 50% of lens	$p = 0.083$
Retinal detachment (preradiation)	$p = 0.017$
Retinal detachment (postradiation)	$p < 0.001$
Tumor base > 16 mm	NS
Tumor apex > 10 mm	NS
< 3 mm from optic disc	$p = 0.034$
Local control	$p = 0.067$

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.

Gragoudas, Munzenrider et al. Arch Ophthalmol 2000, 118(6):773

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**

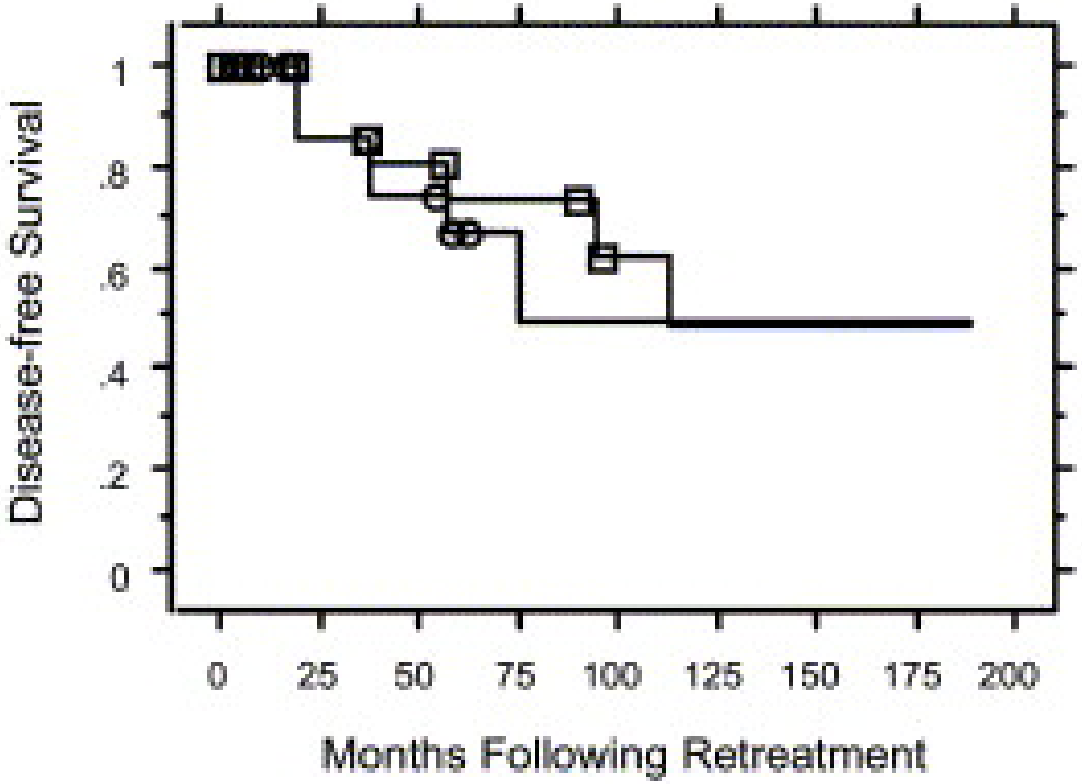
Overlap %	Total dose cobalt Gray equivalent	*n* patients
40–60	120 (70 + 50)	2
40–60	140 (70 + 70)	10
70–90	140 (70 + 70)	5
100	118 (70 + 48)	1
100	120 (70 + 50)	1
100	140 (70 + 70)	12

Marucci et al: **Patient and tumor characteristics at the time of the first treatment and reirradiation**

	Primary tumor	Recurrent tumor
Useful vision	– 39–67 at 3 yrs	27% at 5 yrs
Local control	96% at 5 yrs	69% at 5 yrs
Eye retention	‡76–99% at 5 yrs	55% at 5 yrs
Metastasis-free survival	‡58–97 at 4 yrs	73% at 5 yrs
Overall survival	80% at 5 yrs	64% at 5 yrs

"…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

To develop first class technology

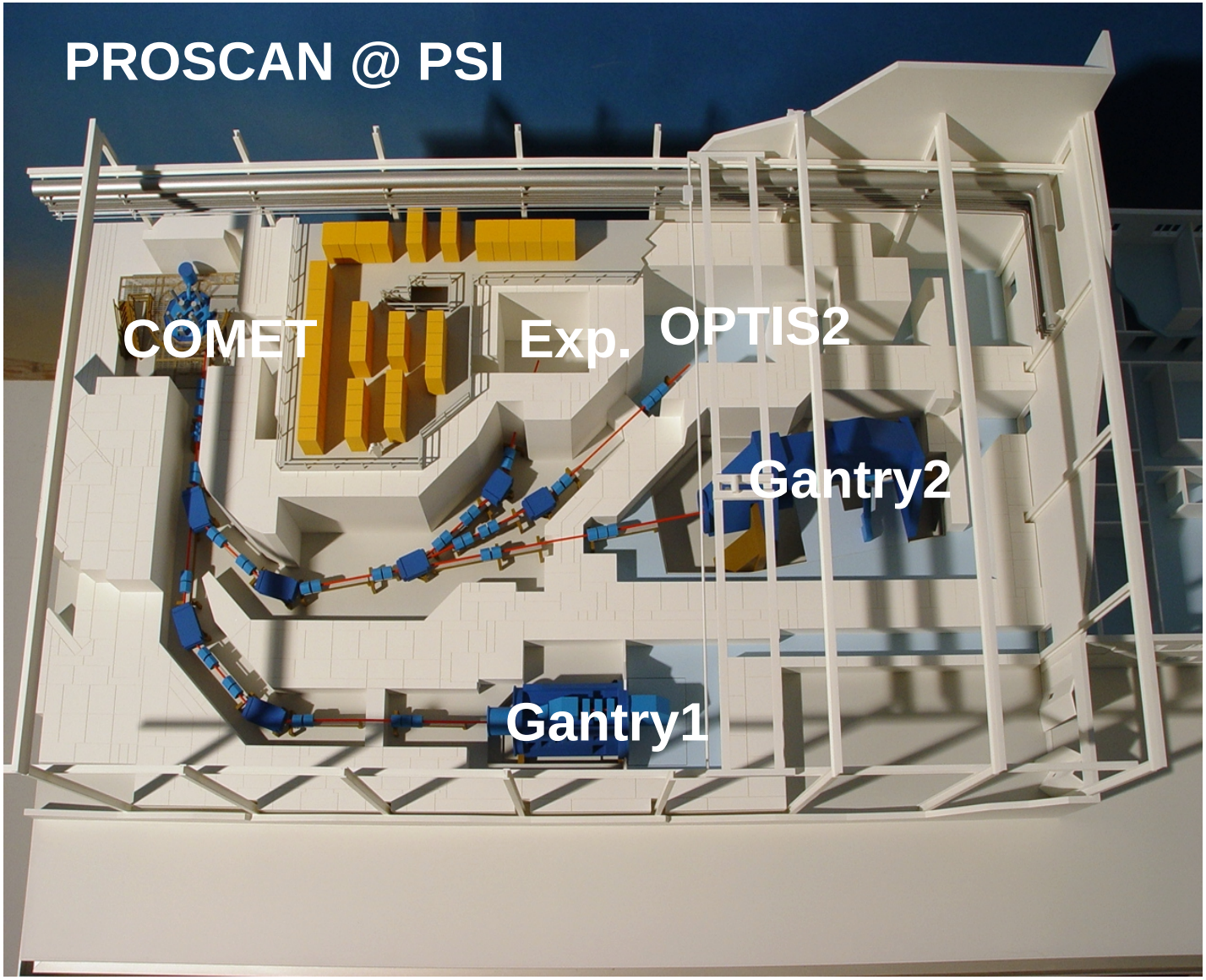
- COMET
- Gantry2
- OPTIS2

- Gating (Gantry2)
- Fast re-scanning (Gantry2)
- Robotchair (OPTIS2)
- Computer aided patient positioning (OPTIS2)

To provide first class clinical care

- Pediatric oncology
- Adult oncology
- Clinical trials

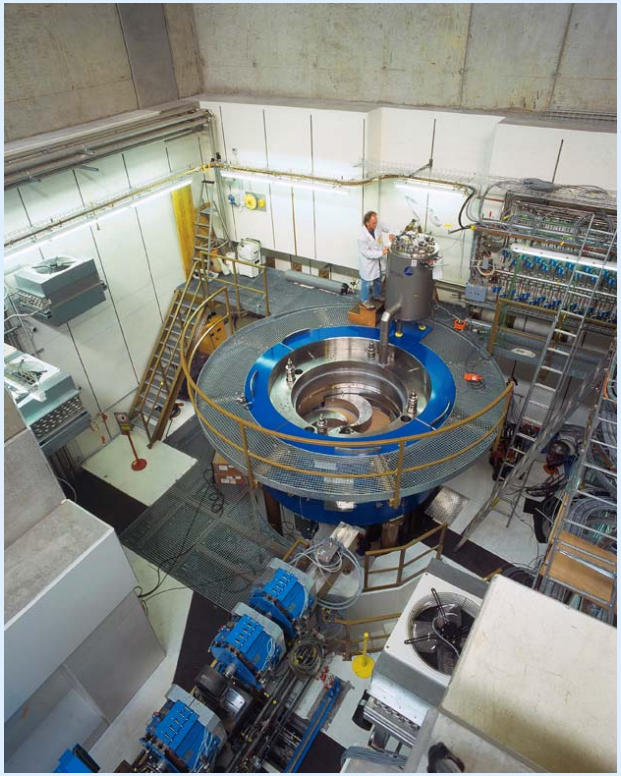
- Chordomas and chondrosarcomas
- Loads of other histologies
- Uveal melanoma


PROSCAN @ PSI
COMET
Exp.
OPTIS2
Gantry2
Gantry1

COMET: patient treatments started Feb. 2007

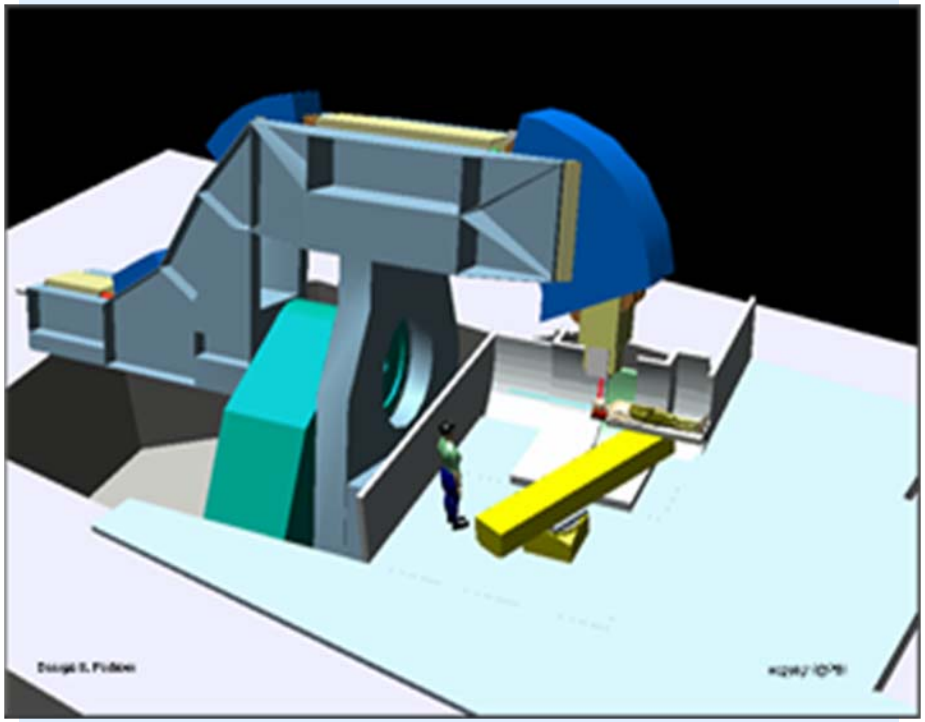
Computer generated (2003)

The real thing at PSI (2006)

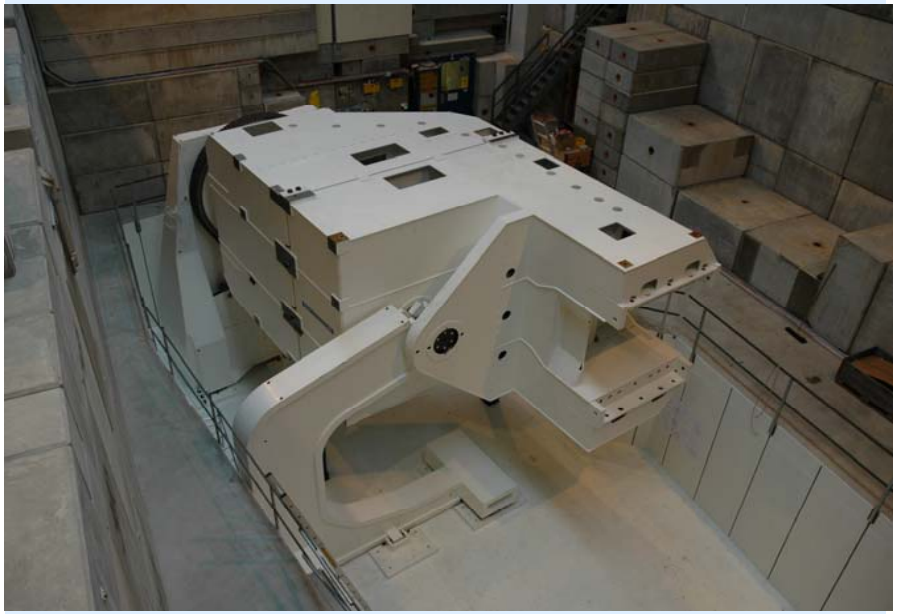


Gantry2

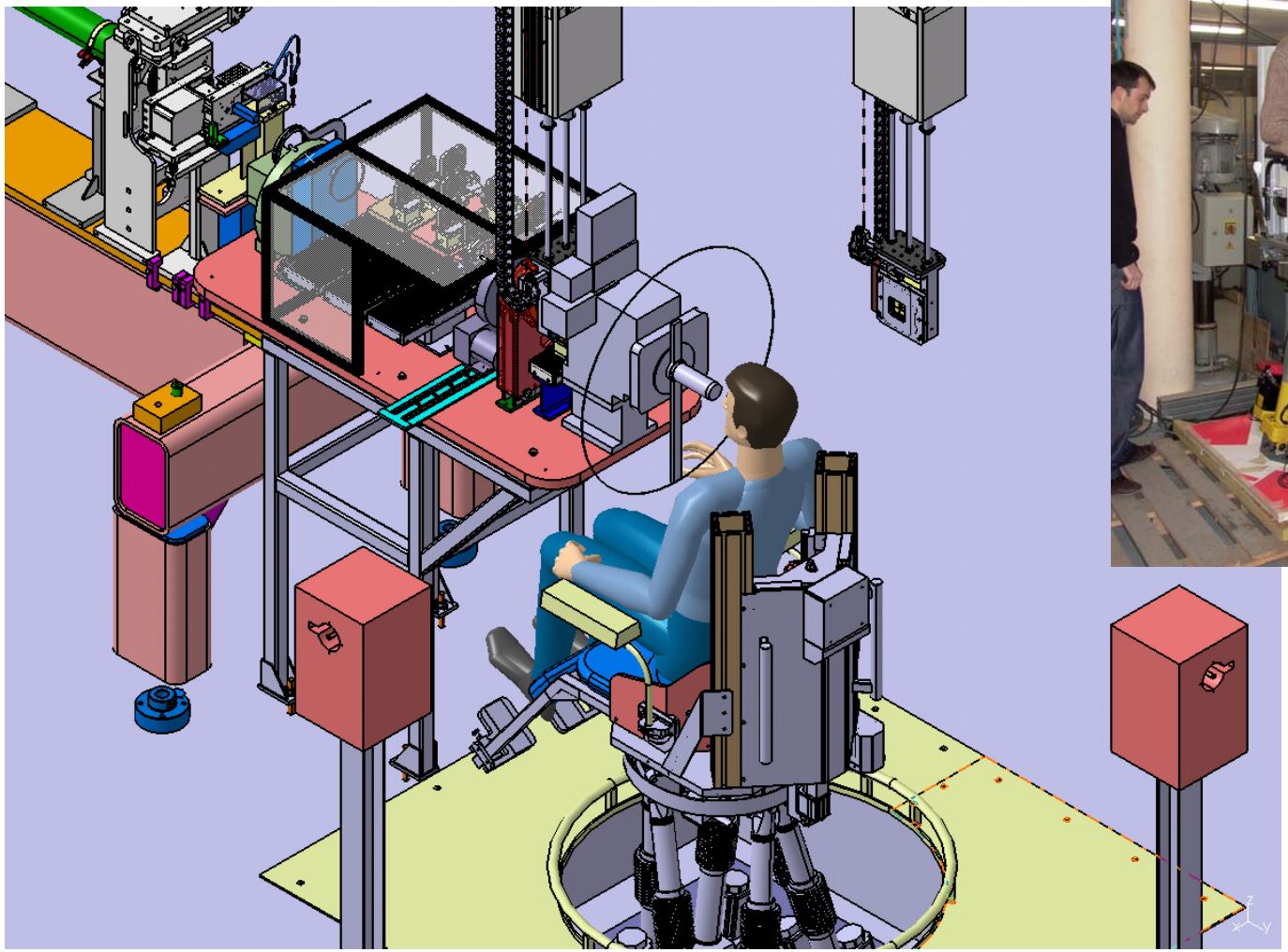
Computer generated



The real thing (late 2006)



OPTIS2 Nozzle with robotchair



Robotchair positioning
< 0.1 mm

Robotchair shown without mask-holder

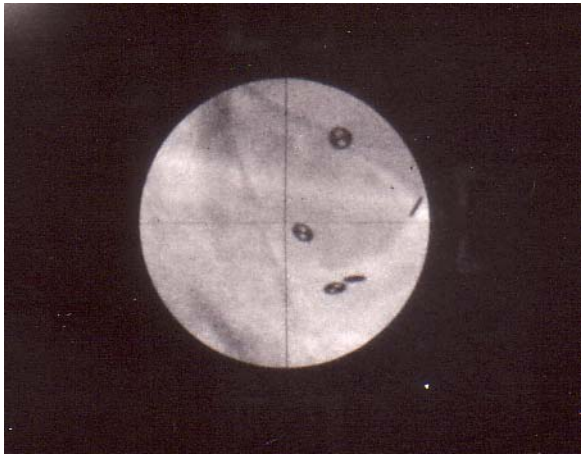
The OPTIS2 Project

sting OPTIS treatment parameters

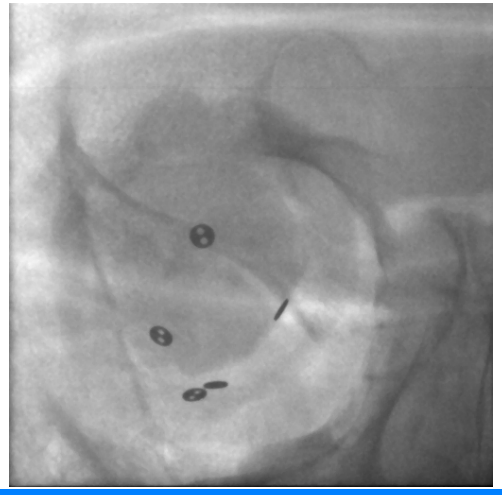
from January 1, 2008

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



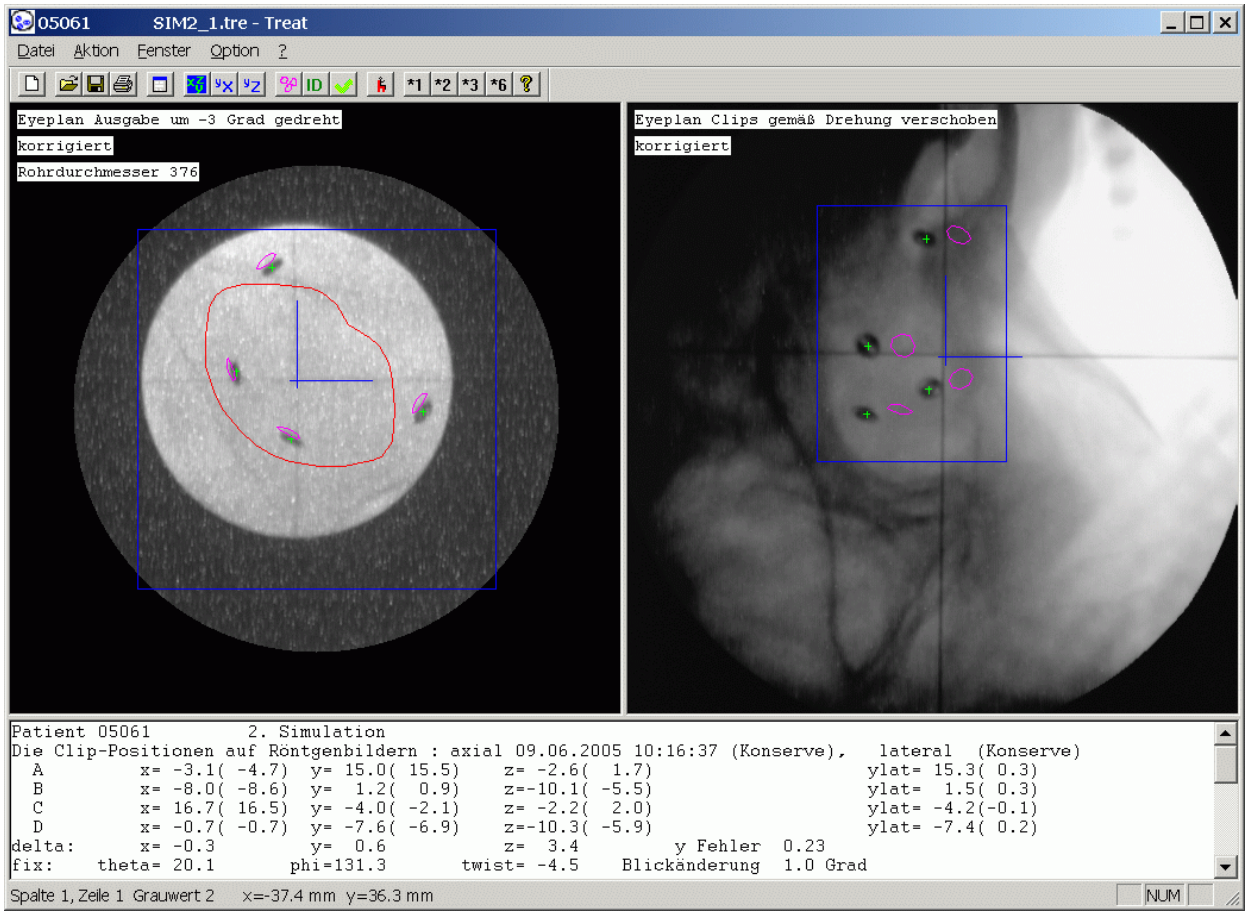
Conventional Polaroid Film



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

igital images of clips

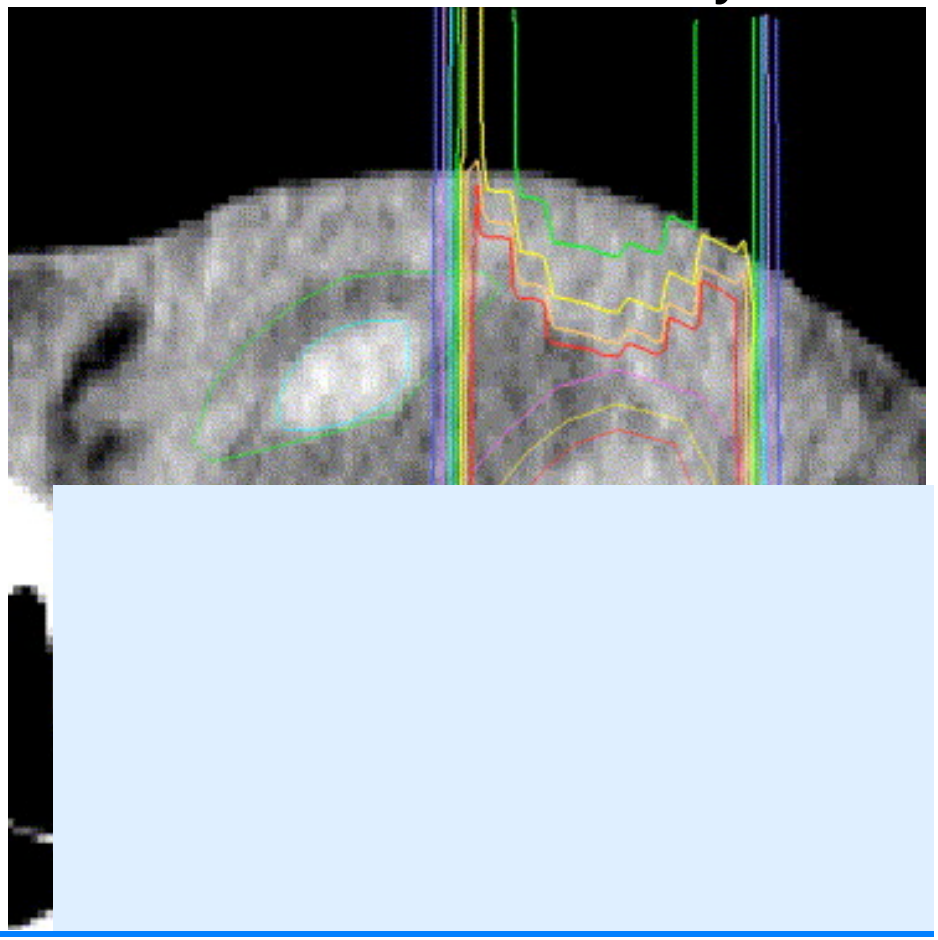
n to position eye of anesthetized patient

- 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 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 years2come (Optis2)