Can Protons replace Eye Brachytherapy?

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Disclosures

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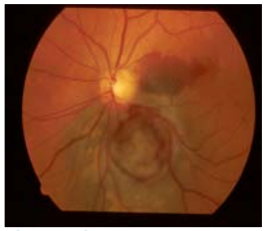
Outline of talk

- Refresher: uveal melanoma
  - ➔ incidence, pathology, treatment options, classification, etc
  - ➔ Ophthalmologic procedures / investigations
  - ➔ Treatment options
- Review of brachytherapy practices
  - ➔ Nuclides, procedures, clinical results
- Review of proton and stereotactic therapy practices
  - ➔ practices, clinical results
  - ➔ Alternative
- Summary / conclusion

Refresher - Uveal melanoma

- Incidence: 6-7 cases per Mill.
- >90% choroidal melanoma
- ciliary body melanoma approx. 9%,
- iris melanoma approx. 1%

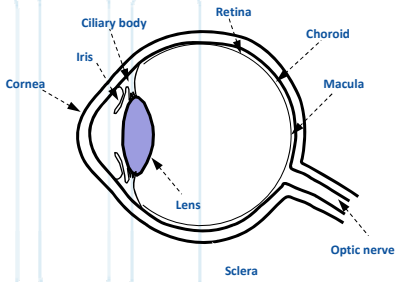


Pathology of Choroidal Melanoma:

- well defined pigmented nodular tumur; dome- (75%) and mushroom-shaped (25%)
- Growth towards the inner part of the globe, along the choroid or sclera
- Serious retinal detachment in most cases: surrounding the tumor and mostly inferior quadrants

Ocular Anatomy

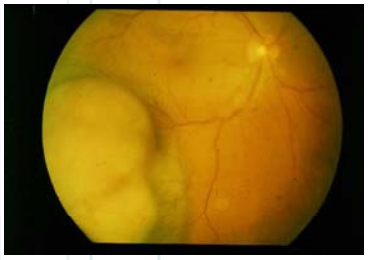
- Sclera: thickness 0.3 - 1 mm - extremely radiation resistant
- Uvea: choroid 0.3 mm
- ciliary body 2.0 mm
- iris 0,5 - 3 mm
- Retina: 0.1 mm



- Optic disc: papilla of optic nerve
- Macula: 3 mm from the optic disc

Ophthalmologic procedures (I)

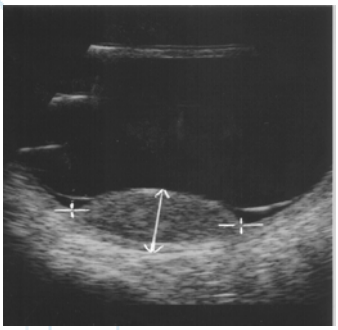
- Clinical examination
- (including screening for metastatic disease)
- Patient history of cancer
- Slit lamp examination
- Indirect binocular funduscopy with photodocumentation (fundus photography)
- morphology, topography
- Schematic drawing
- Prognostic factors (e.g. location)



- Transillumination (if needed)

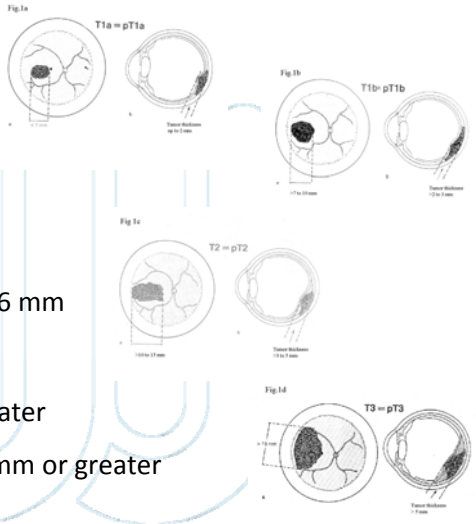
Ophthalmologic procedures (II)

- Fluorescence angiography (if needed)
- Sonography
  - ➔ Differential diagnosis (benign disease)
  - ➔ Tumor dimensions: thickness, diameter
  - ➔ Topography
- Stage: small, medium, large (TNM- and COMS-grading)



Collaborative Ocular Melanoma Study (COMS) Grading

- **Small melanomas**
  - ➔ Apical height: 1–2.5 mm
  - ➔ Largest basal diameter: 5 m
- **Medium melanomas**
  - ➔ Apical height: 2.5–10 mm
  - ➔ Largest basal diameter: 5–16 mm
- **Large melanomas**
  - ➔ Apical height: 10 mm or greater
  - ➔ Largest basal diameter: 16 mm or greater



From: Adult Ophthalmic Oncology: Ocular Diseases

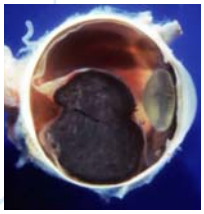
Management of posterial uveal melanoma (I)

- Various factors influencing therapeutic choice
  - ➔ Periodic observation (very flat lesions)
  - ➔ Transpupillary thermotherapy or
  - ➔ photodynamic therapy) (thickness ~ 1mm)
- Radiotherapy
  - ➔ Episcleral plaque radiotherapy (<5-7 mm thick)
  - ➔ Proton radiotherapy or Photon stereotactic radiotherapy
  - ➔ >5-7 mm thick, or >2-2.5mm and juxtapapillary/Juxtamacular

BT versus protons: Rather complementary and not competitive?

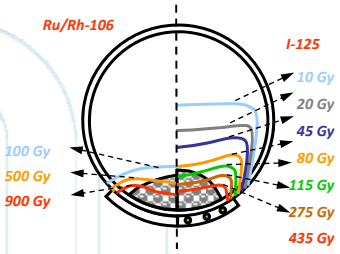
Management of posterial uveal melanoma (II)

- Local resection
  - ➔ complex procedure
  - ➔ highly specialized surgeons
  - ➔ side effects
- Enucleation:
  - ➔ should be avoided if possible
  - ➔ For very large tumours (<10 mm)
- Orbital exenteration
  - ➔ tumors perforating the sclera
  - ➔ extremely rare

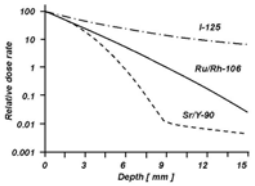


Radiotherapeutic Management

- Eye plaque Brachytherapy
  - ➔ [Cobalt-60 (historical)]
  - ➔ Iodine-125
  - ➔ [Iridium 192]
  - ➔ Ruthenium-106
  - ➔ Strontium 90
- External beam therapy
  - ➔ Proton radiotherapy
  - ➔ Stereotactic photon radiotherapy



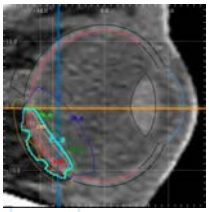
^{90}Sr E_β : 2.2 MeV (1.5 mm)
$^{106}Ru/^{106}Rh$ E_β : 3.5 MeV (2.5 mm)
^{125}I E_γ : 0.03 MeV (16.5 mm)

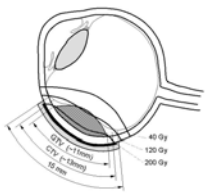


Target Volume Definition

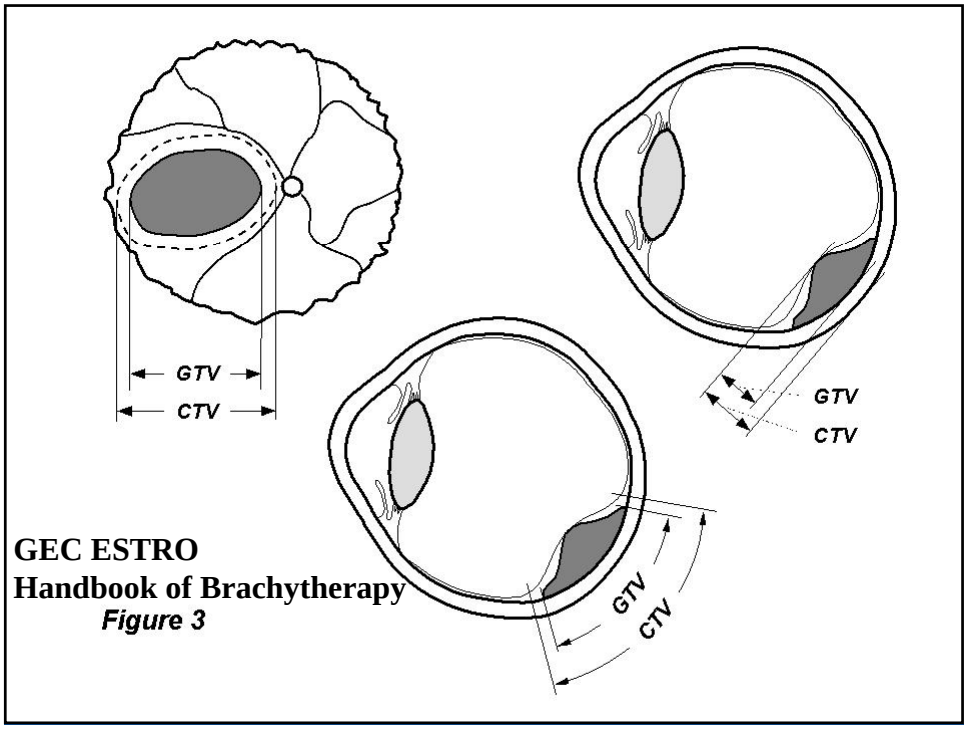
- Basis Diameter of the CTV

  (as determined by MRI/CT)
  - ➔ Tumor basal diameters (echography)
  - ➔ plus 1-2 mm safety margin
- Thickness of the CTV
  - ➔ Tumor thickness (echography, orthogonal)
  - ➔ plus 1 mm „margin“ for the sclera

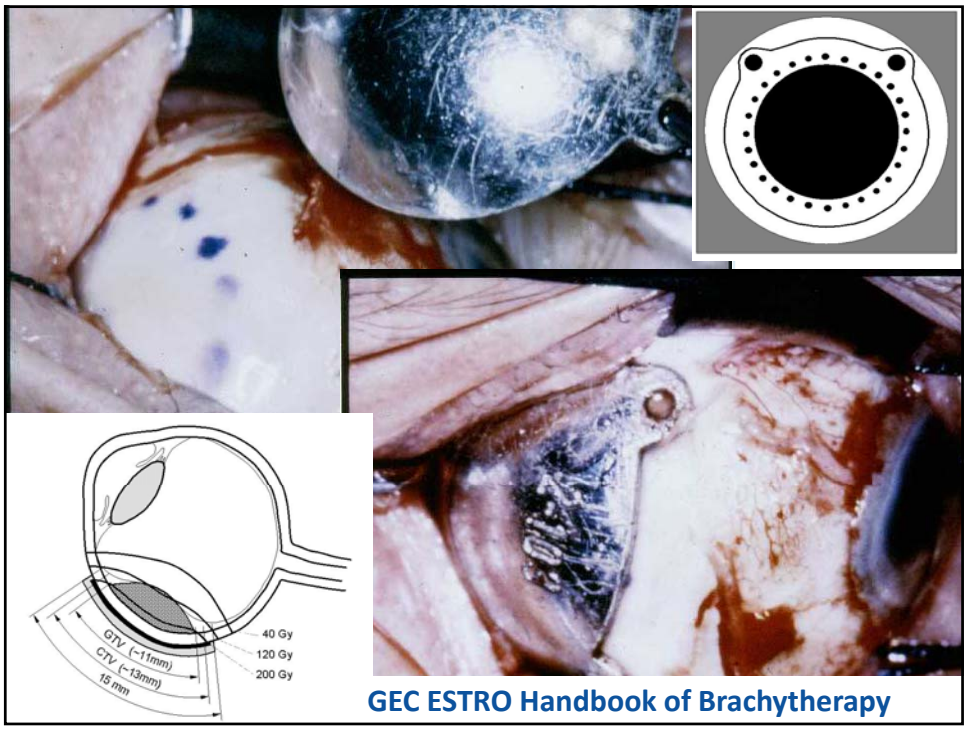




GEC ESTRO Handbook of Brachytherapy



GEC ESTRO
Handbook of Brachytherapy
Figure 3



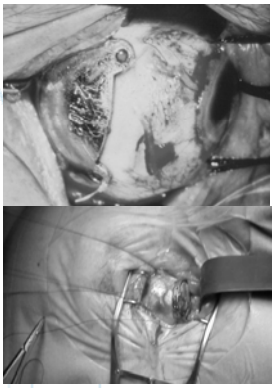
GEC ESTRO Handbook of Brachytherapy

"Typical" Dose in eye melenanoma treatments

Ru-106 (LDR)	**tumor apex 1-10 days**	**70-150 Gy**
I-125 (LDR)	**tumor apex 30-300 hours**	**60-80 Gy**
Sr-90 (HDR)	**tumor base (sclera) 2-3 hours**	**450-600 Gy**
Protons/photons (HDR)	**target volume** ***4-5 fractions each 10-15 Gy 1-2 week(s)***	**50-70 Gy**

Brachytherapy of uveal melanoma

- Surgical procedure
- Excellent clinical results
- (Large) clinical studies
- E.g. Bornfeld, Lomatzsch et al (1991)
  - ➔ 1254 pts with Ru/Rh-106
  - ➔ 87% OS , 12.5% enucleation

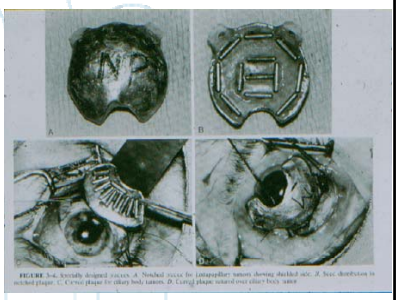


- Reports on **"…. (significantly) higher late recurrence rate with (125)I brachytherapy as compared with charged particle radiation" (?)**

Char DH, Kroll S, Phillips TL, Quivey JM. Late radiation failures after iodine 125 brachytherapy for uveal melanoma compared with charged-particle (proton or helium iontherapy. Ophthalmology. 2002 Oct;109(10):1850-4.

Randomised Trial in North America

- Iodine-125 brachytherapy vs. Enucleation (COMS Trial)
- Brachytherapy (n=657) >10y accrual:
  - ➔ 5 year survival 81%
  - ➔ mortality from melanoma: 9%
- Enucleation (n=653):
  - ➔ 5 year survival 82%
  - ➔ similar melanom mortality
- No statistical difference between treatment arms



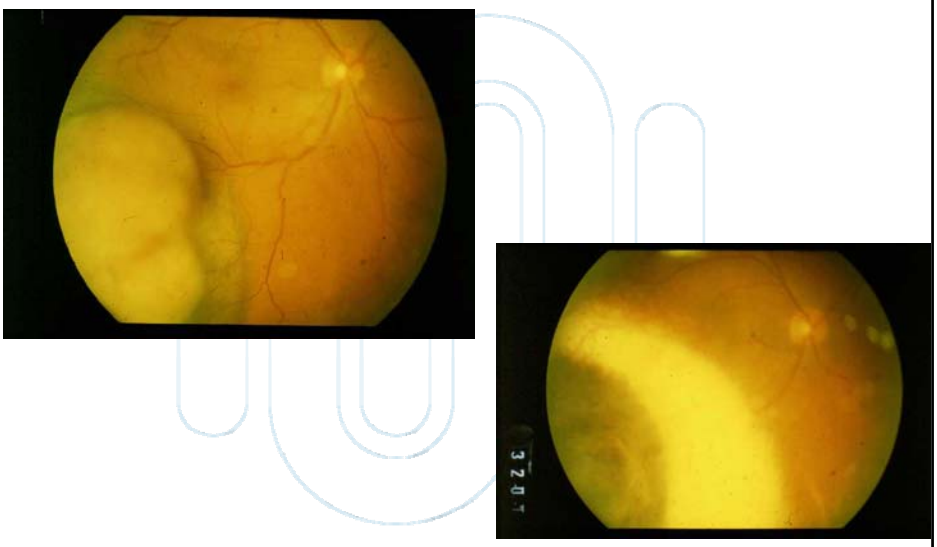
(Shields: Eye tumours 1991)

Clinical Results (1241 pts, Ru-106)

- T1,T2,T3 Tumors Age: 50-60 years
- Apex dose: 70 –150 Gy, Scleral dose: 600-1500 Gy
- Follow-up: 5-7 years
- Local control rate: (selection of patients (!)) ~ 90% (up to 98%)*
- 5y mortality rate (all causes) 11-22%
- 5y mortality rate (tumour related)
  - ➔ T1,T2: 3 - 9%
  - ➔ T3: 13 - 39%

Complete table in GEC ESTRO Handbook of Brachytherapy, Pötter van Limb. 2002
*** Damato et al. IJROBP 2005**

Tumor regression After Eye Plaque BT 12-24 months

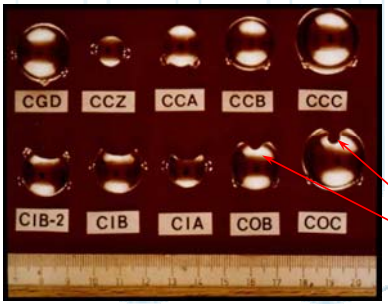


Ru-106 and I-125 Eye applicators

- Various plaque forms for sparing ocular structures (e.g. optic nerve (COB, COC))
- Challenging surgical procedure for posterior tumor location

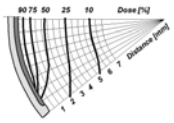
➔ **Alternatives: external beam radiotherapy**

I-125



Ru-106 (1987: former East Berlin)

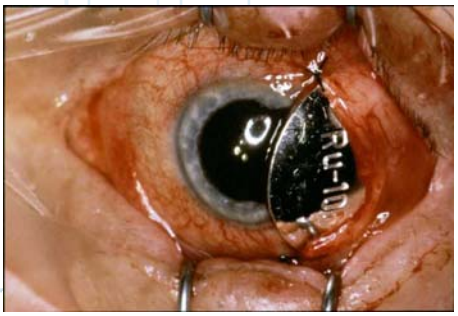
Dose at the edge of Ru-applicator



Ru-106

Disadvantage for targets close to the optic nerve

Iris melanoma

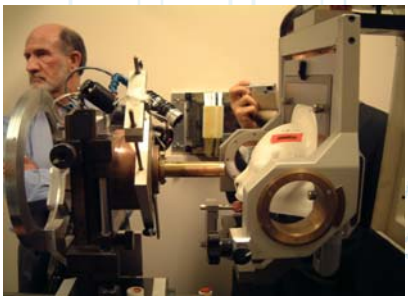


Ru-106
Eye plaque
Brachytherapy

Proton therapy

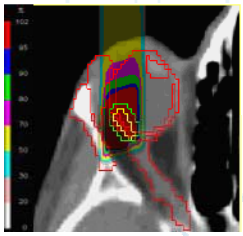
- Fixed single beam
  - ➔ patient in seated position
  - ➔ brass collimators
- Early form of IGRT by X-rays and (tantalum) clips for X-ray verification
- Simple treatment planning (fundoscopy)

courtesy of UCSF



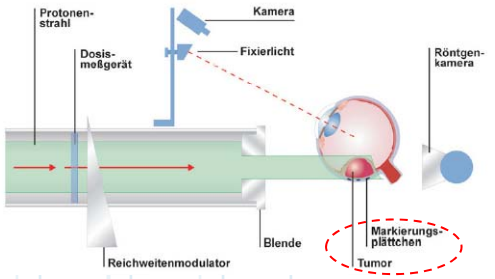
Proton beam radiotherapy

- Surgical application of tantalum markers
- Dose 55-70 Cobalt GyE in 4 fractions (e.g. 5x14 GyE, 5x 12 GyE)
- Single field (passive scattering technique based)



Proton planning and delivery

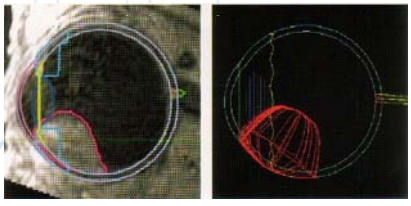
Heufelder et al (HMI), ZMP 2004



courtesy of HMI

Marking clips

Höcht et al (HMI) Berlin, Germany Str & Oncol 2005



Proton therapy for UVEAL MELANOMA

- Considerable number of proton centers treat uveal melanoma
  - → large clinical experience; follow-up critical due to referring structure
  - ➔ Total dose 5 x 12 Gy – 14 Gy in 2 weeks

➔ **Proton RT regarded as golden standard for Uveal Melanoma**

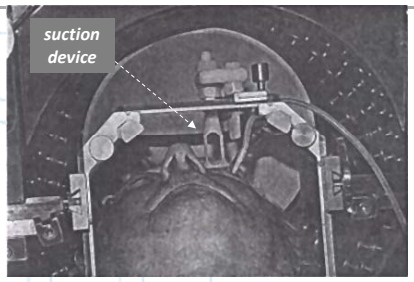
	Center	Year	Patients (n)	Tumor control at 5 years (%)	Eye retention at 5 years (%)
	PSI – CH [11, 12]	2003	*>2800*	95.8	88.9
	MGH – USA [19]	2002	*2568*	97.6	93.1
	Loma Linda – USA [13]	2001	78	90.5	75.3
	Nice – F [7]	1999	538	89	88
	Orsay – F [9]	2003	926	96.0	88.8
	Clatterbridge – UK [43]	1999	267	94.8	89.1
HMI	Present series	2003	245	95.5[a]	87.5[a]

[a] at 3 years

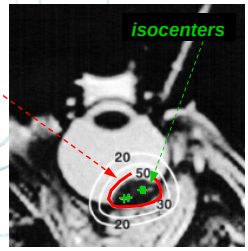
Heufelder et al (HMI), ZMP 2004

Gamma Knife based SRS @ MUW

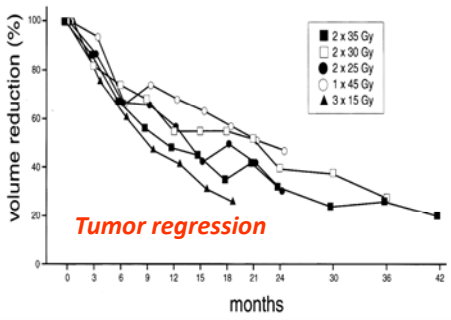
- Treatment technique
  - ➔ Suction device and invasive frame do not allow more than 3 fractions
  - ➔ Inhomogeneous dose



- ***7 patients*** ***TD 45 Gy / SD 45 Gy (50% Isodose)***
- ***41 patients*** ***TD 70 Gy / SD 35 Gy (50% Isodose)***
- ***14 patients*** ***TD 45 Gy / SD 15 Gy (50% Isodose)***
- ***2 Patients*** ***TD 50 Gy / SD 25 Gy (50% Isodose)***
- ***1 Patients*** ***TD 60 Gy / SD 30 Gy (50% Isodose)***
- ***delivery*** ***1 x fraction / week***



Clinical experience - Gamma Knife



Local tumor control and morbidity after one to three fractions of stereotactic external beam irradiation for uveal melanoma☆

Martin Zehetmayer[a,*], Klaus Kitz[b], Rupert Menapace[a], Adolf Ertl[b], Harald Heinzl[d], Irene Ruhswurm[a], Michael Georgopoulos[a], Karin Dieckmann[c], Richard Pötter[c]

[a]Department of Ophthalmology, Oncology Service, University of Vienna, Medical School, Allgemeines Krankenhaus, Währinger Gürtel 18-20, 1090 Vienna, Austria
[b]Department of Neurosurgery, Gamma Knife Unit, University of Vienna, Medical School, Vienna, Austria
[c]Department of Radiotherapy, University of Vienna, Medical School, Vienna, Austria
[d]Department of Medical Computer Sciences/Clinical Biometrics, University of Vienna, Medical School, Vienna, Austria

Radioth & Oncol 61 (2001)

- Tumor control good
  - ➔ 98%
- Side effects „sub-optimal“ compared to protons
  - ➔ Cataract (>60%)
  - ➔ Secondary Glaucoma
  - ➔ Retinopathy
  - ➔ Optic neuropathy
- Effect of tumor height
- Fractionation “challenging” potential

LINAC based SRT @ MUW (I) Vienna

- **Ideas “born” in 1997:**
  - ➔ MR based 3D target definition / CT for 3D planning
  - ➔ Linac based SRT (6MV)
  - ➔ Fractionation scheme as for proton therapy
  - ➔ Stereotactic head fixation with non-invasive eye monitoring

A linac-based stereotactic irradiation technique of uveal melanoma

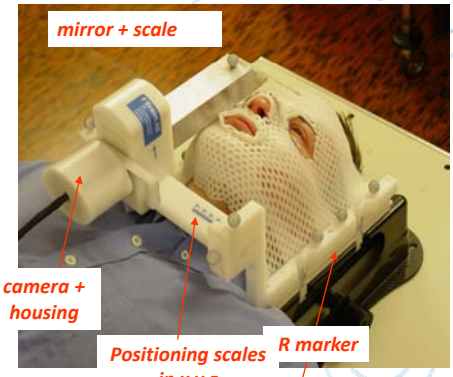
Karin Dieckmann[a,*], Joachim Bogner[a], Dietmar Georg[a], Martin Zehetmayer[b], Gerhard Kren[a], Richard Pötter[a]

[a]Department of Radiotherapy and Radiobiology, University of Vienna, General Hospital Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria
[b]Department of Ophthalmology, University of Vienna, General Hospital Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria

Radioth & Oncol 61 (2001)

LINAC based SRT @ MUW (II) Vienna

- Stereotactic head fixation with non-invasive eye monitoring



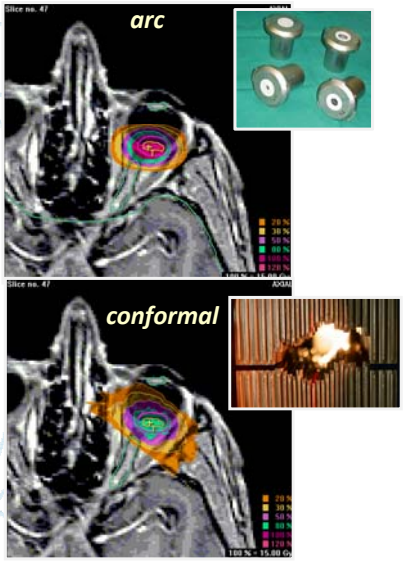
Automatic real-time surveillance of eye position and gating for stereotactic radiotherapy of uveal melanoma

Bernhard Petersch, Joachim Bogner, Karin Dieckmann, Richard Pötter, and Dietmar Georg
Department of Radiotherapy and Radiobiology, Medical University Vienna, Währinger Guertel 18–20, A-1090 Vienna, Austria

Med. Phys. 31 (12), December 2004

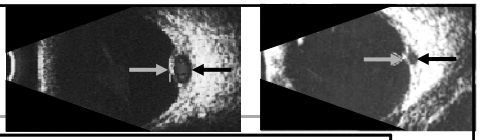
Patient inclusion criteria (since 1997) @ MUW

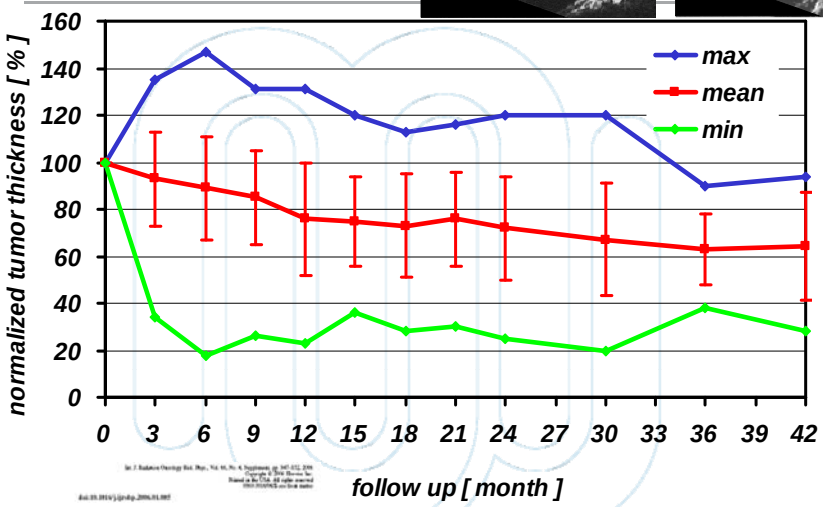
- Melanoma thickness < 10 mm
- OR: unsuitable for Ruthenium-106 Brachytherapy
  - ➔ distance to fovea < 2-3 mm and/or optic disc
  - ➔ thickness > 5mm
- OR: unsuitable for local resection
- "Difficult" cases only
- Important when comparing clinical results



Georg et al UROBP 55; 2003

Slow tumor response





GROSRT SUPPLEMENT

OPTIMIZING LINAC-BASED STEREOTACTIC RADIOTHERAPY OF UVEAL MELANOMAS: 7 YEARS' CLINICAL EXPERIENCE

Karin Dieckmann, M.D.,* Dietmar Georg, Ph.D.,* Joachim Bogner, Ph.D.,* Martin Zehetmayer, M.D.,† Berthold Pötreich, Ph.D.,* Martin Choraut, M.D.,* Hajo Wittmann, M.D.,* and Richard Pötter, M.D.*

Dieckmann et al Int J Radiat Oncol Biol Phys. 2003

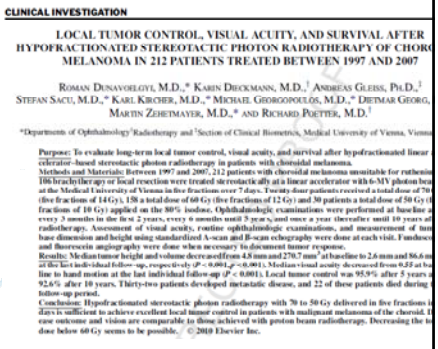
Linac based SRT of uveal melanoma @ MUW

Local Control 96%, 93% at 5/10 years (n=212 pat.)

Visual Acuity: from 0.55 at baseline to hand motion at last follow-up

Metastatic disease: 33 patients

Dead from disease 22 patients



CLINICAL INVESTIGATION

LOCAL TUMOR CONTROL, VISUAL ACUITY, AND SURVIVAL AFTER HYPOFRACTIONATED STEREOTACTIC PHOTON RADIOTHERAPY OF CHOROIDAL MELANOMA IN 212 PATIENTS TREATED BETWEEN 1997 AND 2007

Roman Dunavoelgyi, M.D.,* Karin Dieckmann, M.D.,† Andreas Gleiss, Ph.D.,† Stefan Sacu, M.D.,* Karl Kircher, M.D.,* Michael Georgopoulos, M.D.,* Dietmar Georg, Martin Zehetmayer, M.D.,* and Richard Poetter, M.D.†

Side effects (overall)

Useful vision: majority of patients
in tumors not involving macula, optic disc
if involved, *optic neuropathy*: poor vision - blindness

Radiation retinopathy: frequent in the treated volume
Maculopathy if macula is treated

Cataract: rare after Ru-106, more often after Iodine-125
and possible after proton radiotherapy

Neovascular glaucoma: overall <5% (patient selection)
large tumours, e.g. >10mm: enucleation

Anterior eye damage (e.g. eye lid fibrosis): proton radiotherapy

Advantages of different options

I-125 plaques	Sparing of uninvolved regions because of low energy Individual computer assisted treatment planning. Avoidance of severe radiogenic complications. Precise radiation possible
Ru-106 plaques	Repeated usability (half-life 1 yr.) Limited range of Beta-radiation (10 % in 7 mm). Avoidance of severe radiogenic complications. Precise radiotherapy
External Beam therapy (prot/phot)	Qualified in particular for large tumors and tumors near the posterior pole (optic disc, macula). Fractionated irradiation possible. 3D volumetric treatment planning for SRT

Disadvantages of different options

I-125 plaques	Short half-life (60 days) Plaques be loaded with seeds for every application Higher costs than Ruthenium Radiation exposure of surgical team Scleral necrosis possible; surgical procedure
Ru-106 plaques	Dosimetric difficulties (beta rays) Very inhomogeneous tumor dose Suited for small tumors only (apex <5-7 mm) Complete fibrosis of underlying uvea, retina Scleral necrosis possible; surgical procedure
External Beam therapy (prot/phot)	Significant rate of radiogenic side effects anterior eye (protons) Optic neuropathy due to location (photons, protons); Availability, costs Proton beam: requires exact marking of tumor margins with episcleral fixed tantal rings.

Summary / Conclusion

- Excellent tumour control (>95%) for all RT modalities for uveal melanoma
  - ➔ BT and EBRT rather complementary and not competitive
  - ➔ Posterior Pole (SRT or Protons) other locations BT <5-7 mm
- Side effects moderate (retinopathy) - significant
  - ➔ Depend on tumor location and RT modality
  - ➔ Dose and Dose volume data generally lacking
- SRT photon techniques results in similar levels of dose conformation and clinical local control as protons
- EBRT with photons has most sophisticated planning and dose calculation procedure (R&D for BT (Vienna))

Prior radiotherapy

2 years after RT

Standardised eye model