Ophthalmic tumors

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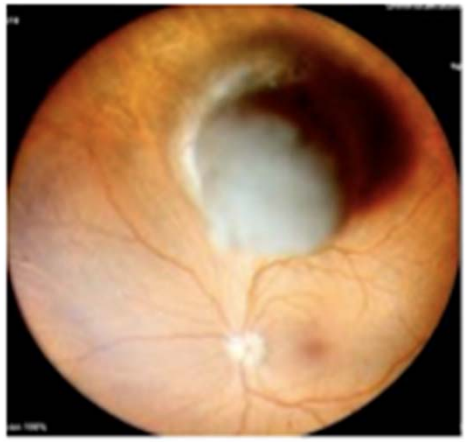
Today's menu

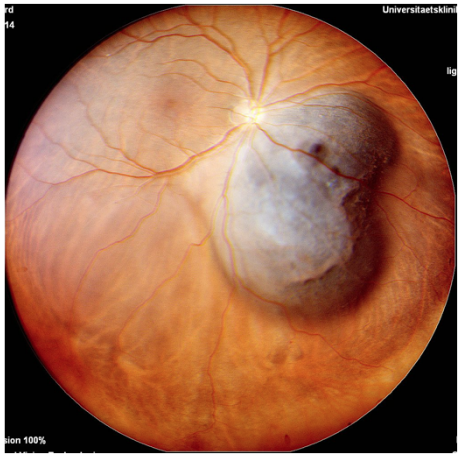
- Introduction and some basics on uveal melanoma
- Brachytherapy for intraocular tumors
- Proton therapy for intraocular tumors
- Proton therapy for melanoma of the conjunctiva
- Future developments in ophthalmic brachytherapy
- High energy beams in ocular tumors
- How to choose the optimal approach in an individual patient?



Ophthalmic tumors

Rare diseases

In Germany 800 new cases per year
(>500 of them treated in Essen)

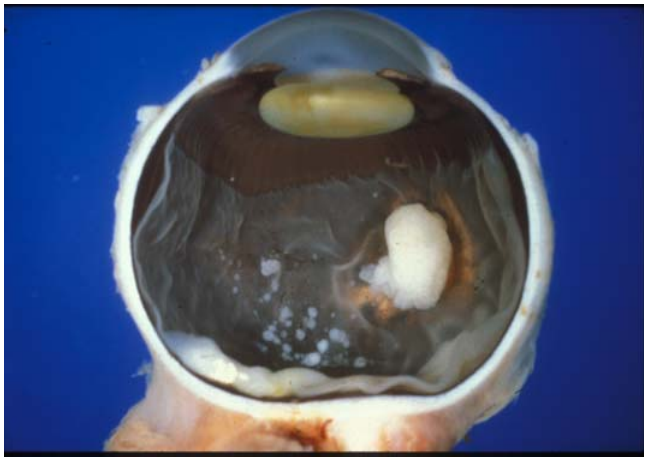


What is different to „normal" radiotherapy?

- Very small treatment volume (electron equilibrium??)
- Very close to important functional structures
- Treated in dedicated centers, which have different equipments

Special techniques are mandatory

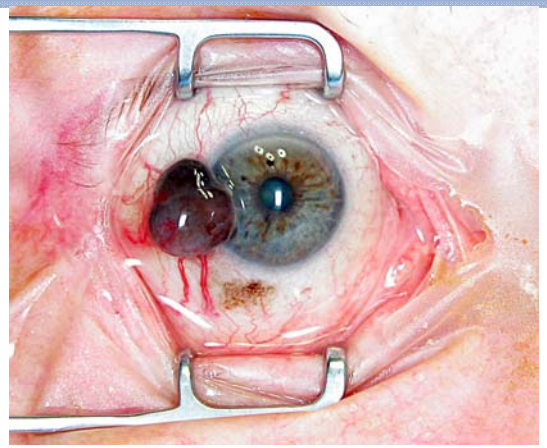
Ophthalmic tumors: Target volumes

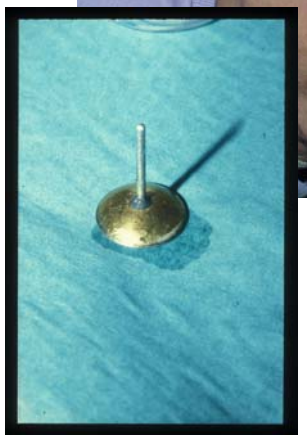


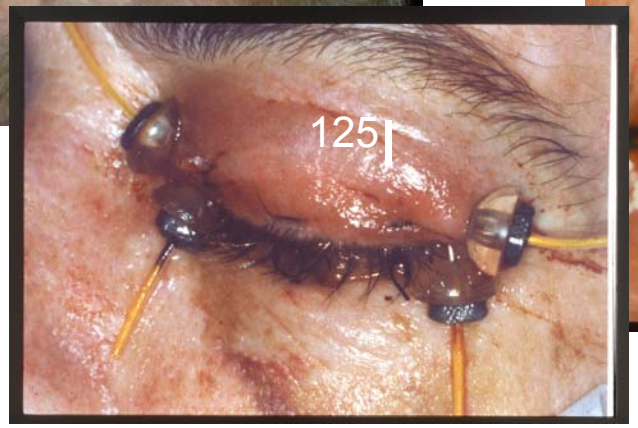
- the entire eye (metastases)
- Localized tumor in the eye (melanoma, retinoblastoma)
- the retina and the vitreous (retinoblastoma, lymphoma)
- the orbit (retinoblastoma, melanoma…)
- others (iris, conjunctiva…)

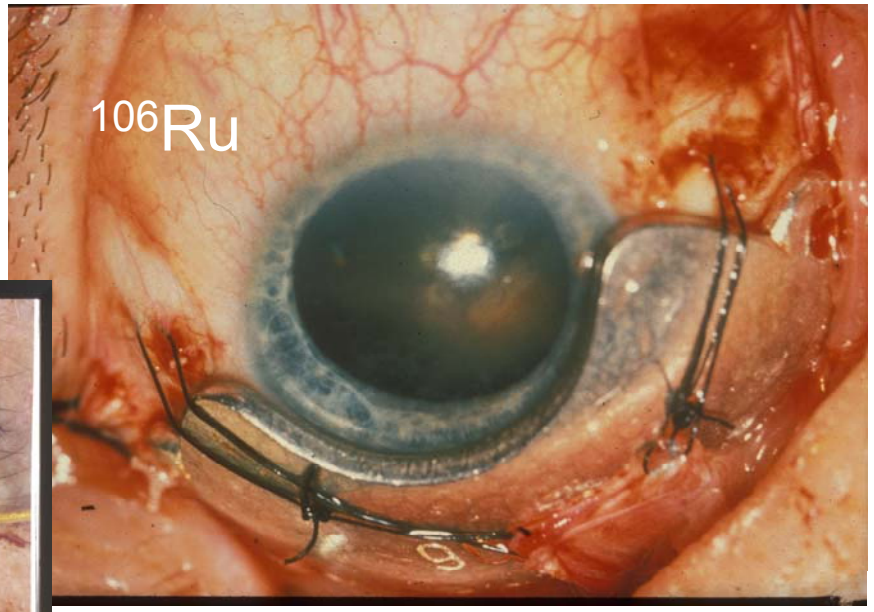
Ophthalmic tumors: Irradiation techniques

Brachytherapy





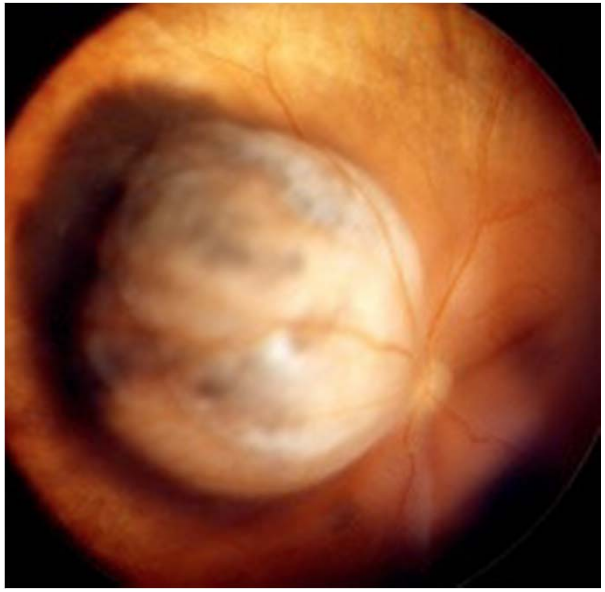


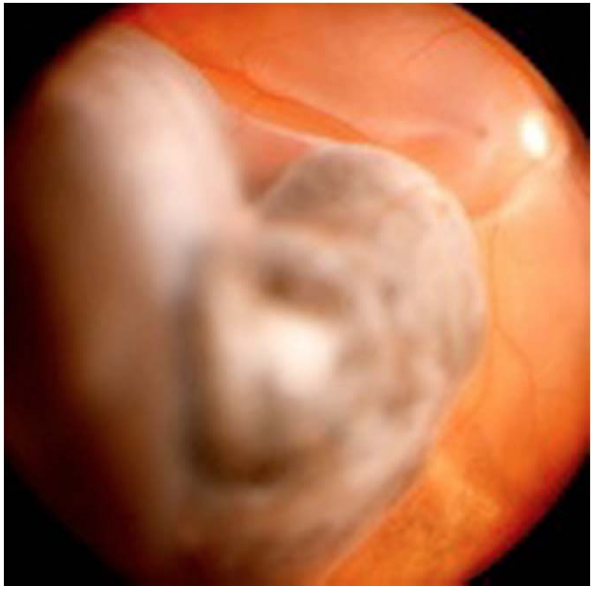


Ophthalmic tumors: Irradiation techniques

External beam radiotherapy

protons



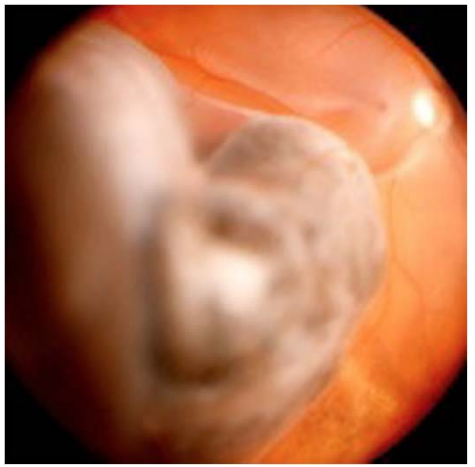


Brachytherapy

INTRAOCULAR TUMORS

Irradiation of a tumor in the eye:

uveal melanoma



Protection
of the optic nerve, the papilla and the macula, the orbit

Dose >100 Gy

Techniques - brachytherapy using radioactive plaques
- protons

Metastases in uveal melanoma

risk factors

genetics

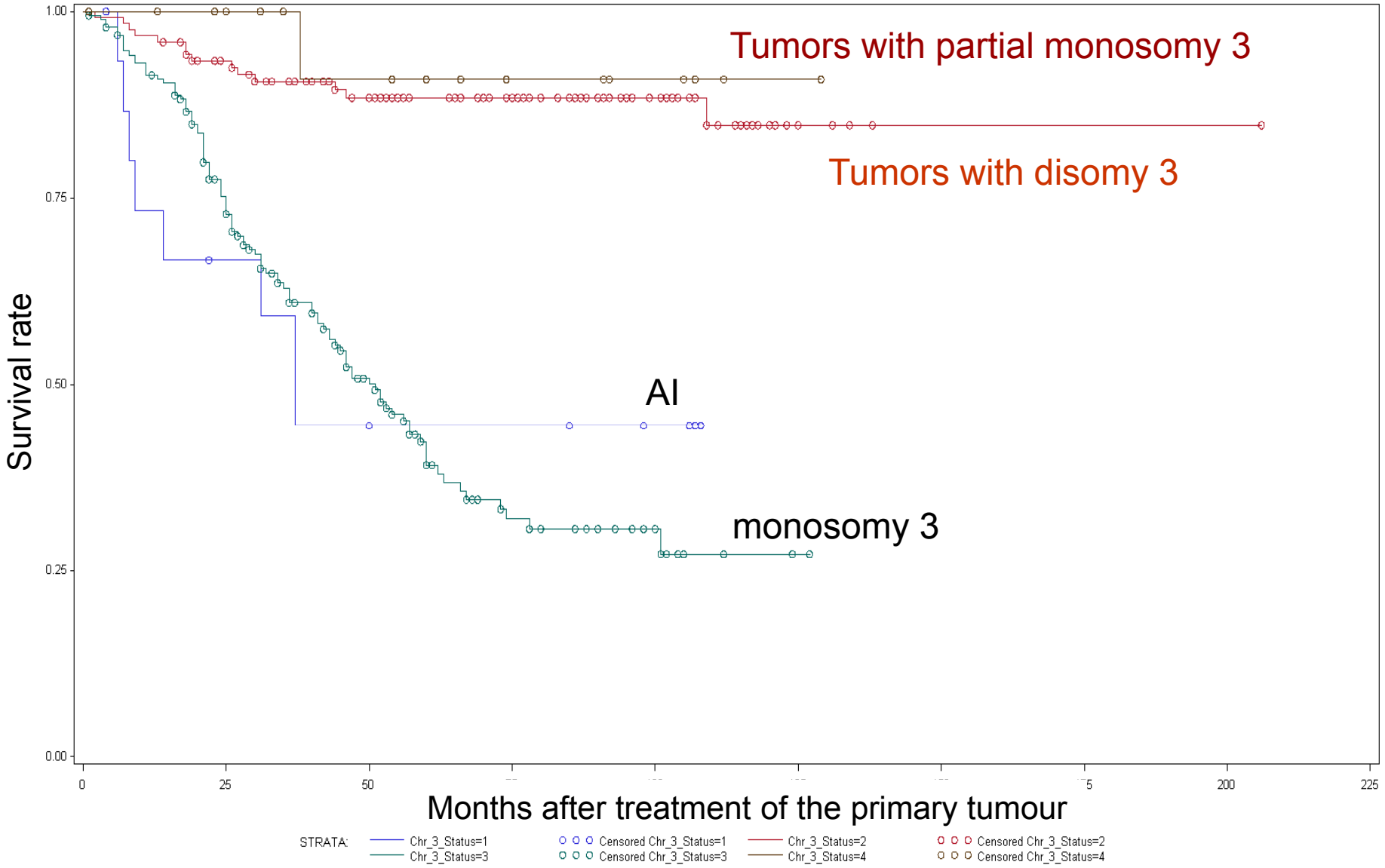
localization

size

extra-ocular growth

Chromosome 3 status predicts survival

Tumour related survival of 374 enucleated patients (1998 – 2008)



Ru-106 plaques

- β-irradiation with a background of γ Bremsstrahlung
- maximal energy of β rays: 3,53 MeV
- half-life: 366 days
- steep dose gradient:
  in 6 mm depth ~ 10% of dose rate at the surface
- big choice of different applicators
- prescribed dose:
  - at the sclera 700 (- 1500)Gy
  - at tumor apex >130 Gy
- indicated for tumors
  ≤ 6 mm height

Ru-106 plaques

I-125 plaques

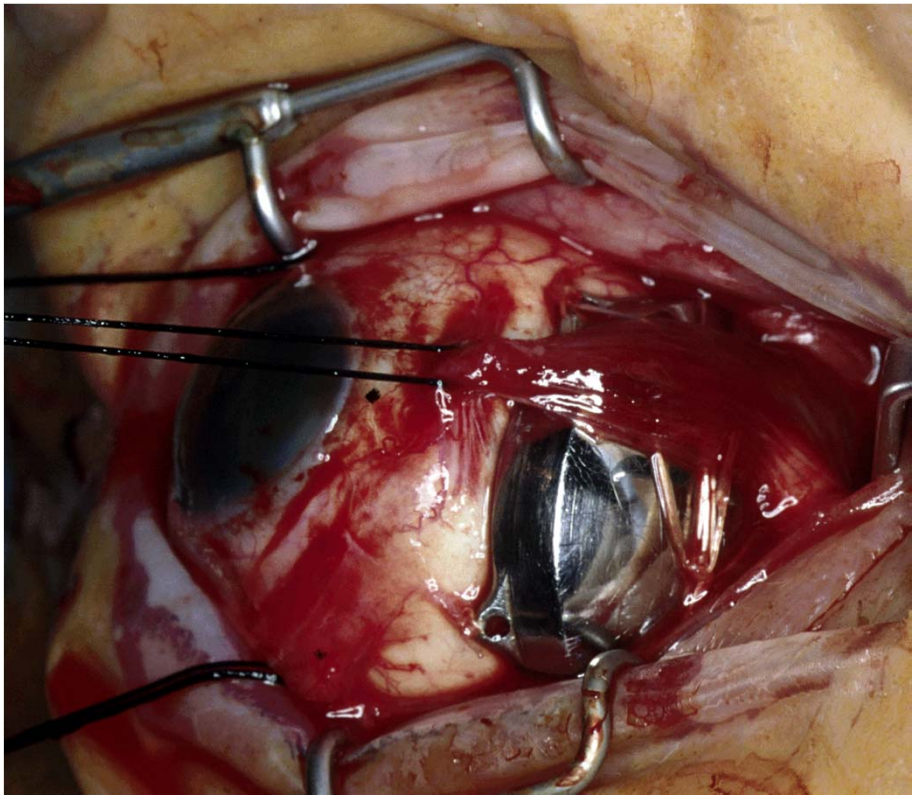
- Photon irradiation mean energy 27 - 35 keV
- Half life: 60 days
- in 10-12 mm depth 10% of dose rate at the surface
- Plaques have to be produced at the hospital (8-12 seeds/plaque)
- Prescribed dose:

  at the sclera 300(- 500)Gy

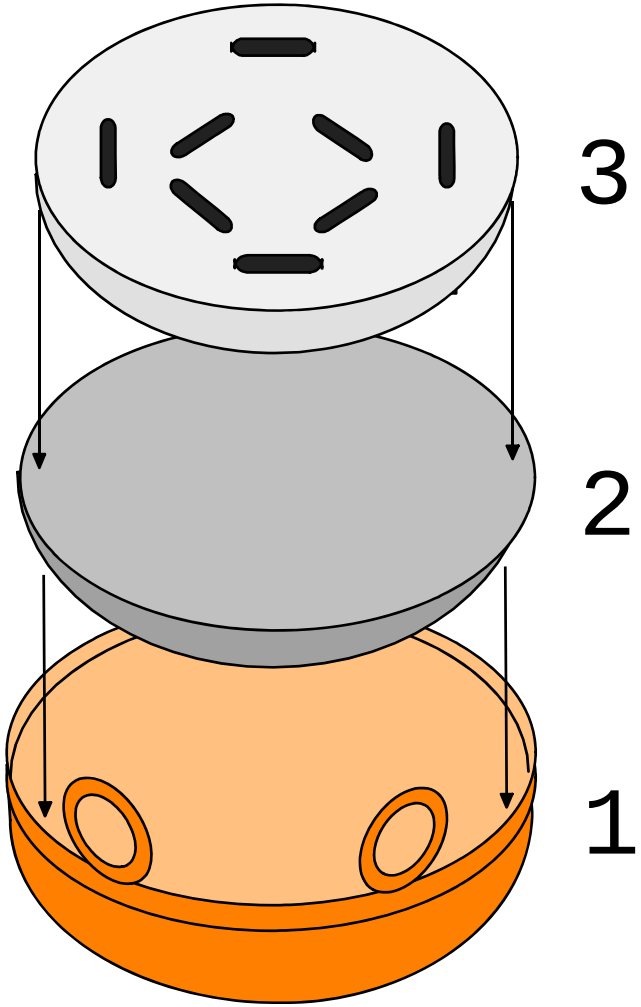
  at tumor apex >80 Gy
- Indication for tumors 8 - 12 mm height

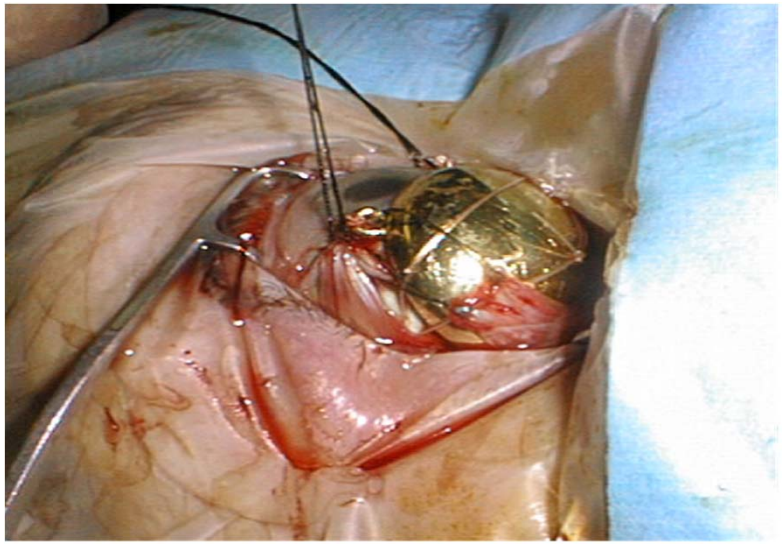
I-125 plaques

plaque in stainless steel with Persepex inlay



I-125 / Ru-106 bi-nuclide-plaque





Dose distribution of a ^{106}Ru-plaque

tumor: 8 mm

dose:

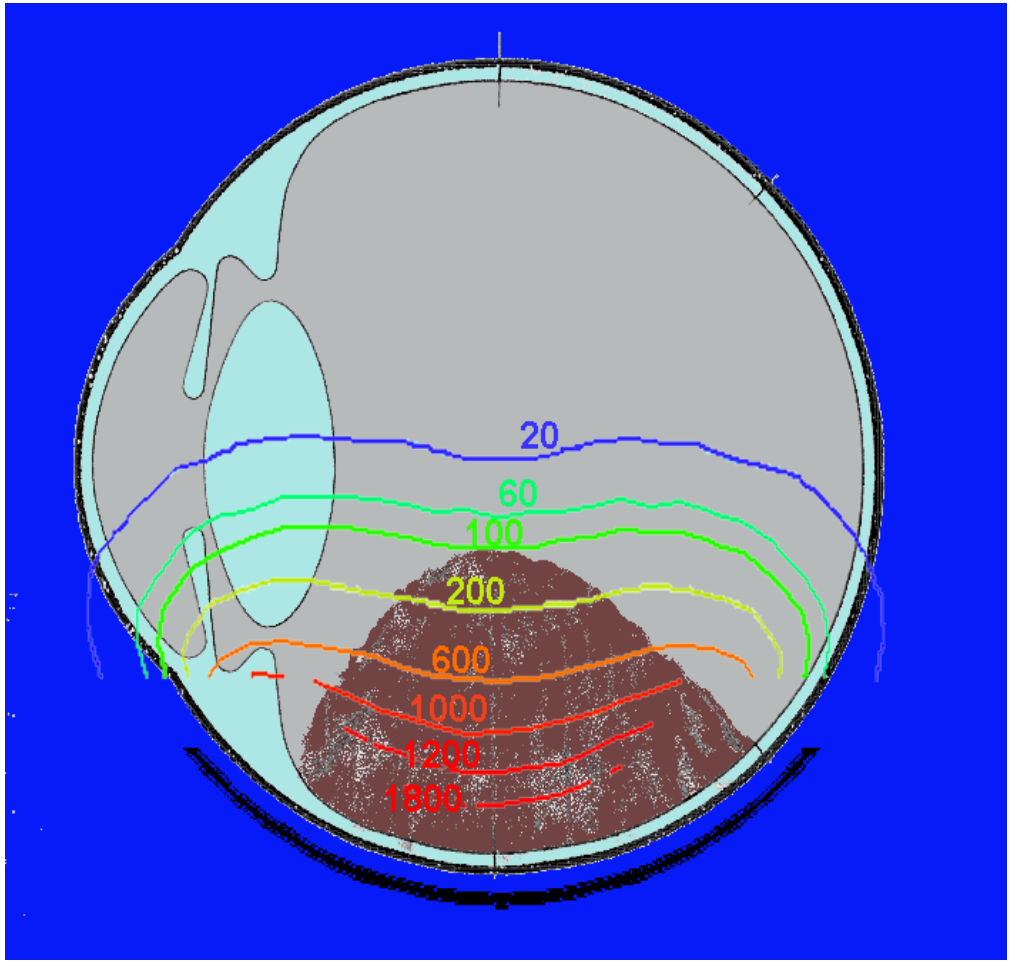
apex: 100 Gy

base: 2200 Gy

sclera

opposite:

1Gy



Dose distribution of a ^{125}I-plaque

tumor: 8 mm

dose:

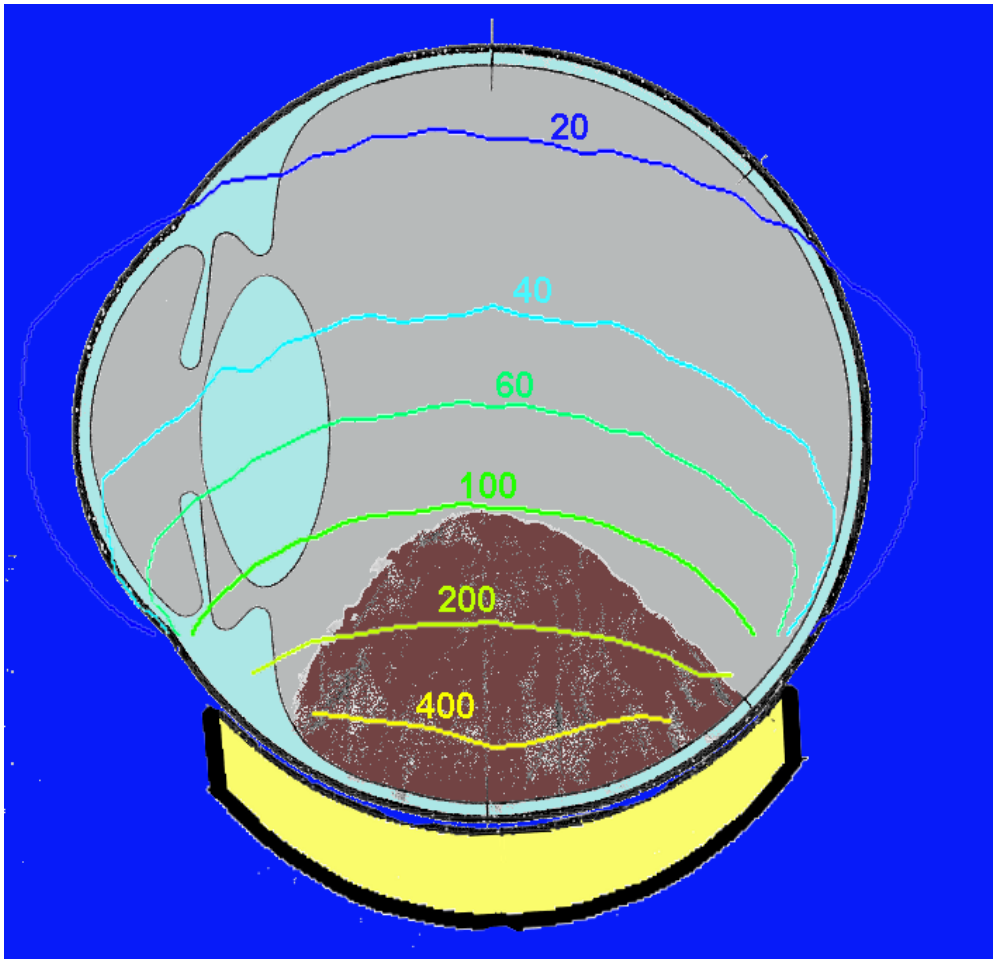
apex: 100 Gy

base : 440 Gy

sclera

opposite:

15 Gy



Dose distribution of a bi-nuclide plaque

tumor: 8 mm

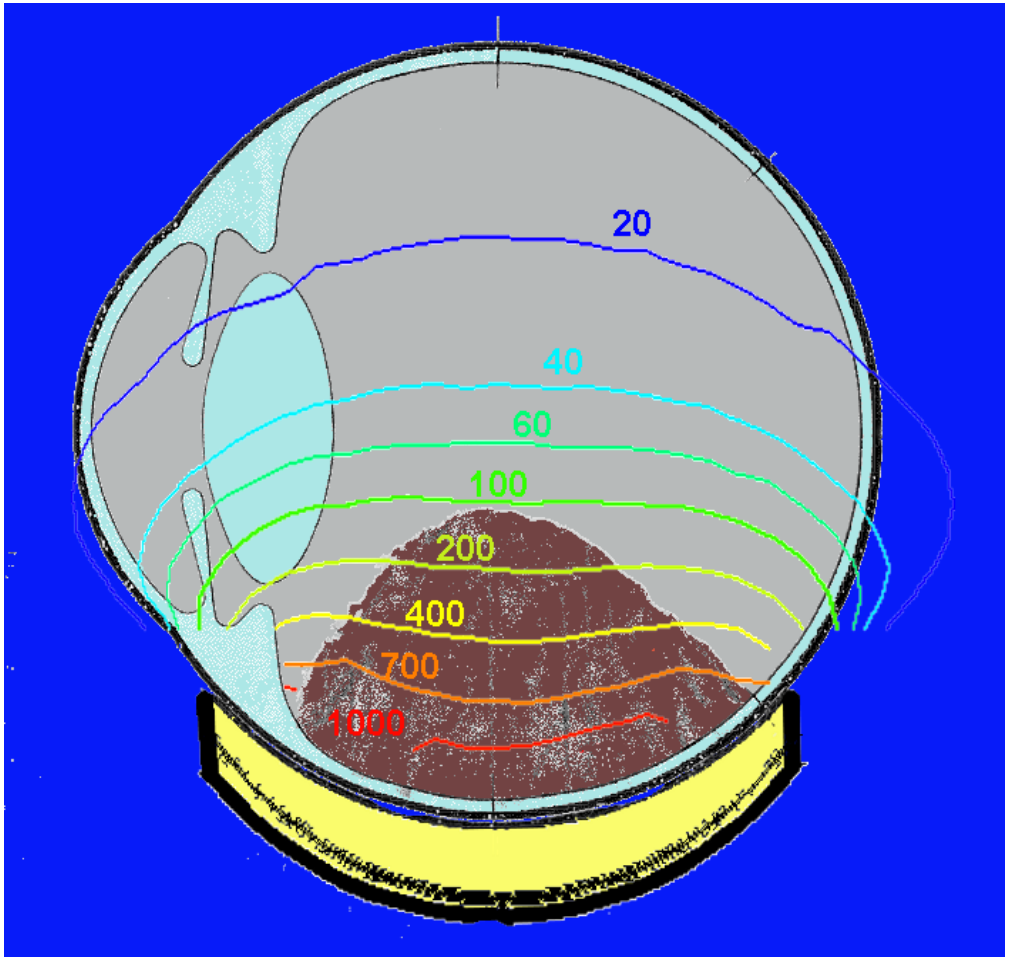
dose:

apex: 100 Gy

base 1200 Gy

sclera

opposite:
9 Gy



I-125 / Ru-106 bi-nuclide-plaque

Advantages as compared to a ^{125}I-plaque

> contact dose

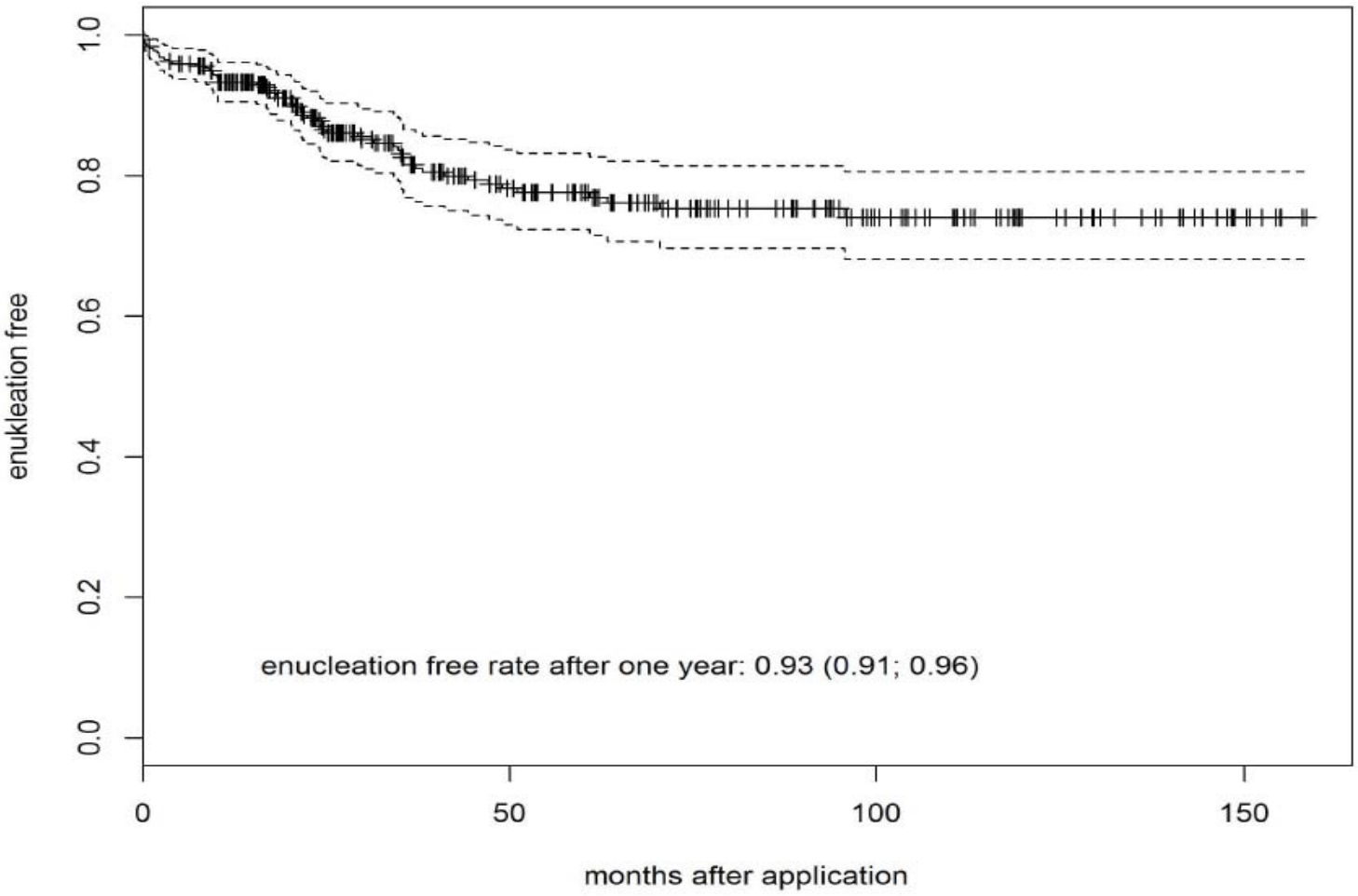
< integral dose

> dose to the tumor

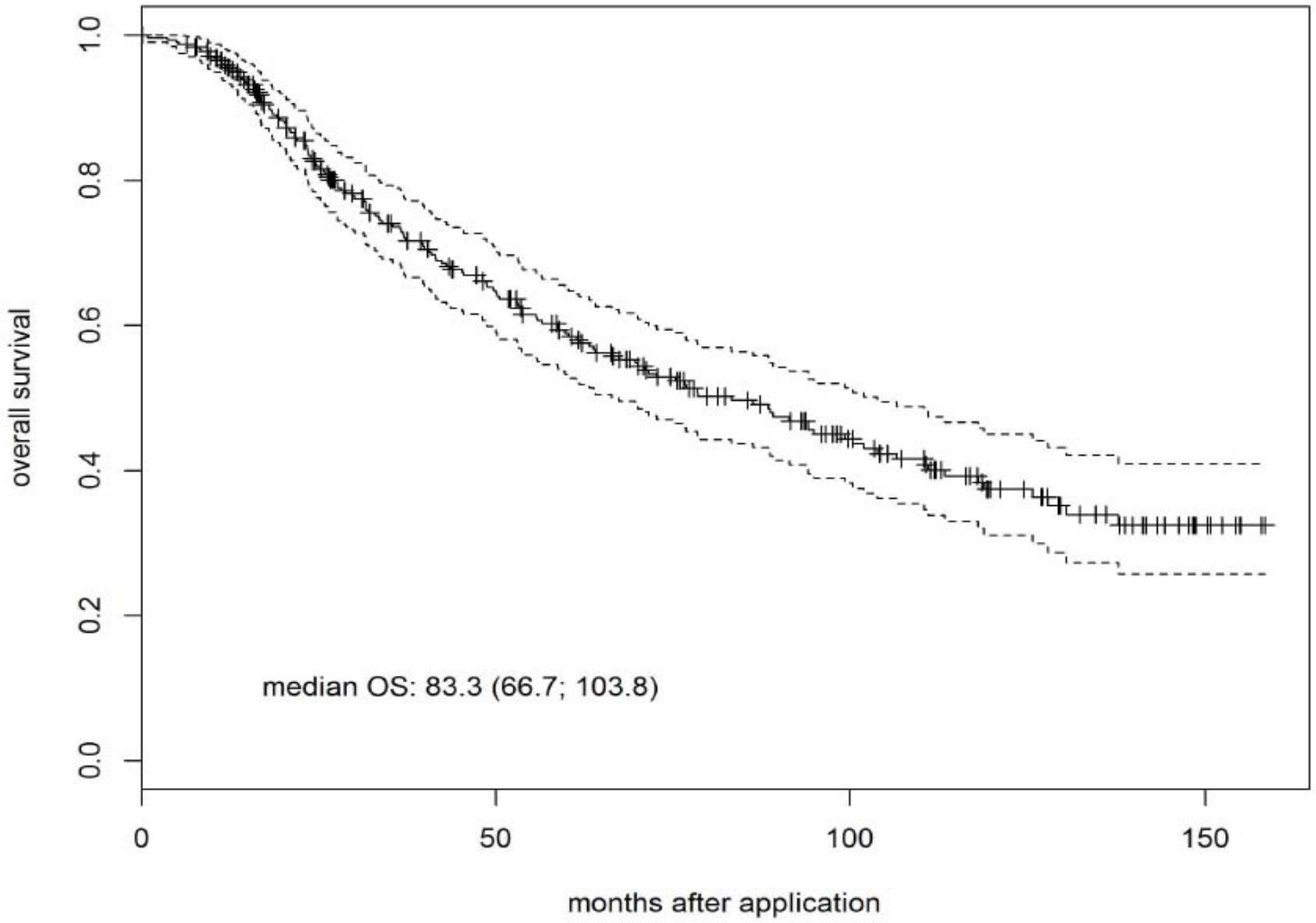
< dose to structures at risk

For tumors with height 7 – 11 mm

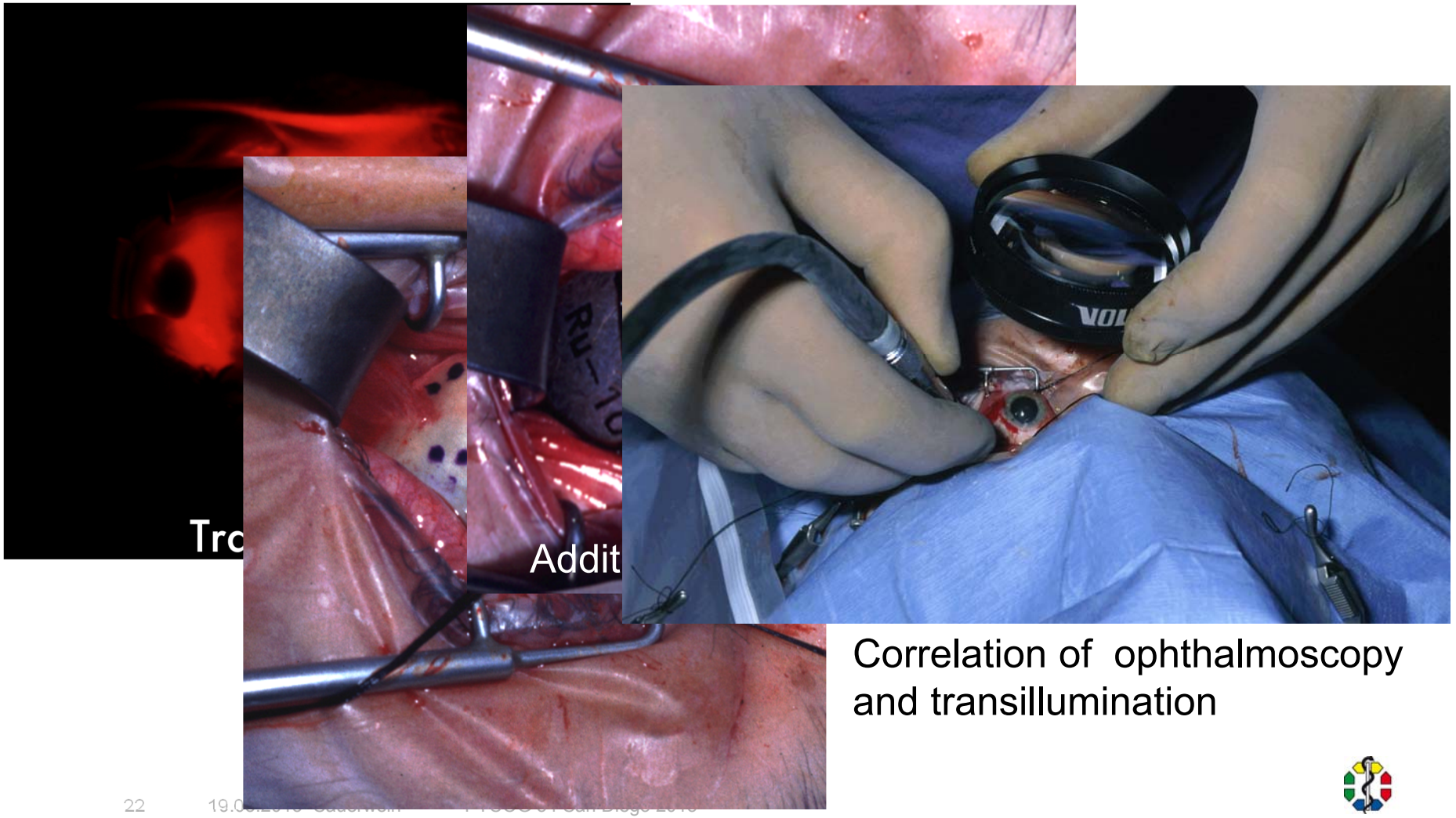
I-125 / Ru-106 bi-nuclide-plaque: Enucleation rate



I-125 / Ru-106 bi-nuclide-plaque: survival

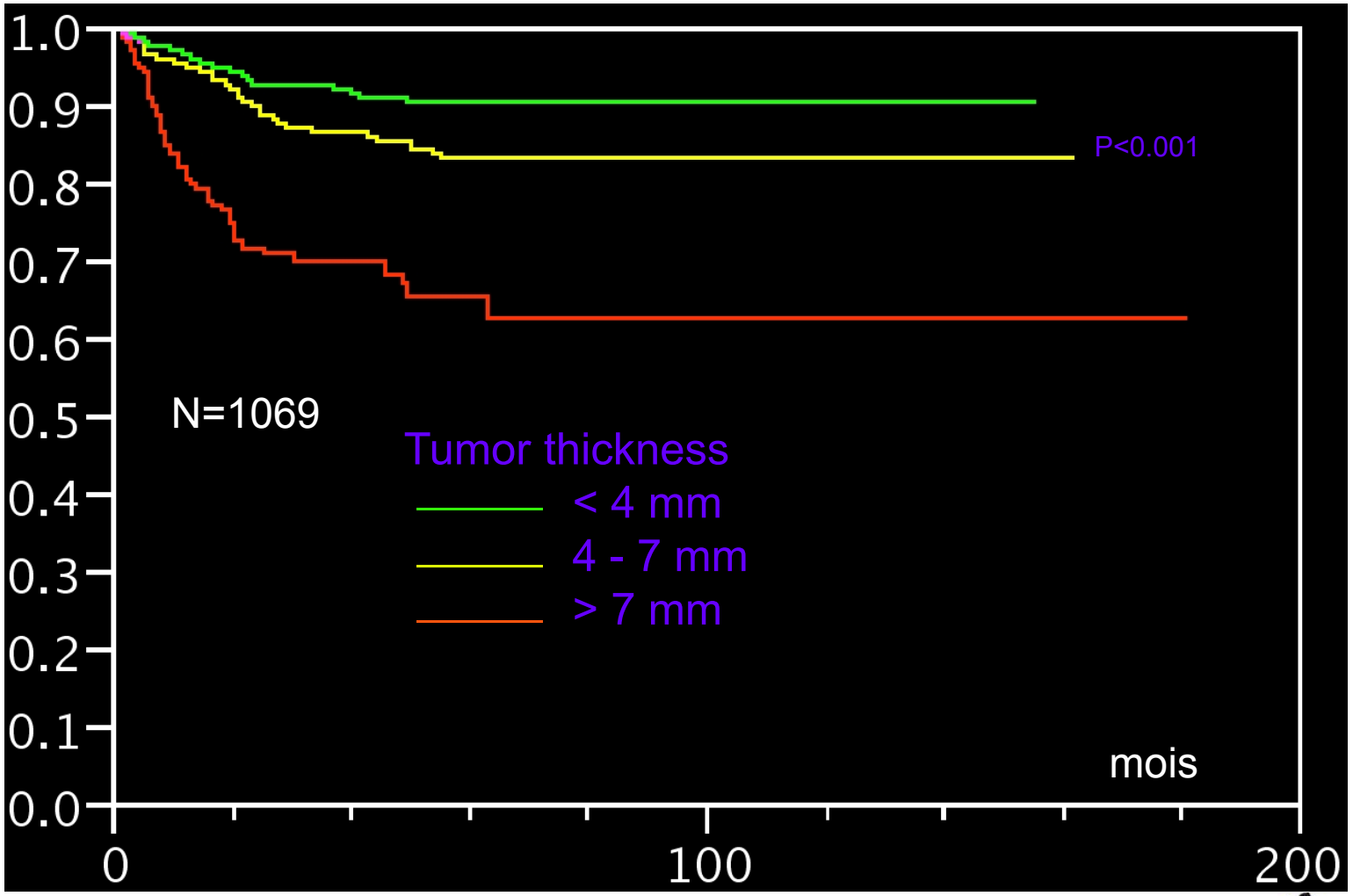


Surgical technique

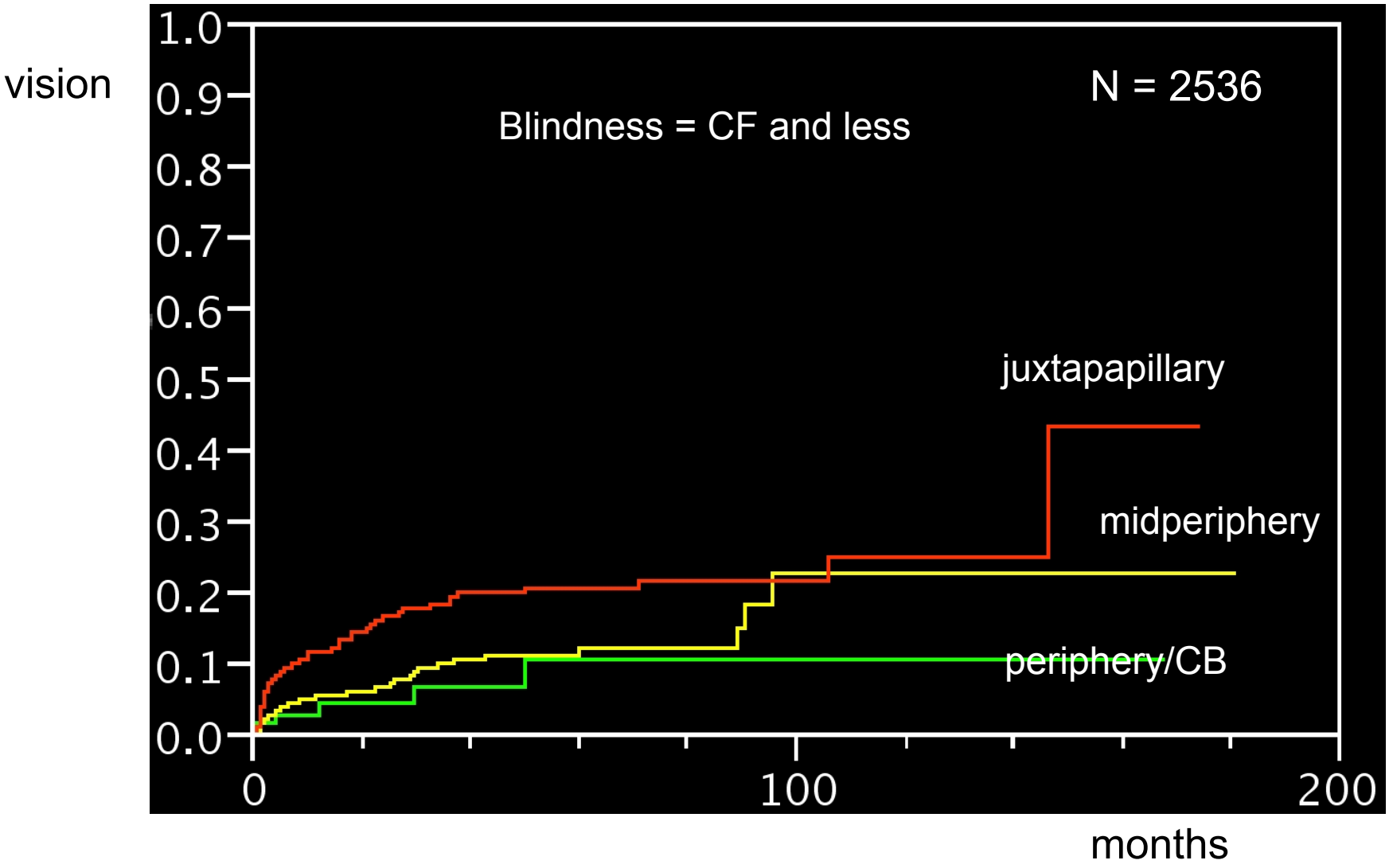


Correlation of ophthalmoscopy and transillumination

Local recurrences after Ru-106



Visual acuity after after Ru-106



Visual acuity after I-125

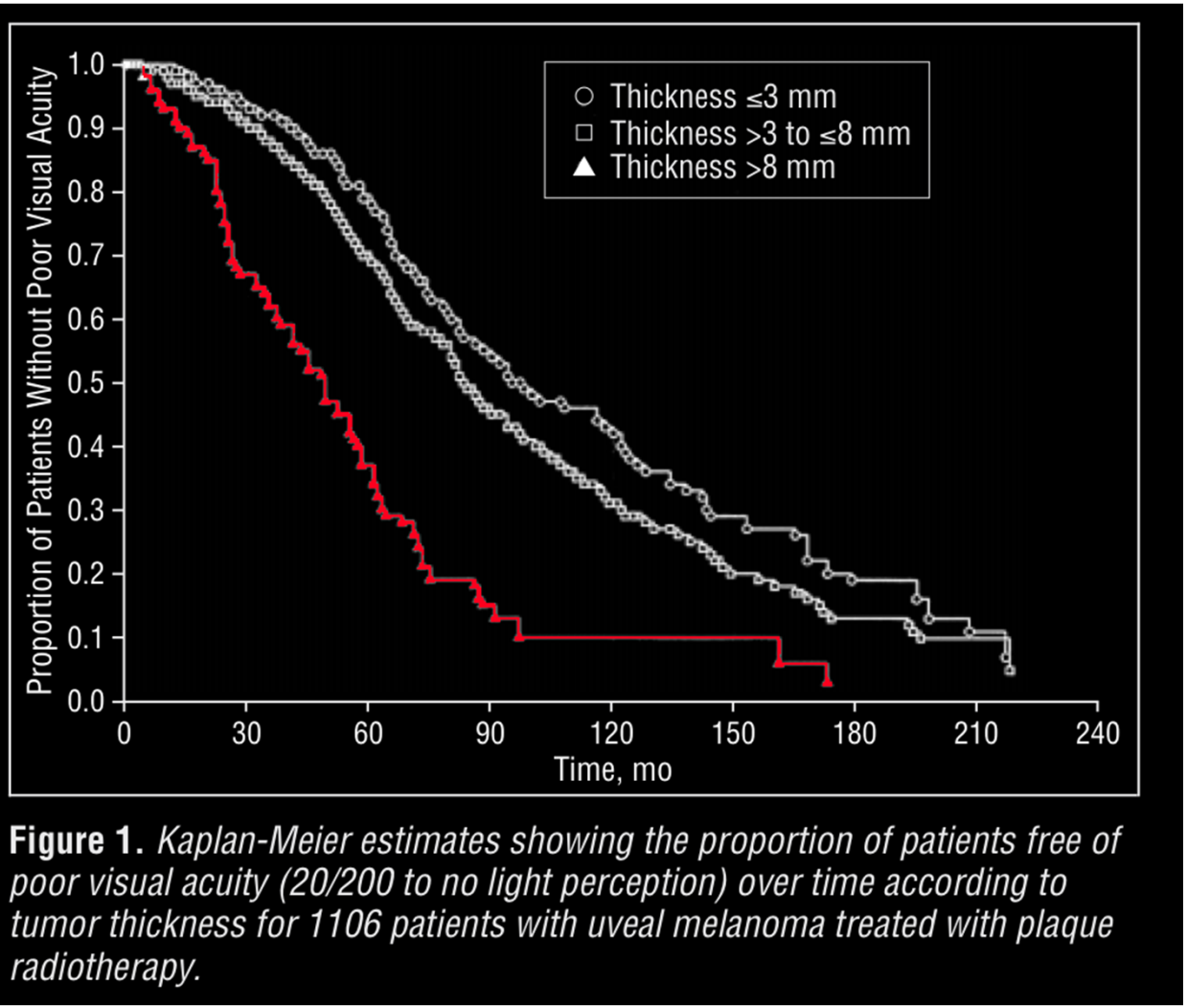
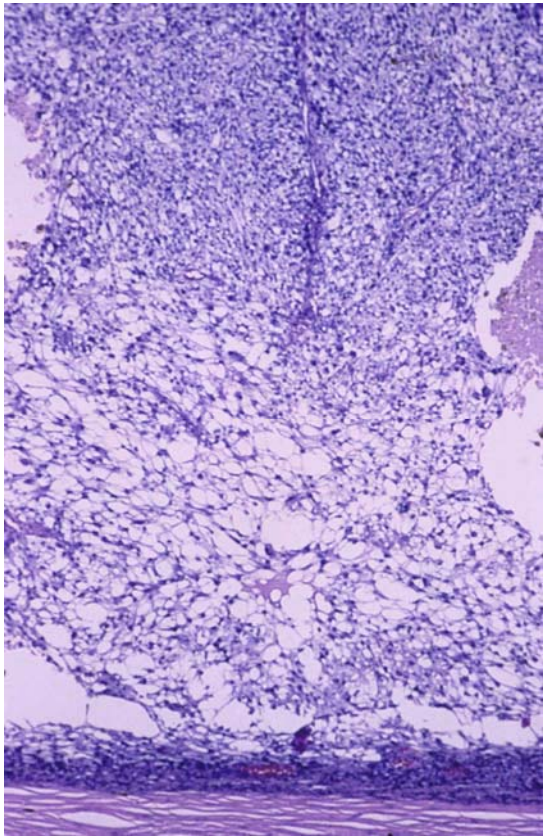


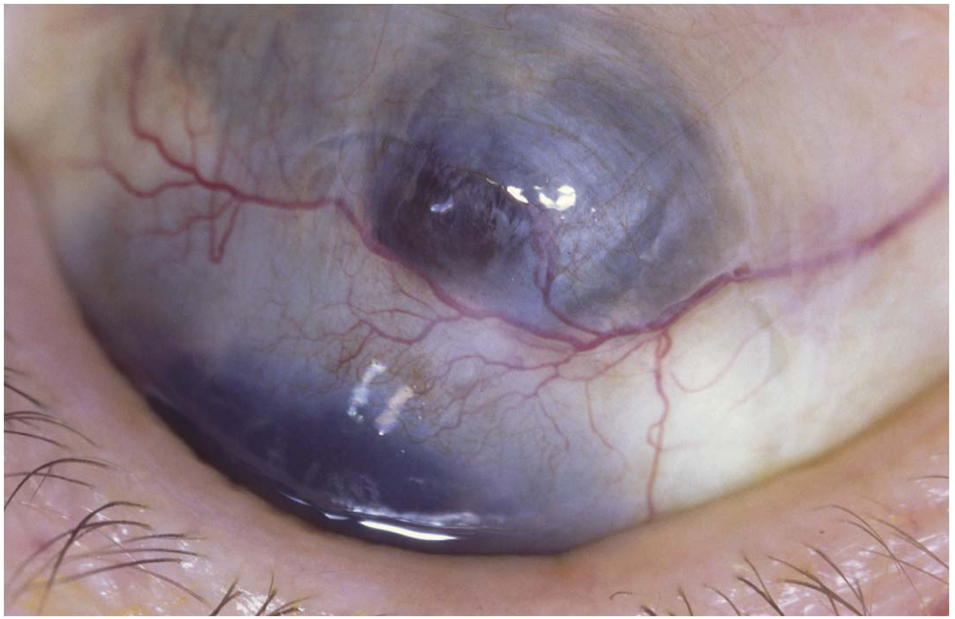
Figure 1. *Kaplan-Meier estimates showing the proportion of patients free of poor visual acuity (20/200 to no light perception) over time according to tumor thickness for 1106 patients with uveal melanoma treated with plaque radiotherapy.*

Shields et al. 2000

Ru-106: limits



incomplete destruction



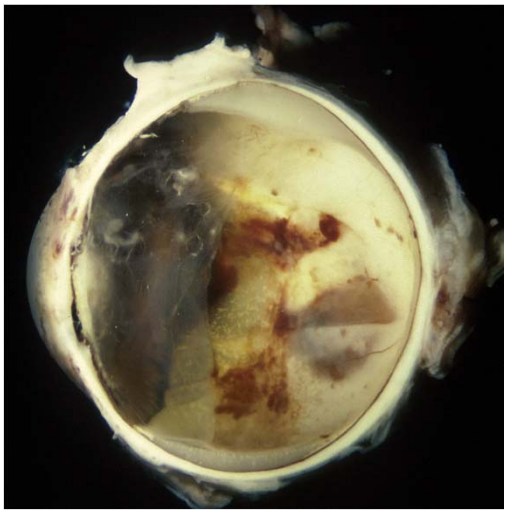
scleral necrosis

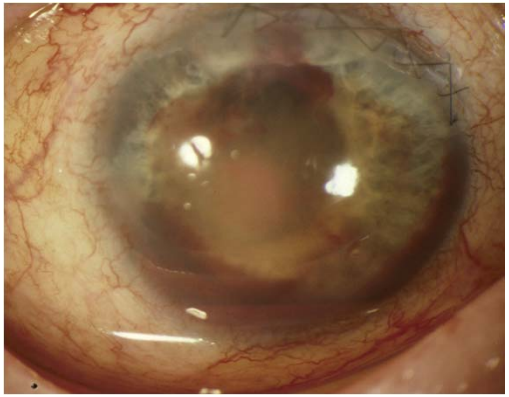
Tumor height

I-125: limits

Complications

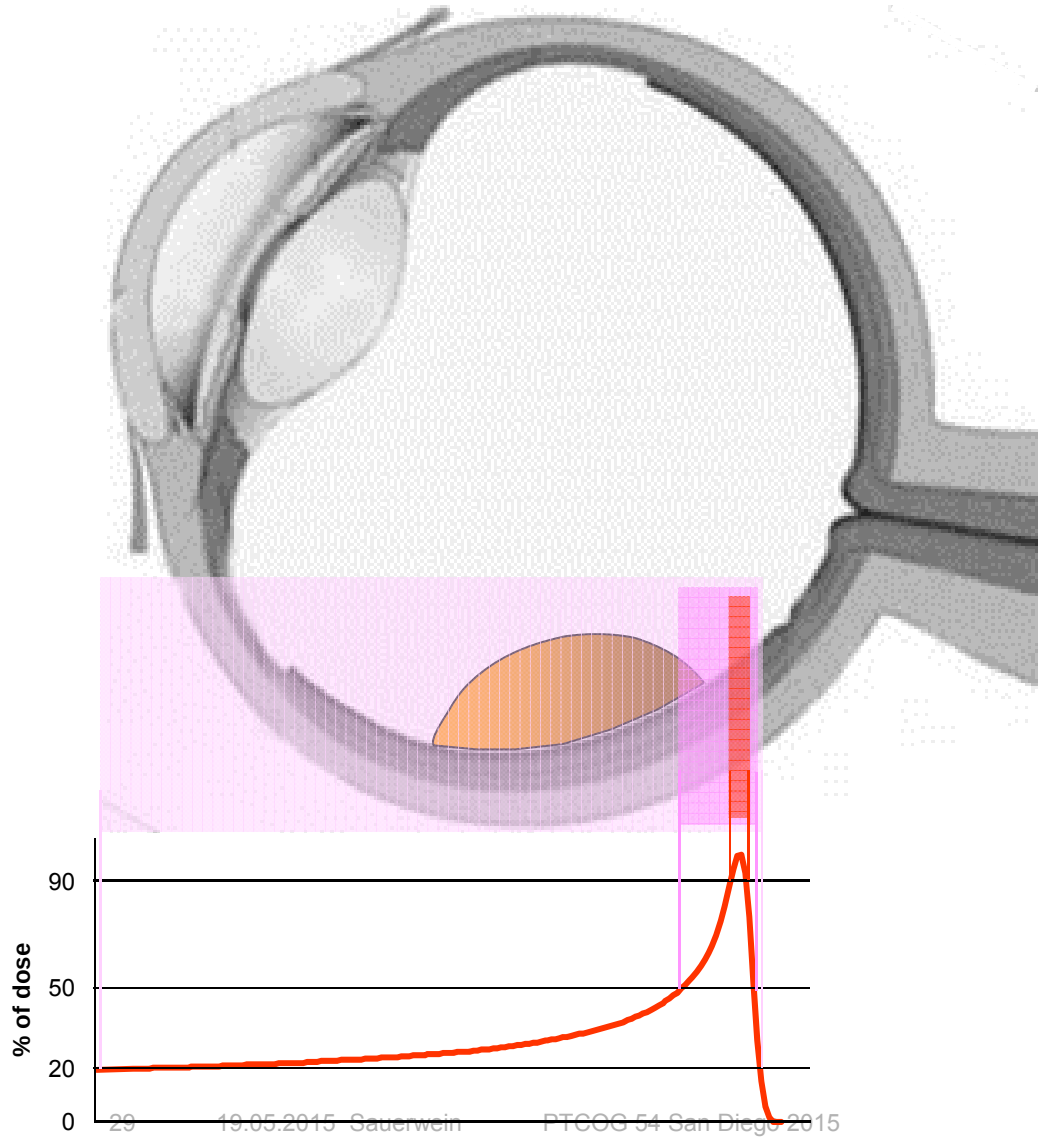
- Long standing exsudative retinal detachment
- Radiation cataract
- Radiation induced optic neuropathy
- Radiation retinopathy, ocular ischemia, neovascular glaucoma





Proton treatment of ocular tumors

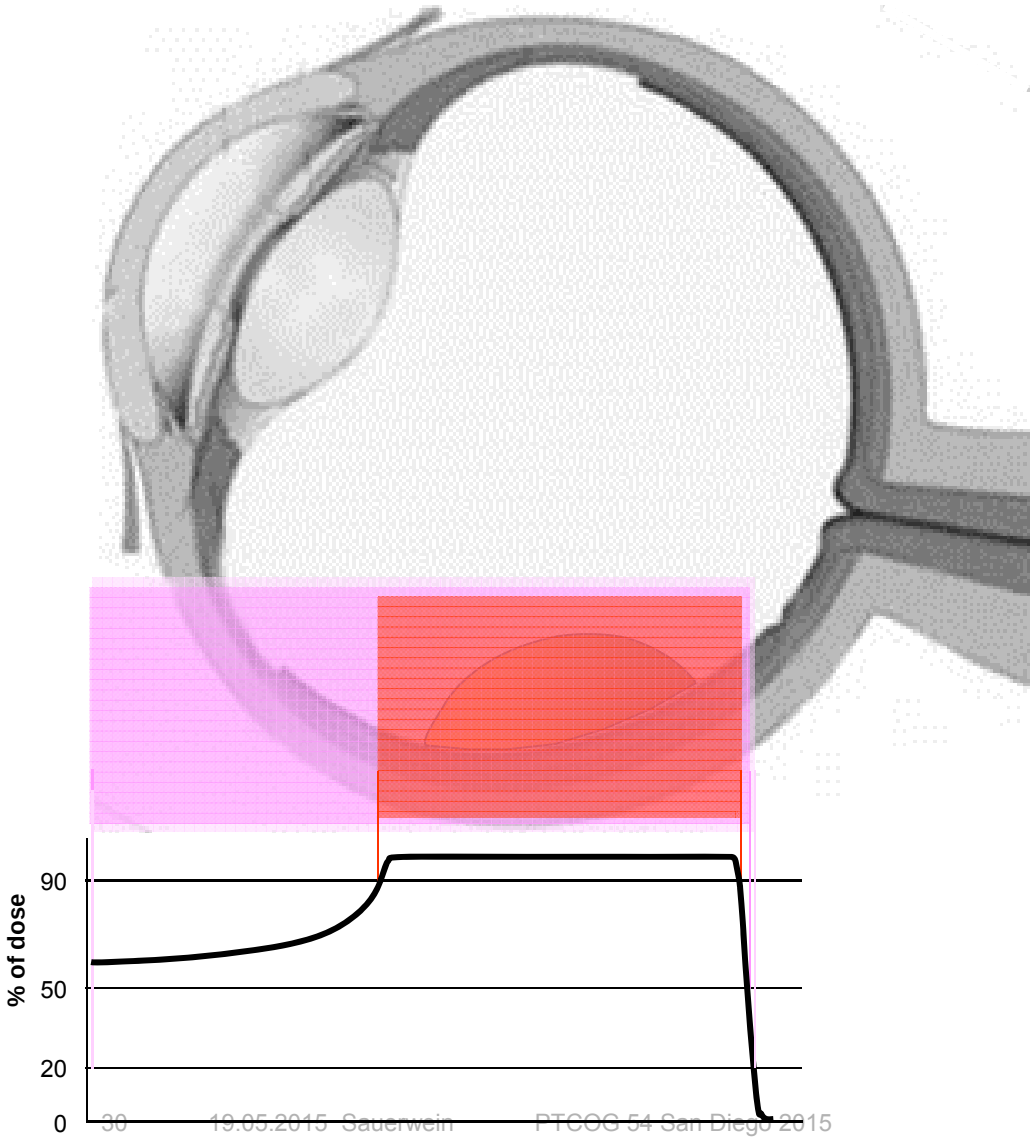
Depth dose distribution



Dose distribution in the Bragg peak:

not convenient to treat a tumor.
The peak needs to be enlarged, (or spread-out, or modulated)

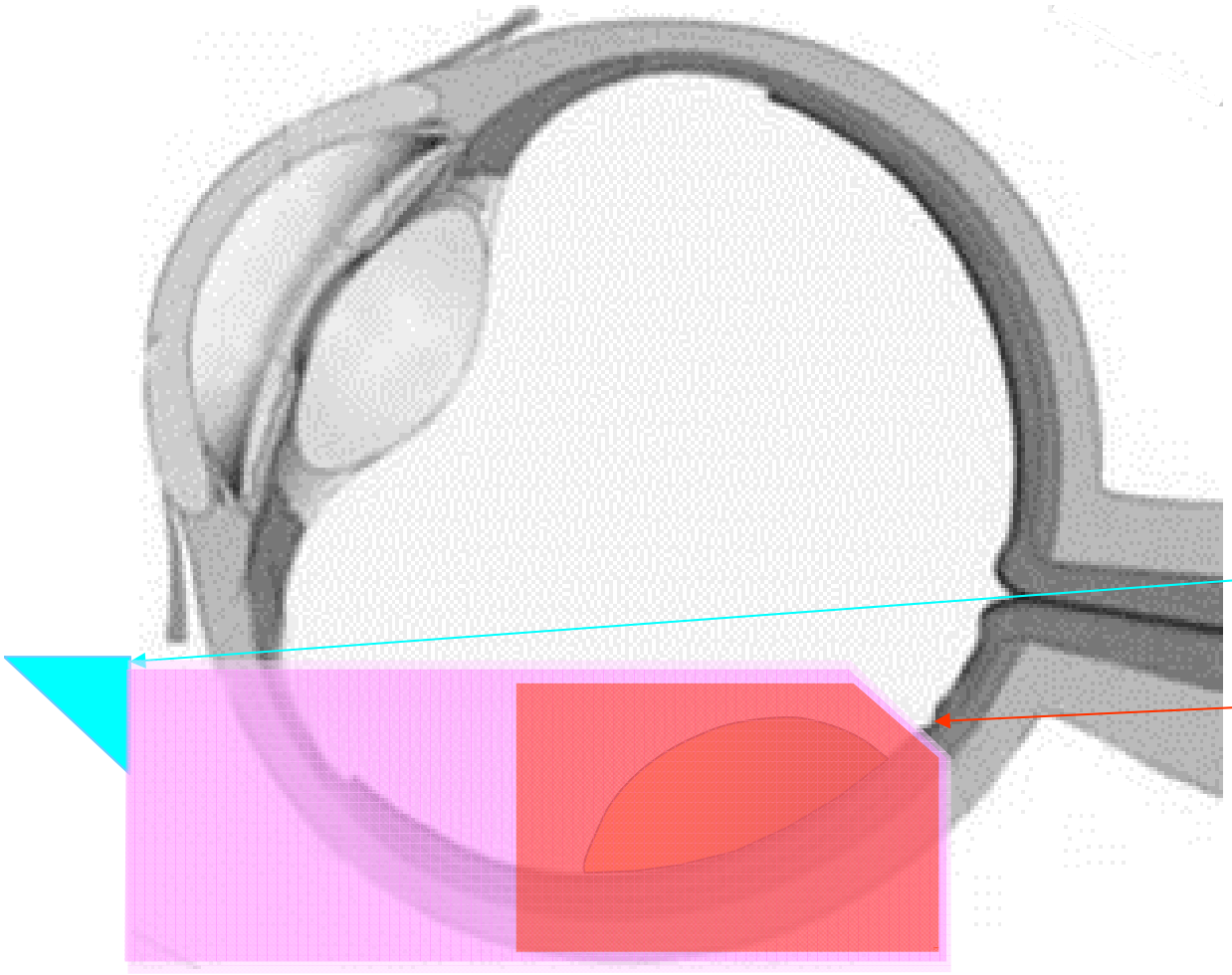
Depth dose distribution



Dose distribution in the spread-out Bragg peak:

now suitable to treat a tumor with safety margins

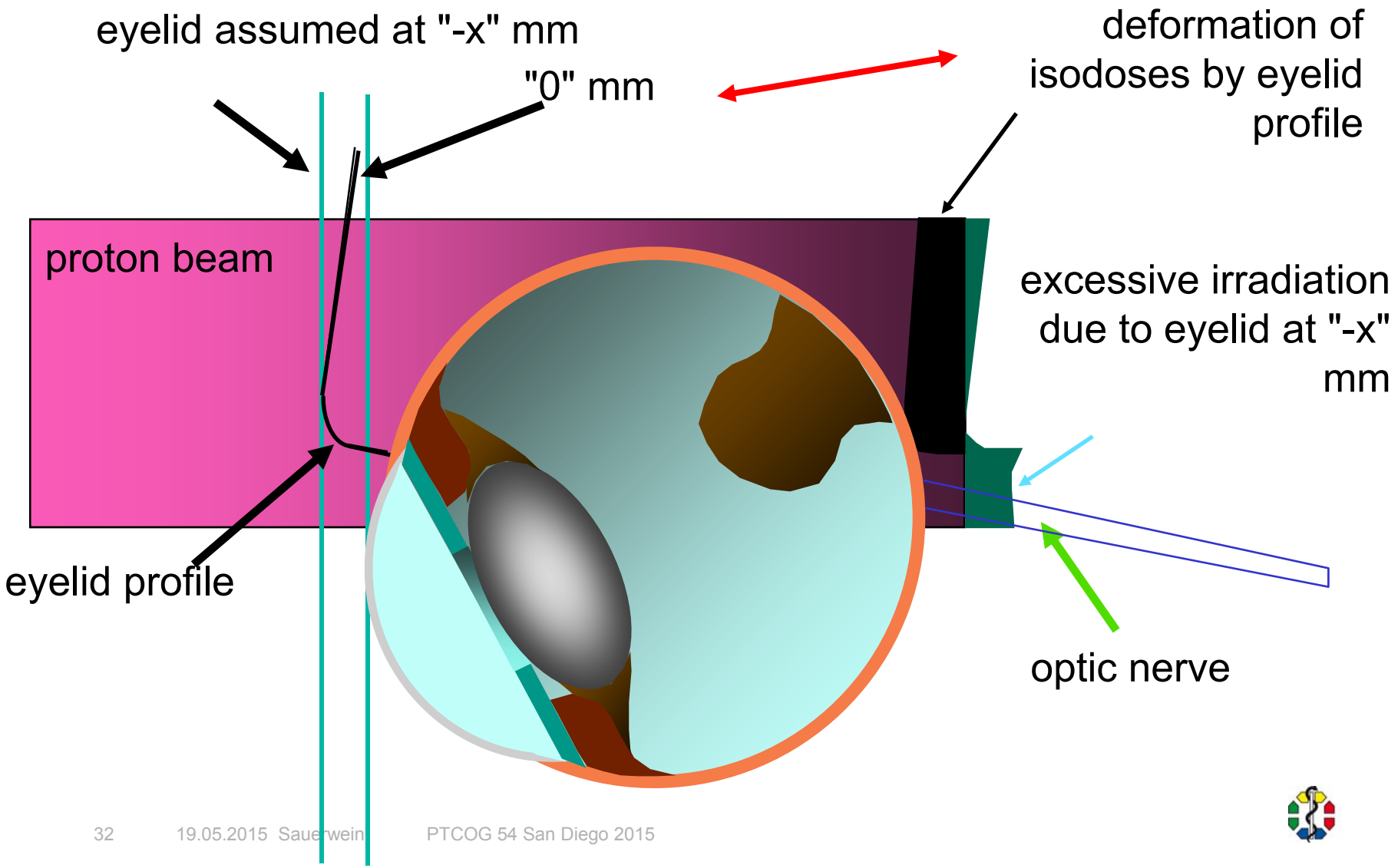
Wedge filter



The dose distribution can be optimized by a wedge filter

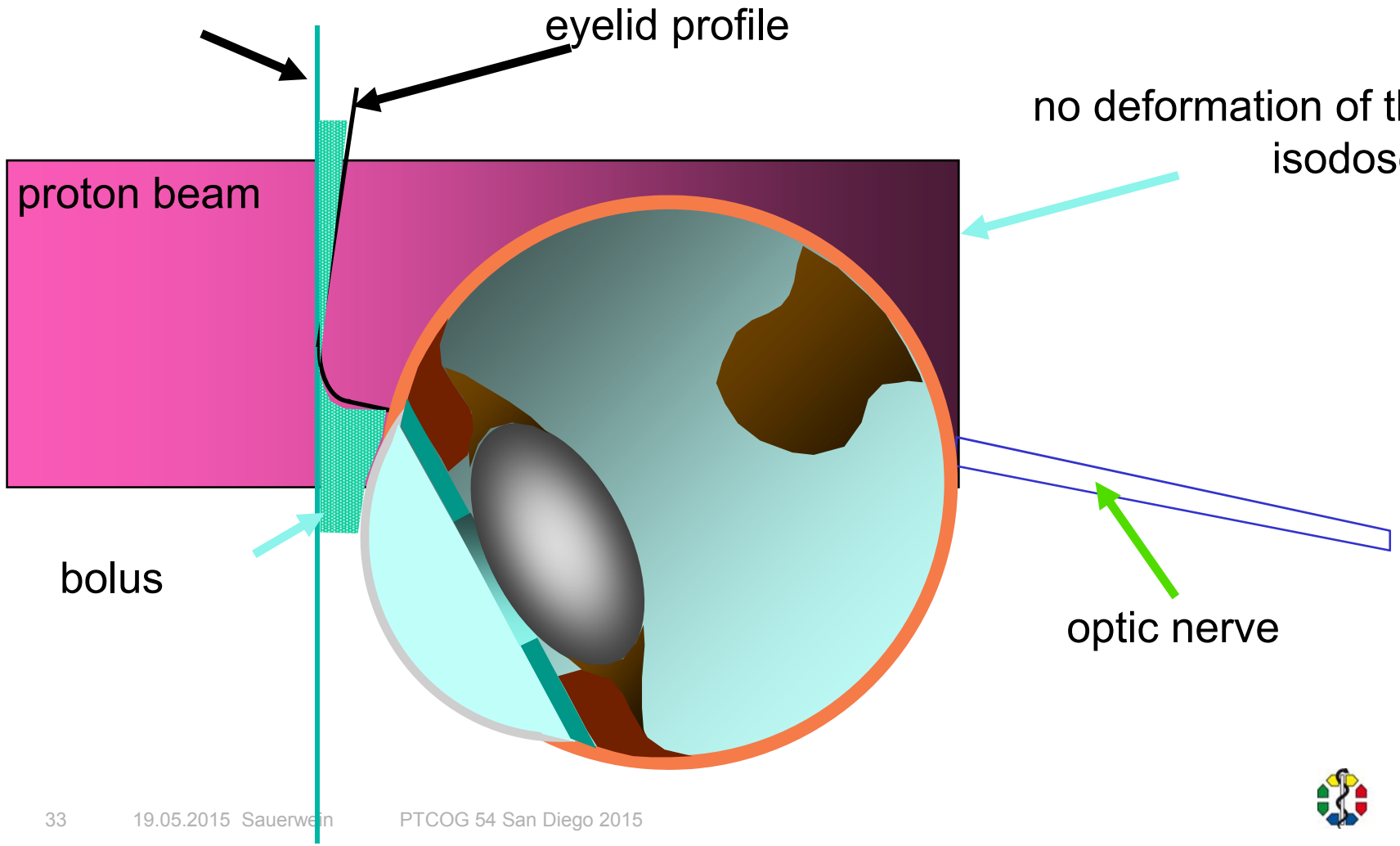
sparing the macula while maintaining a sufficient safety margin

Bolus

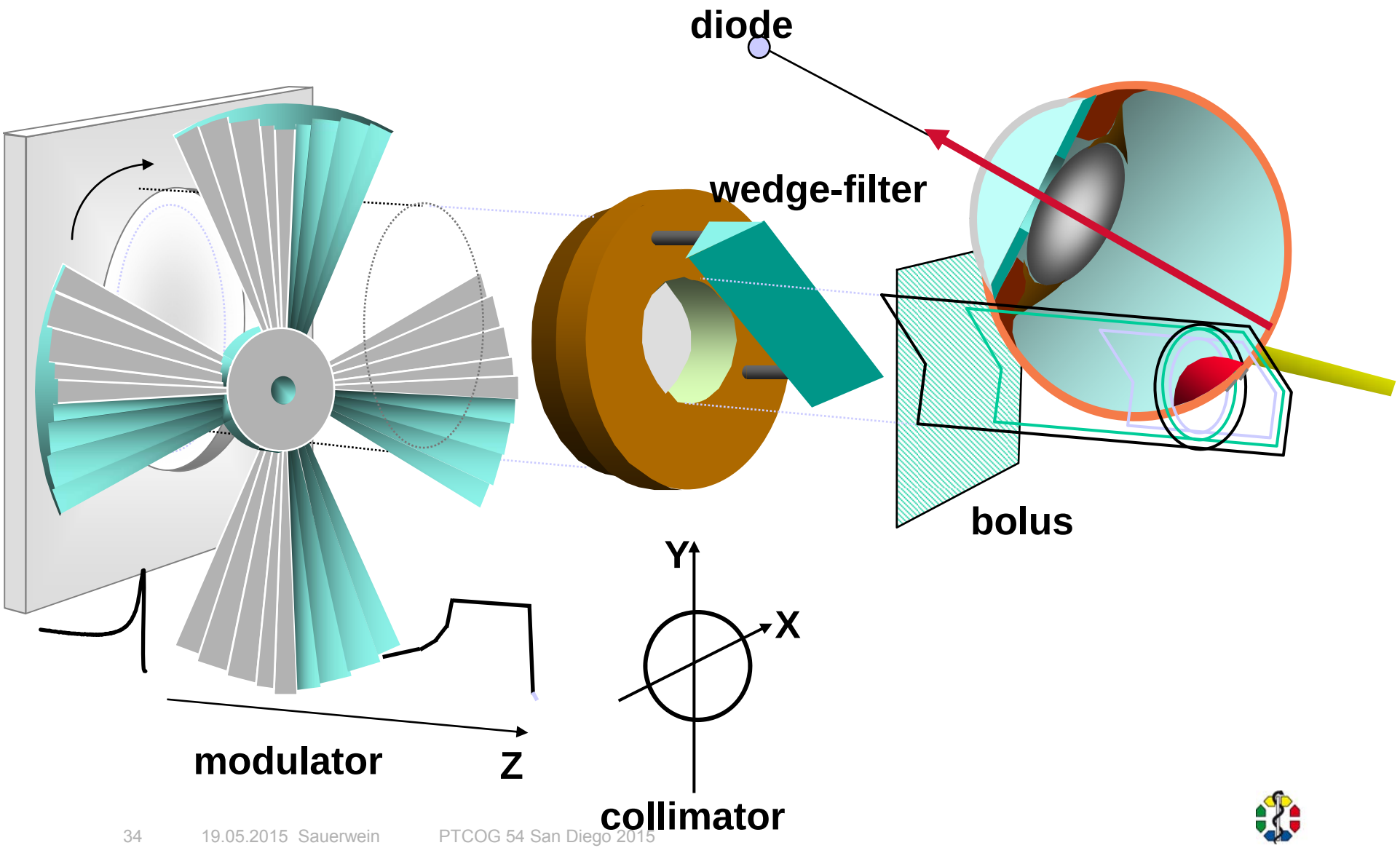

eyelid assumed at "-x" mm
"0" mm
deformation of isodoses by eyelid profile
proton beam
excessive irradiation due to eyelid at "-x" mm
eyelid profile
optic nerve

Bolus

eyelid assumed at – ”x" mm



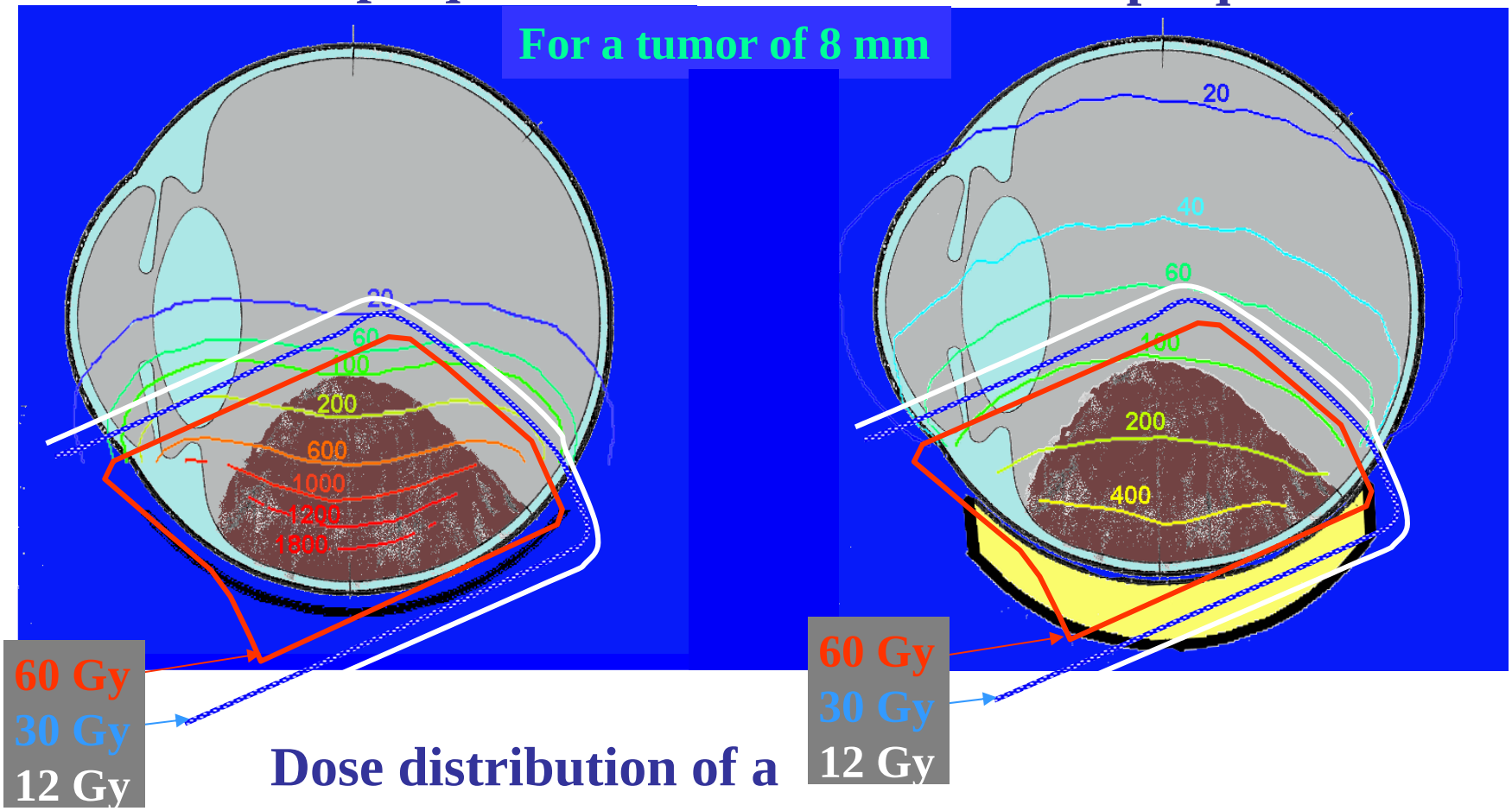
3D Conformation of the proton beam



dose distributions

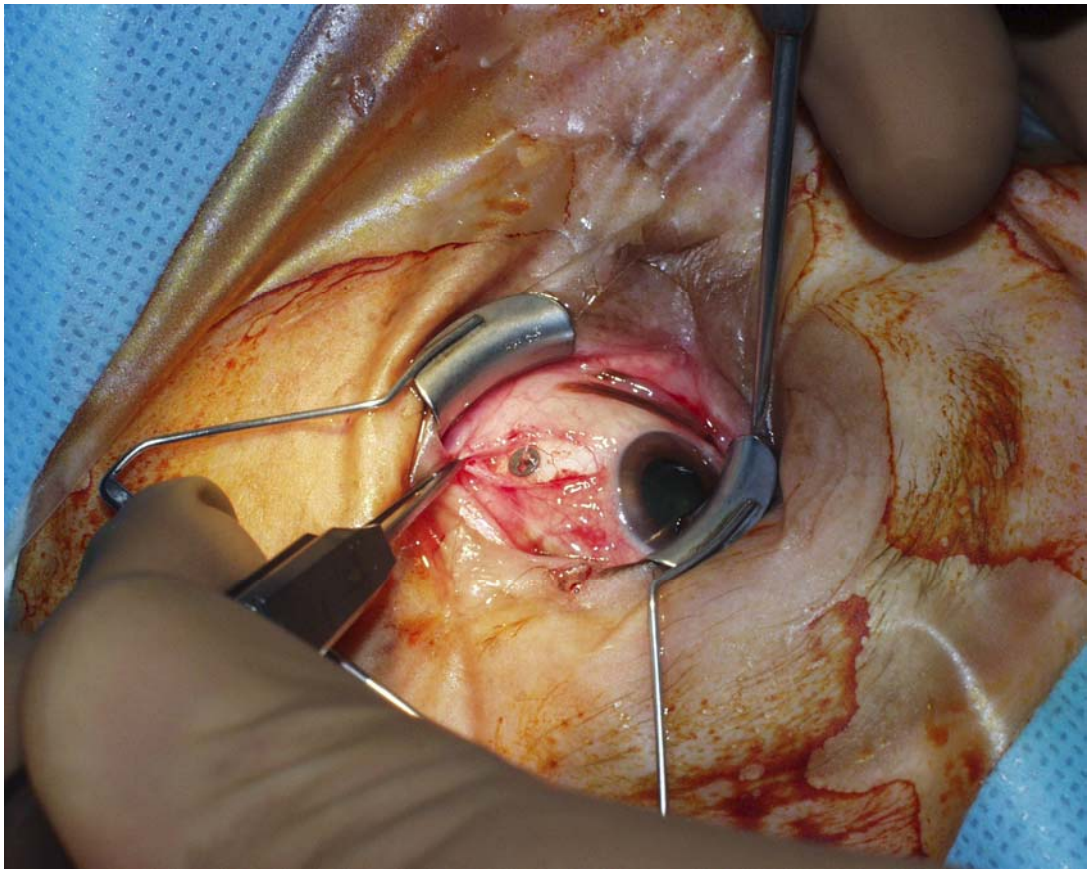
Dose distribution of a ^{106}Ru plaque

Dose distribution of a ^{125}I plaque



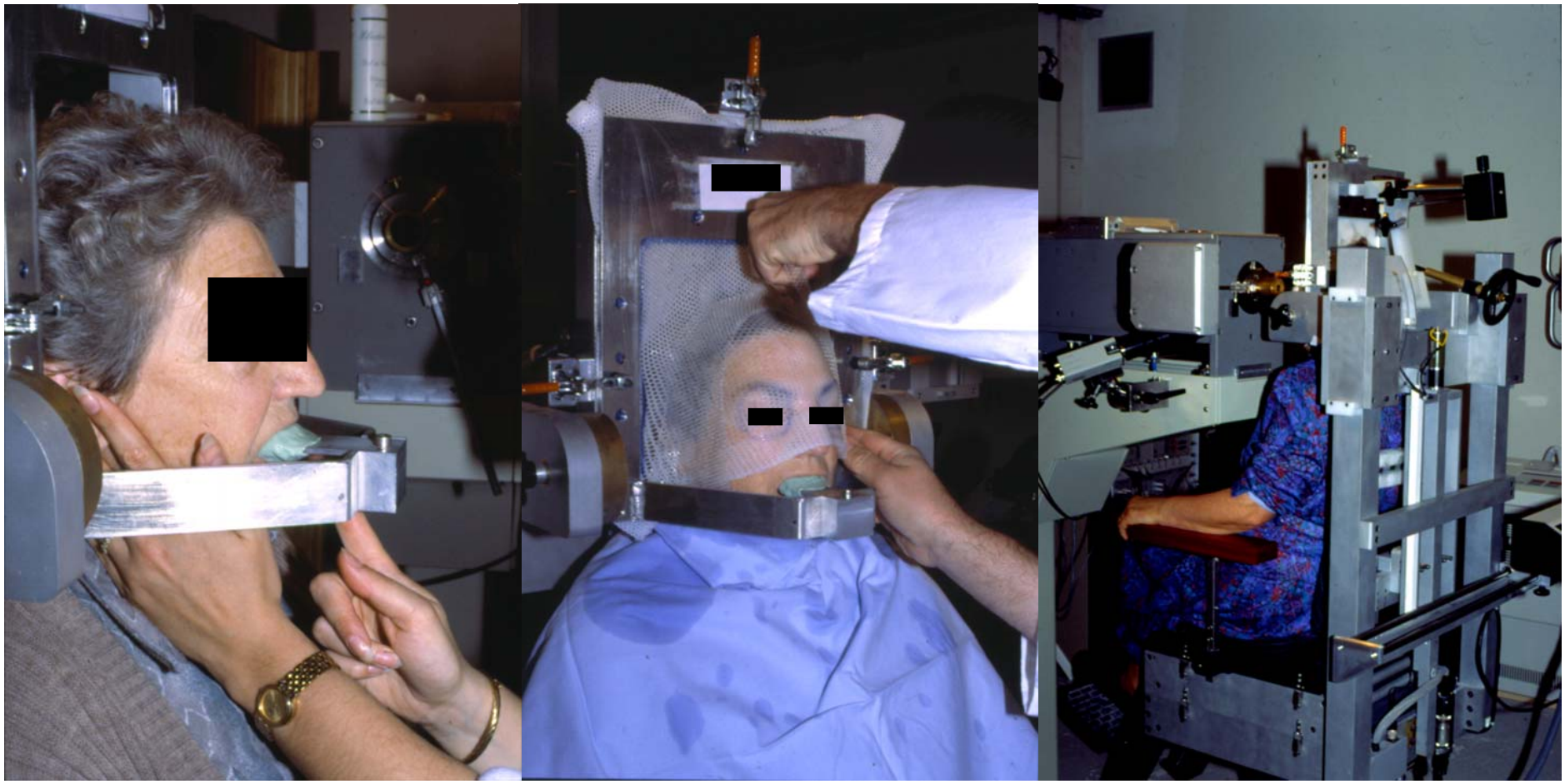
Dose distribution of a proton beam

Preparation of the patient: positioning of markers



CT scan after clipping always included

Positioning devices for the patient

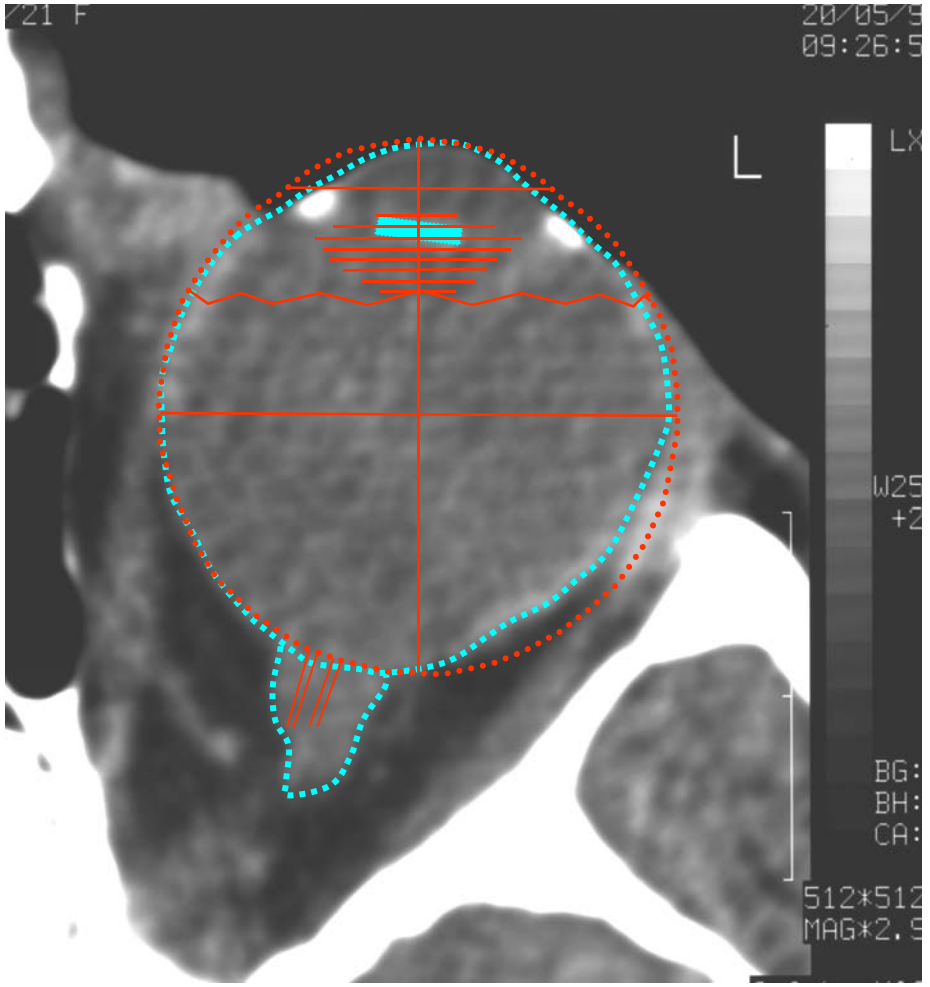


Challenge for treatment planning:

Does the model represent the reality ?

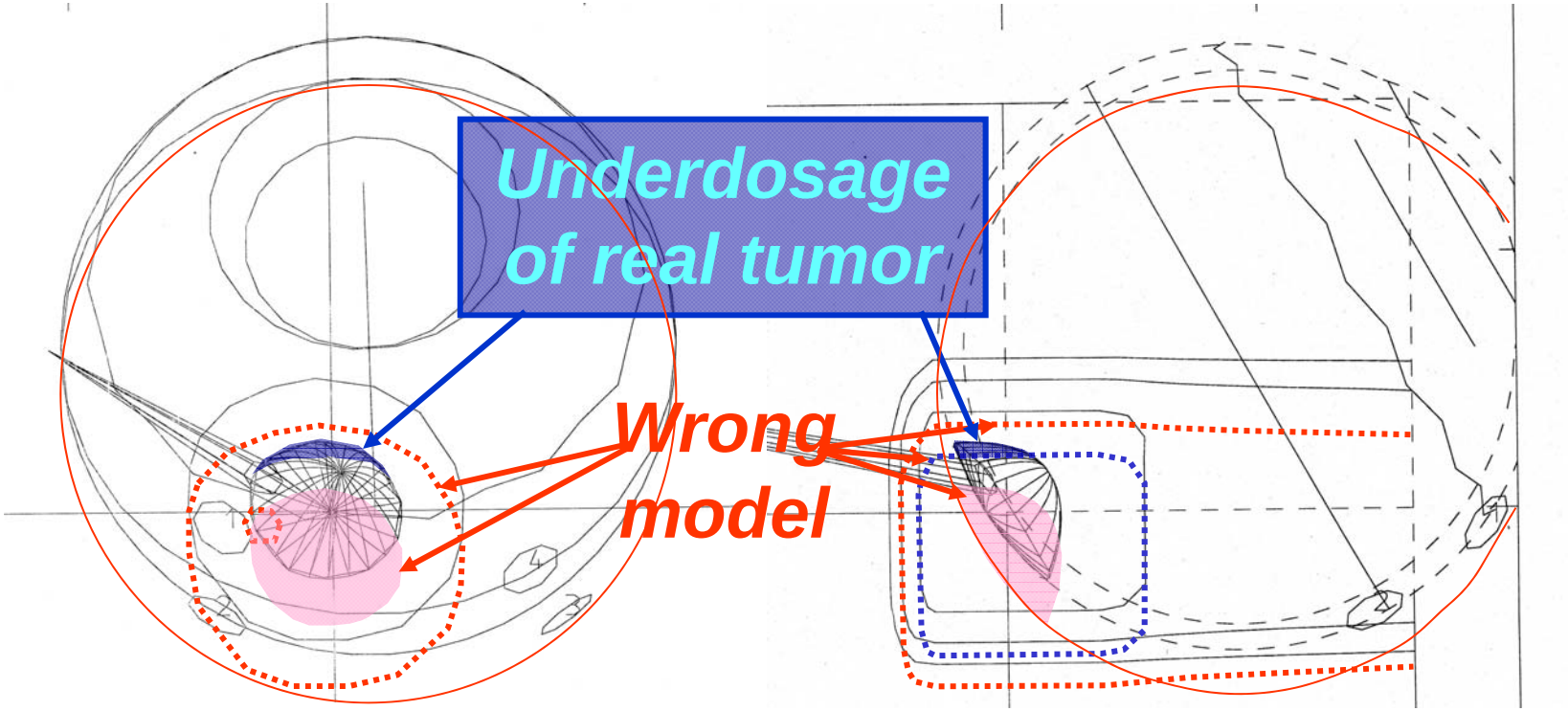
All the calculations made on a relatively simple mathematical model of the eye.

The anatomy may differ from the model. To be accurate, the validity of the model has to be checked by CT and the model to be modified if necessary.

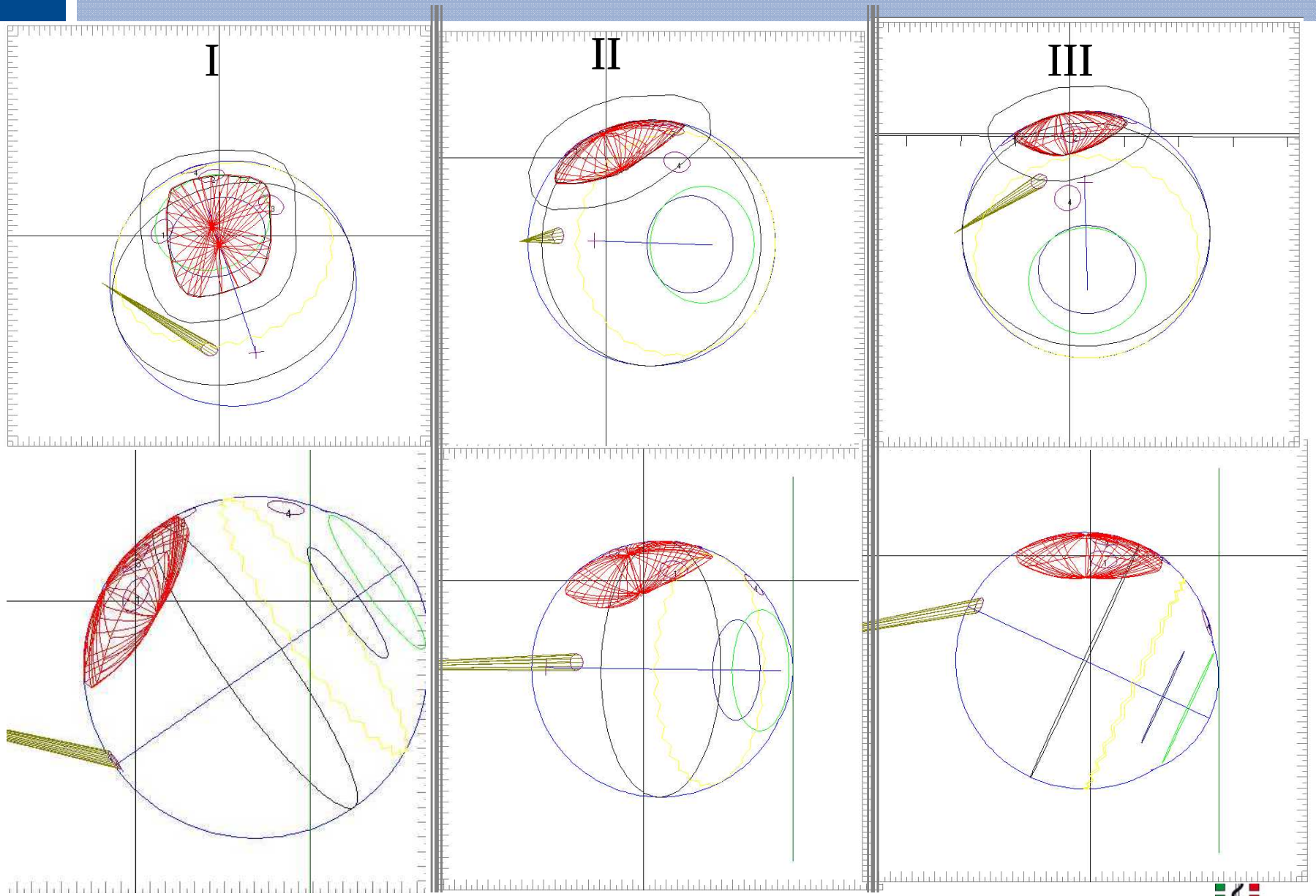


CT-scan

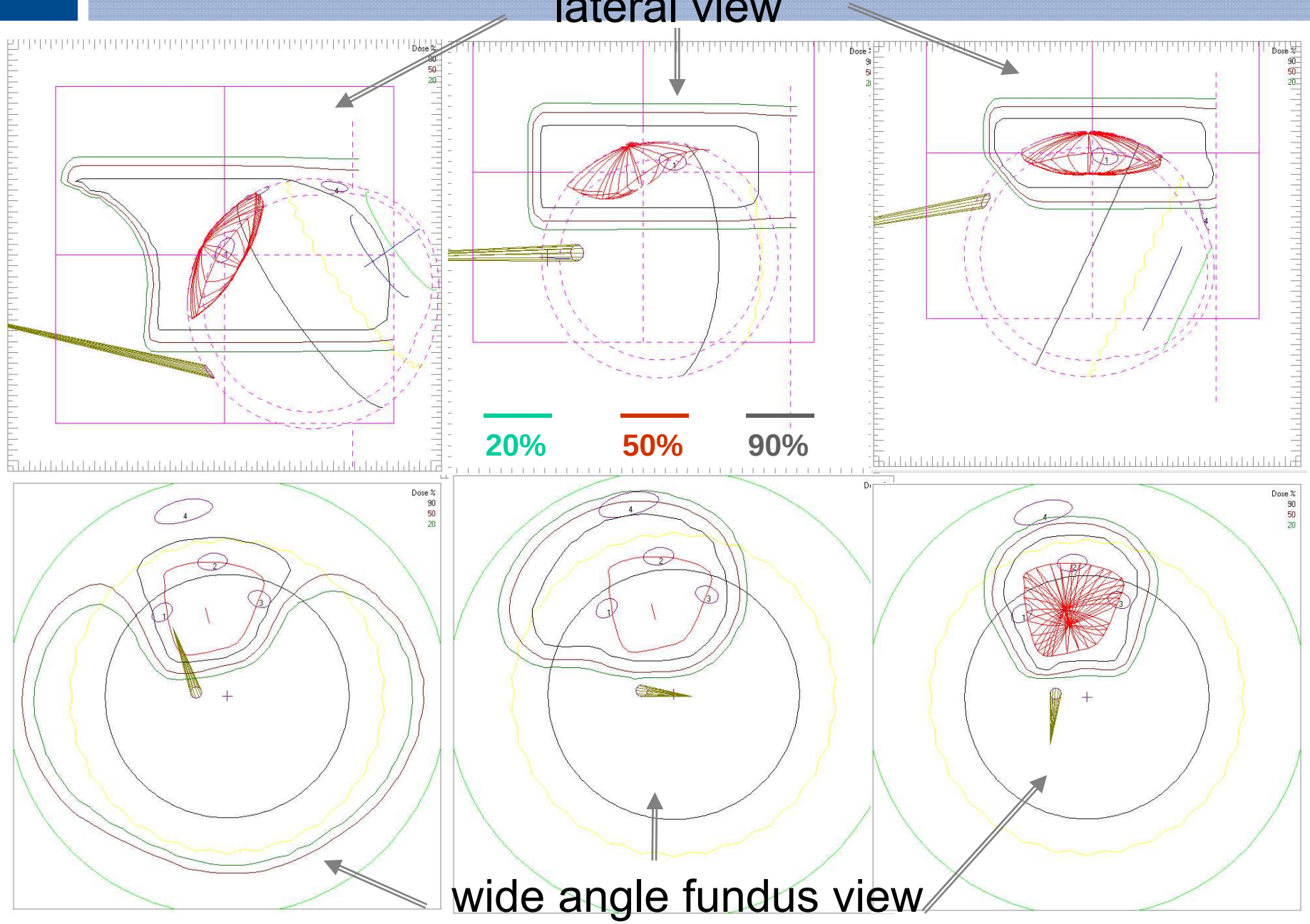
If the model is not accurate, you will not hit the target

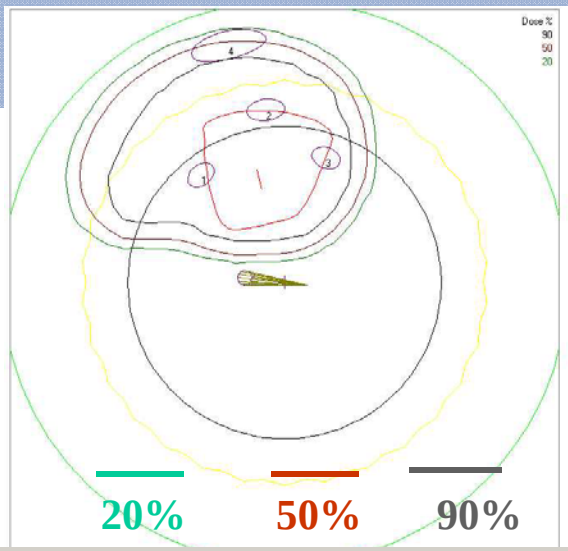


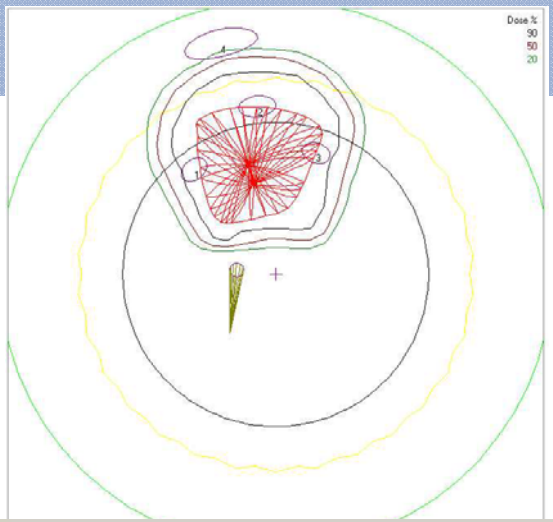
Positioning: same tumor, 3 different positions



Dose distributions for the three different positions







	20%	50%	90%	
Retina	32	27	22	% are
Surface Of The Globe	40	35	13	% are
Volume Of The Globe	3.9	3.4	2.2	cc
Lens Volume	100	100	75	% vol
Lens Periphery	100	100	37	%
Ciliary Body	95	88	11	% vol
Optic Disc	0	0	0	% are
Macula	0	0	0	% vol
Length Of Optic Nerve	0.1	0.0	0.0	mm
Surface Of The Tumor	100	100	100	% are
Upper Eyelid Rim				
Lower Eyelid Rim				

OK

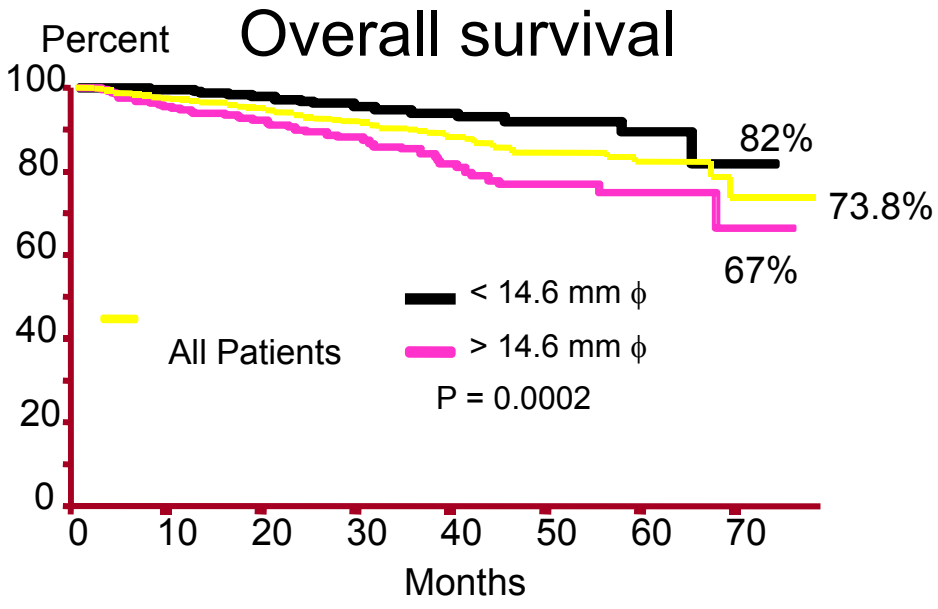
	20%	50%	90%	
Retina	29	26	22	% area
Surface Of The Globe	26	23	19	% area
Volume Of The Globe	1.4	1.2	0.9	cc
Lens Volume	0	0	0	% vol.
Lens Periphery	0	0	0	%
Ciliary Body	12	7	2	% vol.
Optic Disc	0	0	0	% area
Macula	0	0	0	% vol.
Length Of Optic Nerve	0.0	0.0	0.0	mm
Surface Of The Tumor	100	100	100	% area
Upper Eyelid Rim				
Lower Eyelid Rim				

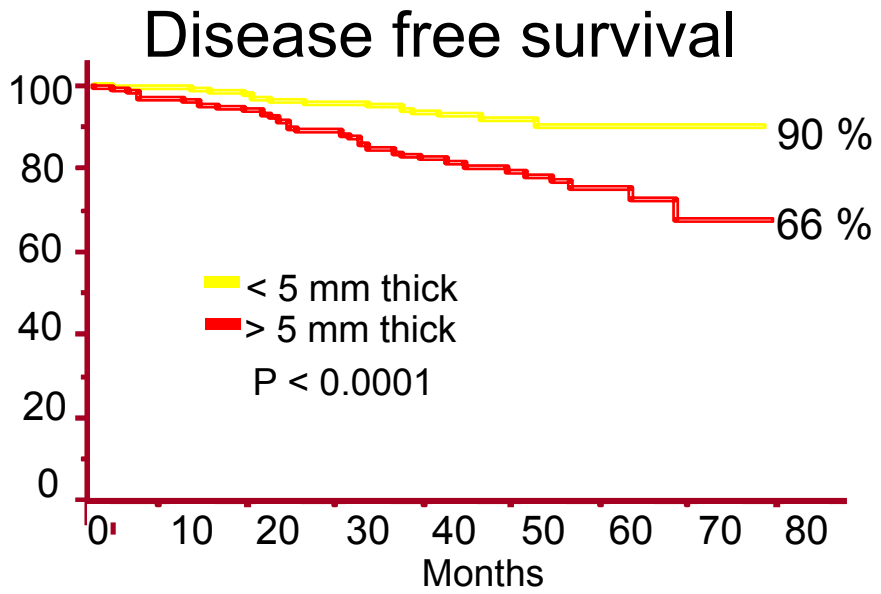
OK

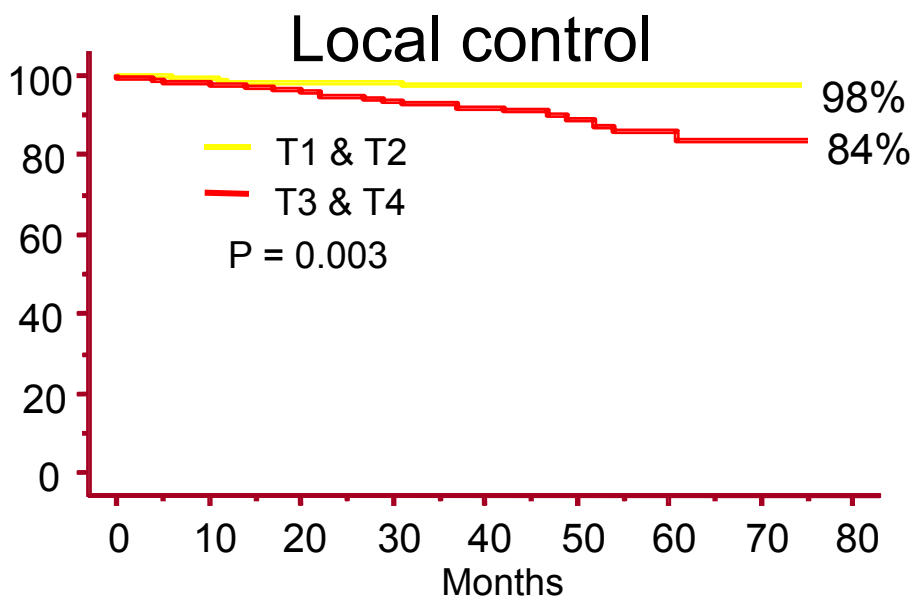
	20%	50%	90%	
Retina	25	22	18	% area
Surface Of The Globe	19	17	14	% area
Volume Of The Globe	1.1	0.9	0.6	cc
Lens Volume	0	0	0	% vol.
Lens Periphery	0	0	0	%
Ciliary Body	1	0	0	% vol.
Optic Disc	0	0	0	% area
Macula	0	0	0	% vol.
Length Of Optic Nerve	0.0	0.0	0.0	mm
Surface Of The Tumor	100	100	100	% area
Upper Eyelid Rim				
Lower Eyelid Rim				

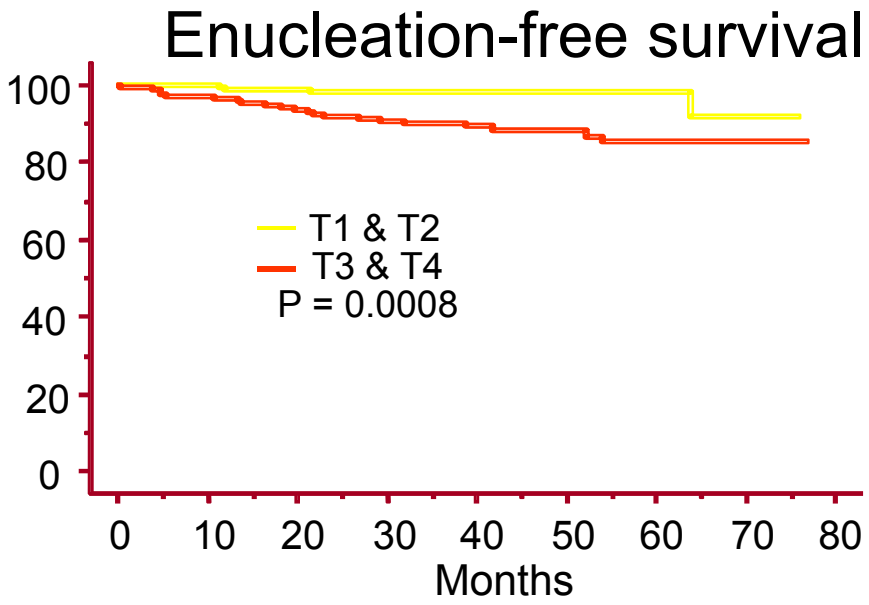
OK

Outcome of Uveal Melanoma treated in Nice (n= 2500)









Tumors of the conjunctiva:

„orphan diseases“

non-Hodgkin lymphoma

malignant melanoma

squamous cell carcinoma

extremely rare lesions:

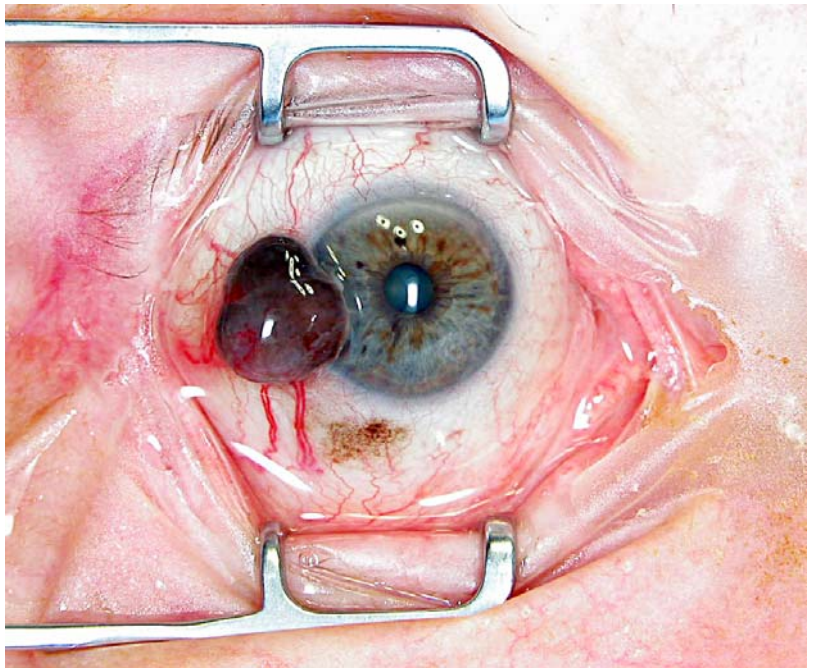
- adeno-squamous carcinoma
- rhabdomyosarcoma
- others…

Complex target volume

Complex geometry

The problem of the fornix

The problem of the depth



Organs at risks in the neighborhood

Target volume is also organ at risk

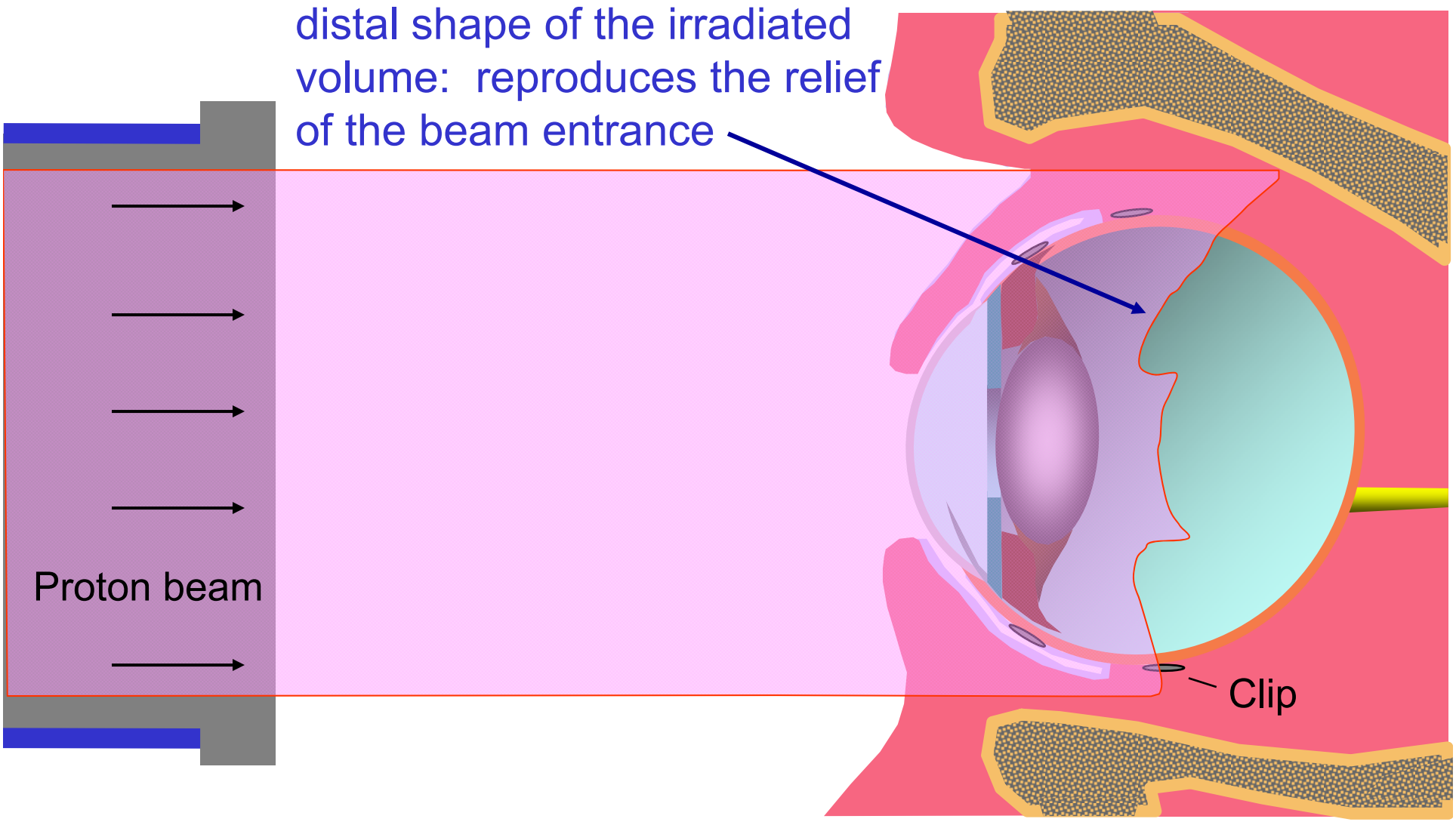
Why protons?

ballistic precision of the proton beam

➡ homogeneous irradiation of a complex treatment volume (necessity to treat large volume of bulbar and tarsal conjunctiva while sparing the internal structures in the eye)

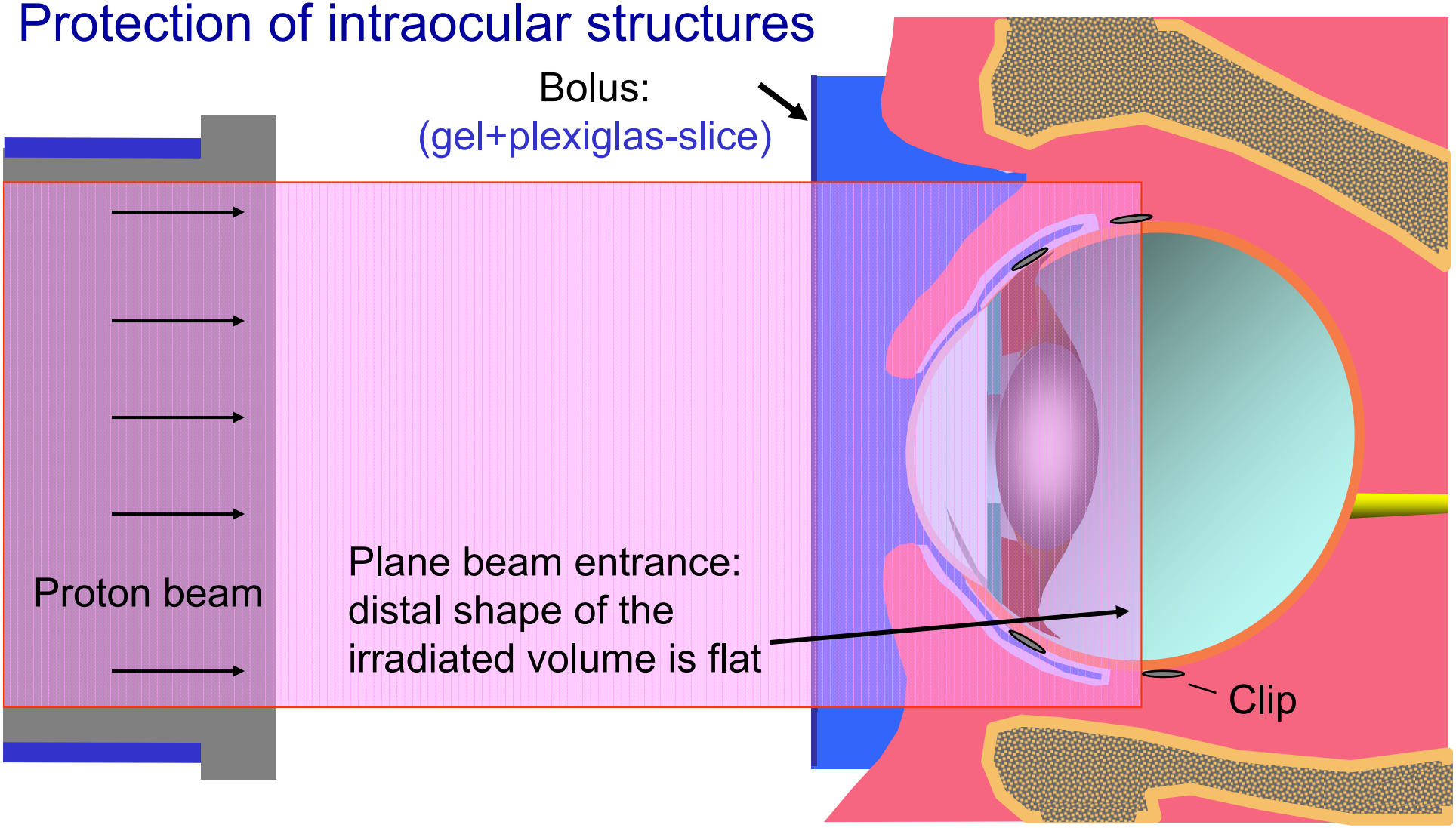
➡ steep dose gradients at the edges and depth: protection of healthy structures

Proton irradiation of conjunctival tumors

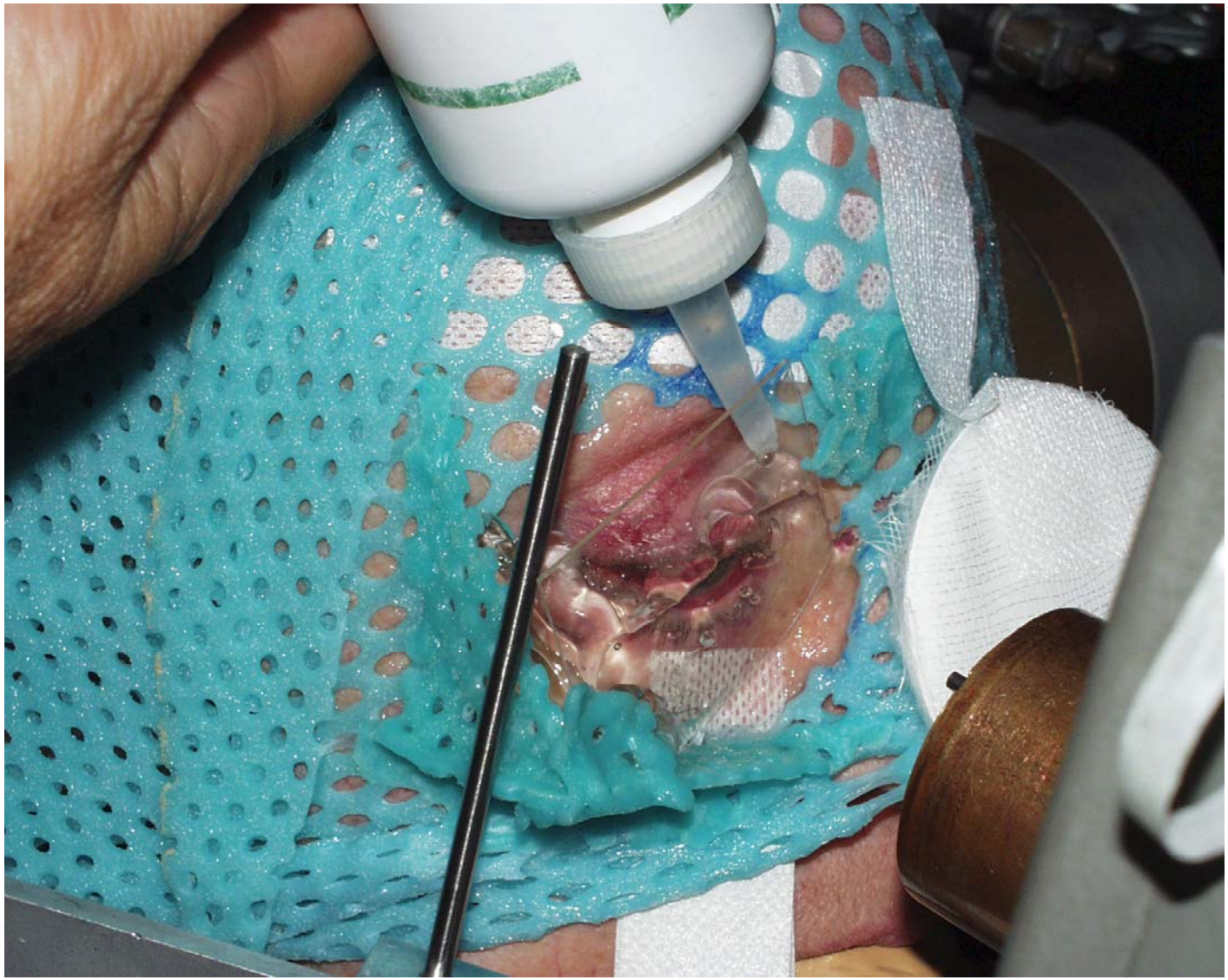


Treatment technique

Protection of intraocular structures

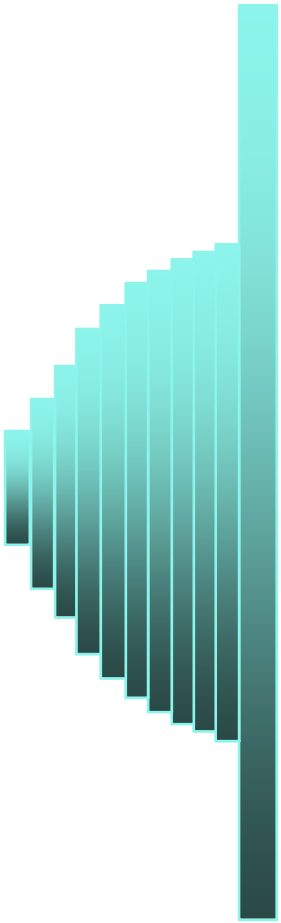


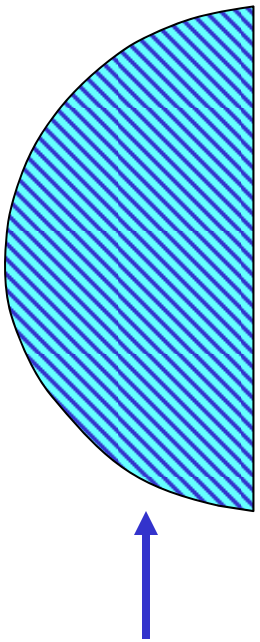
Treatment technique: bolus



Treatment technique

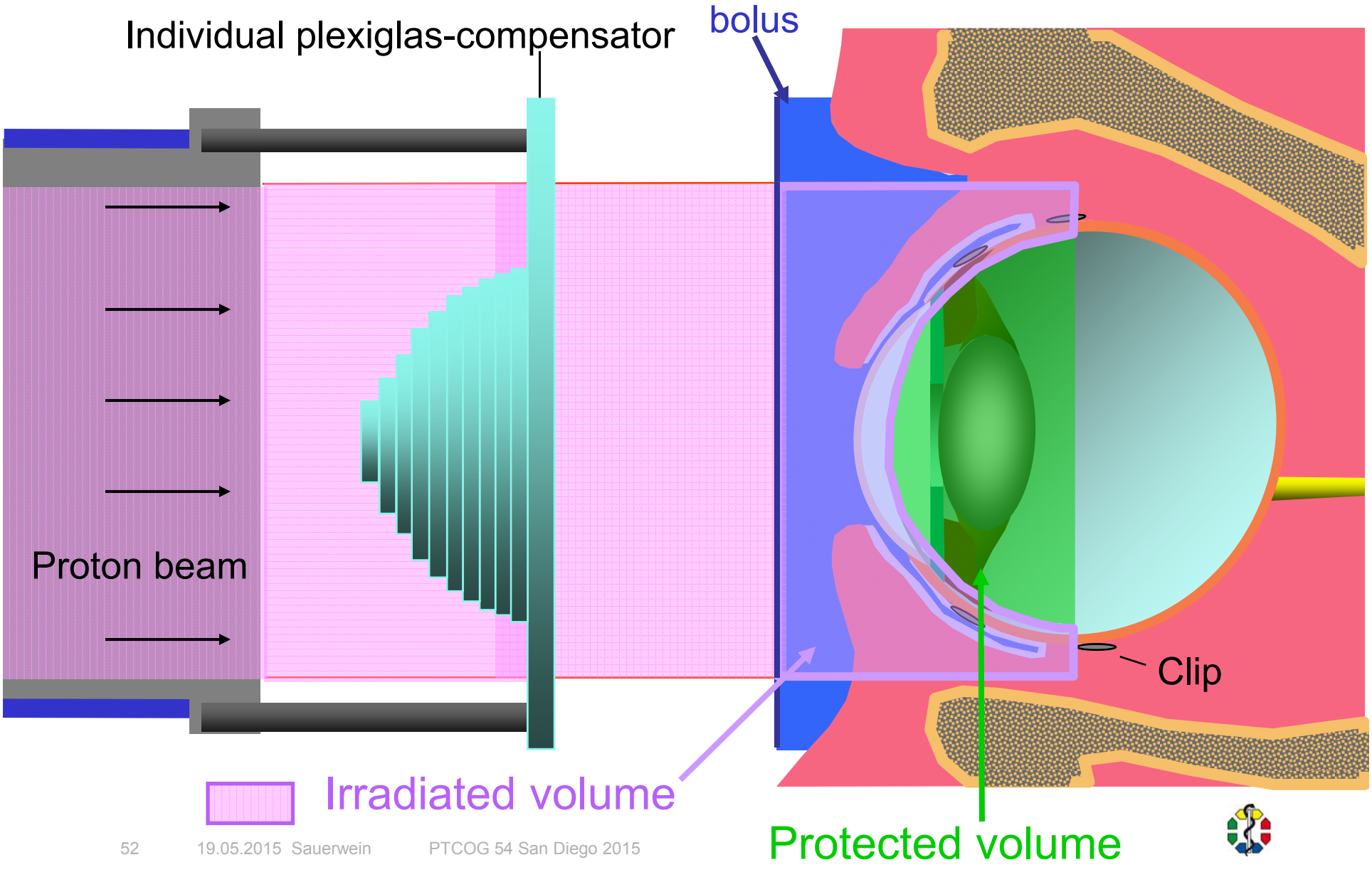
Semi-hemispherical plexiglas-compensator reduces the proton energy and modulates their range to protect healthy structures



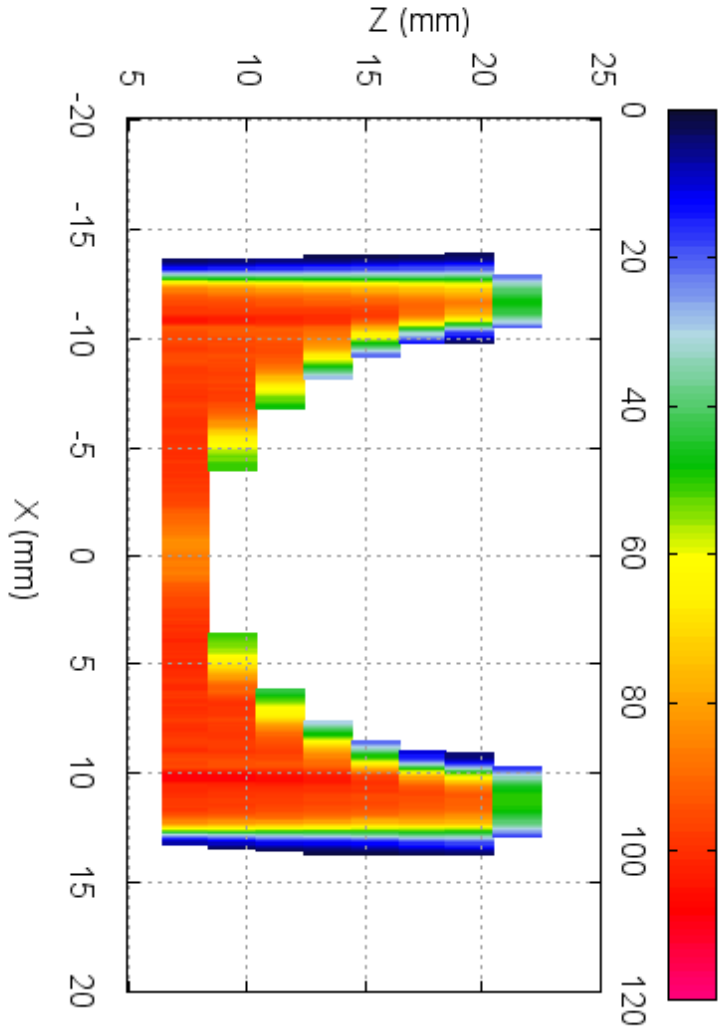


shielded volumen

Treatment technique

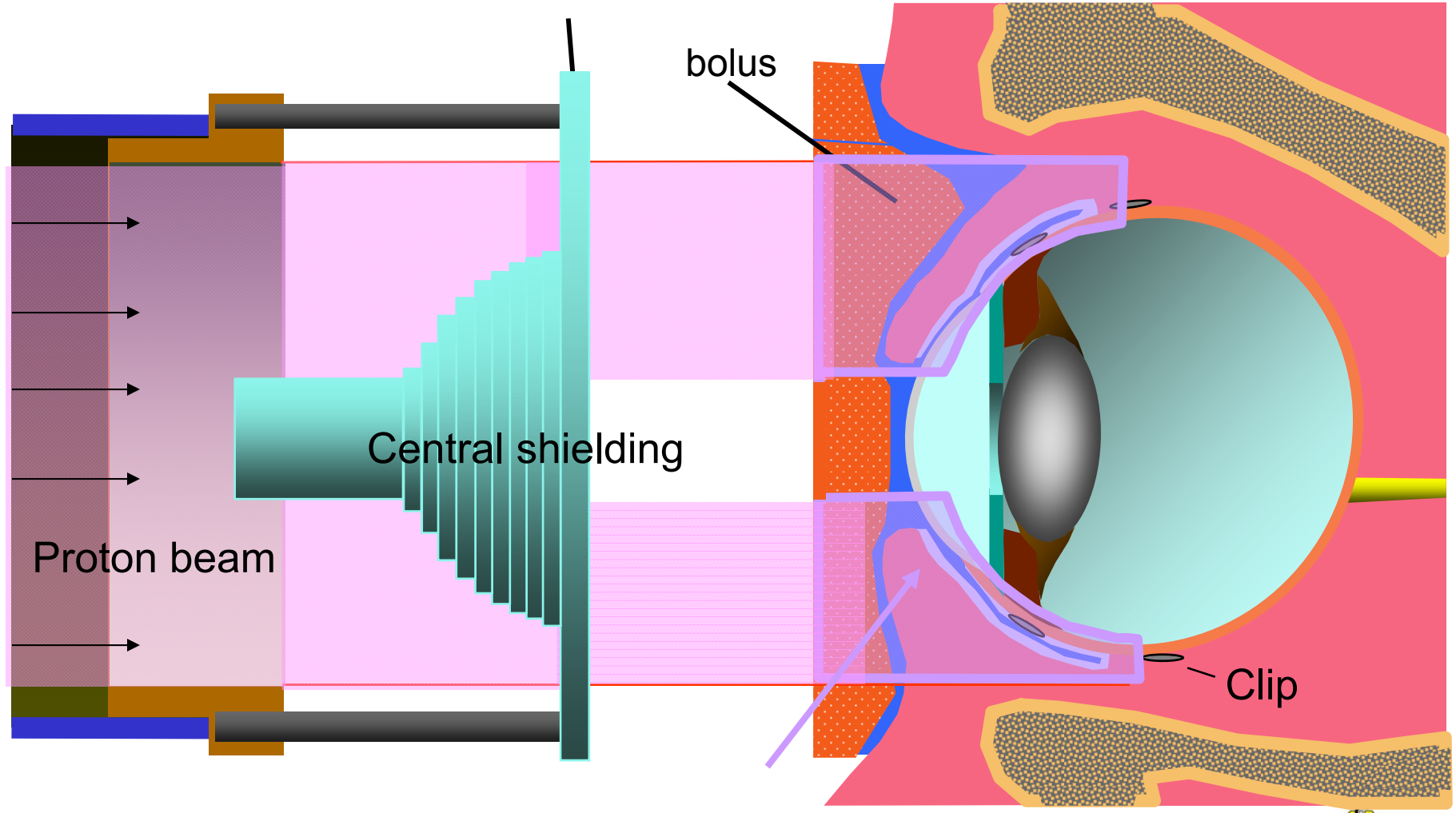


Dose distribution



Treatment technique

Individual plexiglas-compensator

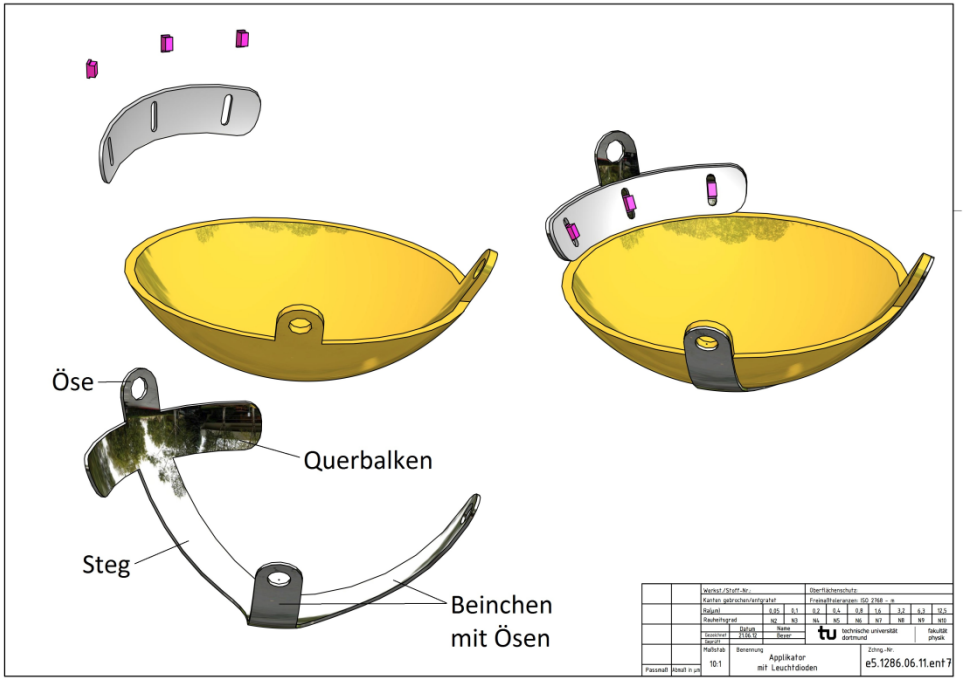


Future developments in brachytherapy: Positioning

Mini-SMD-LEDs

Attached to the plaque

control of localisation of the plauque and it‘s <u>orientation</u>



Easily detectable through the sclera

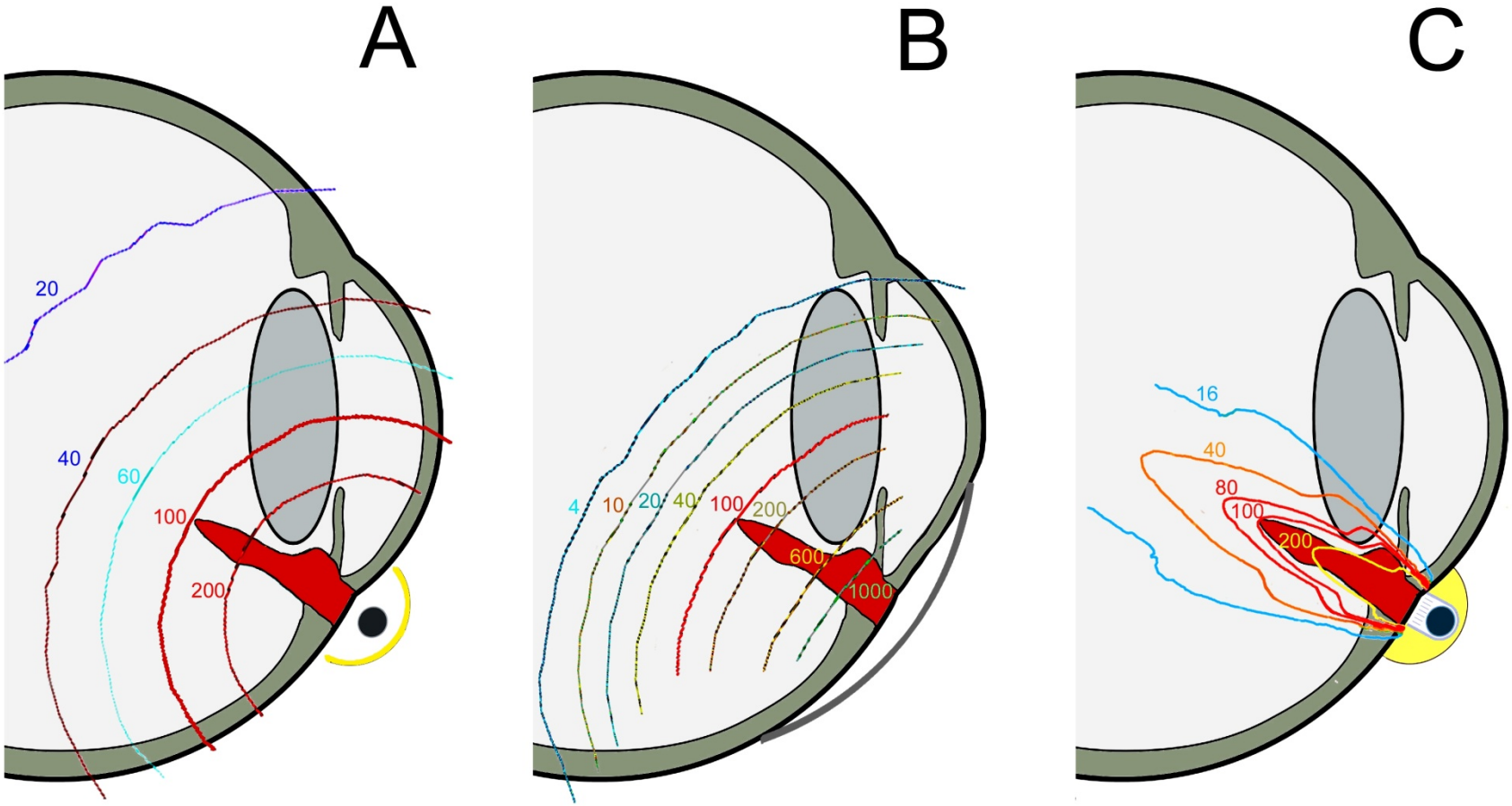
Optimized positioning

Mini-SMD-LEDs

Integrated in the plaque

Offers the possibility to control the postion of the plaque during treatment

Recent developments: highly precise plaques (HPS)



A – ^{125}I-Plaque

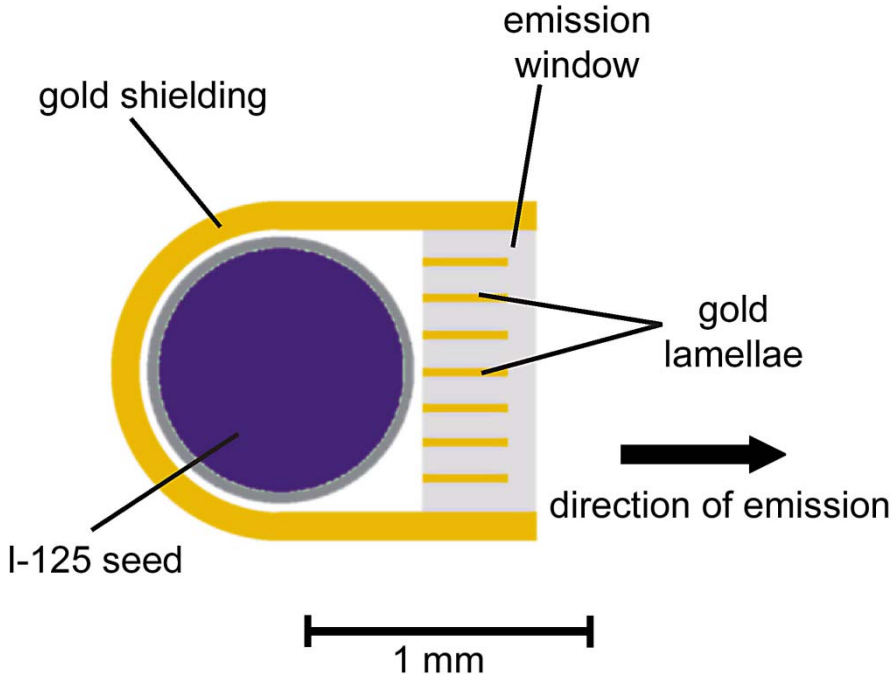
B – ^{106}Ru-Plaque CCX

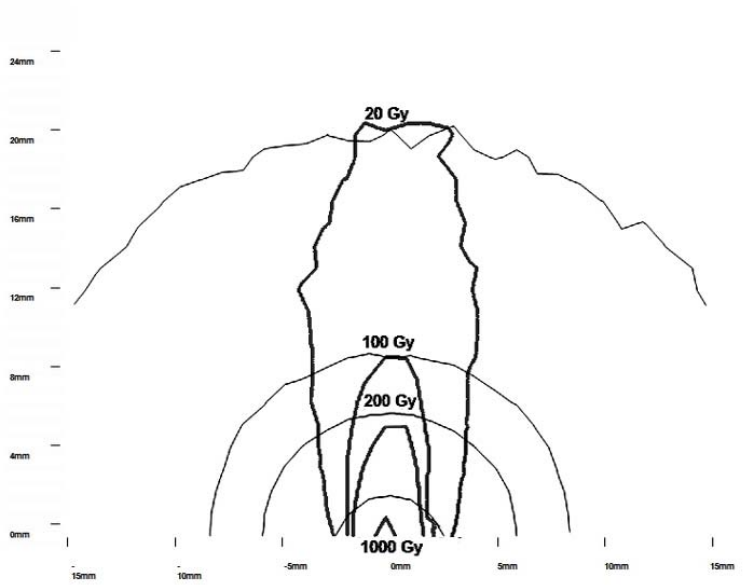
C – ^{125}I-HPS-Plaque

Recent developments: highly precise plaques (HPS)

The principle:

Microcollimation of single seeds





The future of proton therapy for eye tumors?

Dedicated machine
65 MeV
EYEPlan

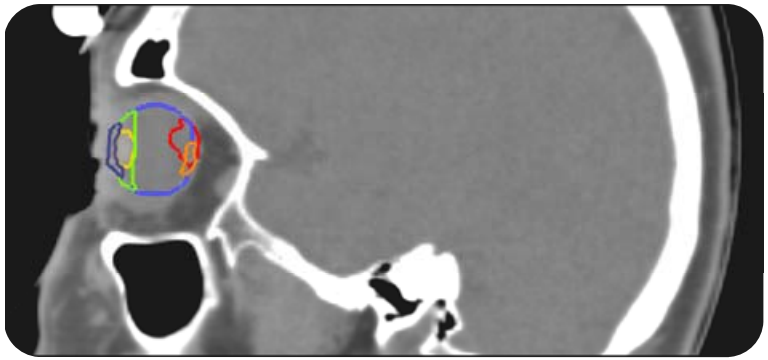
Pulsed beam
Pencil beam scanning
Image based treatment planning
62-230 MeV

High energy beams and PBS for small, superficial tumors

Collaboration

CNAO

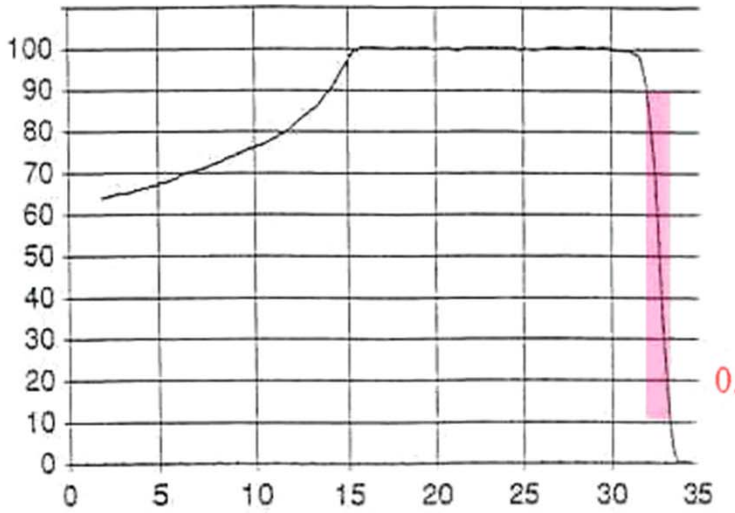
CAL Nice
Centre Antoine-Lacassagne
Centre Régional de Lutte contre le Cancer



“work in progress”

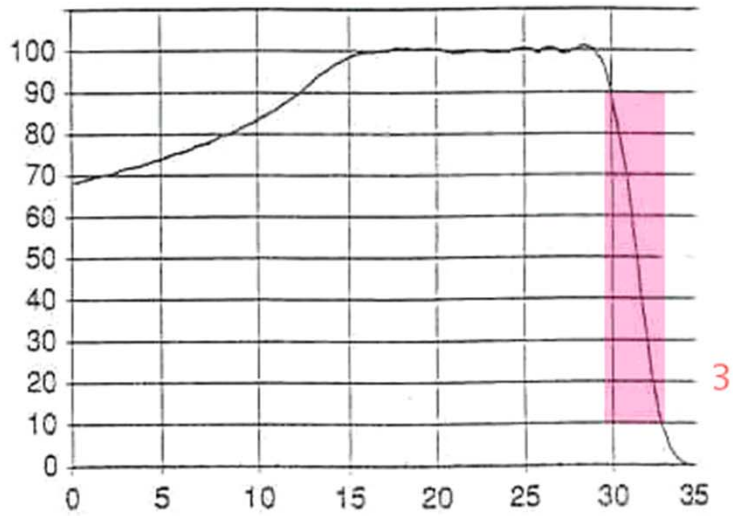
→ R. Via et al.: Patient Setup and Immobilization Session

Cyclotrons with continuous beams



65 Mev without degrader.

0.8 mm fall-off



200 Mev degraded.

3 mm fall-off

Protons
≠
Protons

Dedicated beam vs. degraded high intensity beam

	65 MeV without degrader			200 MeV degraded		
of Dmax	20%	50%	90%	20%	50%	90%
Surface globe [%]	20	13	8	28	25	13
Volume globe [$cm^{2]}$	1.9	1.5	1.0	2.6	2.2	1.5
Volume vitrous [%]	57	37	25	85	61	54
Ciliary body [%]	52	46	36	59	55	45
Cornea [%]	55	47	36	72	64	51

Melanoma of the iris, identical target volume

How to select the optimal radiation technique?

The possibility of a choice between different treatment modalities has not been sufficiently investigated.

Published literature does not give any advice to answer the question:

what is the best solution for an individual patient

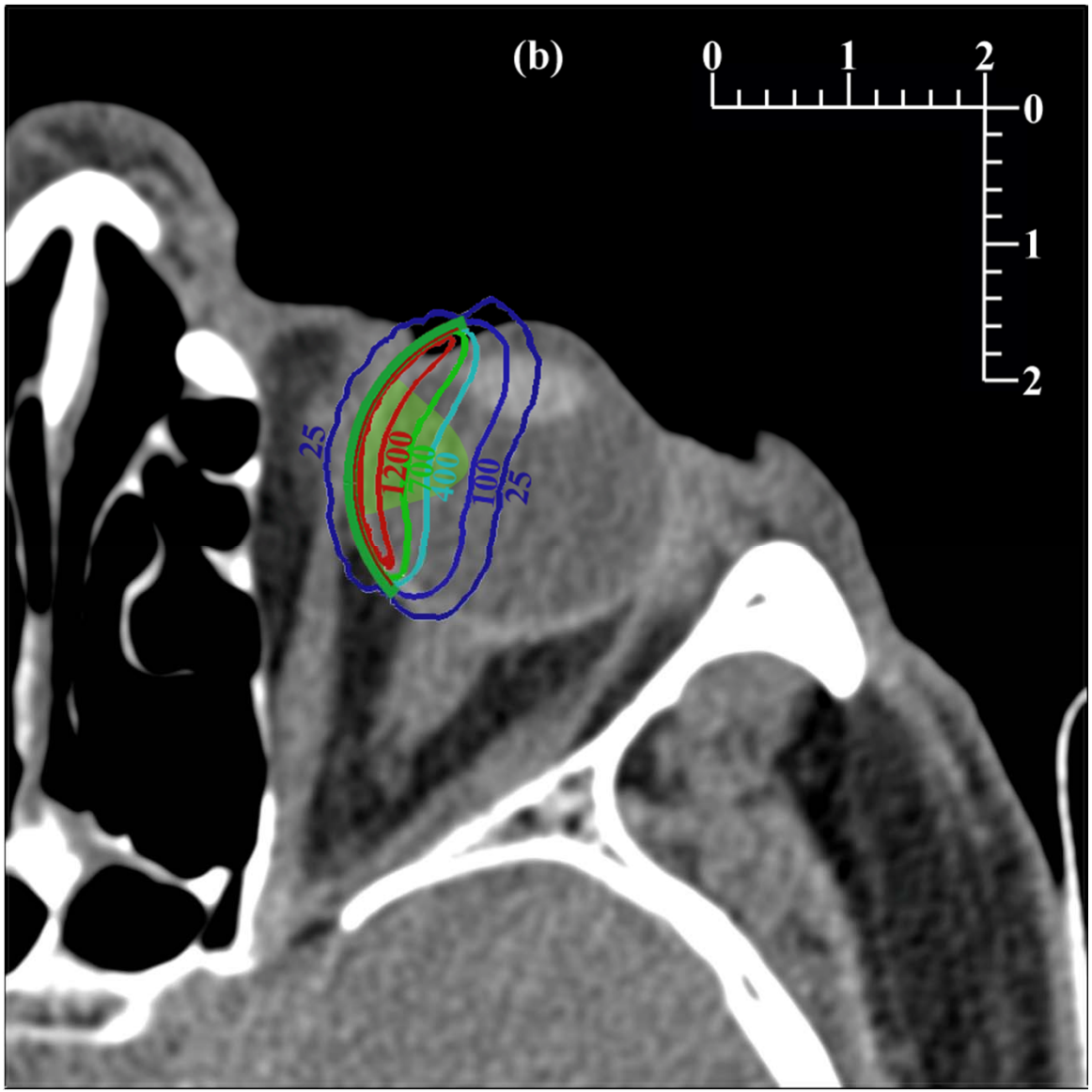
Physical aspects

Type of applicator/ irradiation	^{106}Ru	applicator mixed ^{106}Ru/^{125}I	^{125}I	protons
Maximal tumor thickness allowing an adequate dose distribution	5-7mm (depending from applicator)	6-10 mm (important influence of the activity)	10-15 mm (depending from applicator)	Homogeneous dose distribution always possible
Depth dose distribution behind the target volume (% of dose at the apex)	1 mm: ca. 60% 5 mm: ca. 10%	ca. 75 % ca. 10 %	ca. 80-90% ca. 30-50%	ca. 50% 0
Dose to normal tissues prior the target volume (% of dose at the apex)	0	0	0	ca 30-60%
Lateral dose distribution (% of dose at the apex)	1 mm: ca. 20% 5 mm: ca. 3%	ca. 30-50 % ca. 5-10 %	ca. 20-60% ca. 5-25%	ca. 50% 0

Retinoblastoma

brachytherapy ^{106}Ru vs. ^{125}I	Essen (2005)	Shields et al (2001)
Treatment period	1979 - 2005	1976 - 1999
Treated tumors	175 (^{106}Ru)	178 (^{125}I)
Mean age [months]	23 (0.2 – 150)	12 (1 – 96)
Tumour diameter [mm]	7.5 (1.5 – 22)	7.7 (1-18)
Tumour height [mm|	3.7 (1 - 7.6)	4.1 (0.5 – 12)
Distance to optic disk [mm]	7.2 (0 – 21)	6.4 (0 – 17)
Retinal detachment	22 / 175	31 / 178
Vitreous seeding	37 /175	15 / 178
Primary brachytherapy	56 / 175	60 / 178
Mean duration of radiation	69 h	68 h
Mean dose apex / base (rounded)	**138 Gy / 419 Gy (NIST)**	**42 Gy /155 Gy**
Tumour recurrence / mean interval	**4.6 % / 12.9 Monate**	**17% / 8 Monate**
Radiation retinopathy	**12 %**	**26 %**

Modified penEasy/PENELOPE simulation

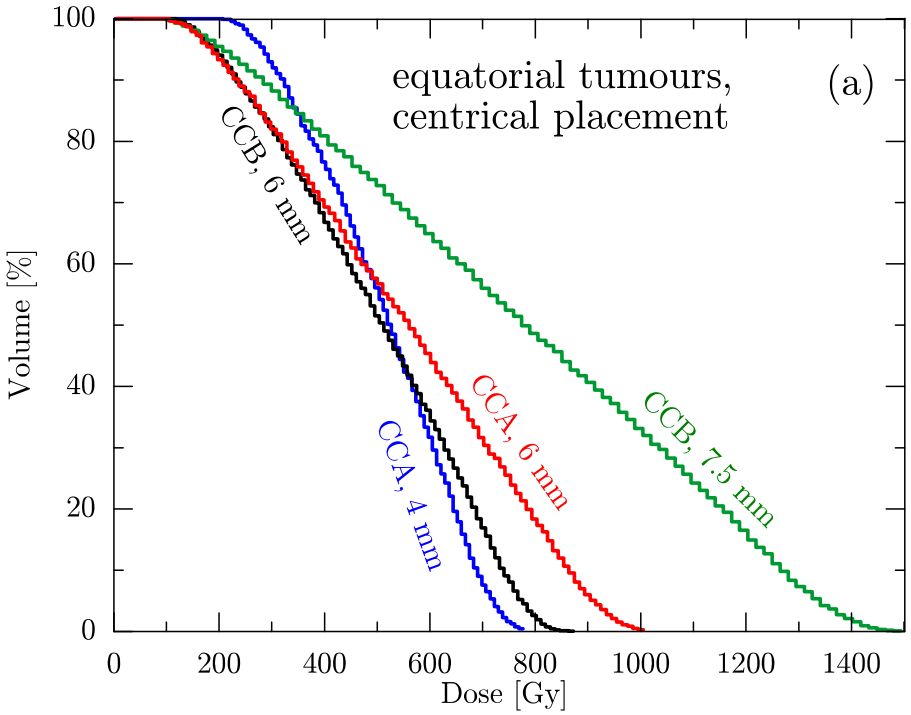


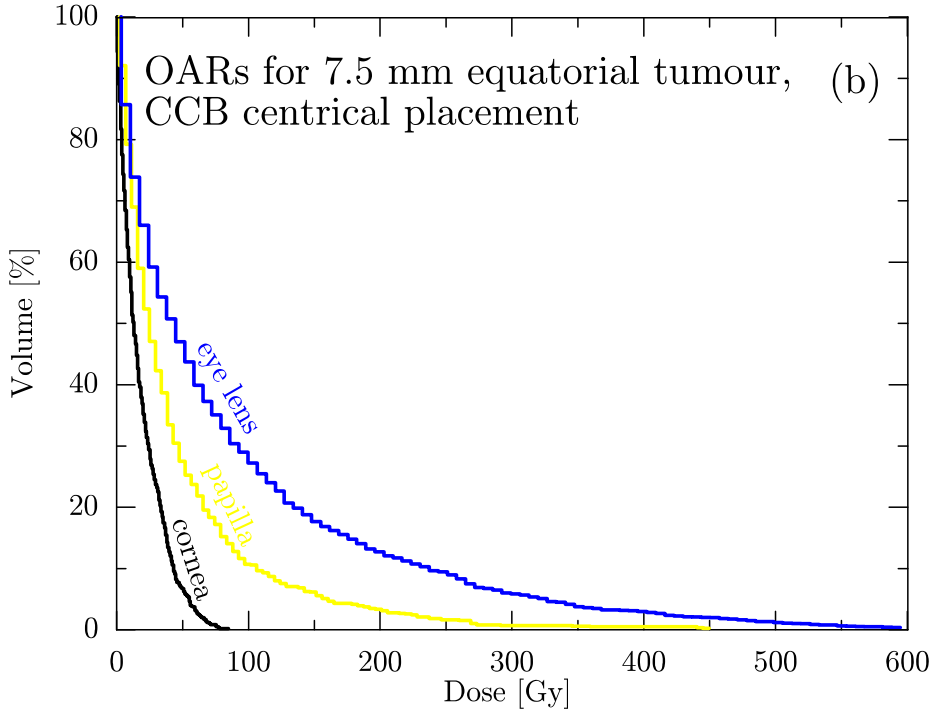
CCB plaque,
7.5 mm apical
height tumour

Strahlenther Onkol (2013)
189, 68-73

Modified penEasy/PENELOPE simulation

Dose volume histograms?

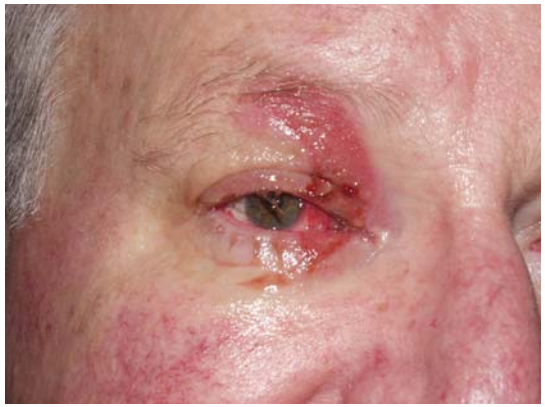




Strahlenther Onkol (2013) 189, 68-73

The evaluation of the clinical outcome

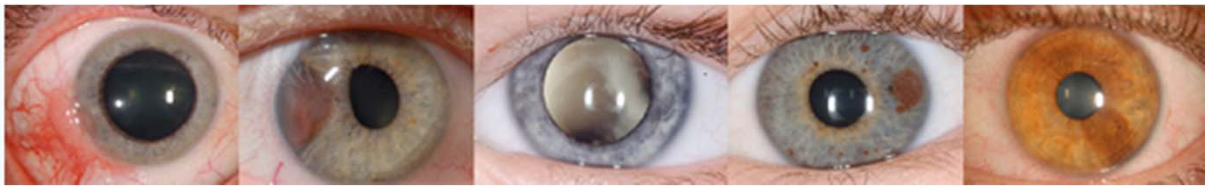
- All authors report excellent tumor control (and good functional outcome)
- Any optimization of ophthalmic radiotherapy has to focus on side effects
- Side effects and damage to normal structures are often not mentioned
- In contrast to other anatomical sites, a standardized reporting system of side effects after ophthalmic radiotherapy does not exist



A standardized reporting of side effects is overdue

The Radiation Side Effect Staging Project of the ISOO

INTERNATIONAL SOCIETY OF OCULAR ONCOLOGY



Join us at

The First Eye Cancer Working Day on June 1, 2015 in Paris

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Jerome Mandrillon
Mario Ciocca
Andrea Wittig

Universitätsklinikum Essen


Thank you!
Proton