Monitoring ocular toxicity of radiotherapy

Stella K. Kim, MD

Ophthalmology Section, Dept of Head and Neck Surgery
Adjunct, Dept. of Radiation Oncology
MD Anderson Cancer Center, Houston, TX

PTCOG 2006

Ocular toxicity from XRT

- Clinical spectrum
- Current reporting metrics of ocular toxicity
  - Common language between ophthalmology and radiotherapy
- Future considerations

Ocular Structures

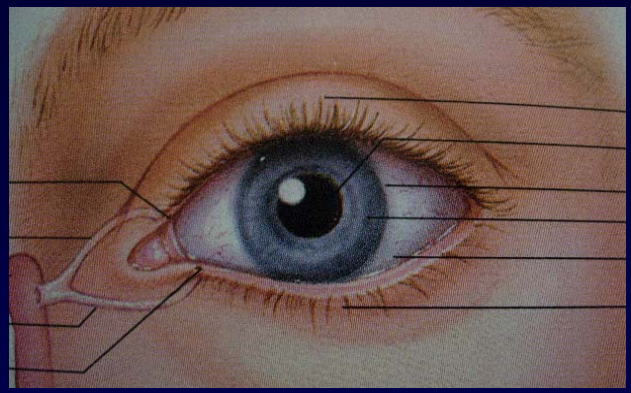
Lid/ Orbit

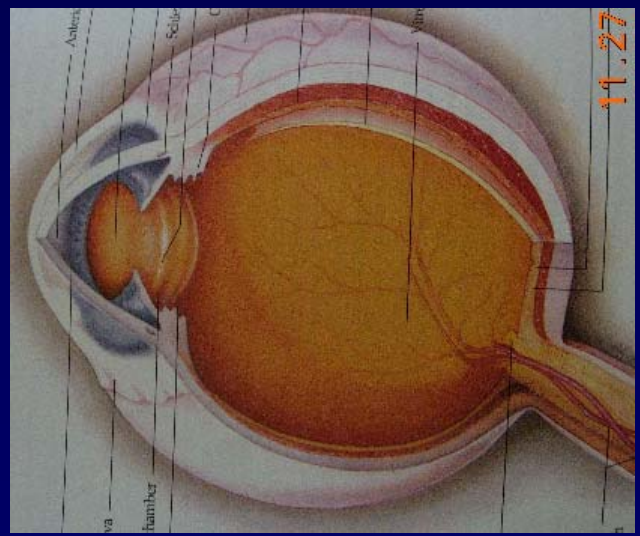
Lacrimal Gland

Nasolacrimal Drainage system

Conjunctiva
Cornea
Lens
Retina

Optic Nerve



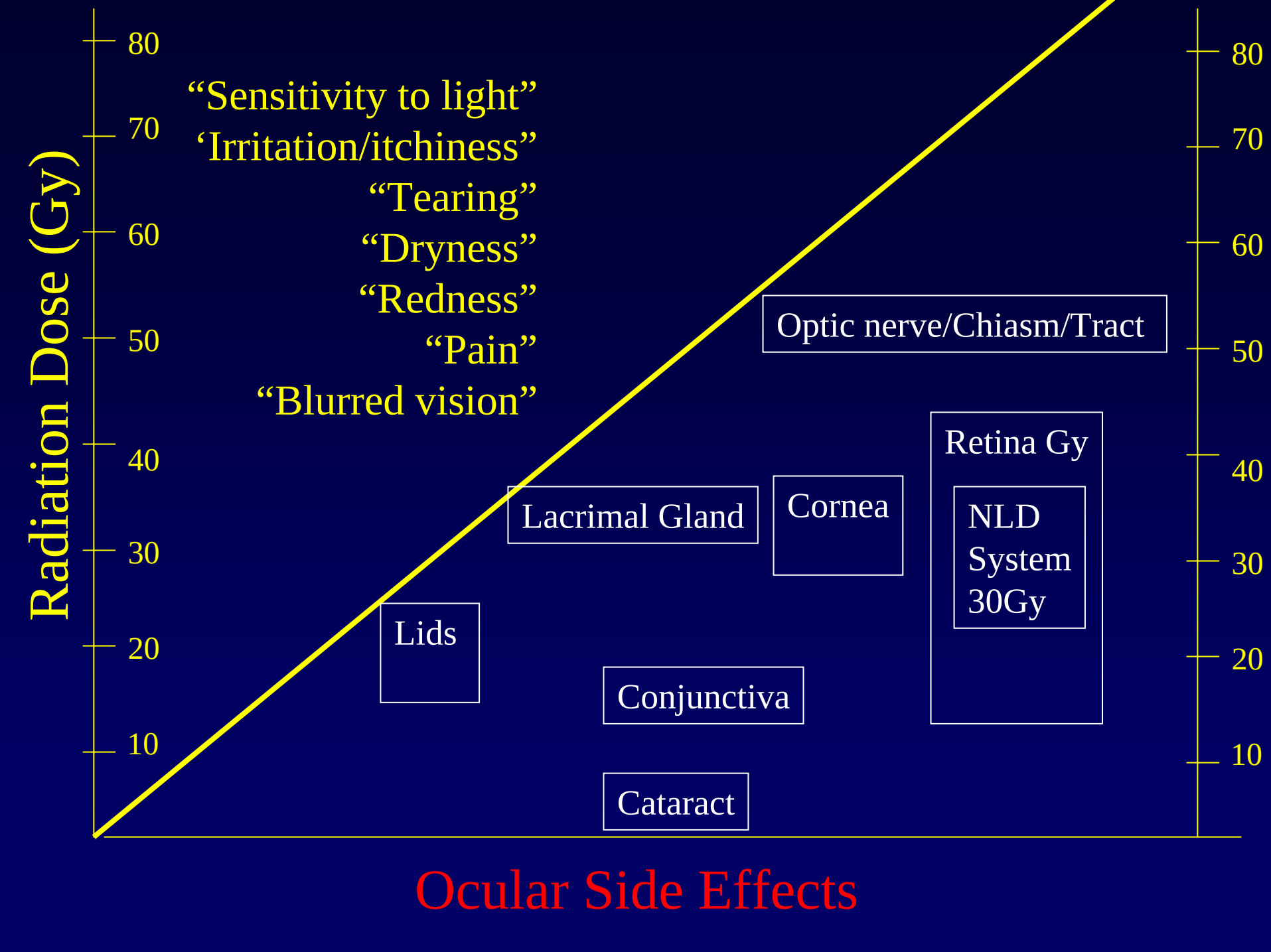


XRT

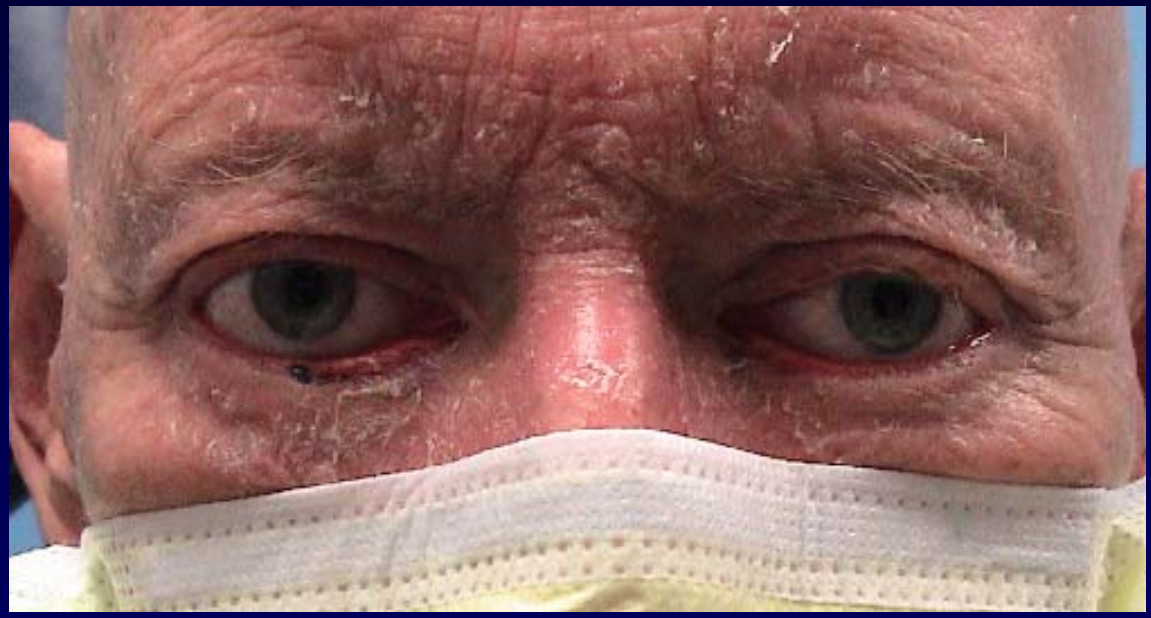
- Ocular/Orbital
- Head and Neck Cancers
  - skull base
  - paranasal sinus CA
- CNS / Pituitary

Proton Eye treatment

- Lacrimal gland/sac tumors (ACC)
- Orbital metastatic disease
- Conjunctival tumors
- Iris Tumors
- Wet age related macular degeneration
- Retinoblastomas
- Angiomas/ Hemangiomas
- Uveal melanoma


Radiation Dose (Gy)
80
70
60
50
40
30
20
10
"Sensitivity to light"
'Irritation/itchiness"
"Tearing"
"Dryness"
"Redness"
"Pain"
"Blurred vision"
Optic nerve/Chiasm/Tract
Retina Gy
NLD System 30Gy
Cornea
Lacrimal Gland
Lids
Conjunctiva
Cataract
Ocular Side Effects

Anterior Eye



Lid (Gy)

30 - 40

Lid erythema, Madarosis

35 -56

Punctual stenosis

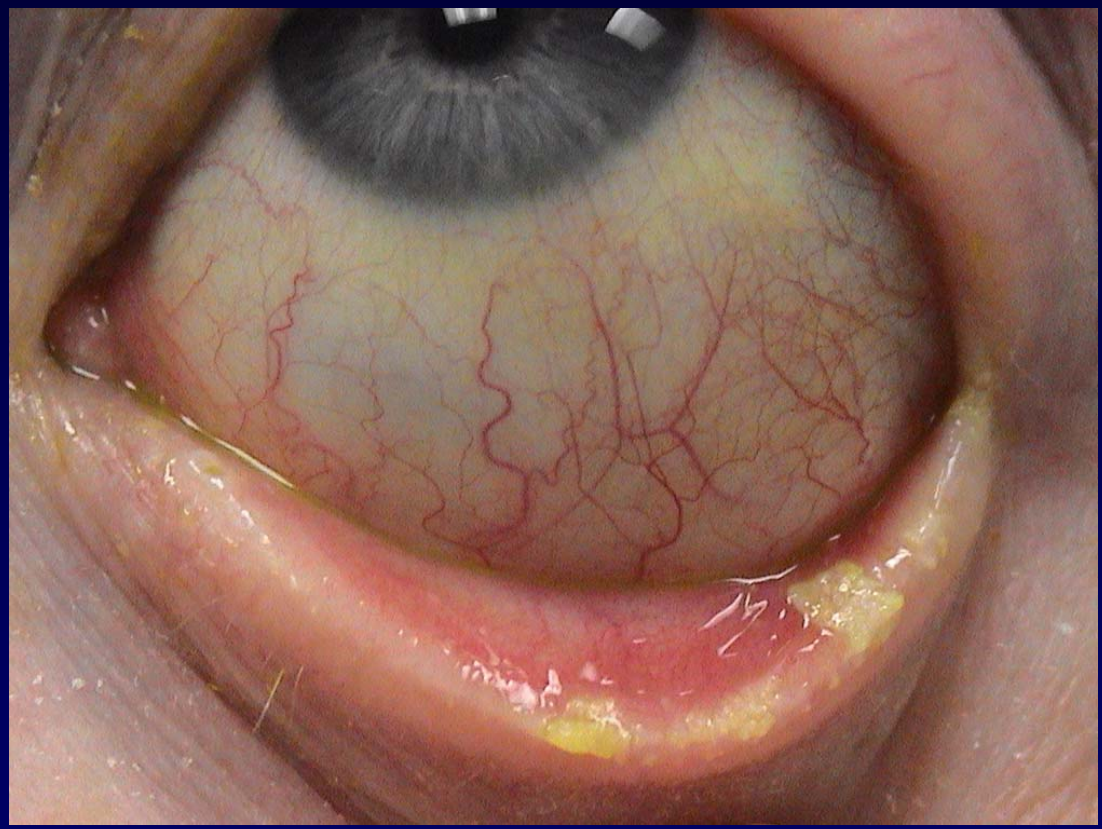
Anterior Eye

Lid (Gy)

> 50 Lid telangiectasis
Ectropion
Entropion
Trichiasis
Hyperkeratosis

Anterior Eye

Lid (Gy)



> 50 Lid telangiectasis
Ectropion
Entropion
Trichiasis
Hyperkeratosis

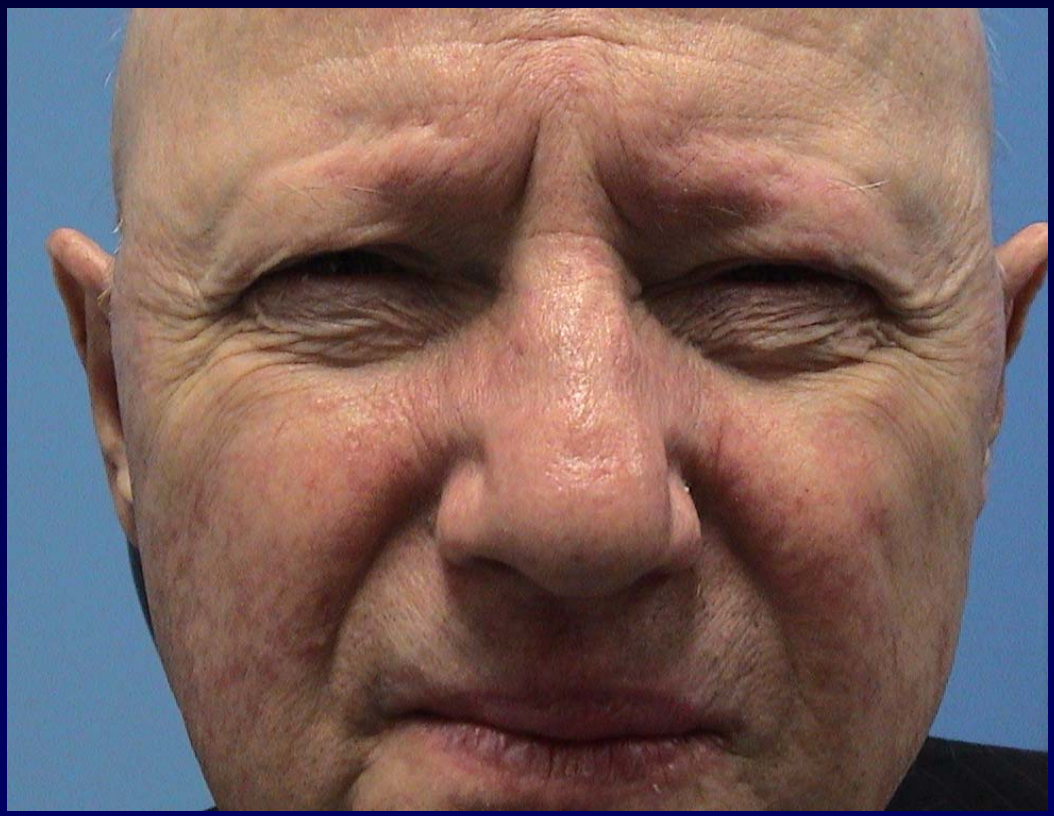
Anterior Eye Lacrimal Glands (Gy)

>30 Sicca syndrome/ Dry Eye

40 =50%

> 60 =100%

Anterior Eye Lacrimal Glands (Gy)



Keratoconjunctivitis Sicca/ DES

>30 Sicca syndrome/ Dry Eye

40 =50%

>60 =100%

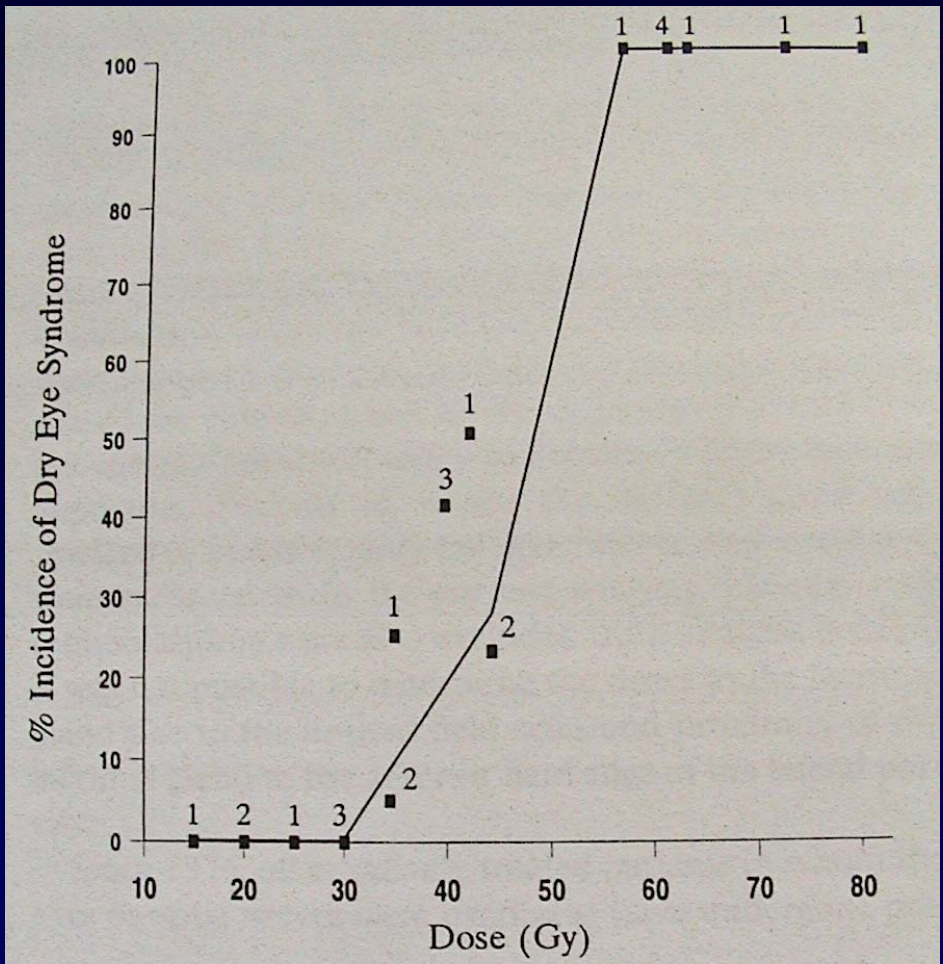


Fig. 3. Sigmoid dose response curve for production of dry-eye complications. Points are numbered to correspond with authors: 1, Parsons *et al.* (current series); 2, Bessell *et al.* (1); 3, Letschert *et al.* (6); and 4, Morita *et al.* (7). Dose ranges are shown in Tables 3 and 5.

Table 3. Incidence of severe dry eye syndrome according to total dose (University of Florida data)*

Dose range (Gy)	Incidence (%)
10–20	0/4 (0)
20.01–30	0/2 (0)
30.01–40	2/8 (25)
40.01–45	1/2 (50)
45.01–56.99	No data
57–60	3/3 (100)
60.01–70	5/5 (100)
70.01–80	8/8 (100)
80.01–83	1/1 (100)

SEVERE DRY-EYE SYNDROME FOLLOWING EXTERNAL BEAM IRRADIATION

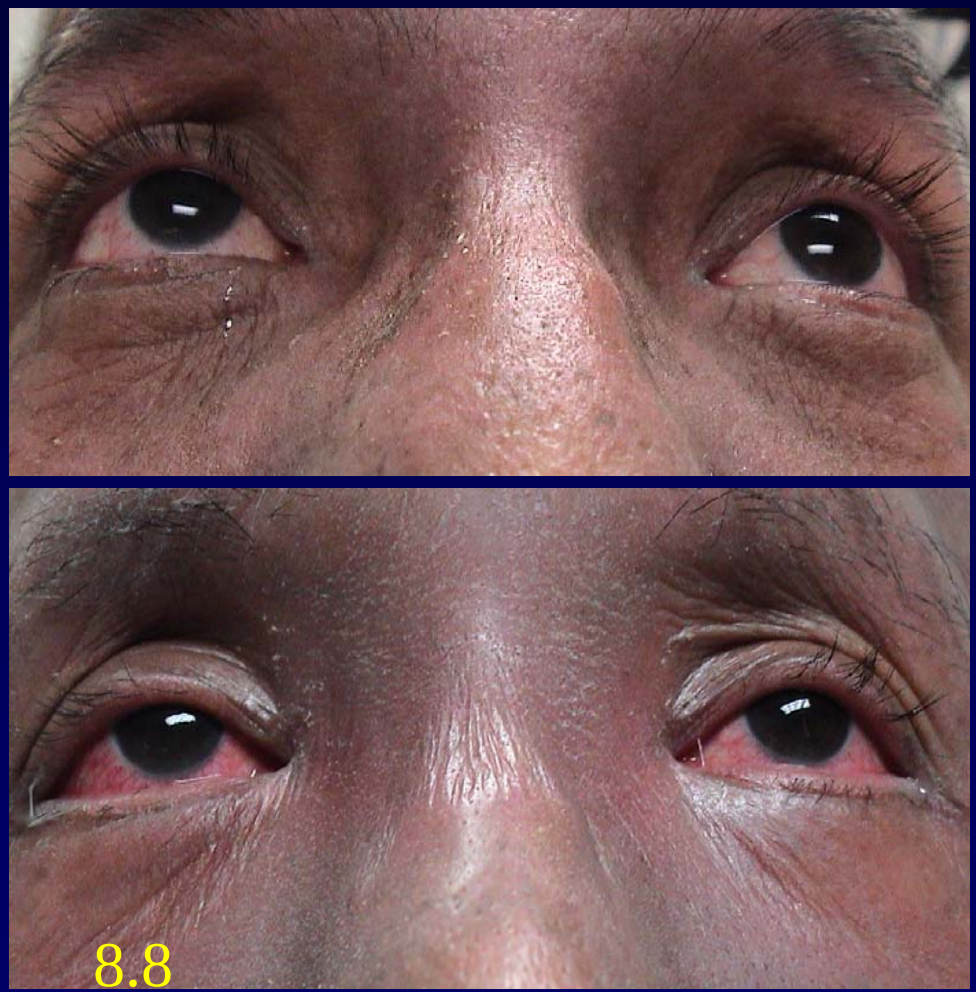
JAMES T. PARSONS, M.D.,* FRANK J. BOVA, PH.D.,* CONSTANCE R. FITZGERALD, M.D.,† WILLIAM M. MENDENHALL, M.D.* AND RODNEY R. MILLION, M.D.*

*Department of Radiation Oncology, University of Florida College of Medicine; and †Private Practice of Ophthalmology, Gainesville, FL

IJRO, 1994

Anterior Eye

Conjunctiva (Gy)



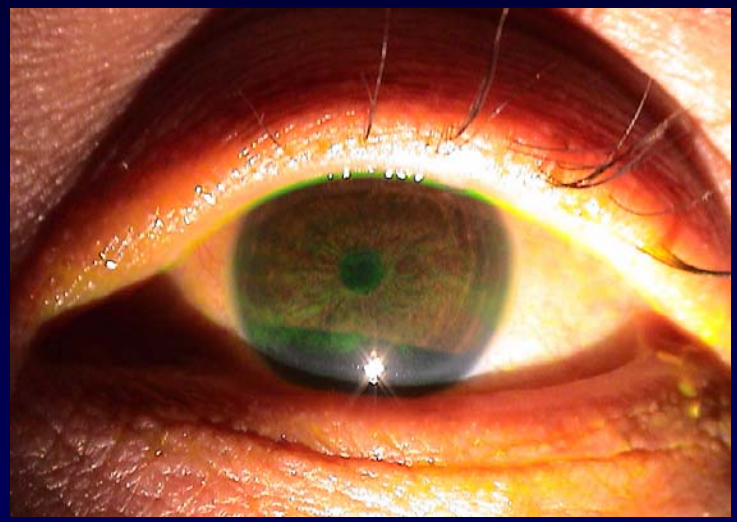
10 – 21 Ocular surface disease

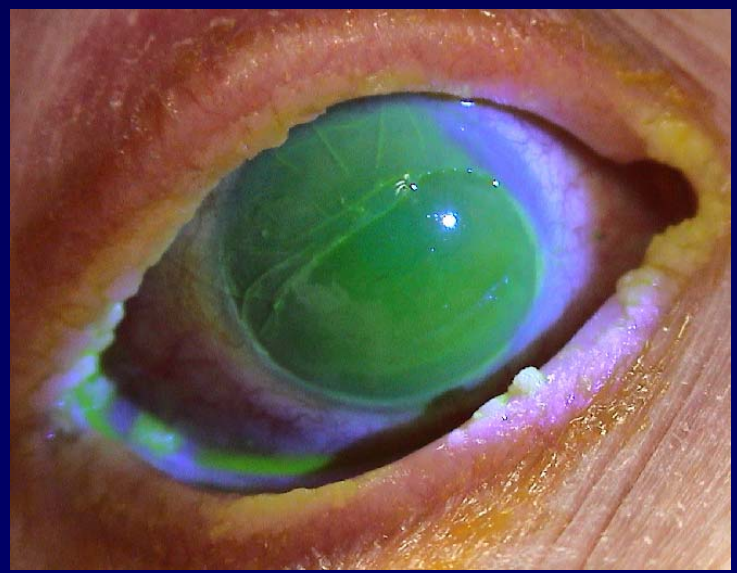
37 (200-250 cGy fractions) Conjuctivitis

55 – 75 Conjunctivitis, symblepharon

Anterior Eye

Cornea (Gy)





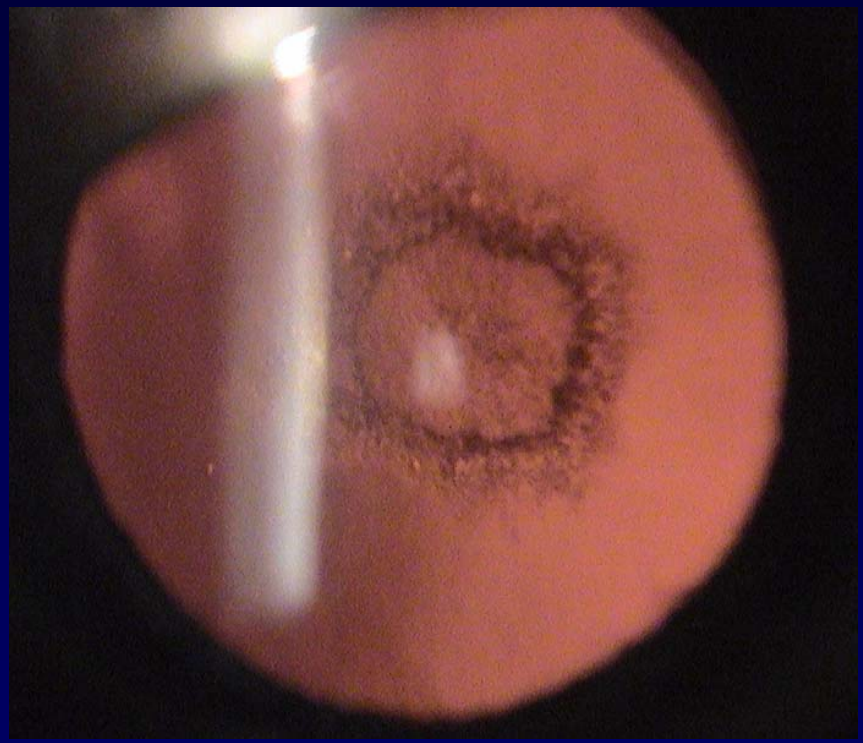
30 – 50 Keratitis, corneal edema, small ulcer

35 Blindness, severe keratitis (orbital lymphoma)

> 60 Corneal ulcer, perforation

Posterior Eye

Lens (Gy)



200 cGY Threshold- Cataract (no shield)

2.0-11.5 Gy, 1/3 developed cataract (<6.5 in 8yr; >6.5 in 4 yr)

10 Gy – 21Gy TBI Cataract, (TBI fractionation better than single dose)

Baseline cataract evaluation is important

Posterior Eye

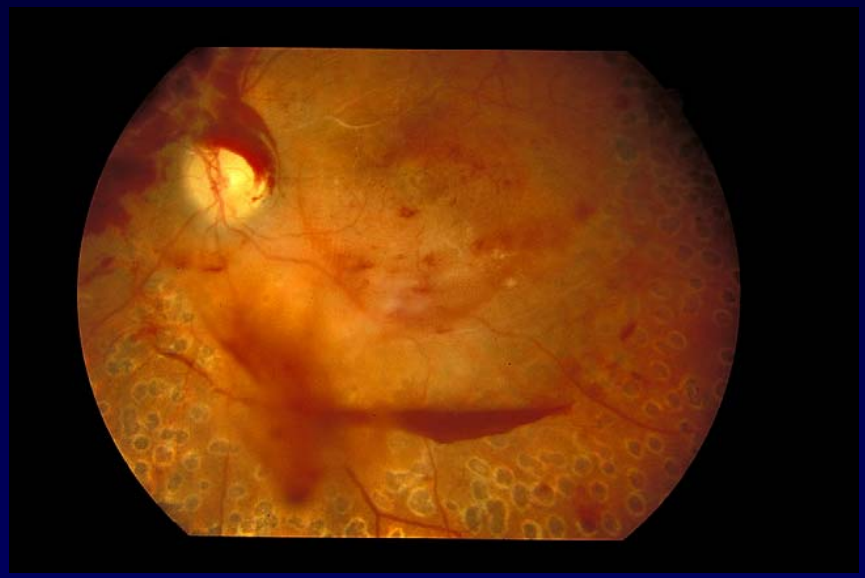
Retina (Gy)

>40 Gy Retinopathy
(2-3 yrs; 1-6 yr range)
< 20-30 Gy if
comorbidity exists

- Diabetes
- Vaso-occlusive dz
- Hypertension

Posterior Eye

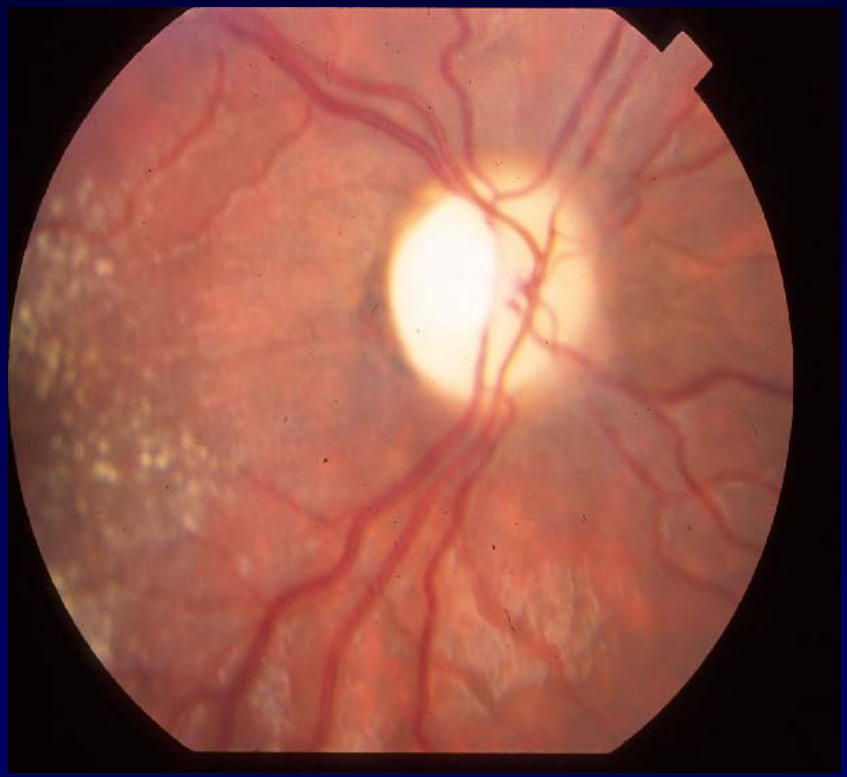
Retina (Gy)



- Anterior segment neovascularization may lead to neovascular glaucoma
- Leads to “Blind painful eye”
  - Enucleation
  - EtOH retrobulbar injection

Posterior Eye

Optic neuropathy (Gy)



>50 Gy (variable)

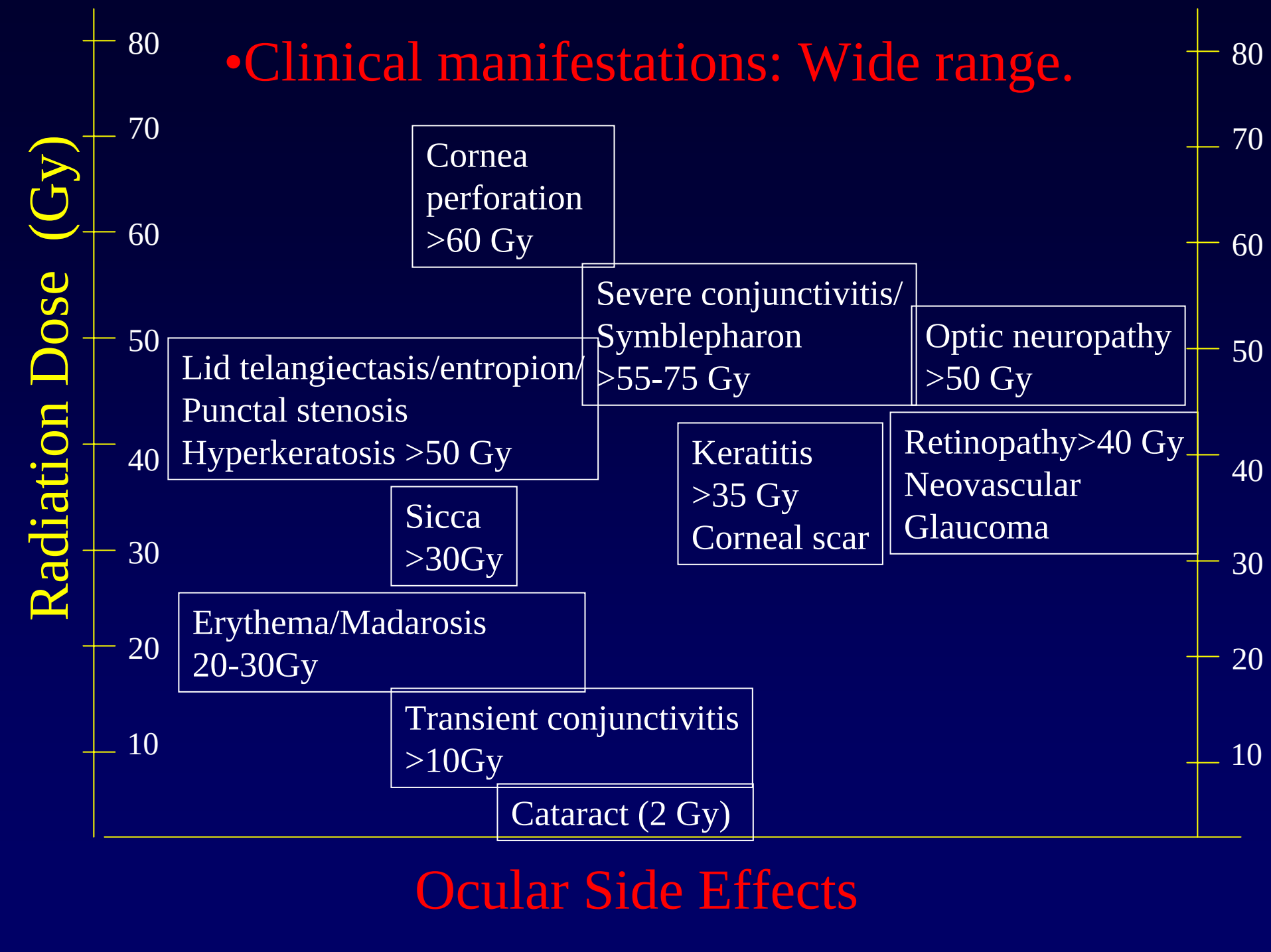
≥2Gy Daily fractionation

Total dose (>65Gy, <2Gy daily dose)

Tissues volume

Age (>50)

Chemo-radiation


•Clinical manifestations: Wide range.
Radiation Dose (Gy)
80
70
60
50
40
30
20
10
Cornea perforation >60 Gy
Severe conjunctivitis/ Symblepharon >55-75 Gy
Optic neuropathy >50 Gy
Lid telangiectasis/entropion/ Punctal stenosis Hyperkeratosis >50 Gy
Keratitis >35 Gy Corneal scar
Retinopathy>40 Gy Neovascular Glaucoma
Sicca >30Gy
Erythema/Madarosis 20-30Gy
Transient conjunctivitis >10Gy
Cataract (2 Gy)
Ocular Side Effects

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Organ Tissue	0	1	2	3	4
EYE	-	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panopthalmitis / Blindness

Challenges in Grading Ocular Side Effects

- Common language needed.
  - For ocular tumors, primary treating physician is a non-radiotherapist. Capturing toxicities in context of grade I, II, III, IV not commonly done in ophthalmology

- Clinical manifestations: Wide range.
  - transient non-vision threatening ocular surface disease to severe optic neuropathy and blindness.
  - Real time assessment is optimal

NCI/CTEP Common Toxicity Criteria for Adverse Events, Version 3.0

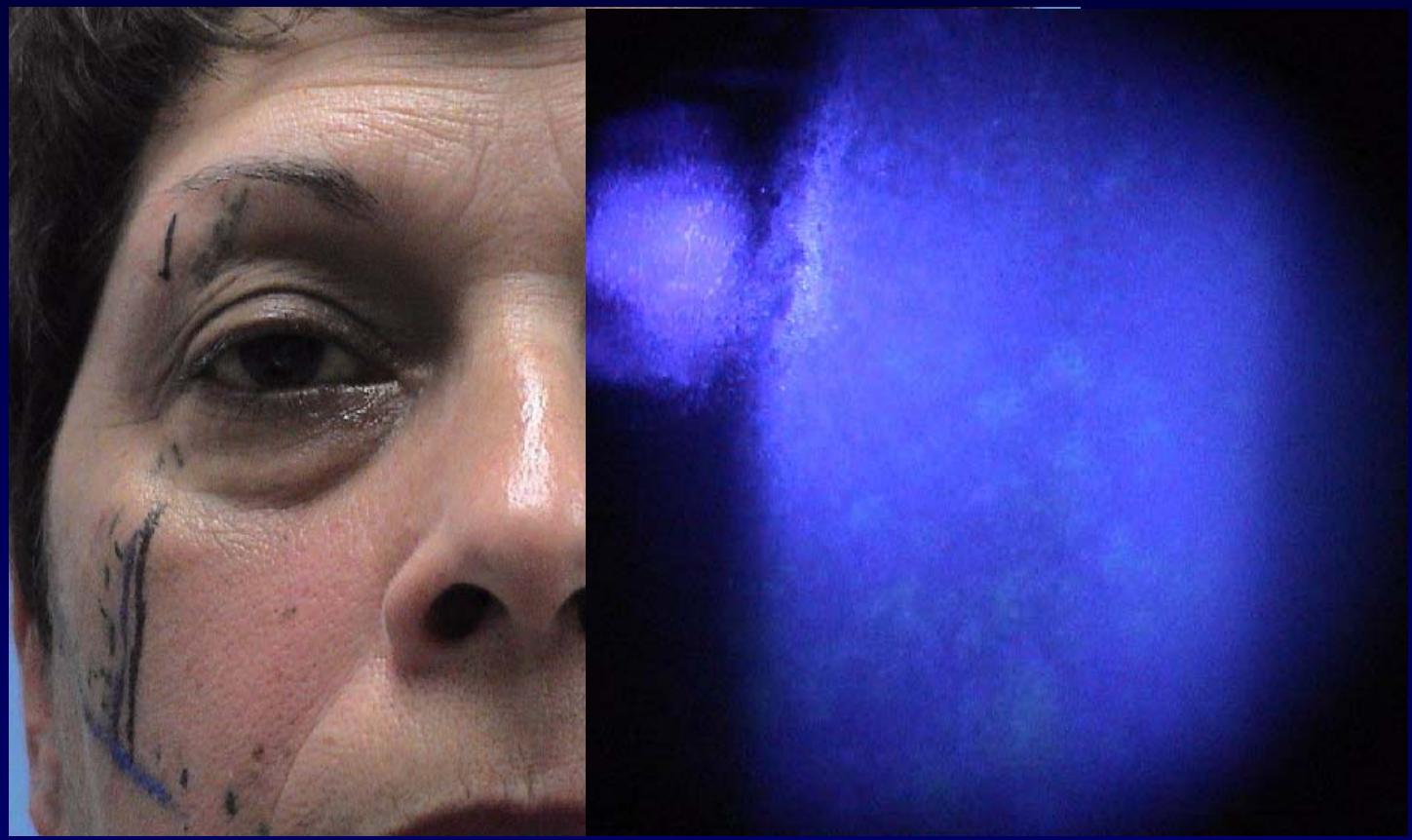
CTC AEv3.0 grading system for toxicity for a given sign or symptom	General guideline used to grade toxicity.	General guideline used to grade a given sign or symptom as it relates to eye or vision
Grade 1	Present. Asymptomatic.	No vision loss. Asymptomatic.
Grade 2	Symptomatic. Requiring medical intervention. Affecting function of the organ but not interfering with activities of daily living	Vision loss present. Visual acuity greater or equal to 20/40.
Grade 3	Symptomatic. May require surgical intervention.Affecting function of the organ and interfering with activities of daily living (ADL).	Vision loss present. Visual acuity less than 20/40 and greater than or equal to 20/200.
Grade 4	Complete loss of function or loss of organ.	Blindness and/or events leading to blindness such as perforation or enucleation.

Grade I –Ocular surface disease

Grade II

Severe photophobia

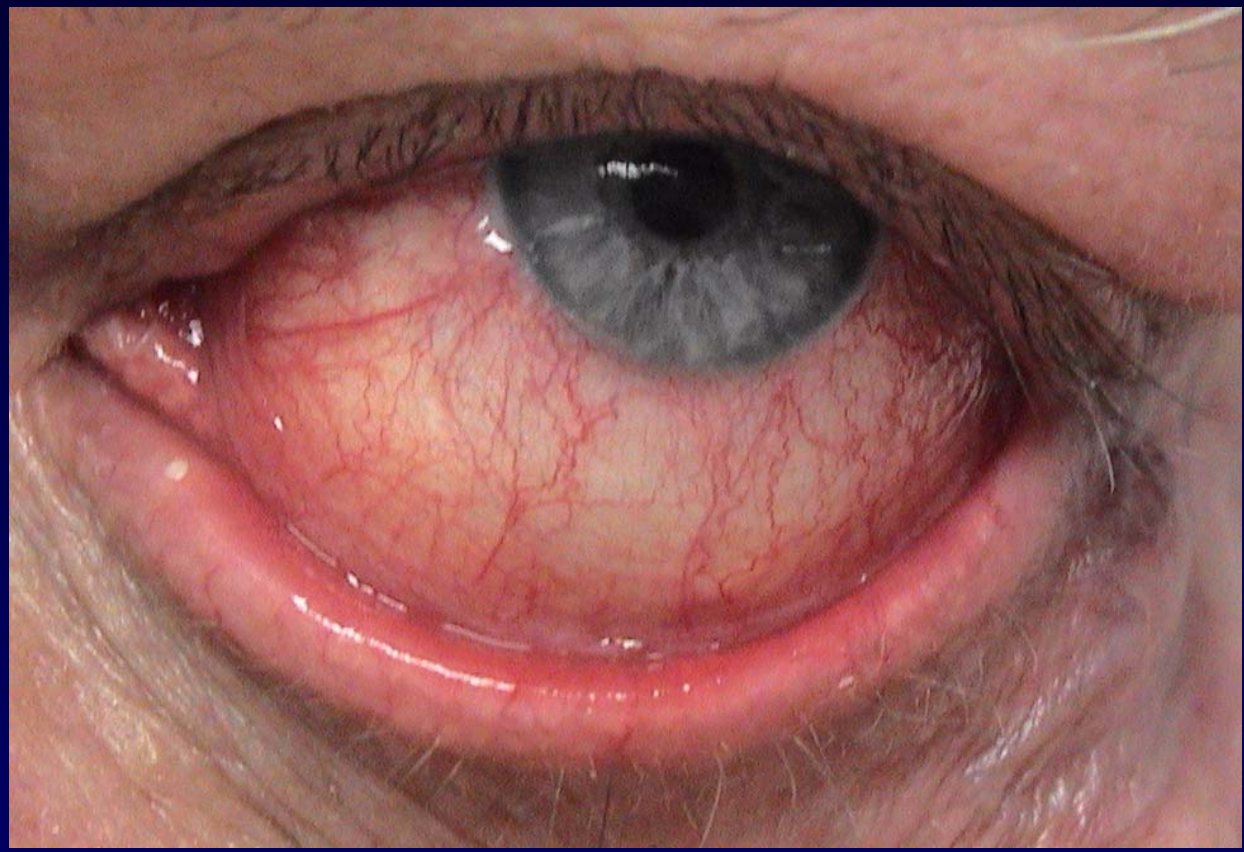
Grade II Ocular surface disease



Severe keratitis

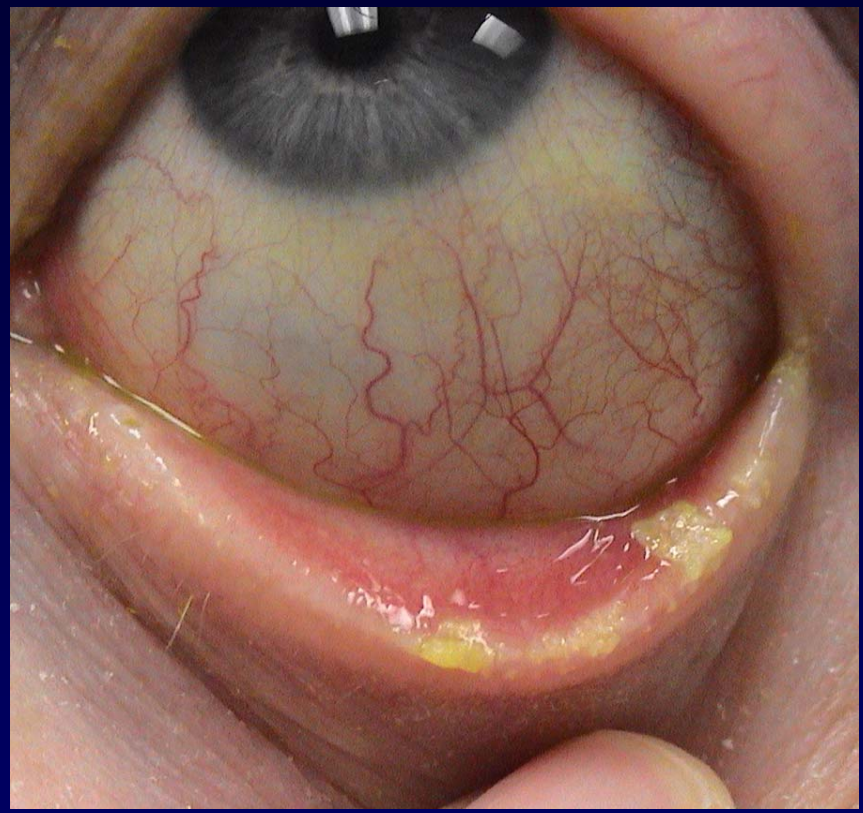
Grade II – Ocular Surface disease

Lid telangiectasis, symblepharon of lower lid with shortened inferior fornix, chronic kerato-conjunctivitis sicca/



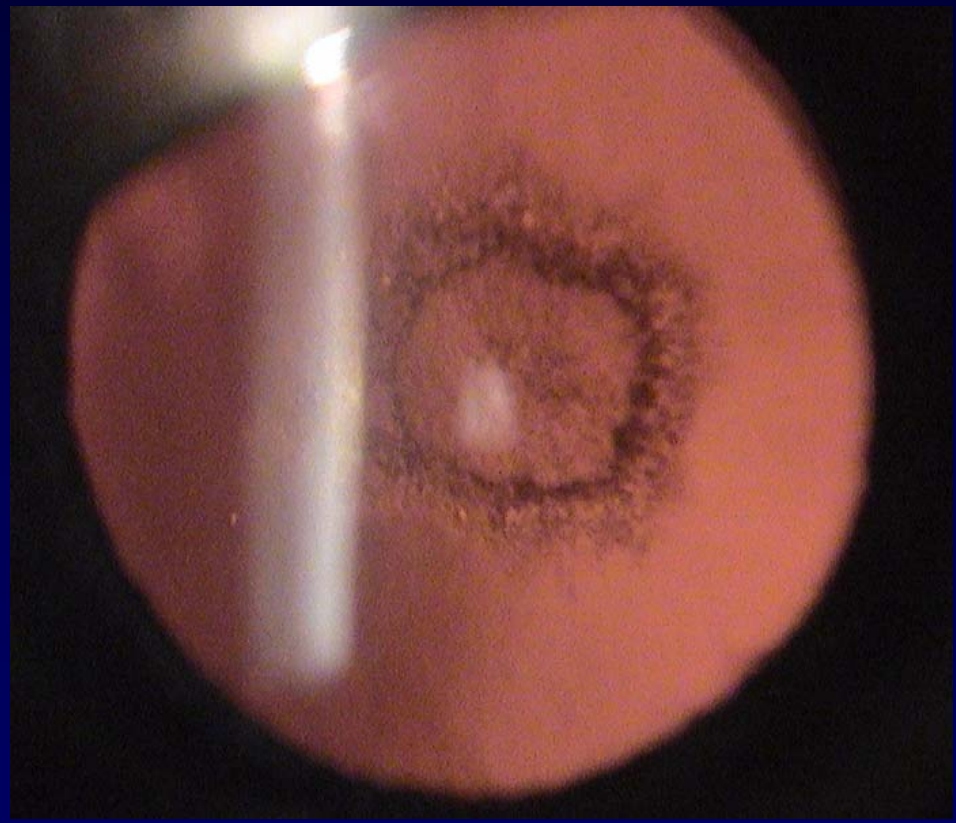
Requiring punctual plugs, aggressive lubrication and occasional topical steroid medication. Not affecting activities of daily living.

Grade III



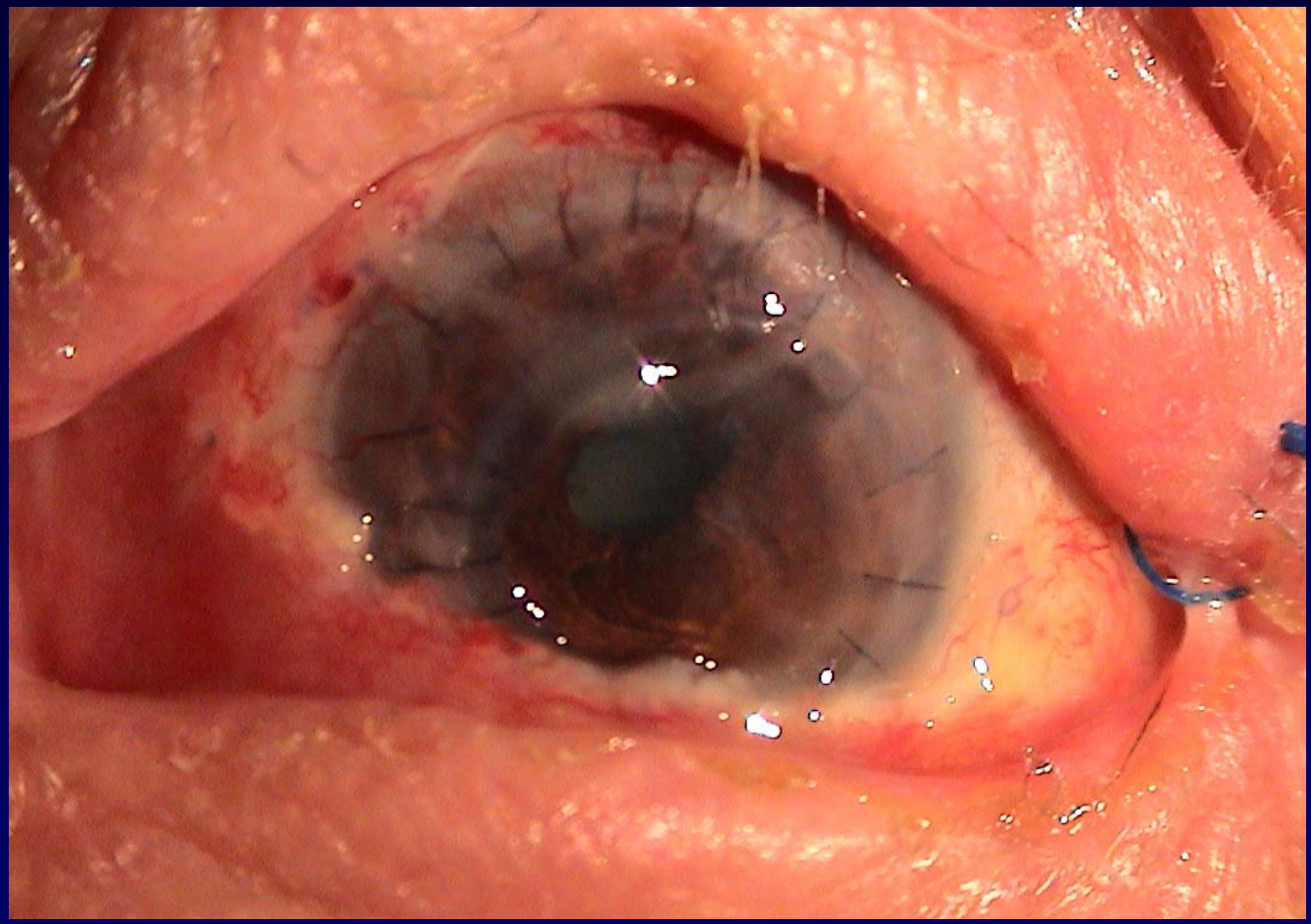
Lower lid palpebral conjunctival keratinization with severe keratopathy, leading to visual acuity of 20/50 and affecting ADL. Status post multiple surgical debridement. In need of amniotic membrane graft.

Grade III



Posterior subcapsular cataract in 21 year old woman. Visual acuity 20/200 by bright acuity test, affecting ADL. Requiring surgery.

Grade IV



Neurotrophic cornea, leading to persistent corneal epithelial defect. Status post corneal transplantation, with progressive corneal graft thinning, resulting in perforation (see iris plug coming though the corneal tissue).

Grade IV

Corneal perforation with
pan-endophthalmitis

MDACC Eye Treatment System

Ocular Proton Therapy: Can we do better?

- Reduce local toxicity
  - Enucleation rate; vision loss, etc.
  - Hyperfractionation ?
  - Deduced dosing for patients with co-morbidity?
- Quality of life
  - validated surveys ?

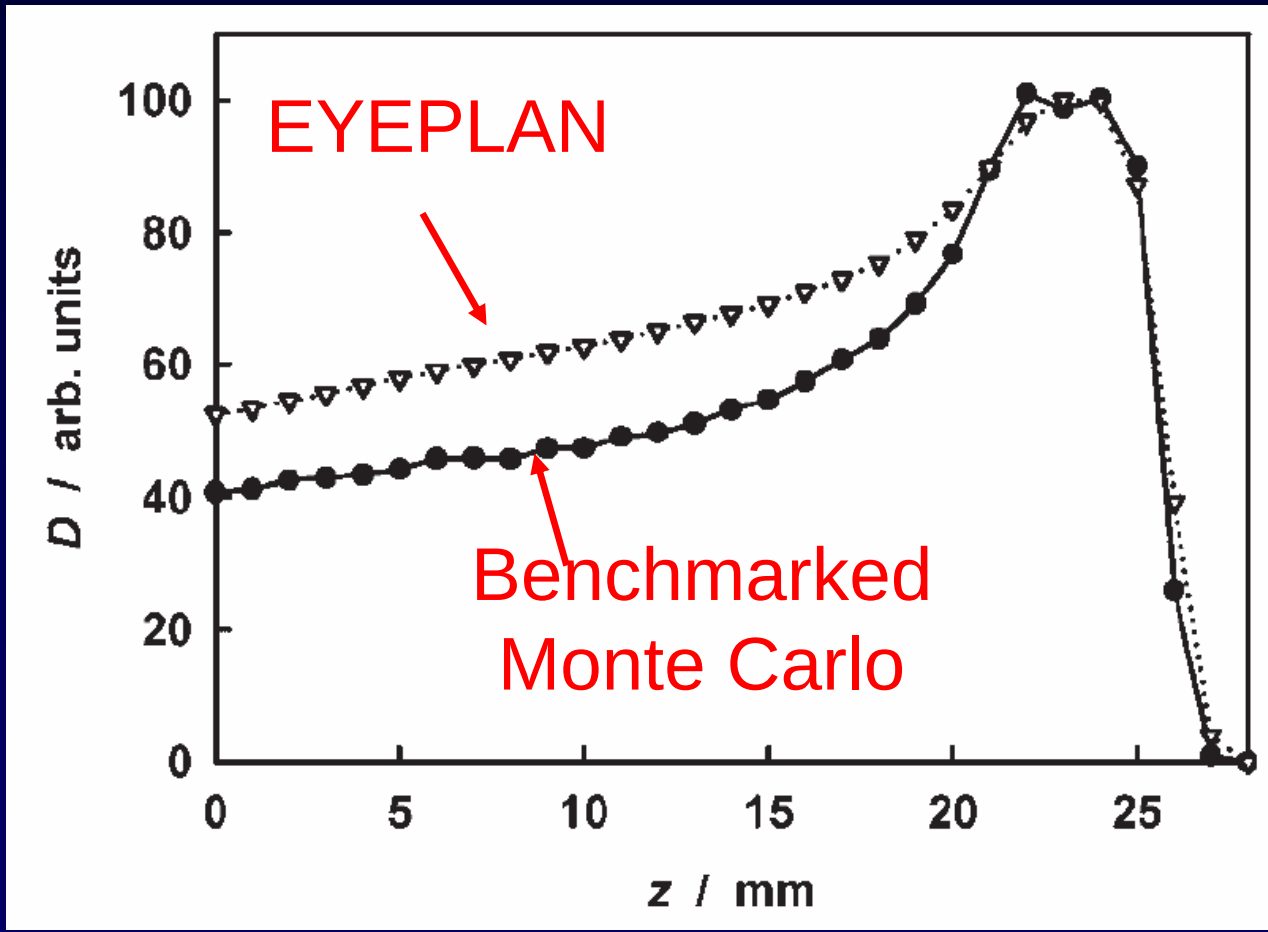
Ocular Proton Therapy: Can we do better?

- Increase local control
  - Planning systems ?
  - Improved homogeneity of treatment dose in the tumor ?
- Late effects (2nd CA, especially in patients < 50 y old)
  - Neutrons ?

Toxicity: Can we improve quality of dose response functions?

Dose difference due to overly simplistic modeling of beam modulation.

Modulation width = 4 mm



Koch and Newhauser. *Rad. Prot. Dosim.* (2005)

Newhauser, Koch, Hummel, Ziegler, Titt. *Phys. Med. Biol.* (2005)

Toxicity: How accurate is the Eyeplan dose prediction for other modulation widths?

Mod. width

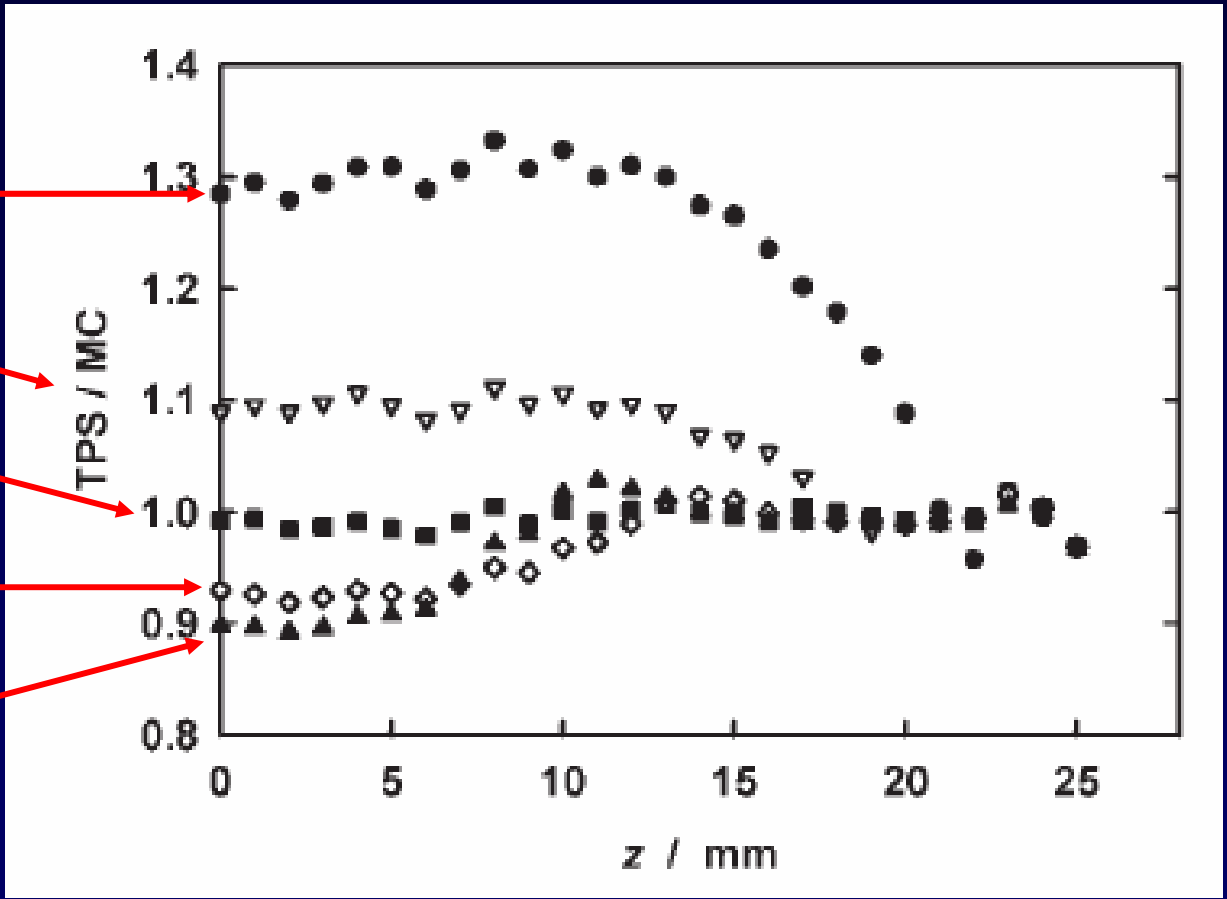
4 mm

7 mm

10 mm

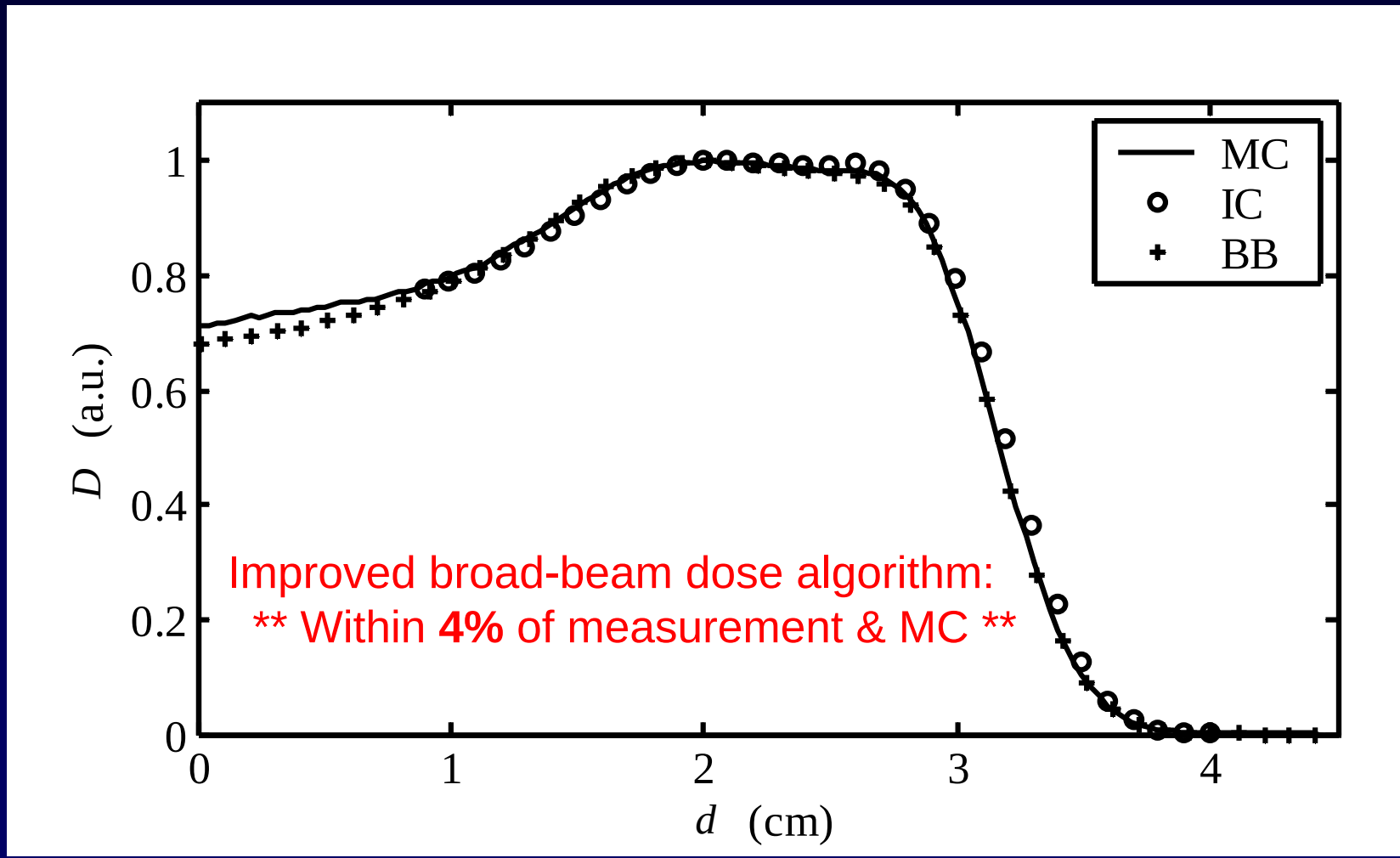
14 mm

17 mm



Koch and Newhauser, Rad. Prot. Dosim. (2005)

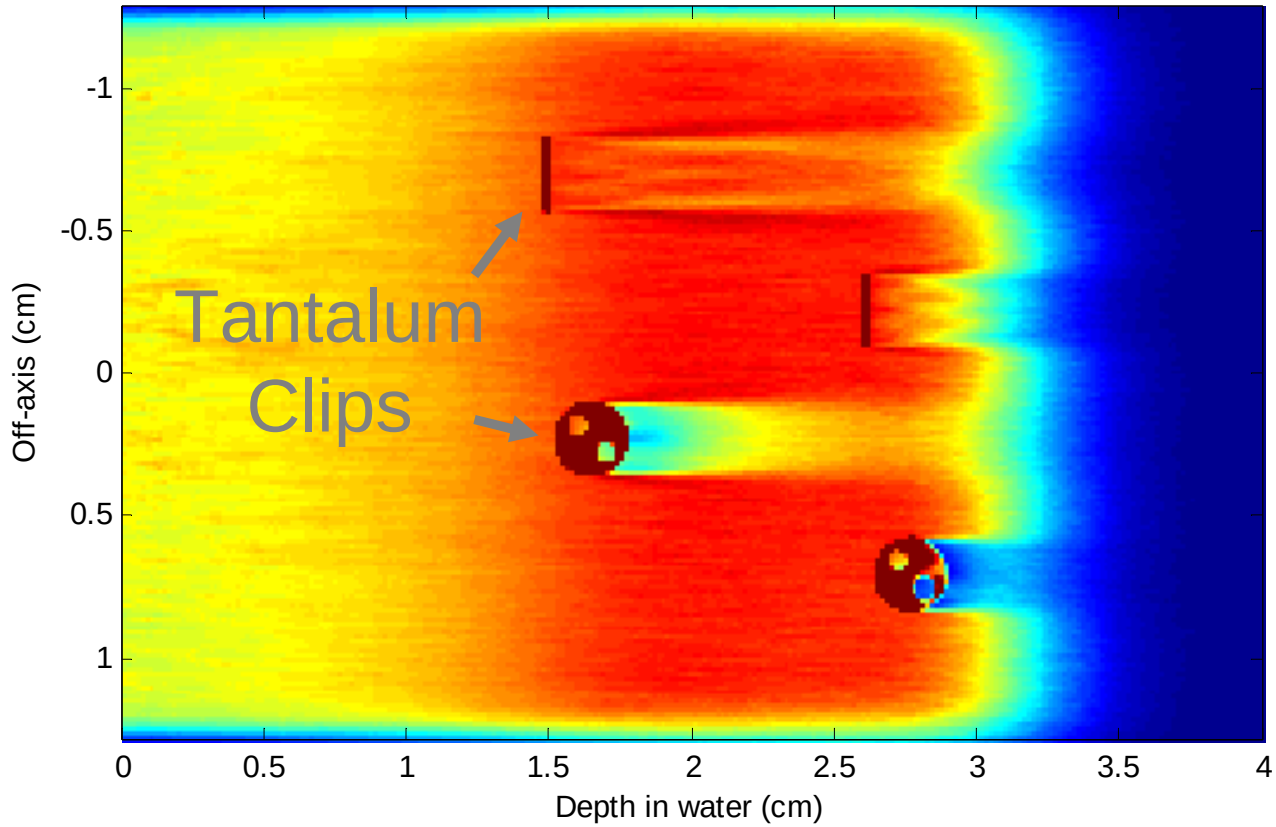
Toxicity: More accurate dose predictions will translate to more accurate dose response functions



Nich Koch. Ph. D. doctoral dissertation, UTMDACC 2006.

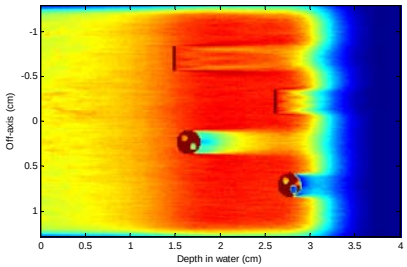
Local Control: Can fiducial markers cause shadows?

Beam



Newhauser, Koch, Gombos, et al. (in preparation)

Local Control?: Big shadows => placement strategy is key



Normalized to Control Maximum

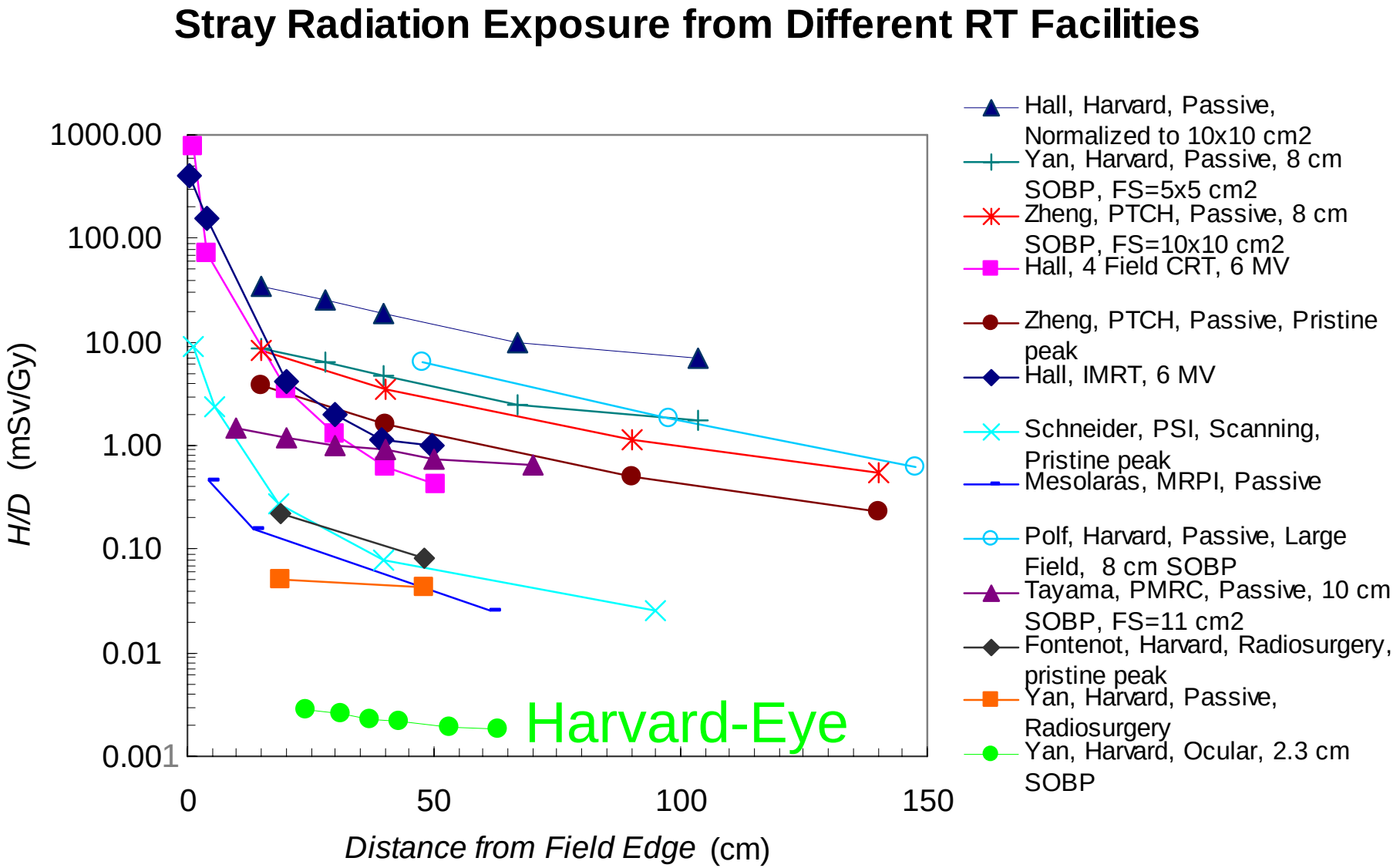
Depth in water (cm)

Perp. Distal end
Perp. Proximal end
Parallel Distal end
Parallel Proximal end
Control

Dose Shadows

Newhauser, Koch, Gombos, et al. (in preparation)

Late Effects: Neutron dose small, but uncertainty large



Zheng, Newhauser, Fontenot, Mohan, et al. (in preparation)

Summary

Ocular toxicity from radiotherapy can impact patients' quality of life.

Using expanded metrics for grading ocular toxicity may provide for easier comparison between treatment modalities.

Strategies to reduce local toxicity while retaining and/or improving local control should be considered.

skim@mdanderson.org

Choroidal Hemangioma

Irradiation treatment of choroidal hemangiomas

Zografoz L et al. J Fr Ophtalmol. 1989;12(11):797-807

24 patients -

Proton beam therapy for posterior pole circumscribed choroidal haemangioma.

Lee V, **Hungerford JL**. Eye. 1998;12 (Pt 6):925-8.

3 patients – similar toxicity as conventional low-dose, lens sparing external beam treatment or brachytherapy

Sturge-Weber syndrome: medical management of choroidal hemangiomas

Reuman, F et al J Fr Ophtalmol. 2002 Apr;25(4):399-403

7 patients: 2/7 with proton – good for well circumscribed hemangioma.

5/7 External beam for diffuse disease

Low-dose proton beam therapy for circumscribed choroidal hemangioma.

Frau E et al Arch Ophthalmol. 2004 Oct;122(10):1471-5

17 patients, 12 mo followup, no toxicity, 94% with >2 Snellen Va improvement

Choroidal Hemangioma

Low-Dose Proton Beam Therapy for Circumscribed Choroidal Hemangiomas

Eric Frau, MD; Frank Rumen, MD; George Noel, MD; Sabine Delacroix, PhD; Jean-Louis Habrand, MD; Hervé Offret, MD

ARCH OPHTHALMOL/VOL 122, OCT 2004

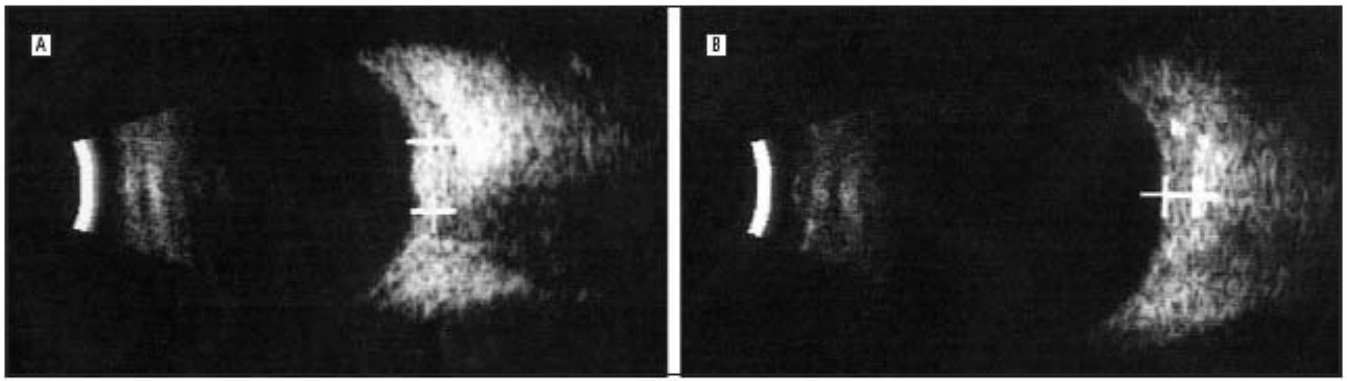


Figure 2. Ultrasonographic study, A, showing a solid choroidal lesion, high internal reflectivity, and a thickness of 2.5 mm. B, Echographic aspect 3 years after proton beam therapy. The tumor is almost flat; the patient's final visual acuity was 20/25.

20 CGE in 5 fractions

Proton radiotherapy as an alternative to exenteration in the management of extended conjunctival melanoma

Graefe's Arch Clin Exp Ophthalmol

Henrike Wuestemeyer
Wolfgang Sauerwein
Daniel Meller
Pierre Chauvel
Andreas Schueler
Klaus-Peter Steuhl
Norbert Bornfeld
Gerasimos Anastassiou

Nice, France

Essen, Germany

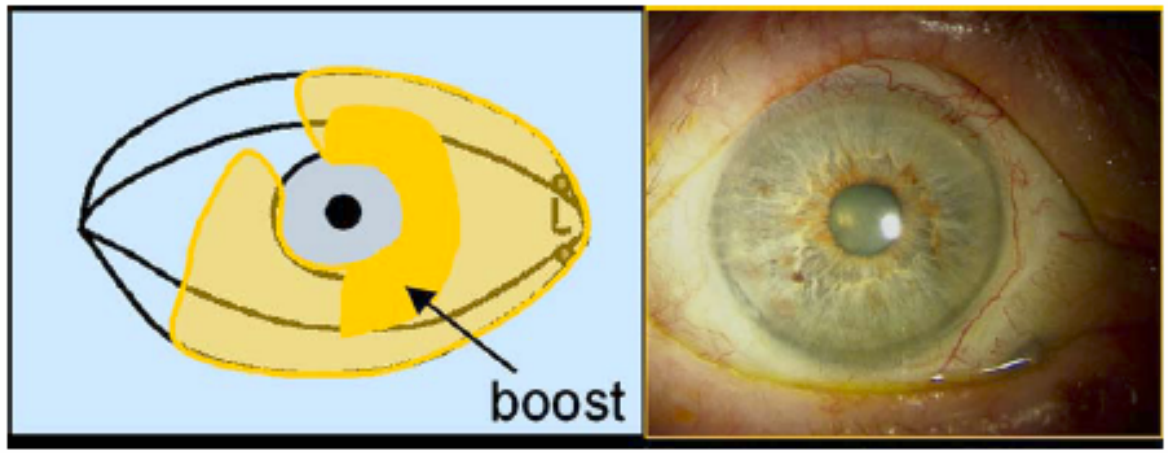


Fig. 1 This is a case of a de novo conjunctival melanoma. The colour draw shows the large target area, because of the diffuse extension, and the smaller boost field including almost 50% of the limbus. The clinical picture shows the eye at 27 months after treatment. So far no recurrence has occurred. The visual acuity has remained stable (0.4). The patient reports only mild sicca-symptoms

PHASE I/II STUDY OF PROTON BEAM IRRADIATION FOR THE TREATMENT OF SUBFOVEAL CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION: TREATMENT TECHNIQUES AND PRELIMINARY RESULTS

LESLIE T. YONEMOTO, M.D.,* JERRY D. SLATER, M.D.,* ERIC J. FRIEDRICHSEN, M.D.,† LILIA N. LOREDO, M.D.,* JEFFREY ING, M.D.,† JOHN O. ARCHAMBEAU, M.D., F.A.C.R.,* SANDRA TEICHMAN, B.S.N.,* MICHAEL F. MOYERS, PH.D.,* PAUL A. BLACHARSKI, M.D.† AND JAMES M. SLATER, M.D., F.A.C.R.*

Int. J. Radiation Oncology Biol. Phys., Vol. 36, No. 4, pp. 867–871, 1996

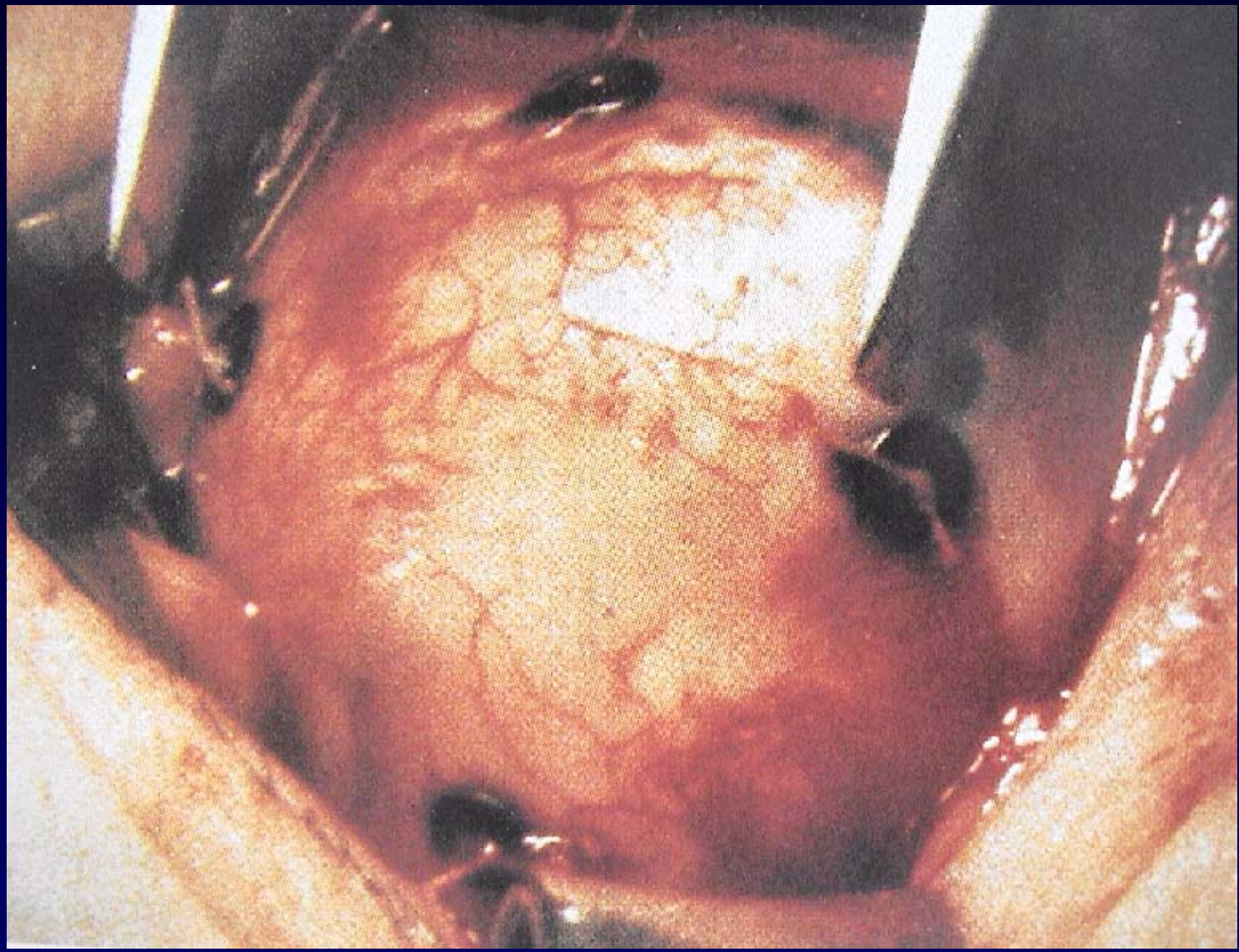
20 patients; 8 Gy single fraction;

Proton Therapy for Exudative Age-related Macular Degeneration: A Randomized, Sham-controlled Clinical Trial

Thomas A. Ciulla, MD, Ronald P. Danis, MD, Susan B. Klein, PhD, Victor E. Malinovsky, OD, P. Sarita Soni, OD, Linda M. Pratt, RN, Newell O. Pugh, MD, James G. Morphis, MD, Charles Bloch, PhD, and John Cameron, PhD

Am J Ophthalmol 2002

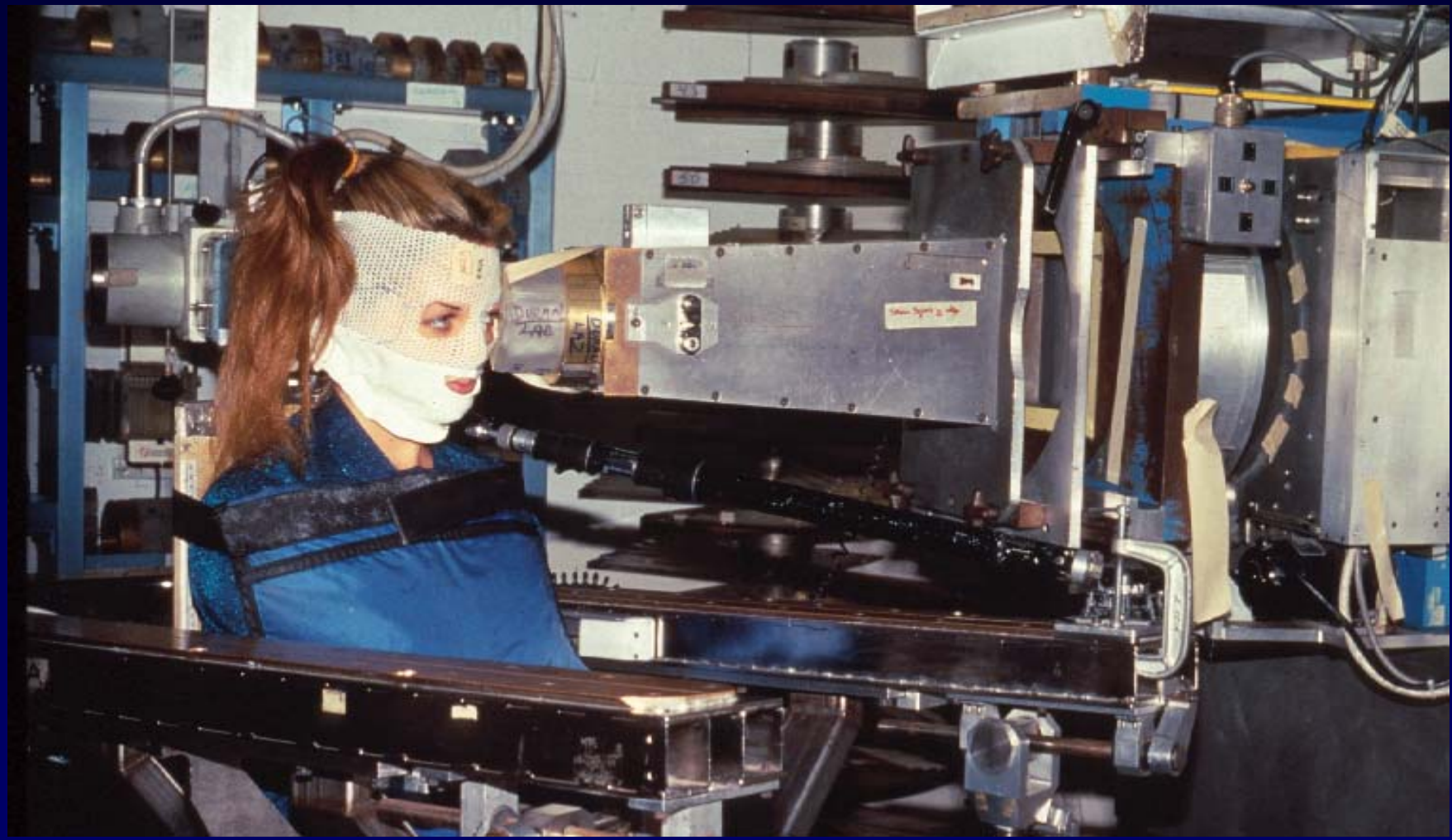
Eye Treatment Nozzle Factory Tests



Intra-operative placement of tantalum rings

From Albert and Jakobiec 2nd Ed.

Lacrimal tumors (Adenoid cystic carcinoma)



Courtesy of Drs. Sutula and Libsche
Harvard cyclotron

Advantage of Proton Therapy

- Reduces damage to surrounding tissues
- Greatly reduces side effects
- Treatment of choice for lesions close to sensitive areas of the body