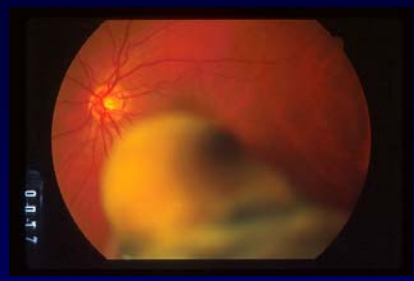
PROTON BEAM IRRADIATION OF CHOROIDAL MELANOMAS



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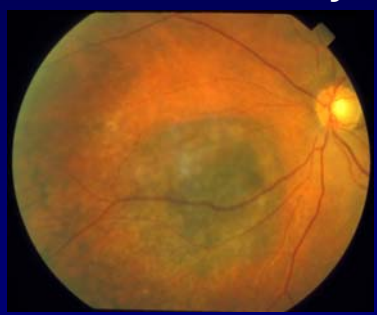
INTRODUCTION

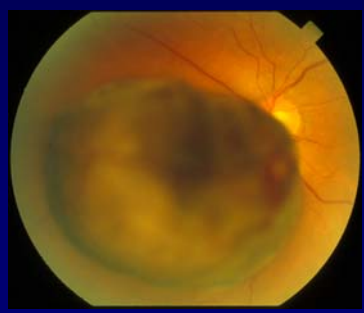
- Rare malignancy (6 cases per million in the US)
- Most common primary intraocular malignancy in the adult
- Threatens both sight and life

NATURAL HISTORY

- Intraocular melanomas may arise from benign pigmented lesions
- 1 in 5000 choroidal nevi will transform to melanoma in one year



9/17/1992



7/19/1993

RADIOTHERAPY

Radiotherapy has replaced enucleation as standard treatment modality

Advantages:

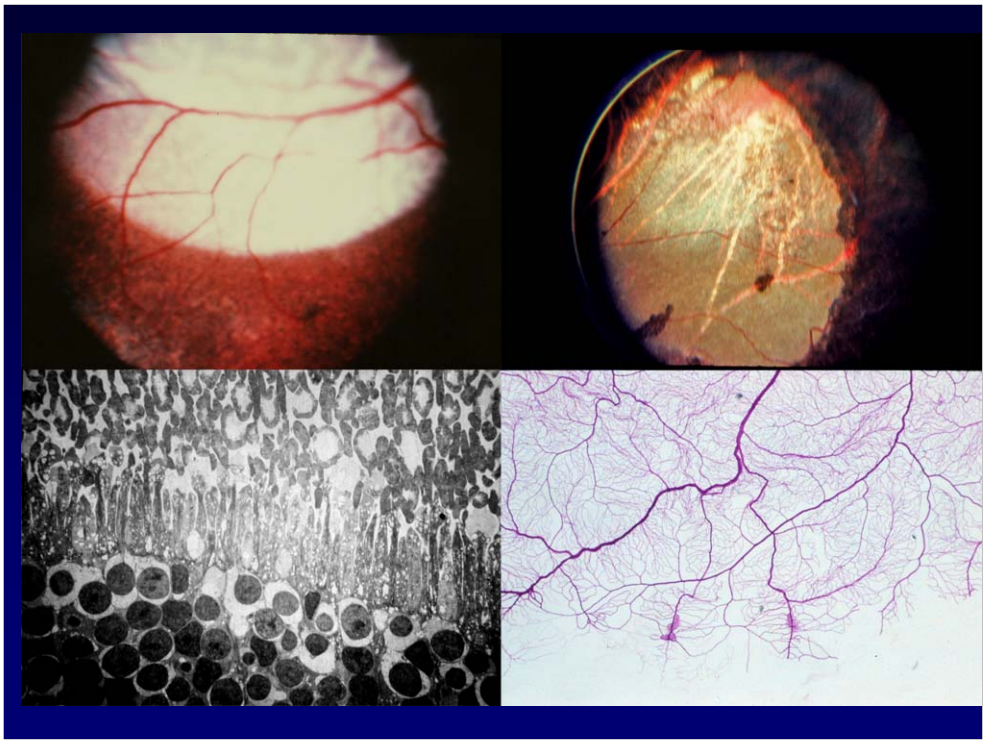
- preservation of eye
- retention of useful vision
- no increased risk of metastasis

RADIOTHERAPY

- Radioactive plaques (sutured to sclera)
  - iodine 125
  - ruthenium
- External beam radiation
  - protons
  - Gamma knife

PROTON THERAPY

- Proton beam irradiation
  - offers more uniform and highly localized dose distributions
  - tumors near macula and optic nerve may be treated while preserving vision in some patients
  - large tumors can be treated

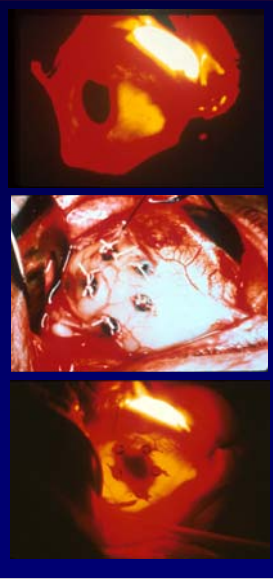


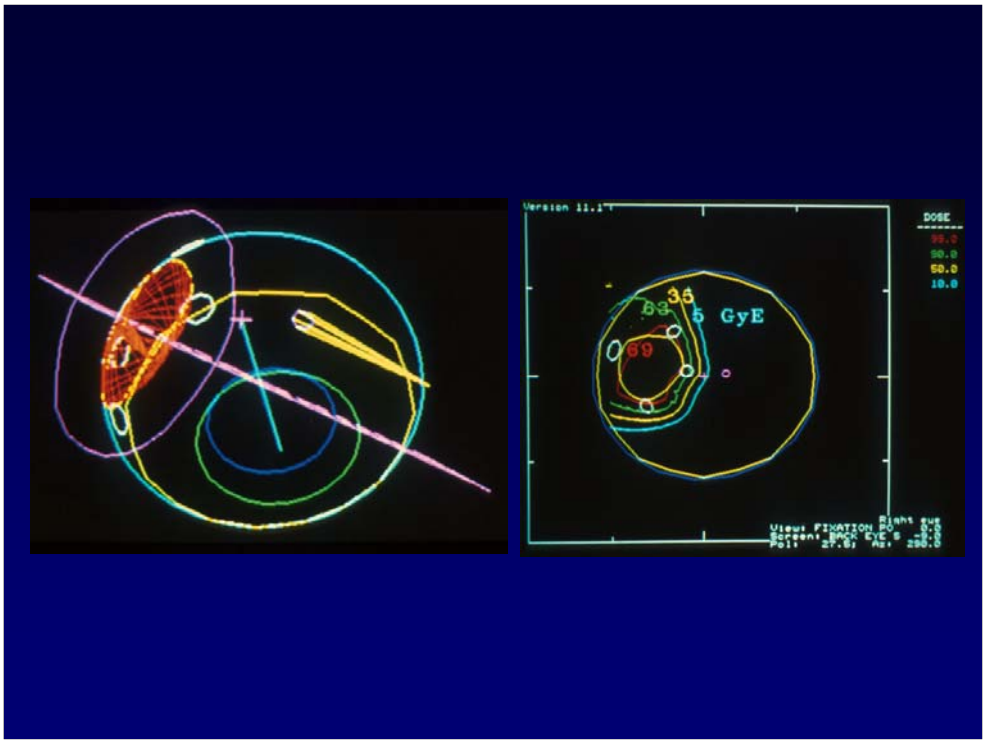
TREATMENT PROTOCOL

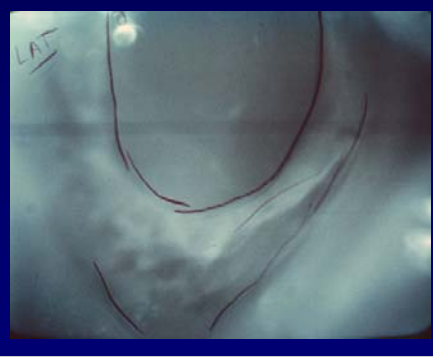
Proton Irradiation

- Tumors localized through surgical placement of tantalum rings

- 70 cobalt Gy equivalent delivered in 5 fractions




Version 11.1
DOSE
90.0
50.0
10.0
35
53
5 GyE
69
Right eye


LAT

PROTON THERAPY AT MEEI

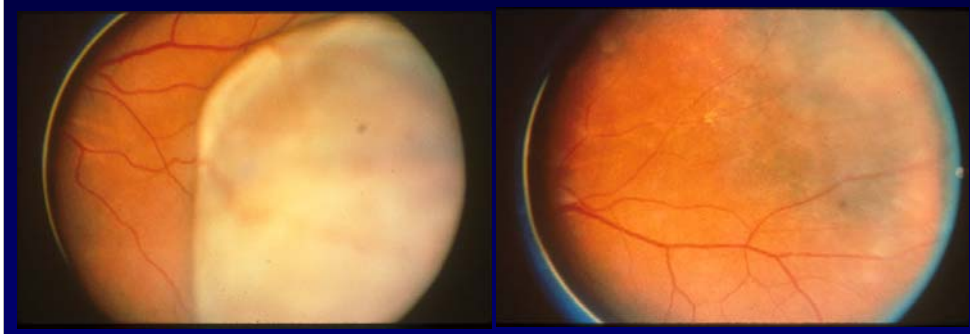
2069 patients treated with proton irradiation for intraocular melanoma between 1975 and 1997 were evaluated for the following outcomes:

- local recurrence
- survival
- vision loss
- eye retention
- radiation complications

PROTON THERAPY AT MEEI TUMOR CHARACTERISTICS

Pigmentation	34% heavy
Origin	7% ciliary body
LTD	13.2 mm (median)
Height	5.3 mm (median)
Posterior margin	68% within 2 DD of optic nerve or macula

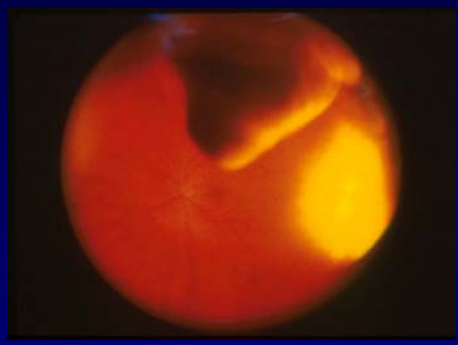
COMPLETE REGRESSION CHOROIDAL MELANOMA



Before proton therapy

After proton therapy

PARTIAL REGRESSION CHOROIDAL MELANOMA

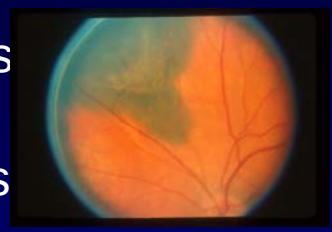


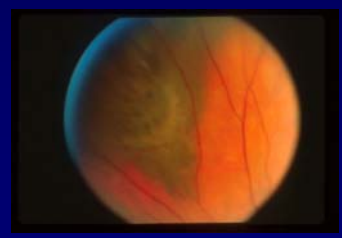
Before proton therapy

5 years after proton therapy

LOCAL RECURRENCE

- 60 (2.9%) recurrences
  - 45 documented cas
  - 15 suspect cases
- Earliest: 5.2 months
- Latest: 10.5 years





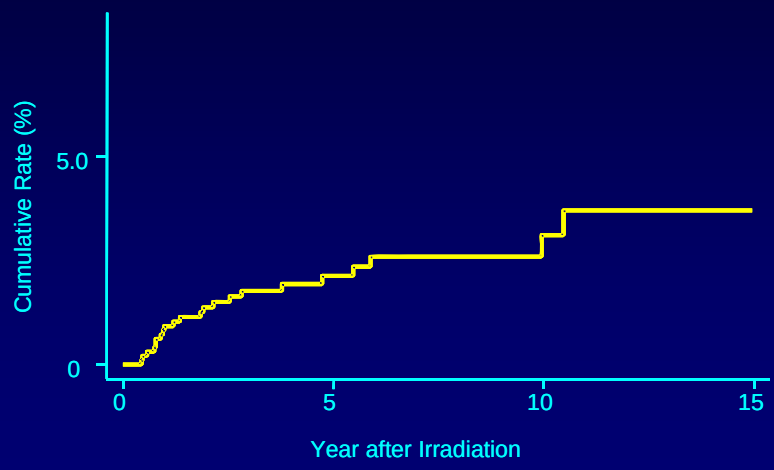
RISK FACTORS FOR LOCAL RECURRENCE

- Larger tumors (LTD)
- Anterior tumor margin involving ciliary body or iris
- Lighter irises

CUMULATIVE RATES OF LOCAL RECURRENCE

year post-rx	percent	95% CI
5	3.0	2.3-4.0
10	4.2	3.2-5.5
15	4.8	3.6-6.5

CUMULATIVE RATES OF LOCAL RECURRENCE



METASTATIC MELANOMA

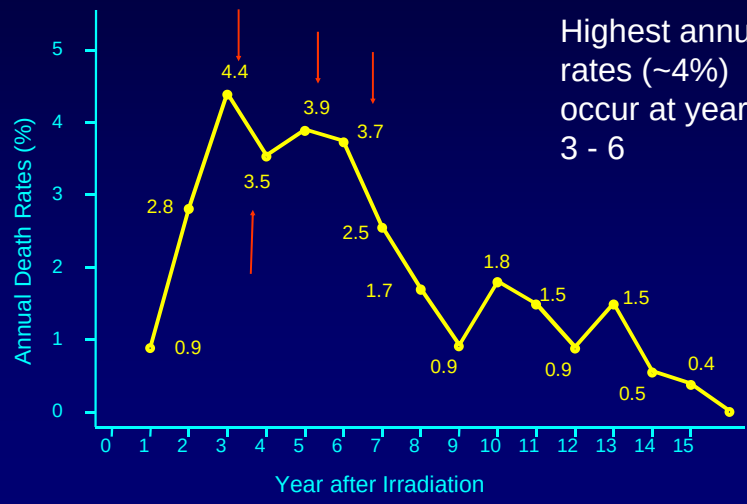
- 408 patients died of metastatic melanoma
- 89% with liver metastasis
- Earliest death: 3 months post therapy
- Latest death: 16 years post therapy
- Survival rates after diagnosis of metastasis were poor: 20% at 1 year
  6% at 2 years

METASTATIC MELANOMA

Cumulative Mortality Rates

Year post-rx	All cause	Metastatic melanoma
5	21%	14%
10	36%	23%
15	48%	27%

ANNUAL MELANOMA-RELATED MORTALITY RATES



Highest annual rates (~4%) occur at years 3 - 6

RISK FACTORS FOR METASTATIC DEATH

- LTD
- more pigmented tumor
- symptoms at presentation
- older age at dx
- ciliary body tumor origin
- extrascleral extension
- light iris color (green or blue)

EYE LOSS

- 179 patients (8.7%) underwent enucleation
  - 42 due to tumor regrowth
- Earliest enucleation: 2 months post therapy
- Latest enucleation: 14 years post therapy

RISK FACTORS FOR EYE LOSS

- Larger tumor size (height and LTD)
- Tumor near macula and optic disc (within 2 dd)
- Heavily pigmented tumor
- Bilobed or diffuse tumor

CUMULATIVE RATES OF EYE LOSS

year post-rx	percent	95% CI
5	9	7-10
10	12	10-14
15	16	13-20

CUMULATIVE RATES OF VISION LOSS*

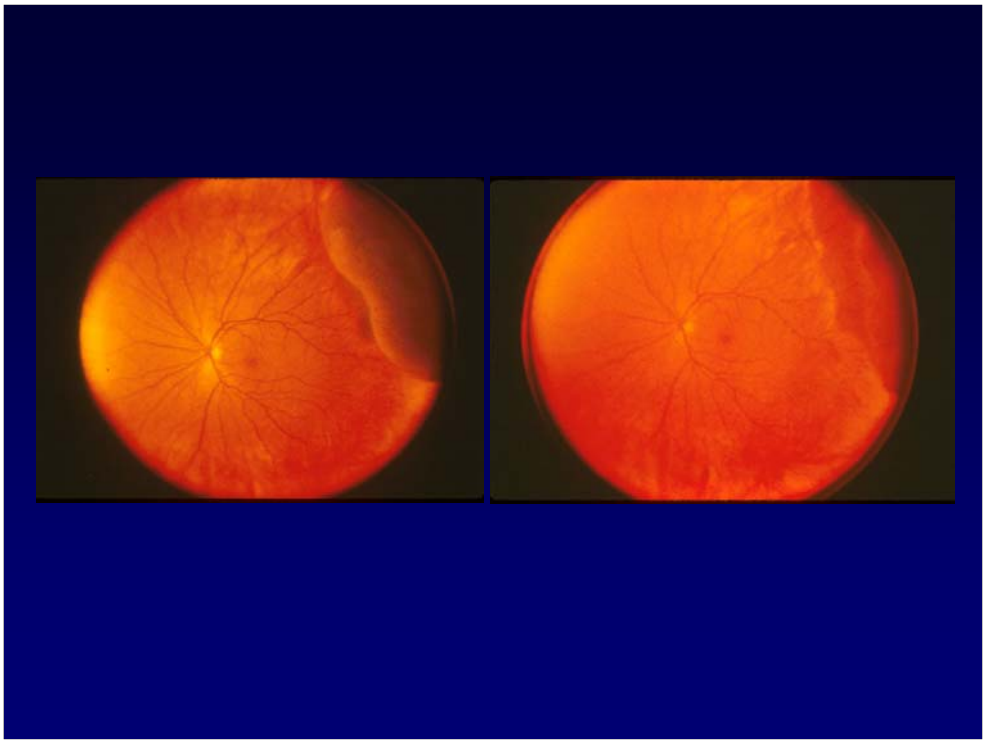
Patients with BLVA of 20/100 or better

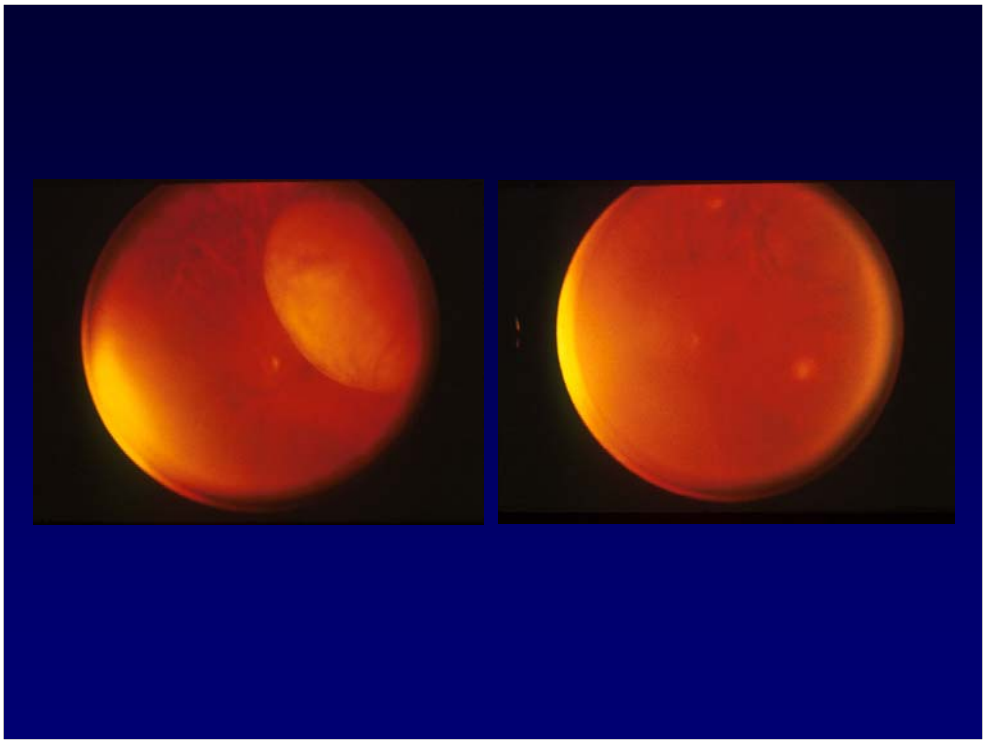
year post-rx	percent	95% CI
5	52	50-55
10	65	62-68
15	71	66-75

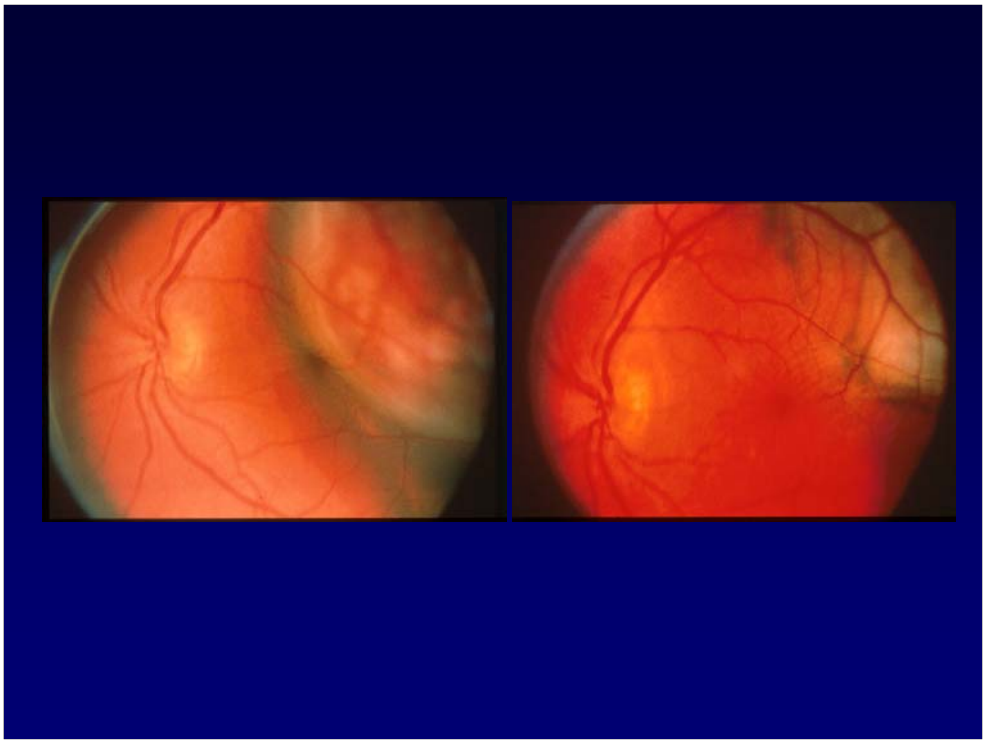
*to worse than 20/200

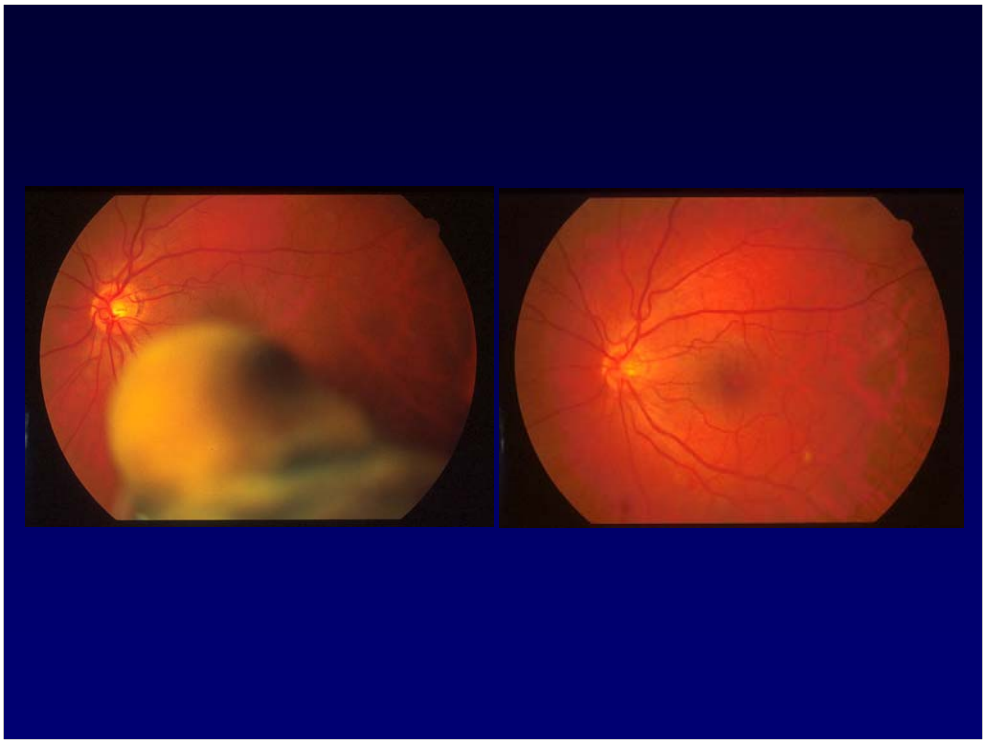
RISK FACTORS FOR VISION LOSS

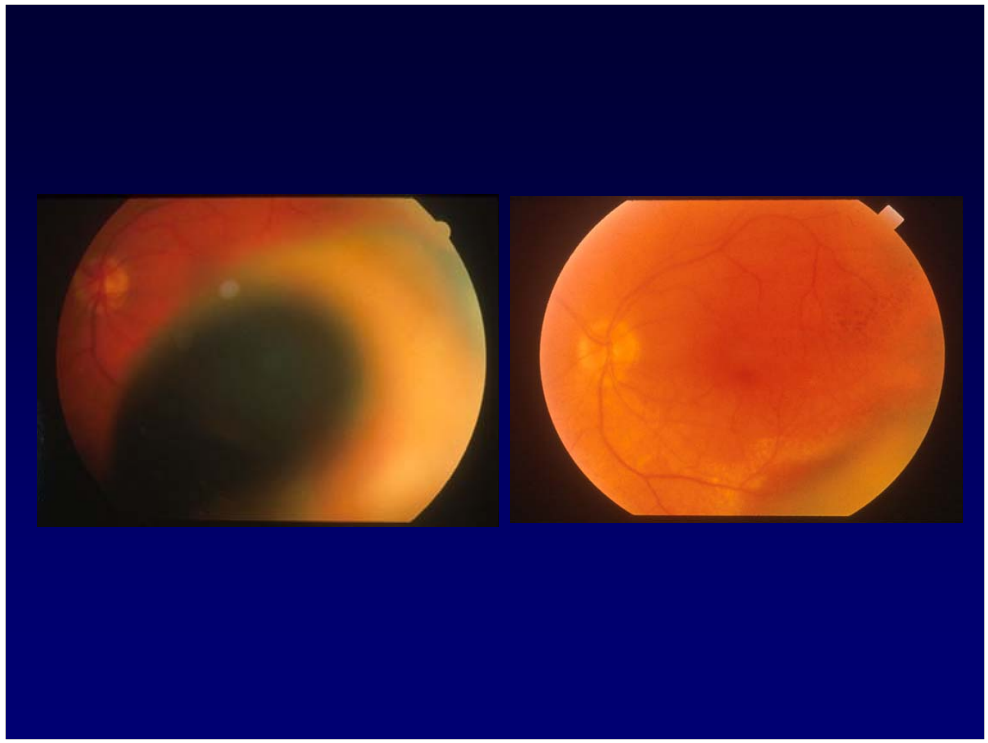
- Larger tumor size (height & LTD)
- Tumor near macula or optic disc (within 2 dd)
- Complications, e.g., retinal detachment
- Poorer pre-treatment visual acuity (20/30 or worse)
- Diabetes

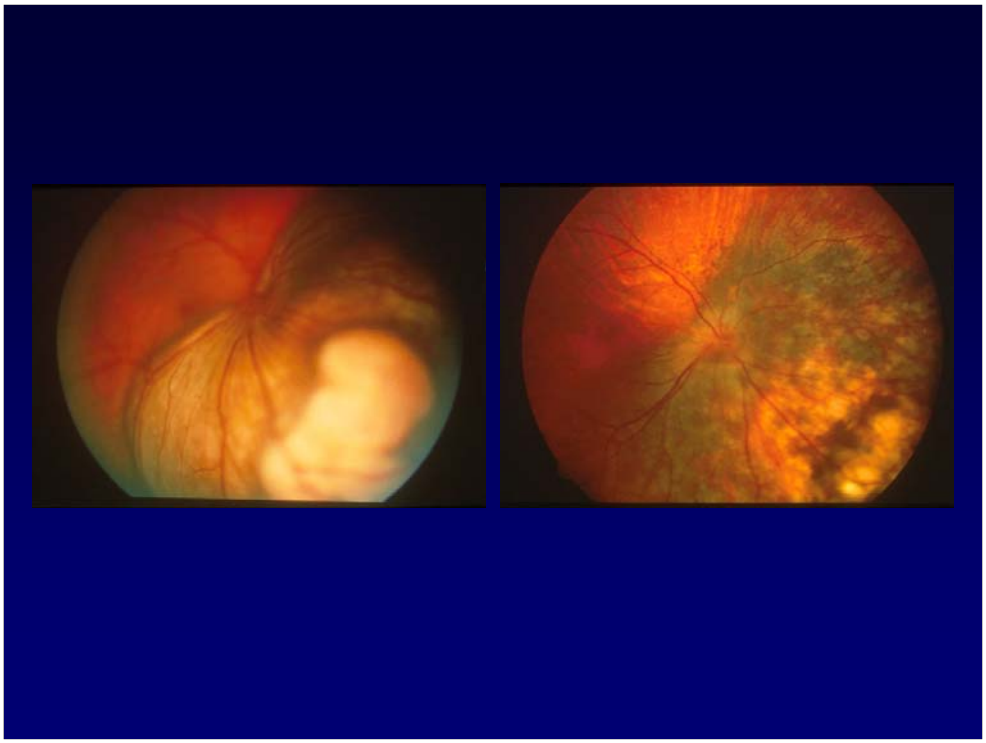








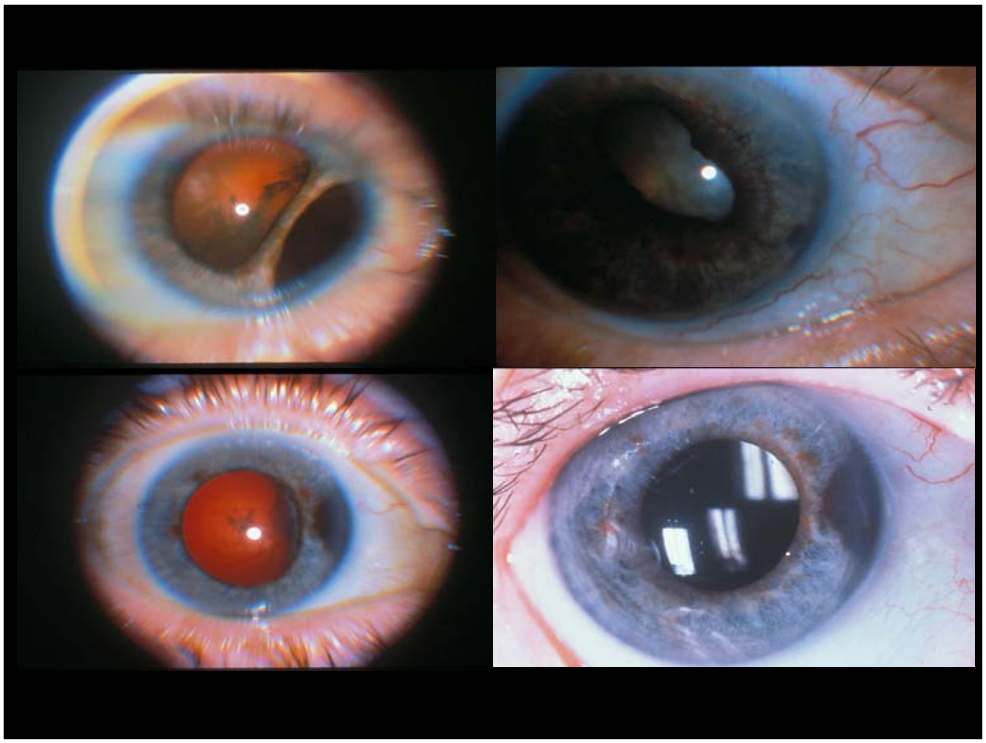




CUMULATIVE RATES OF OCULAR COMPLICATIONS

Anterior Segment

year post-rx	NVG	PSC
3	12.8	18.8
5	15.9	27.9
10	17.6	35.3



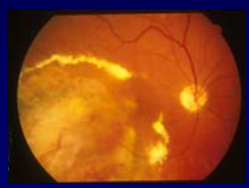
CUMULATIVE RATES OF OCULAR COMPLICATIONS

Posterior Segment

Year post-rx	Maculopathy	Papillopathy
3	30.6	19.7
5	39.8	23.9
10	48.3	27.0

RADIATION VASCULOPATHY

Radiation maculopathy and papillopathy were associated with distance of tumor from macula and optic disc respectively.



	Maculopathy		Papillopathy	
	0 DD	≥ 4 DD	0.5 DD	> 3 DD
% of patients	69	8	65	1

SUMMARY

- 4.2% of patients experienced tumor regrowth at 10 years post irradiation
- 23% of patients died from metastasis at 10 years post irradiation
- 34% of patients retained visual acuity of 20/200 or better at 10 years post irradiation
- <10% of patients underwent enucleation

PARAPAPILLARY TUMORS
Subgroup analyses

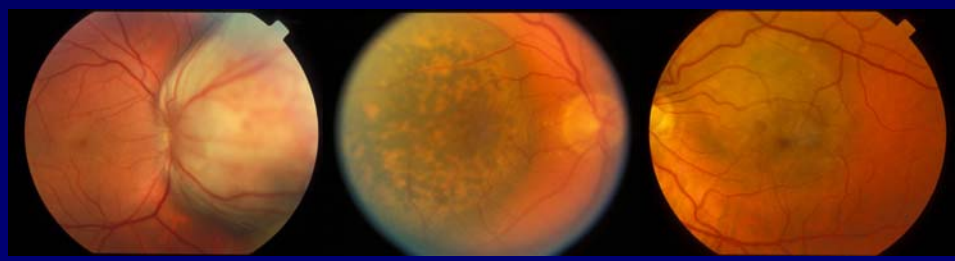
Inclusion criteria:

- Patients with tumors $\leq$ 1 DD from optic nerve
- Treated with protons between January 1985 and December 1997

STUDY SUBJECTS

573 patients

- 306 (53%) had tumors touching the optic nerve
- 240 (42%) had tumors also extending into the macula
- 128 (22%) had tumors touching both structures



RESULTS

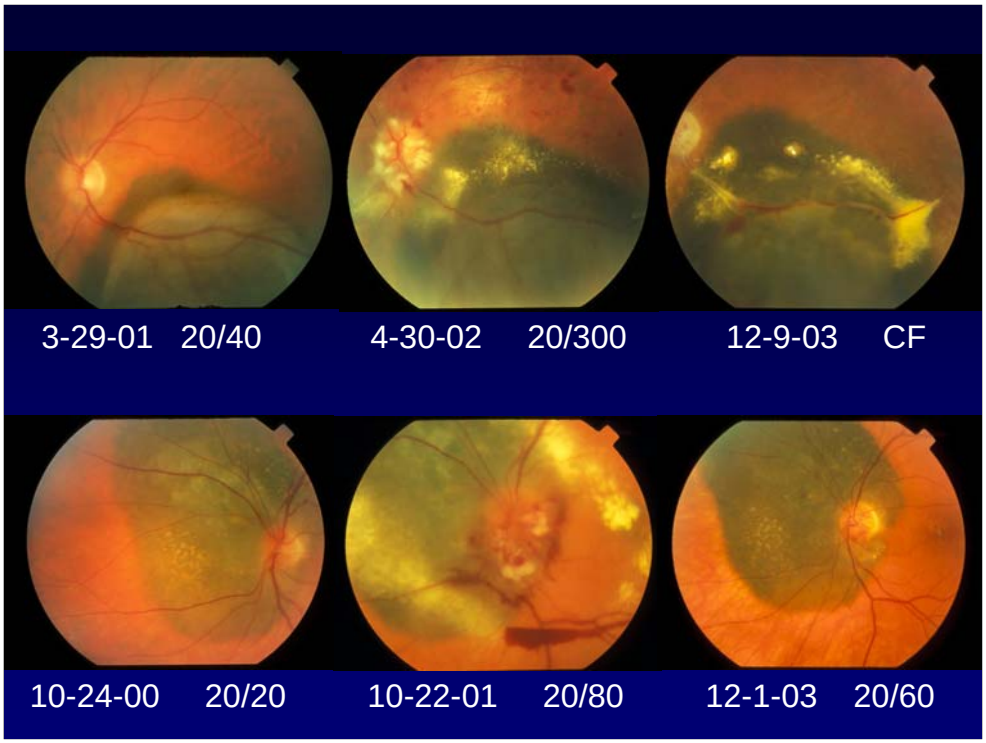
Tumor Recurrence

- 13 (3%) patients with definitive regrowth
- 5 (<1%) patients with suspected regrowth (diagnosed outside MEEI)

RESULTS

Complications

- Radiation papillopathy developed in 258 (45%) eyes
- Radiation maculopathy developed in 276 (48%) eyes
- Most cases occurred 2-3 years after irradiation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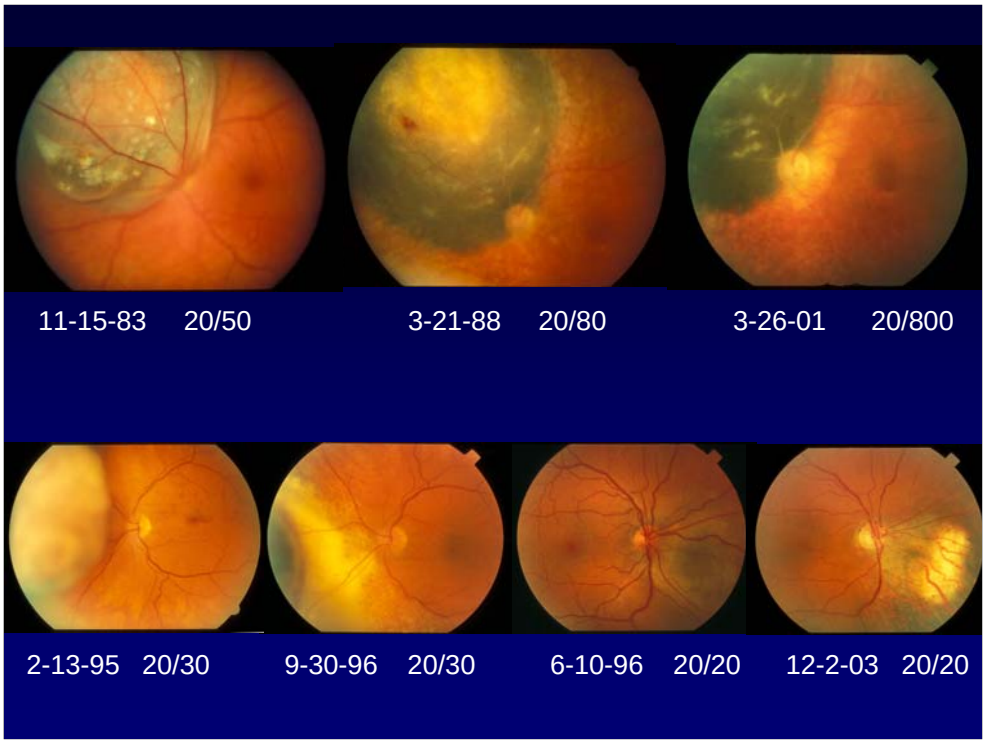
4-30-02 20/300
12-9-03 CF
10-24-00 20/20
10-22-01 20/80
12-1-03 20/60


11-15-83 20/50
3-21-88 20/80
3-26-01 20/800
2-13-95 20/30
9-30-96 20/30
6-10-96 20/20
12-2-03 20/20

RESULTS

Visual acuity of counting fingers or better was retained in many patients

- 85% at 2 years post irradiation
- 67% at 5 &10 years post irradiation

RESULTS

10 year rates of outcomes (%)

	COMS-Ineligible	All Patients
Mortality	21	23
Regrowth	6	4
Eye Loss	18	12
Vision Loss†	91	65
Maculopathy*	60	40
Papillopathy*	57	24

† worse than 20/200 * 5 year rate

TUMORS AT HIGH RISK OF PAPILLOPATHY

Parapapillary tumors without macular involvement :

- LTD ≤ 15 mm
- Height ≤ 8 mm
- ≤ 1 DD from optic disc
- ≥ 2 DD away from the fovea

CUMULATIVE RATES OF RADIATION PAPILLOPATHY

Patients with parapapillary tumors (N=93)

Distance to disc	percent	95% CI
0 DD	81	68-91
>0 DD	67	51-82

RADIATION PAPILLOPATHY

Vision changes at 5 years after onset of papillopathy

- 69% (N=38) of eyes permanently lost ≥ 3 lines of vision after papillopathy diagnosis
- 42% (N=34) of patients retained visual acuity of CF or better

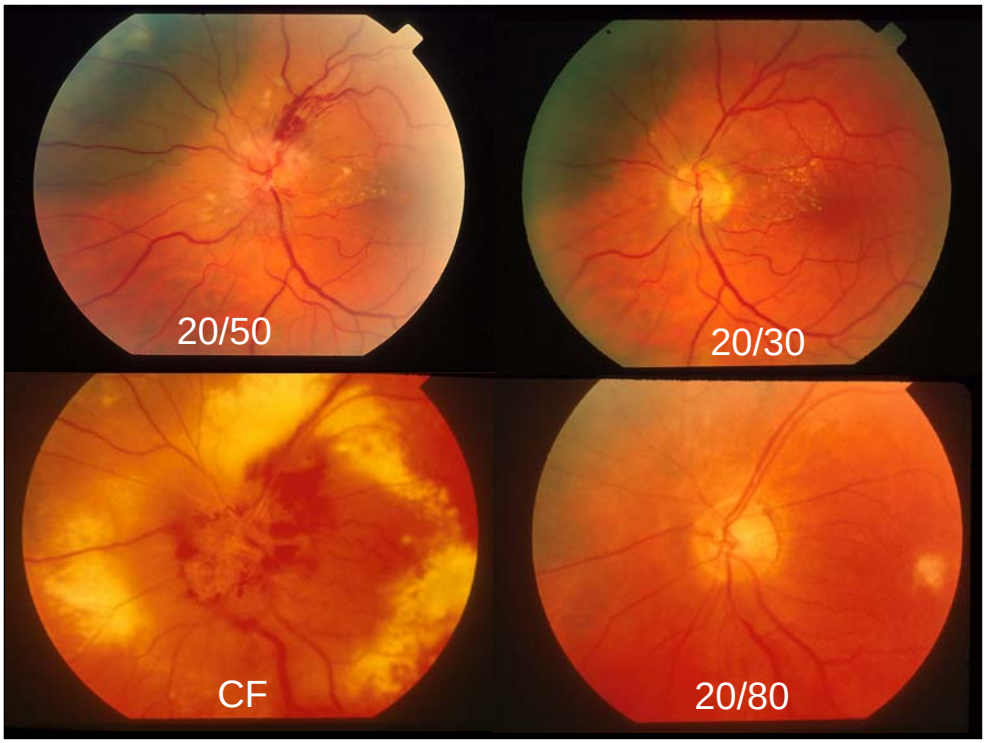
RADIATION PAPILLOPATHY

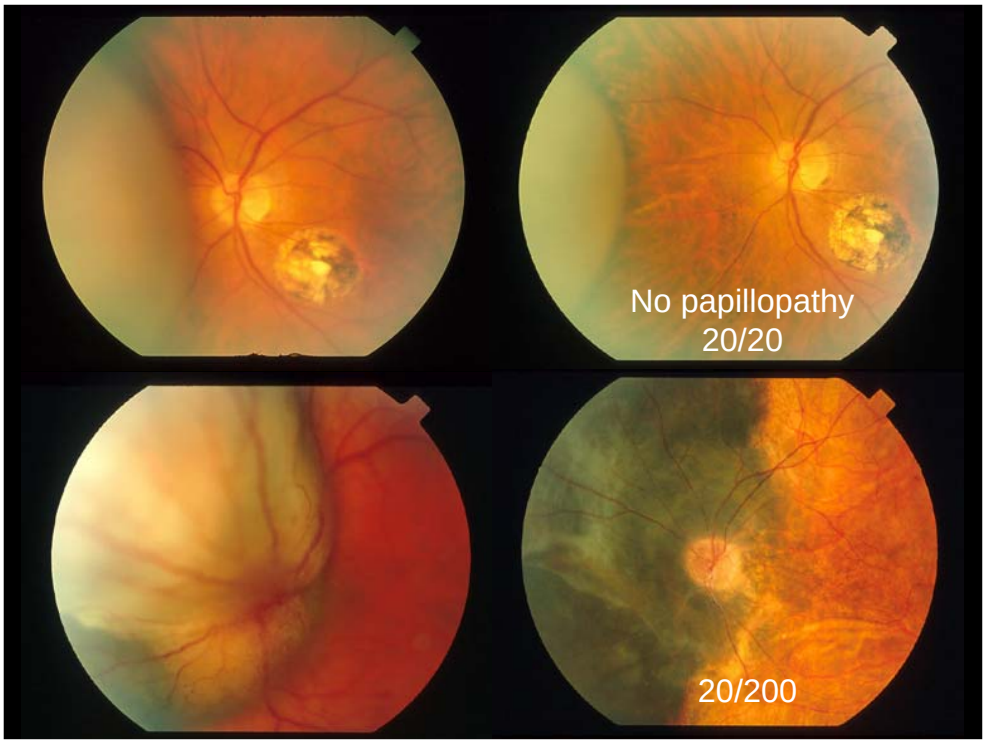
Recovery of visual acuity post papillopathy (n=13, 31%)

12 patients sustained improvement ≥ 2 years

- VA at diagnosis
  - 20/100 or better (N=4)
  - 20/126 -20/500 (N=8)
- VA at last follow-up
  - 20/100 or better (N=10)
  - 20/160 (N=2)

1 patient sustained improvement 15 months


20/50
20/30
CF
20/80


No papillopathy
20/20
20/200

GENERAL RECOMMENDATIONS

Radiotherapy should be considered for:

- Small melanomas with documented growth
- All medium sized melanomas
- Most large melanomas
- Tumors contiguous to the optic nerve (ineligible for COMS)

GENERAL RECOMMENDATIONS

For COMS-ineligible patients, eye conservation is possible

- low rates of recurrence
- no increased risk of metastasis
- visual acuity of CF or better is retained in many patients
- recovery of vision is possible in some patients

GENERAL RECOMMENDATIONS

Enucleation

- Large melanomas (>30% of ocular volume)
- Large extrascleral extensions
- Extensive neovascularization in a painful eye