Ocular Melanoma: Leave it in or take it out

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Mark Dunbar: Disclosure

- Optometry Advisory Board for:
  - Allergan
  - Carl Zeiss Meditec
  - ArticDx
  - Sucampo

Mark Dunbar does not own stock in any of the above companies

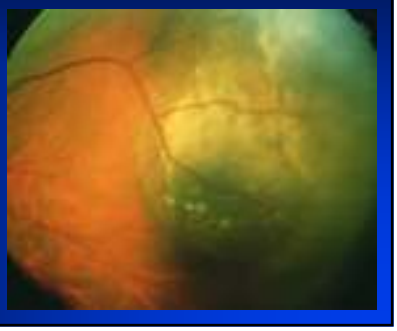
Choroidal Melanomas

It is the most controversial topic in the history of ophthalmology

More has been written about choroidal melanomas then any other topic

How Do I Find It?

- Careful, thorough, routine eye exam
- Pupillary dilation
- Slit lamp exam
- Binocular Indirect Ophthalmoscopy
- Echography
- Orbital Imaging?



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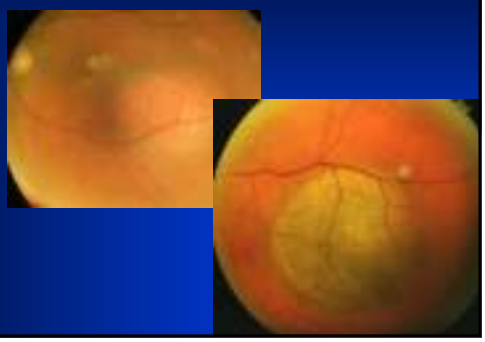
Ocular Melanoma

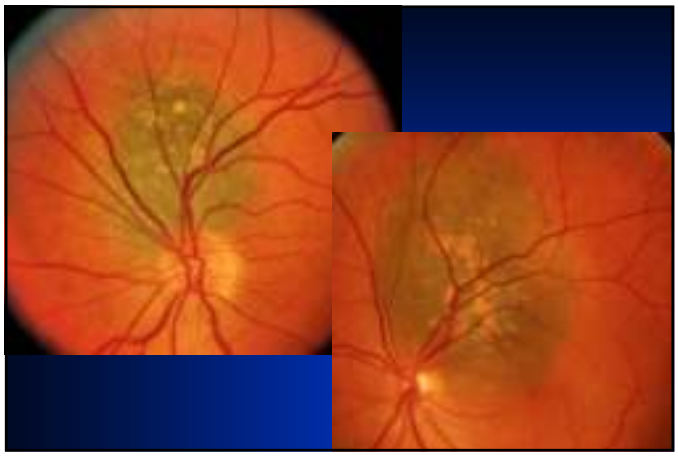
- Most common site for primary malignant intraocular tumor
- Most frequent site of noncutaneous melanoma
- Most controversial topic in the history of ophthalmology
  - For more than 100 years, standard to care was enucleation
  - Inaccurate diagnosis: 20% of eyes enucleated for melanoma did not have melanoma

Choroidal Melanoma

- Color
- Size
- Shape
- Location

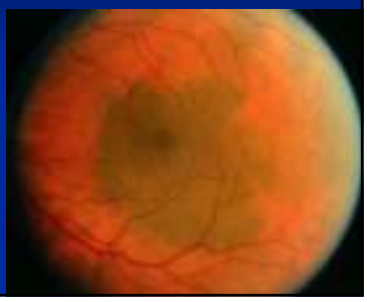


Suspicious Nevi Vs Small Suspicious Choroidal Melanoma



Choroidal Nevi

- < 3 mm elevation
- < 3 DD in size
  - 95% are less than 2 DD
- Slate gray
- Drusen
- SRF associated with drusen
- CNVM



Features Suggesting Nevi

- Drusen
- Overlying neurosensory detachment
- Choroidal neovascular membrane
- Circinate exudate
- Bony pigment spiculing
- Zones of RPE atrophy
- Orange pigment assoc. with drusen

Choroidal Melanoma

- >3 mm elevation
- Variable pigment
- Multiple areas of orange pigment (lipofuscin)
- Serous fluid (detachment) in absence of drusen
- Unequivocal evidence of growth

Ciliary Body Melanoma

- Sentinel vessels
- Protrusion of CB seen with slit lamp through dilated pupil
  - may see while performing retinoscopy
- Sectoral cataract

Diagnosis

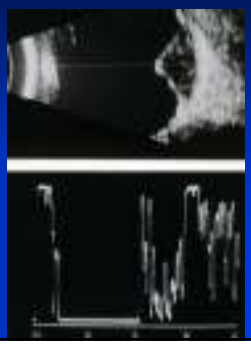
- Clinical
- Standardized ultrasonography
- Fluorescein angiography
- Transillumination
- CT/MRI - no value
- Biopsy

Ultrasonography

- Biometric ultrasound (A-Scan)
- B-Scan echography
- Standardized echography

Standardized Echography

- Most effective, reliable, accurate method
- Designed for tissue differentiation
- Reliability and accuracy of 99.52%
  - (413 eyes, 3 year period)



Standardized echography

- Tissue differentiation
- Document size from one visit to the next
- Opaque media

Standardized Echography

A-Scan: Choroidal Melanoma

- Regular internal structure
- Low to medium reflectivity
- Solid consistency
- Vascularization
- Scleral infiltration
- Extraocular extension

Standardized Echography

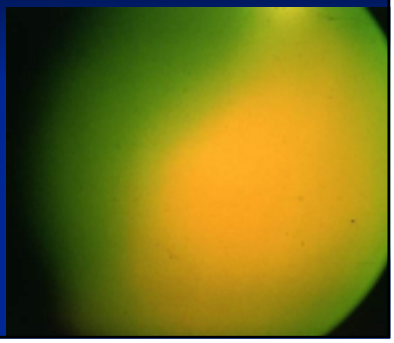
B-Scan: Choroidal Melanoma

- Size
- Shape
- Maximal elevation
- Scleral infiltration
- Extraocular extension

Misdiagnosis of Melanoma

False Positives

- 1959 -> 10.9%
- 1985 -> 1.7%
- 1990 -> 0.48%



Fluorescein Angiography

- Patchy hyperfluorescence
- Areas of pinpoint staining
- Sometimes double circulation seen
- Nevi: blockage vs. pinpoint staining
- Not reliable tool to differentiate melanoma from choroidal nevi

Differential Diagnosis

- Choroidal nevi
- Cavernous hemangioma of the choroid
- Eccentric disciform process (peripheral CNVM)
- CNVM with dense hemorrhage
- Metastatic Ca
- RD
- Hemorrhagic RD

Management

- Flat choroidal nevi: follow yearly
- Suspicious nevi:
  - photo
  - follow q 3-6 mo, depending on findings
  - evidence of growth -> early melanoma
- Lesions > 3 mm thickness: probably early melanoma

Choroidal Melanoma

What is the best management?

- Enucleation?
  - It's a "cancer," get it out of the eye!
  - Why wouldn't you…?
- Observation?
  - Pathologic studies show not all eyes removed for melanoma, are melanomas
  - Low malignant potential for many tumors

Observed Growth
116 Patients, 5 yr F-up

No Growth: 69 pts
- 64 small
- 5 medium
- 0 large
- 8 yr F-up

Growth: 47 pts
- 36 small
- 6 medium
- 5 large
- 35 enucleated
- 7.8 yr F-up

Gass, Ophth. 87: 523-538, 1980

Prognosis and Histology

1931 Callendar Classification
- Spindle A
- Spindle B
- Fasicular
- Mixed
- Epitheloid
- Necrotic

1931 Am Acad of Oph & Otol Callander

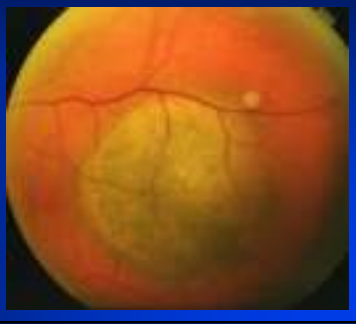
Mortality

5 Year Prognosis
- Highest with epitheloid cells 69%
- Mixed 51%

1931 Am Acad of Oph & Otol Callander

Revised Callendar Classification

- Spindle B
- Epitheloid
- Mixed



Prognosis

- Histology
- Tumor size
- Observed growth of the tumor
- Location
- Rupture thru Bruch's membrane
- Extrascleral extension

Prognosis

Size

- 70% when diameter > 12 mm
- 13% when diamete < 10 mm
- Most small tumors are spindle cell
- Large tumors likely to contain epitheloid cells

McLean, Zimmerman, Arch of Oph 1977

Mortality and Location

- 58% anterior to equator
- 29% ciliary body
- 33% posterior pole
- 83% filling the vitreous cavity

Shammas, Blodi. Arch Ophth. 1977

Metastasis

- Liver 75%
- Subcutaneous tissue and bone
- Time from Dx to metastasis = 4 yrs
- Survival with hepatic met = 7 months
- Chemotherapy is Tx of choice

History of Enucleation

- Prior to 1970's enucleation was the standard of care for all melanomas
- 1978 Zimmerman, McLean challenged the traditional beliefs regarding enucleation:

"Does enucleation of the eye... prevent or accelerate dissemination of tumor cells"

Br J Ophthalmol 1978 Jun;62(6):420-5

History of Enucleation

- 1882 Fuch's indicated all melanomas were treated by enucleation
  - Untreated cases were reported in "older literature"
  - Fuch's cure rate: 25% (259 cases)
- 1891 Lawford & Collins reported 79 cases
  - 3 yr recovery rate of 25%
  - 20% extraocular extension, 22% ON invasion, 66% with glaucoma

History of Enucleation

- In the "early days;"
  - Most tumors advanced when diagnosed
  - Many pts had symptoms and often blind
  - No instances of preop metastatic disease at the time of diagnosis
  - 3 Cases of untreated metastatic disease recorded

Enucleation Accelerates Metastatic Death

- Low mortality rate before enucleation
- Patients rarely found to have metastatic disease at time of diagnosis
- Abrupt increase in mortality following enucleation
- 2/3 of fatalities due to disseminated tumor cells during enucleation

Zimmermans theory

Treatment: Choroidal Melanoma

- Enucleation
- External beam radiation
- Plaque radiation
- Local excision/eye wall resection
- Photocoagulation

Plaque Radiation (Ionizing Radiation)

- Iodine-125
- Seeds of radioactive material implanted into a plaque
- Sewn onto the globe and left on for 3 d
- Dosage: 8-10 rads reach apex, 40-50,000 reach the base

Plaque Radiation

- Survival rate is approximately equal to enucleation
- Rapid regression of melanoma post Tx is an unfavorable prognosis
  - Indication of tumors malignant potential

Enucleation vs. Plaque

- Nonrandomized
- Small numbers in both groups
- Greater frequency of anterior location of tumors in the Co Plaque group (72% vs 22%)

Gass. Arch of Ophth. 103: 1985

Leave it in or take it out?

- Many tumors have uncertain growth potentials
- Inadequate length of follow up
- Deficiencies inherent in retrospective studies
- Insufficient patient numbers
- Loss of patients to follow up
- Inaccuracy in information re "cause of death"

Collaborative Ocular Melanoma Study (COMS)

- International, multicentered randomized controlled clinical trial
- Supported by NEI: 32 centers
- Primary outcome: overall survival p Tx
- Secondary: metastatic free survival, preservation of vision

COMS: Results:

Diagnostic Accuracy

- 1527 of 1532 enucleations resulted in resulted in correct Dx 99.7% Accuracy

Cell Type

- Spindle Cell = 9%
- Mixed Cell = 86%
- Epitheloid = 5%

Histopath Characterist. COMS Report #6 AJO June 1998

COMS Results: Medium Tumors

- Enucleation vs I_{125} Brachytherapy
- 1317 Enrolled: 660 Enucleation 657 plaque
- 1072 (91%) followed for 5 yrs
  - 416 (32%) 10 yrs
- 364 pts died:
  - 188 Enuc (28%); 176 (27%) Plaque

Arch of Ophthalmol July 2001 119(7):969-982

COMS Results: Medium Tumors

- Unadjusted 5 yr survival: 81% vs 82%
- 5 yr adjusted rate of death from metastatic melanoma:
  - 11% Enucleation
  - 9% Plaque
- Conclusion: Mortality rates do not statistically differ b/w the 2 treatments for up to 12 years

Arch of Ophthalmol July 2001 119(7):969-982

COMS Results: Medium Tumors

- Baseline Visual Acuity:
  - Median VA: 20/32
  - 70% with $\geq$ 20/40, 10% $\leq$ 20/200
- 3 yrs Post I_{125} plaque
  - Median VA: 20/125
  - 34% $\geq$ 20/40; 45% $\leq$ 20/200
  - 43-49% impairment in VA (> 6 lines of acuity loss from pretreatment)

Ophthalmology Feb 2001 108(2):348-366

Large Choroidal Melanomas
COMS Report # 10

Pre-enucleation Radiation vs Enucleation

- Randomization 11/86 to 12/94: 1003 Pts enrolled
  - 506 Enucleation alone vs 497 Pre-enucleation Radiation
  - 5 year outcome known for 80%
- 5 Year survival
  - 57% Enucleation alone vs 62% Pre-Enuc Rad
    - Includes all causes of death

Initial Mortality, COMS Report # 10 AJO June 1998

Large Choroidal Melanomas
COMS Report # 10

Pre-enucleation Radiation vs Enucleation

- Total 435 deaths classified by Mortality Coding Committee
  - 269 had histologically confirmed melanoma metastases (166 died from other causes)
- 5 yr survival = 72% Enuc vs 74% PERT
  - No statistical survival difference b/w 2 groups

Initial Mortality, COMS Report # 10 AJO June 1998

Assessment of Metastatic Death: Large Tumors

- 1003 enrolled in trial
- 457 deaths – disease status avail on 435
  - Median survival from time of enrollment 7.4 yrs
- 361/435 (83%) confirmed death metastatisis
  - 62% Histopathologic confirmed, 21% suspected
- 93% Liver, 24% lung, 16% bone

Arch of Ophthalmol May 2001 119(5):670

Large Choroidal Melanomas
COMS Report # 10

Conclusion - Summary - What Next?

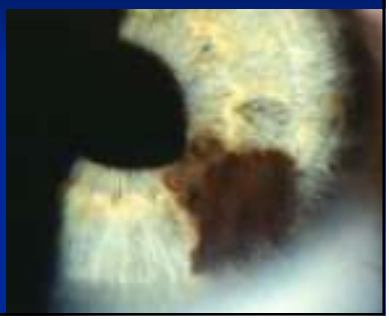
- Radiation was successful in reducing mitotic activity
- Existing micrometastases was clinically undetectable at the time of enucleation
- All cause mortality both groups = 40%
  - To reduce mortality, enucleation must be combined with other systemic measures to control metastatic disease

Iris Nevus

- Pigmented lesion of the iris stroma
- Relatively flat
- Focal
- Avascular
- Noninvasive

Iris Nevus

- 5% will grow in 5 years
- Ectropion uvea
- Sector cataract
- Malignant transformation



Iris Melanoma

May be impossible to differentiate from benign iris nevi

- Growth over time
- Variable pigment
- Nodular
- Vascular
- Invasive
- Tapioca appearance

Iris Nevus

Diagnosis

- Old Photographs
- Gonioscopy
- Careful follow up over time

Iris Melanoma

Management

- Local excision
- Enbloc resection
- Enucleation

Ocular Melanomas Take Home Message

- Choroidal Melanomas
  - Most picked up on routine eye exam
  - Prompt diagnosis is critical for survival
  - Large tumors: PERT = Enucleation (60%)
  - Medium tumors: Plaque therapy is as good as enucleation
- Suspicious iris lesions: growth over time may be the only way to determine difference b/w nevi vs melanoma

Thank You!