UPDATE ON UVEAL MELANOMA

Presented by Dr. Carlo J. Pelino
Assistant Professor
Retina / Emergency Service
The Eye Institute
Philadelphia Pa

April, 2017
Tumor Definition

tumor /tu·mor/ (too´mer)
also called neoplasm. a new growth of tissue characterized by progressive, uncontrolled proliferation of cells. The tumor may be localized or invasive, benign or malignant. A tumor may be named for its location, for its cellular makeup, or for the person who first identified it.

Lecture Outline

• Choroidal Nevus
• Choroidal Melanoma
• Congenital Hypertrophy of the RPE
• Choroidal Metastasis
• Melanocytoma
• Combined Hamartoma of the Retina & RPE
• Choroidal Hemangioma
• Choroidal Osteoma
• Retinal Astrocytic Hamartoma
• Retinoblastoma
Updated ways to diagnose uveal melanoma

New treatment plans for uveal melanoma

Gene expression profiling

Adjuvant treatments - liver metastasis
Retinal and Choroidal Anatomy
Protect p 53 = Natural food sources include:

- Glutathione found in sulfur foods such as onions, garlic, milk thistle
- Curcumin (23) found in turmeric
- Anthocyanins (24) found in berries, red cabbage & red onions among others
- Resveratrol found in berries and grape skins
- Carotenoids (27) found in a number of fruits, vegetables and pasture-raised animal foods
Longevity:

• Insulin is very low

• IGF is low

• mTORC1 is low

• AMP kinase is high

• Ras is low
Constitutive activation of pathways can lead to autocrine growth factor production. Both pathways activated in HCC also effects of HBx protein on pathway activation.

- EGF-R mutated in brain cancers & NSCLC
- HER2 is increased in 30% breast and 15% gastric cancers
- Mutations at Fit-3 detected in ~20% AMLs
- Kit & PDGF mutated in AML, GIST
- High frequency of Ras mutations detected in many human cancers
- Mutations at PI3K present in ~25% breast cancers
- Akt overexpressed in many cancers
- SOS, PTPN11, HRAS mutations in Noonan and Costello syndromes

- BCR-ABL translocation detected in ~100% of CML also in some ALLs

EGF-R, HER2, IGF1-R, VEGF-R, Fit-3, Kit, PDGF-R, BCR-ABL

- Other mutations/translocations
- Mutations at B-Raf frequent in ~70% melanomas
- MEK1/2 mutations in Cardio-facio-cutaneous syndrome also mutations at KRAS and BRAF

- Ras
- B-Raf
- Raf-1
- PI3K
- PTEN
- MDM2
- p53

- MEK1/2
- Akt
- TSC1/2
- ERK
- Rheb
- mTOR
- p70S6K

Increased protein translation & accelerated aging

PTEN & p53 loss present in many different cancers

TSC1/2 mutations in with tuberous sclerosis than develop hamartomas

Rheb & p70S6K overexpressed in different cancers

http://archive.impactaging.com/
Uveal melanoma is the second-most common form of melanoma and the most common primary intraocular malignancy.

Up to one-half of patients are at risk for fatal metastatic disease.
Population by Race for the US: 2012

RACE

Total population .......... 313,914,040 100.0%

Caucasian ................. 244,852,951 78.0%

Source: quickfacts.census.gov
Ocular Melanoma

- **Uveal Tract**
  - >95% of ocular melanomas

- **Conjunctiva**
  - <4% of ocular melanomas

- **Orbit/Eyelid**
  - <1% of ocular melanomas
## Gene Mutations in Cutaneous Melanoma

### Table 2. Oncogene mutations in melanoma

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Incidence (%)</th>
<th>Type of melanoma</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>40–50</td>
<td>Cutaneous</td>
<td>Found most frequently in sites where sun damage is intermittent and not chronic</td>
<td>22</td>
</tr>
<tr>
<td>NRAS</td>
<td>15–30</td>
<td>Cutaneous</td>
<td>NRAS mutations are mutually exclusive of BRAF mutations</td>
<td>23, 24</td>
</tr>
<tr>
<td>c-KIT</td>
<td>5–10</td>
<td>Acral and mucosal</td>
<td>Found more frequently in chronic sun damaged skin</td>
<td>25</td>
</tr>
<tr>
<td>GNAQ and GNA11</td>
<td>80</td>
<td>Uveal (almost exclusively)</td>
<td>Uveal melanomas are very rare</td>
<td>16</td>
</tr>
</tbody>
</table>

*BRAF = v-raf murine sarcoma viral oncogene homologue B1; c-KIT = v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue; GNA11 = guanine nucleotide-binding protein subunit alpha-11; GNAQ = guanine nucleotide binding protein (G protein), q polypeptide; NRAS = neuroblastoma RAS viral (v-ras) oncogene homologue*
Intrinsic Blood Vessels
Uveal Melanoma
Stats – SEER Database

Incidence: 4.3 cases per million

Gender: Male / Female 52:48

Race: W / B 150:1

Age: Overall 60.4 mean

Incidence of uveal melanoma has remained the same over the last 25 years.
WHAT WE KNOW

- Rare cancer
- Most common primary intraocular tumor
- Incidence: 7 per million per year in US
- Approximately 2000 new cases diagnosed annually in the US
- Median age 60yrs
- Overall Survival varied

*Above based on what is reported to SEER/CINA national databases / single center experiences
Where does uveal melanoma come from - Choroidal Nevus

- Most common intraocular tumor
- Proliferation of choroidal melanocytes
- Present in ~ 7.9% of Caucasians
- Growth is rare after puberty
Nevus of Ota have increased amounts of melanin (pigment) and melanin producing cells (melanocytes) in and around their eyes. This includes the intraocular blood vessel layer called the uvea (choroid, ciliary body and iris), on the sclera, and in the eyelids.
• Baseline fundus photography
• Consider OCT if location permits
• Consider B-Scan if suspicious
• Yearly dilated fundus examination

Choroidal Nevus: Treatment & Management
- Caucasian ethnicity
- Light colored eyes (blue)
- Fair skin
- Propensity to burn when exposed to UV light
- Cutaneous nevi or freckles
- Iris nevi
- Welders

Risk Factors of Melanoma
BOX 31.2 Symptoms and Signs Indicating the Presence of an Intraocular Tumor

- Melanoma or other tumor visible externally in the iris or episclera
- Eccentric visual phenomena, such as photopsia, floaters, and field loss
- Lens abnormalities, such as cataract, astigmatism, and coloboma
- Afferent pupillary defect, mostly caused by secondary retinal detachment
- No optical correction with spectacles because of blurring or metamorphopsia
- Ocular hypertension, especially if asymmetrical
- Melanocytosis, predisposing to melanoma
- Asymmetrical episcleral vessels, indicating a ciliary body tumor
Nevoma

Make sure to photodocument and measure
To Find Small Ocular Melanoma

- \( T = \) thickness
- \( F = \) subretinal fluid
- \( S = \) symptoms
- \( O = \) orange pigment
- \( M = \) tumor margin touches disk

- No risk factors (<4%)
- 1 risk factor (36%)
- 3 risk factors (50%)
- 5 risk factors (70%)

DOCUMENTED GROWTH - MEANS EVERYTHING

Using Helpful Hints = Ultrasound hollow, Halo absent

7/29/2016
Nevus to melanoma

“To Find Small Ocular Melanoma Using Helpful Hints Daily” (TFSOM-UHHD)

T  →  *thickness greater than 2 mm*,
F  →  *fluid subretinally*
S  →  *symptoms*
O  →  *Orange pigment present,*
M  →  *margin with in 3 mm of the optic disc*
UH  →  *USG hollowness (versus solid/flat)*
H  →  *halo*
D  →  *drusen absent*

**DIFFERENTIATION.** (1) Choroidal nevus with drusen. (2) Choroidal melanoma with orange pigment and subretinal fluid.
Special Testing

**OCT**
- Can detect sub-retinal fluid
- Has been shown to detect early seeding
- Helpful in monitoring response to treatment
- Enhanced depth imaging

**B Scan**
- Acoustically hollow
- Choroidal excavation with orbital shadowing
- Classic mushroom appearance (less common)
- Can identify extraocular extension

**FA**
- No pathognomonic pattern
- Typically, mottled fluorescence during arteriovenous phase followed by leakage and staining
Nevus in 2004?  Nevus in 2009?

Nevus vs Melanoma?
Collaborative Ocular Melanoma Study

- Organized and funded in 1985 to address issues related to the management of choroidal melanoma. > 4000 patients. 65% pts eligible

- Primarily to study the overall survival of patient following treatment

**Small** melanomas  < 2.5 mm in height

**Medium** melanomas  2.5 – 10.0 mm in height

**Large** melanomas  > 10.0 mm in height

- Secondary outcomes = metastasis-free survival, years of useful vision
Treatment & Management

- Enucleation
- Radioactive plaques
- Proton beam radiotherapy

Most widely accepted

- Local resection

Less common

Treatment depends on...

1. state of other eye  2. location  
3. extent of tumor    3. vision  
4. size              5. health    6. age of pt
Treatment Options for Uveal Melanoma

It is left in place for 4 to 7 days to provide 8,000 centigray of radiation to the entire tumor. The remainder of the body receives a small amount of radiation, about the equivalent of 1 chest x-ray.
Trans pupillary thermotherapy

Silicone Oil

Avastin & Lucentis
...not just for AMD
BOX 40.1 Essential Features of Transpupillary Thermotherapy

- Indicated for small, posterior tumors not involving the optic disc
- Administered with a 3mm diode laser beam
- Heats the tumor to 60–65°C for about 1 minute
- Is preferably administered with adjunctive radiotherapy
- Is useful after radiotherapy for tumor recurrence or exudation
- Can be augmented using indocyanine green
BOX 48.1 Sites for Metastatic Uveal Melanoma

- Liver 93%
- Lungs 24%
- Bone 16%
- Skin 11%
- Lymph nodes 10%
- Brain 5%
- Fellow eye 0%

Multiple sites involved in about half the cases. In an atypical case consider a second primary tumor.
• **AFIP Classification** of uveal melanomas.

1) Spindle cell nevi
2) Spindle cell melanomas (mixture of spindle A and B cells).
3) Mixed cell melanomas in which there is a mixture of spindle and epithelioid cells.
4) Epithelioid cell melanoma

Last two types has poorer survival prognosis
Other type - necrotic melanoma
Using fluorescence in situ hybridization and molecular assay techniques, several genetic abnormalities in uveal melanoma were found on chromosomes 1, 3, 6, and 8.

Monosomy 3

- Found in up to 50% of uveal melanomas.
- Imparts a worse prognosis.
- In small melanoma it provokes the argument for earlier treatment than observation.

Role of Cytogenetics
Gene expression profiling (GEP) divides uveal melanoma into 2 molecular subgroups:

**Class 1 A and B** (low risk) and **Class 2** (high risk)

GEP allows oncologists to accurately predict which patients with uveal melanoma will get metastatic disease.

Technology is now available as a routine clinical test (DecisionDX-UM, Castle Biosciences)

**Improving the prognosis for uveal melanoma**
Cell-Signaling Advances in Uveal Melanoma
Cell-Signaling Advances in Uveal Melanoma
Mutations in the $G_q$ alpha subunits $GNAQ$ and $GNA11$ are mutually exclusive and represent early or initiating events that constitutively activate the MAPK pathway.

Mutations in BRCA1-associated protein-1 ($BAP1$) and splicing factor 3B subunit 1 ($SF3B1$) also appear to be largely mutually exclusive, and they occur later in tumor progression.

$BAP1$ mutations are strongly associated with metastasis (liver)

$SF3B1$ mutations are associated with a more favorable outcome.

$BAP1$ mutations can arise in the germ line, leading to a newly described BAP1 familial cancer syndrome (mesothelioma, cutaneous melanoma, basal cell carcinoma and renal cell carcinoma)
Types of Choroidal Melanoma

Class 1A tumors account for about 45% of all uveal melanomas.

Class 1B tumors about 15%.

Class 2 about 40%.

The five-year risk of metastasis is less than 5% for Class 1A, about 15% for Class 1B, and 70-80% for Class 2.

The goal is to be able to offer adjuvant therapy to all Class 2 patients and to selected Class 1B patients in the near future.
Adjuvant Therapy

**Adjuvant:** A substance that helps and enhances the effect of a drug, treatment, or biologic system.

From the late 16th century: from Latin *adjuvant*- 'helping toward', from the verb *adjuvare*, from *ad-* 'toward'

The first class of compounds consists of various types of agents that activate the patient’s immune system to kill tumor cells.

Such agents include interferon and ipilimumab or Yervoy.
Choroidal Melanoma

- **10 year mortality for uveal melanoma**
  - Large 50%
  - Medium 25%
  - Small 12%

- **Most common sites of metastasis for uveal melanoma**
  - Liver 89%
  - Lung 29%
  - Bone 17%
  - Skin / Subcutaneous 12%

- **Pattern of metastasis**
  - Uveal: hematogenous
  - Cutaneous: lymphatic

- **Median survival after dx of metastasis - 6 months**
Chemoembolization

Immunoembolization – GM-CSF

Radioembolization
Adjuvant Therapy
Adjuvant Therapy

The second class of compounds consists of inhibitors of proteins that promote cell growth, such as mitogen activated protein kinases (MAP K pathway).

The goal of treatment with such compounds is primarily to shrink large, proliferating tumors.

Selumetinib
Adjuvant Therapy

The third class of compounds could be referred to as “epigenetic modifiers” because they alter the expression of many proteins.

Such compounds include histone deacetylase (HDAC) inhibitors, which appear to work by delaying or preventing tiny, undetectable metastatic deposits from growing by causing them to go into a dormant state.
Class 2 uveal melanoma = Micrometastasis to the liver
Melanoma Summary

- Most often seen in **caucasians**
- Usually in adults
- **80 % choroid, 2 % iris, 18 % ciliary body**
- 2,500 cases per year compared to 32,000 cases of cutaneous melanomas.
- ~ 5 cases per million people annually
- Classification = small < 3 mm
  medium 3-8 mm
  large > 8 mm
GENE EXPRESSION PROFILING

A. Fine-needle aspiration of tumor

B. Analysis of tumor cells

C. Tumor classified into one of four categories

D. Survival probability over time for different classes:
   - Class 1A
   - Class 1B
   - Class 2A
   - Class 2B

Tumor classification helps predict patient survival.
• Common benign lesion

• Focal area in which the RPE cells are taller and more densely packed with melanosomes

Congenital Hypertrophy of the Retinal Pigment Epithelium
Familial Adenomatous Polyposis (FAP)
- AD inheritance
- Adenomatous polyps throughout rectum & colon
- Starts to develop in adolescence (15-40 yrs)
- If untreated – all pts will develop colorectal cancer

>80% of patients with FAP have atypical CHRPE lesions
Lung Metastasis

Choroidal Metastasis
Metastatic Prostate Cancer
Metastatic Tumors

• Breast cancer is the most common tumor to metastasize to the eye - followed by lung cancer

• 85% of patients with breast cancer metastases will have a known history of breast cancer

• Breast cancer metastases tend to be bilateral and multiple

• 40% of these patients have a brain metastasis
Retinoblastoma – life threatening disease

Most common intraocular malignancy in children / dx=18 month

300 new cases of retinoblastoma diagnosed each year in the US
# International Classification of Retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Small RB $&lt; 3$ mm size</td>
<td>Plaque, TTT</td>
</tr>
<tr>
<td>B</td>
<td>Larger RB $&gt; 3$ mm size</td>
<td>Chemoreduction W / WO EBRT</td>
</tr>
<tr>
<td>C</td>
<td>Contained seeds</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Diffuse seeds</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Extensive $&gt; 50%$ globe, NVI, Opaque media</td>
<td></td>
</tr>
</tbody>
</table>

Recurrences = within 1\textsuperscript{st} year
Uveal Melanoma Resources

- AIM at Melanoma

- Melanoma International Foundation
  - [www.melanomainternational.org](http://www.melanomainternational.org)

- Melanoma Research Foundation: Cure OM
  - [http://www.melanoma.org](http://www.melanoma.org)

- Ocular Melanoma Foundation
  - [http://www.ocularmelanoma.org](http://www.ocularmelanoma.org)

- Melanoma Research Alliance
  - [http://www.melanomaresearchalliance.org](http://www.melanomaresearchalliance.org)

- National Cancer Institute
The End!

Any Questions ????

Special Thanks to Dr. Lauren Richards