Uveal melanoma: Risk factors, Treatment and Survival

EFTHYMIA PAVLIDOU
CHOROIDAL MELANOMA

- Is the most common primary intraocular disease which can be fatal in adults
- Has an incidence of 6 cases per 1 million per year
- It is usually diagnosed in the sixth decade of life and its incidence rises steeply with age
- There is no known family history of the disease
- Pigmented individuals rarely get skin or choroidal melanomas
- Similar incidence in Europe/US (low UV exposure) to Australia/NZ (higher UV)
- M>F, 4.9 vs 3.7 per million population
Choroid 80%

Iris 5%

Ciliary Body 15%
The incidence of uveal melanoma has remained stable for many years.

- USA mean age adjusted incidence is 5.1 per million.
- Northern Europe > 8 cases per million.
- Southern Europe > 2 cases per million.
RISK FACTORS

• **Age**
  – Is rare in children

• **Race**
  – 150 x times more common in whites than blacks
  – Light skin color
  – Blonde hair
  – Blue eyes

• **Environmental**
  – Sunlight exposure not significant

• **Hormones**
  – Not good evidence

• **Patients with ocular or oculodermal melanocytosis are at a greater risk as are melanocytoma and neurofibromatosis.**

• **Genetics**
  – Presence of germline BRCA1- associated protein 1 (BAP1) mutations
COMS : SIZE OF MELANOMA

• **Small CMM**
  – 5 to 16 mm in basal diameter
  – Up to 2.5 mm in height

• **Medium CMM**
  – <16 mm in basal diameter
  – 2.5 to 10 mm in height

• **Large CMM**
  – >16 mm in basal diameter
  – >10 mm in height
COMS SMALL CMM

OBSERVATIONAL STUDY

• Tumor growth
  – 31% grew by 5 years
  – 63% no growth

• What is a small melanoma?
  – Suspicious naevus or small MM or indeterminate lesion?

• Risk factors:

• To Find Small Ocular Melanoma
  – T thickness > 2 mm
  – Fluid
  – Symptoms
  – Orange pigment
  – Margins within 3 mm of the optic disc
  – >2 risk factors 50% risk of growth
COMS SMALL CMM
OBSERVATIONAL STUDY

• Mortality
  – For MM specific deaths
  – 1% at 5 years
  – 8% at 8 years

• Low risk of death from small melanoma, even though 59% of patients were not treated
SMALL MM

• Why treat small MM?

• Mortality not changed over last 30 years

• Tumor doubling time (Kivela, 2000)
  – Metastasis detected clinically 2.2 years after primary site
  – Micrometastases occur earlier
  – Calculated size of primary is $7\text{mm}^3$ when micromетastases occur
  – 3 mm in diameter
  – 1.5 mm in height
Does conservative treatment promote mortality?

RCT
- Enucleation vs Iodine-125 plaque brachytherapy

MM specific
- 11% for enucleation
- 9% for iodine plaque
- Associated with larger tumor diameter and shorter distance to optic nerve

No significant difference

Confirmed at 12 years follow up
COMS LARGE MM RCT

- Does enucleation promote metastasis?
- Can pre-operative EBRT reduce that effect?
- RCT
  - Enucleation
  - Enucleation with pre-op EBRT

- Mortality MM specific
  - 28% enucleation alone
  - 26% EBRT & enucleation
  - Confirmed at 10 years follow up
Treatment Options
Goals of treatment

Save your life

Save your eye

Save your sight
- Observation – iris lesions/ suspicious naevi
- Transpupilllary diode thermotherapy
- Photodynamic Therapy
- Plaque brachytherapy
- Proton Beam Radiotherapy
- Surgical Resection
- Enucleation
- Exenteration (orbital spread)
- Palliative external beam radiotherapy
SMALL MM MANAGEMENT

- Some small melanocytic tumors are best managed by periodic fundus photographs and US to document growth.

- Tumors that show highly suspicious features or unequivocal evidence of growth should be treated.

- Recently identified risk factors for metastasis include greater tumor thickness, tumor proximity to the optic nerve, presence of visual symptoms and prior documented growth.

- Since documented growth may be associated with a worse systemic prognosis, there is a trend to treat patients who have the other risk factors, without necessarily waiting for documentation of growth.
Plaque brachytherapy

- Transpupillary ThermoTherapy
  - TTT delivers heat to the tumor using a modified diode laser delivery system
  - It is used frequently as a supplement to plaque radiotherapy

RBRT
Plaque brachytherapy

- First choice treatment
- Relatively straightforward procedure
- High success rate
- Ruthenium-106 emits high energy $\beta$ and small degree $\gamma$ radiation
- Has less scatter and thus less side-effects than Iodine
- Time dependant on dose, tumour thickness and age of plaque
- Takes several months to see effect
RUTHENIUM PLAQUE
CASE
CASE
CASE
MEDIUM CMM

• Radiotherapy
  — Plaque radiotherapy
  — Proton beam

• Surgical resection
Proton Beam Radiotherapy

- Delivers protons (charged hydrogen particles) by use of cyclotron unit
- Fractionated over 4 days
- Area defined by tantalum marker clips
- Used for peripapillary tumours
- Significant minority develop retinal ischaemia and neovascular glaucoma
Planning for Proton Beam

Transillumination for anterior lesions and ‘marking’ during surgery to indicate position of tumour
Proton therapy

Planning, Simulation and Treatment
Positioning of eye and monitoring during treatment
Proton Beam Radiotherapy

- 98% tumour control

- 40% developed NVG in large lesions with RD

- 10% NVG in smaller lesions
LARGE CMM

• Radiotherapy
  – Proton beam

• Enucleation
Enucleation

- Large tumours not amenable to plaque due to either diameter or thickness
- Hydroxyapatite orbital implant
- Some movement of prosthesis
- Temporary prosthesis 3-4 weeks
- Moulded prosthesis thereafter
- Orbital radiotherapy if signs of ESE or spread to cut optic nerve
Enucleation
• Sample from the tumor

• For genetic testing only and not to make a diagnosis
  
  – Abnormalities in chromosomes 3, 6 and 8 in the tumor itself have been linked to metastatic death
  
  – A loss of chromosome 3 is associated with a poor prognosis
  
  – Gains in chromosome 8 are associates with bad prognosis

  – Abnormalities in chromosome 6 are associated with a good prognosis
GENETICS

- The molecular profile of uveal melanoma is composed of a number of chromosomal abnormalities and somatic gene alterations.

- 10 year Disease Specific Mortality rate varies with abnormality.

- Monosomy 3 is observed in 50% of tumors and is associated with metastatic disease, while simultaneous chromosome 8 alterations are associated with a worse prognosis.

- Oncogenic mutations in genes associated with the G-protein a subunits GNAQ are observed in > 80% of UM.
HIGH RISK PATIENTS

• Gene expression profiling tests are one way to determine a patient’s risk of progressing

• Class 1: low metastatic risk
  – 15% metastatic disease

• Class 2: high metastatic risk (85%)
  – Associated with mutations
  – BAP1
  – GNAQ
  – GNQ11
FACTORS PREDICTIVE OF METASTASIS

• Extrascleral extension
  – No statistically significant advantage for exenterosis

• Tumor size

• Location of anterior tumor margin
  – Tumors extending into the anterior choroid have been associated with a worse prognosis
  – Ciliary body involvement seems to be a poor prognostic sign

• Weaker factors:
  – Older age at diagnosis
  – Greater tumor pigmentation
  – Higher number of mitoses
  – Retinal detachment
METASTATIC DISEASE

• Despite the development of effective local therapies, 5 year survival rate have not changed in the past three decades

• No effective adjuvant systemic therapy could reduce the risk of metastasis

• One year survival of patients with metastases is reported to be 15%, with reported median survival ranging from 4 to 15 months
OBJECTIVE:

To determine the rate of metastasis of uveal melanoma on the basis of tumor thickness in millimeters.

METHODS:

Retrospective medical record review.

RESULTS:

The mean (median) patient age was 58 (59) years. A total of 8033 eyes were examined. Of the 285 eyes with iris melanoma, the mean tumor thickness was 2.7 mm and metastasis occurred in 0.5%, 4%, and 7% at 3, 5, and 10 years, respectively. Of the 492 eyes with ciliary body melanoma, the mean tumor thickness was 6.6 mm and metastasis occurred in 12%, 19%, and 33% at 3, 5, and 10 years, respectively. Of the 7256 eyes with choroidal melanoma, the mean tumor thickness was 5.5 mm and metastasis occurred in 8%, 15%, and 25% at 3, 5, and 10 years, respectively. For all uveal melanoma, metastasis at 5, 10, and 20 years was 6%, 12%, and 20% for small melanoma (0-3.0 mm thickness), 14%, 26%, and 37% for medium melanoma (3.1-8.0 mm), and 35%, 49%, and 67% for large melanoma (>8.0 mm). More specifically, metastasis per millimeter increment at 10 years was 6% (0-1.0 mm thickness), 12% (1.1-2.0 mm), 12% (2.1-3.0 mm), 16% (3.1-4.0 mm), 27% (4.1-5.0 mm), 28% (5.1-6.0 mm), 29% (6.1-7.0 mm), 41% (7.1-8.0 mm), 50% (8.1-9.0 mm), 44% (9.1-10.0 mm), and 51% (>10.0 mm). Clinical factors predictive of metastasis by multivariate analysis included increasing patient age, ciliary body location, increasing tumor diameter, increasing tumor thickness, having a brown tumor, and the presence of subretinal fluid, intraocular hemorrhage, or extraocular extension.

CONCLUSION:

Increasing millimeter thickness of uveal melanoma is associated with increasing risk for metastasis.
METASTASIS

- Haematogenous dissemination
  - Liver
  - Lung

- At the presentation we perform abdominal ultrasound and a whole body PET CT scan

- Also blood tests for liver function and a CXR

- Screening with blood tests and abdominal ultrasound every 6 months

- Mortality up to 50% at 5 years
The value of whole body 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) / computed tomography (CT) and abdominal ultrasound in staging of patients with uveal melanoma

E. Pavlidou, V. Cohen et al. IOVS, April 2014, Volume 55, issue 13,

- **Abstract**
- **Purpose**: To determine the value of whole body (18) fluorodeoxyglucose (FDG) positron emission tomography (PET)/ computed tomography (CT) and abdominal ultrasound in staging of patients with uveal melanoma.
- **Methods**: From January 2012 patients with uveal malignant melanoma over 4 mm in thickness, were staged with whole body (18) fluorodeoxyglucose (FDG) PET/CT and abdominal ultrasound. The incidence and location of metastatic disease at diagnosis was recorded. The imaging findings were compared.
- **Results**: 108 patients had a whole body FDG PET/CT and abdominal ultrasound at primary diagnosis. 3 patients (2.8%) were found to have metastatic disease. All 3 had liver metastases, confirmed with biopsy in only one case. 1 of 3 had additional extrahepatic widespread metastases in the lungs, lymph nodes and bone seen on whole body FDG PET/CT. In the 3 patients with metastatic disease, the liver findings using both imaging techniques were consistent in one patient. In the second case abdominal ultrasound misdiagnosed metastatic disease as liver cysts; however, FDG PET/CT revealed several foci of intense metabolic activity in both lobes of the liver. In the third case, PET/CT missed the presence of liver metastases as no metabolic activity was detected, however a hypodense liver lesion was identified on abdominal ultrasound. An abdominal CT scan with contrast confirmed the presence of an enlarging liver metastasis. PET/CT identified second primary malignancies in 9 patients (8.3%) and incidental extrahepatic pathology in another 9 patients (8.1%). Coincidental liver findings, such as fatty liver and haemangiomata, were seen in 20 patients (18.5%) using abdominal ultrasound but only 4 (3.7%) using whole body PET/CT.
- **Conclusions**: Whole body PET/CT and abdominal ultrasound complement each other in the staging of uveal melanoma. PET/CT is useful to detect extrahepatic disease including widespread metastases and other primary malignancies. The metabolic activity of uveal melanoma metastases is variable. Abdominal ultrasound provides more detailed description of the liver and detected an abnormality in all 3 cases with liver metastases.