Course Title: Cancer and the Eye
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Cancer factoids
- Can affect any tissue or organ at any age
- All cancers begin with a defect in a single cell (monoclonal)
- This is followed by unrestrained growth

Cancer factoids
- A one cm. tumor contains one billion cells
- One trillion cells usually means a lethal tumor
- BENIGN tumors may damage local tissue by occupying space but they do not spread
- MALIGNANT tumors invade surrounding tissue and may metastasize

Cancer factoids
- Cell division is controlled by genes that promote it and genes that suppress it
- Cancer is the result of some combination of defects in this genetic functioning

Cancer types
- General types of cancer include:
  - Melanomas (melanin)
  - Sarcomas (connective tissue)
  - Carcinomas (epithelial tissue)
  - Leukemias (bone marrow)
  - Lymphomas (lymphoid tissue)
- Adenocarcinoma: Glandular tissue
Leading Cancers in US

- Men:
  1) Prostate
  2) Lung
  3) Colon
  4) Urinary
  5) Skin melanoma

- Women:
  1) Breast
  2) Lung
  3) Colon
  4) Uterine
  5) NHL lymphoma

But the most common malignancy in humans is..............Basal Cell Carcinoma!

Cancer mortality (M & F)

- 1) Lung
- 2) Colorectal
- 3) Breast
- 4) Pancreatic (#12 in frequency)
- 5) Prostate

Skin cancer

- In the US 50% of all cancer is skin cancer.............and 80% of skin cancer is BCC.
- Kidney transplant = 20 X risk for ocular SCC
- 50% of BCC patients and 75% of SCC patients develop a second within 5 years
- Hydrochlorothiazide (HCTZ) for HTN is a photosensitizer: significantly increases risk of BCC and SCC, especially SCC

American Cancer Society Report

2018
- 1,735,350 new cases of cancer excluding SCC and BCC, > 4700/day
- 13.7 million living Americans with a history of cancer (active or remission)
- 609,640 deaths: about 1700/day

Combined M & F Rank
- Prostate
- Breast
- Lung
- Colon
- Lymphoma
- Skin melanoma

2018 cancer statistics

- Cancer deaths peaked in 1991, had dropped 26% by 2016
- The most important reason............a decrease in cigarette smoking
- 42% of new cancer diagnosis in males = P, C, L
- 50% in women = B, L, C
- Liver cancer on the rise in both sexes

2018 cancer statistics

- 39% decrease in breast cancer from 1989-2015
- 52% decrease in prostate cancer from 1993-2015
- 52% decrease in colon cancer from 1970-2015
- Cancer is the second leading cause of death in children under 14, 1180 deaths per year

- All cancers 5 year survival rate is 66% in whites, 81% in African Americans
- Five year survival rates: Prostate 99%, melanoma 92%, breast 92%, pancreatic 8%, lung 18%, and liver 18%
Obesity and cancer
- 2017 study in *Lancet Diabetes and Endocrinology*
- Used 2012 data
- Worldwide, 5.6% of cancer cases directly attributed to diabetes or high BMI

Cancer epidemiology
- Cancer screenings are driven by several factors...........
  1) Is it a common cancer ?
  2) Can we detect it ?
  3) Can we treat it ?
  4) How much does the screening cost?

Cancer epidemiology
- It is generally worth screening for prostate, colon, breast, cervical, and skin cancer
- Cancer increases with age due to increased length of exposure to carcinogens

Cancer screenings
- 1) Blood tests
- 2) Bone scans
- 3) Biopsies
- 4) X-ray, CT, MRI and other imaging
- 5) Observation
Growing movement that says cancer screening of healthy individuals does not decrease mortality, causes harm, and costs a tremendous amount of money

Cancer
- Leading cause of death worldwide
- It accounts for ¼ of deaths in the US......Only heart disease kills more.

Cancer treatment
- CHEMOTHERPY:
  - Drugs that interfere with cell division
  - Multiple drugs available, oral and IV
- RADIATION:
  - Damages cellular DNA
- SURGERY:
  - Removes the tumor
Cancer treatment

- Chemotherapy targets all cells in the body that are actively dividing...abnormal and normal!
- Hair follicles > loss of hair
- Intestinal mucosa > diarrhea, vomiting, nausea
- Bone marrow > anemia

Cancer treatment

- Radiation results in the damage of cellular DNA > cell death
- Need to be focal with treatment because all cells are affected
- Both radiation and chemotherapy can lead to retinal complications

Interferon chemotherapy

Cancer itself can cause CWS too.......

Help from a tree?

- Beta-lapachone from the South American lapacho tree
- Cytotoxic effects shown (due to induced apoptosis) to cancer cells: retinoblastoma, lung, breast, prostate, many others

Beta Lapachone

- Usefulness in humans limited thus far by toxicity
- Also has antibacterial and antiviral properties, including activity against HIV
Did you know..........  

- Metformin (Type II DBM drug) is proving to be very protective against lung cancer  
- It activates an enzyme ........ that inhibits a protein ........ that is needed for the growth of cancer cells

Paraneoplastic syndrome

- CAR (cancer associated retinopathy)  
  - Rare: antibody mediated  
  - Associated with many types of cancer  
  - Photopsia and progressive bilateral vision loss  
  - Normal fundus appearance then RPE changes, etc.  
  - Confirm with ERG

- MAR (melanoma associated retinopathy)  
  - Rare, more common in males  
  - Associated with cutaneous melanoma  
  - Photopsia, night blindness, loss of vision  
  - Normal fundus appearance then RPE changes, etc.  
  - Antibodies target rods

Case Report

- A 55 year-old white female reported to our clinic with a complaint of blurry vision in her left eye for about one month  
- She also complained of dizziness, nausea, and a “pressure” behind her left ear  
- Her medical history was significant only for a family history of colon cancer

- An eye exam performed in our clinic three years prior was remarkable only for refractive error  
- Entering acuity with correction was 20/20 OD, 20/40 OS and BCVA was 20/20 OD, 20/25 OS  
- Entrance testing was unremarkable as was the anterior segment OU

Case Report

- DFE OD was remarkable for an isolated cotton-wool spot in the superior arcade  
- All other fundus findings OD were normal  
- DFE OS revealed a large (2.5 disc diameter) cream colored mass inferotemporal to the macula which was encroaching on the foveal region but did not involve the foveal center

Amelanotic Lesion OS (whitening in arcades is a camera artifact)
Case Report

- Screening and threshold Matrix FDT VF results were normal OU
- B-scan ultrasound of the left eye revealed a solid lesion with 1.5-2.0mm of elevation and moderately high internal reflectivity with no evidence of overlying retinal detachment

Threshold VF OS

B-scan ultrasound of lesion (note elevation and internal reflectivity)

Systemic Work-up

- Due to the appearance of the retinal lesion, metastatic disease was strongly suspected
- The patient was counseled earnestly regarding this fear and referred for a consultation with a retinal oncologist

Systemic work-up

- A systemic work-up revealed previously undiagnosed large cell carcinoma of the lung with multiple lesions
- There were metastases detected in the liver, spleen, and kidneys
- Chemotherapy was begun at this time

Therapy

- The ocular lesion in the left eye continued to be problematic despite chemotherapy and the vision deteriorated to 20/100 over the course of one month
- The retinal surgeon decided to proceed with a course of external beam radiation ocular therapy in addition to the chemotherapy. Ultimately successful with acuity recovery to 20/25
Another example……

- The following set of pictures represent another patient.
- Once again, the patient reported with a complaint of blurry vision OS and no known cancer.

Multiple Metastatic Lesions OU

Early IVFA OS

- Note blocking of the background hyperfluorescence in multiple areas including large central lesion.

Late IVFA

- Note late staining of large central lesion secondary to leakage from lesion’s blood supply.

Another Example……..

- In this case, systemic evaluation revealed multiple, subcutaneous adenocarcinomas with several intracranial metastases and lymph node involvement.
- No primary tumor site was able to be identified.
- Management with radiation and chemotherapy was undertaken and the ocular lesions responded well but ultimately the patient did not survive.

Several weeks later….systemic chemo and radiation
Uveal Metastatic Lesions
- Most common intraocular tumor
- Number one primary site in women is the breast, in men it is the lung
- Choroid around 90%, ciliary body about 8%, iris 1-2%
- Up to 10% of cancer patients get uveal metastases: often not diagnosed
- Primary site is often never determined

Uveal Metastases
- Located in posterior pole (blood supply)
- Unilateral or bilateral (unilateral 3 to 1)
- Breast metastases most likely to be bilateral; lung unilateral
- Single lesion or multiple lesions
- RPE detachments
- Creamy yellow in color (may have orange hue)
- Oval to placoid
- Relatively flat (rarely break through Bruch's membrane)
- High internal reflectivity on ultrasound
- Typically irregular or lobulated surface on OCT

Management of Metastatic Tumors
- Metastatic lesions tend to be detected sooner because their posterior pole location leads to earlier symptoms (countered by life expectancy)
- Systemic work-up is critical
- Average survival time of 9 months after Dx
- Systemic chemotherapy
- Radiation via external beam (outpatient) or plaque (hospital)
- PBT (protons)
- Photocoagulation
- Enucleation
- Anti-VEGF injections
- Must consider life expectancy

Differential Diagnoses of Metastatic Tumors
- Primary uveal melanomas
- Hemangiomas
- Osteomas
- Posterior scleritis
- Inflammatory disorders

Other Examples of Ocular Neoplasms
- Choroidal nevi
- Primary Choroidal / CB Melanomas
- Melanocytomas
- Iris melanomas
- 6.5% of whites in 2011 study: <1% AA, 2% Hisp
- Flat or minimally elevated (< 2.0 mm)
- < 6 mm in diameter: Average 4.5 mm
- Melanotic (75%) or amelanotic
- Overlying drusen: usually indicate longstanding inactivity: lipofuscin?
- Possible overlying serous RD
- RPE disturbance / atrophy over time
- Conversion to uveal melanoma: 1 in 8000 average over lifespan
- Some will grow without undergoing malignant conversion: 2011 study showed growth in 31% over 15 years.

Choroidal nevi
- Possible overlying serous RD
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- Conversion to uveal melanoma: 1 in 8000 average over lifespan
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Choroidal Nevi

- Photodocument (include FAF when possible)
- B-scan
- If small, follow annually
- If suspicious, more frequent observation
- Significant elevation rare with nevi

Small choroidal nevus with FAF

Choroidal nevus FAF

Choroidal nevus

Peripheral choroidal nevus
Longstanding, Large Choroidal Nevus

- Overlying PED / RD
- B-scan revealed no growth compared to baseline; retinal oncologist chose to monitor closely

B-Scan

Melanoma

- Later, decision was made that malignant transformation had occurred
- Treatment was undertaken with brachytherapy

Primary Uveal Tumors

- Unilateral & solitary
- Pigmented but may be amelanotic
- Relatively elevated
- Can break through Bruch’s membrane “Collar Button”
- Rare in non-caucasians (C19 X AA; H 5x AA).
- Second most common primary ocular tumor
- Low internal reflectivity with ultrasound
- Typically smooth surface on OCT
- Can be located anywhere……no posterior pole predilection
- About 2000 new cases per year in US

Environmental factors?

- “Auburn cluster”
- Incidence of uveal melanoma is roughly 5 people in one million
- At least 19 individuals with uveal melanoma who attended Auburn University between 1983-2001
- Investigation ongoing

Melanoma vs. nevus

- Important risk factors for possible malignant transformation….
  - Thickness > 2mm (>3mm nearly 100% melanoma)
  - Symptoms
  - Orange Pigment
  - New onset of subretinal fluid / serous RD, especially in the absence of drusen
  - Ultrasound hollowness / no halo
  - Location within 3mm of ONH
  - Diameter of 12mm or more
Shields

- “To find small ocular melanomas using helpful hints daily”
- Thickness > 2mm
- Fluid
- Symptoms
- Orange Pigment
- Margin near ONH (3mm)
- Ultrasound Hollow
- Halo absent
- Drusen absent

EDI SD-OCT feature of small melanomas vs. nevi

- Shaggy photoreceptors
- Loss of PIL
- Disruption of IPL, GCL
- Loss of ELM
- FAF also excellent: little to no AF with nevi, significant AF with melanomas

SD-OCT and FAF of suspicious nevus

Primary uveal tumors

- Can metastasize (but often not yet detectable at the time that the ocular tumor is found). 75% to the liver first
- Gene mutations that cause metastasis have been discovered (Dr. J. William Harbour at Bascom Palmer)
- Systemic work-up a must, but may not find metastases at time of diagnosis
- 2X risk of colon cancer compared to general population

Deep DNA sequencing: Dr. Harbour

- Class 1A: 35% of uveal melanomas, 1% 5 year risk of metastasis
- Class 1B: 25% of uveal melanomas, 35% 5 year risk of metastasis
- Class 2: 40% of uveal tumors, 70% 5 year risk of metastasis

Radiation risk

- For a 50 year old diagnosed with an ocular melanoma, the cancer risk from 10 years of radiation exposure with abdominal scans is.....
- CT scan around 1% lifetime risk
- CT plus PET scan around 2% lifetime risk
- This is average for both sexes, women slightly higher risk
Pathology

- Three main tumor types based upon cell morphology:
  - Spindle (relatively benign)
  - Epithelioid (most large tumors)
  - Mixed

Choroidal Melanoma With Intravitreal Extension

Early choroidal melanoma (courtesy Dr. Diana Shechtman)

“Collar Button” Melanoma

57 year old WF
57 year old white female

2016

2018: symptoms of blur

57 year old white female

Bile Duct Liver Cancer with no ocular history

Lesion edge

Atrophic area and border

Could the liver cancer have been metastatic from the eye?
Peripheral Exudative Hemorrhagic Chorioretinopathy

Treatment options for tumors

- Systemic radiation / chemo if metastatic disease involved
- Brachytherapy (radioactive plaque): requires two surgeries and sometimes a hospital stay. Local recurrence rate of 10% @ 5 years. 12.5% end up enucleated
- Photocoagulation- replaced by TTT. 20% recurrence rate, but limited “down side”
- Cryotherapy, stereotactic radiotherapy
- Enucleation

EBRT (external beam radiation therapy)
3-4 weeks of daily treatment

PBT (proton beam therapy)
Two treatment sessions only
Less readily available
Lowest local recurrence rate: 3.5% @ 5 years, 5% @ 10 years

PBT in Scotland

- 2012 retrospective study
- 147 patients who had medium and large uveal (most all choroidal) melanomas
- Treated with PBT between 1993 and 2008
- 23% eventually required enucleation
- Disease specific 5 year survival rate of 88%
- Most common reasons for eventual enucleation were tumor recurrence and NVG

Treatment side effects

- Main side effect of focal ocular treatment is ...
- Radiation retinopathy!
- NVD / NVE
- Exudative changes
- Macular edema
- Occurs several weeks to months after therapy
Radiation retinopathy

- Can combine plaque brachytherapy with TTT and anti-VEGF injections (Shields)
- Highly effective with decreased risk of radiation retinopathy

Exciting trial (AU-011)

- New therapy called AU-011
- Granted fast track and orphan drug status by the FDA
- Derived from the capsid of papilloma virus
- Binds only to the heparan sulfate proteoglycans expressed on the surface of the tumor cells

Exciting trial (AU-011)

- Drug injected intravitreally, then activated by a 689 nanometer wavelength near infrared laser similar to PDT
- Causes tumor cell necrosis with no damage to any ocular structure
- In rabbit trials, led to complete tumor necrosis with no collateral damage
- In early human trials currently to first assess safety, then efficacy
- Very promising

Treatment options

- Rapid shrinkage of the tumor with treatment may be bad news........indicates substantial malignant (and metastatic) potential
- No response to treatment also indicates high metastatic potential

Causes for secondary enucleation

- Main causes for secondary enucleation after attempted treatment (in order of incidence):
  - Tumor recurrence
  - NVG
  - Tumor non-response

COMS and other studies

- Five year survival rates for........
  - Small melanomas (< 10 mm): 94%
  - Medium melanomas (10-15 mm): 70-90%
  - Large melanomas (> 15 mm): 40-60%
- Enucleation does NOT appear to increase metastatic risk
Choroidal Melanoma ("George")
Post Photocoagulation Therapy

Melanoma: photos courtesy of Dr. Vic Malinovsky

Melanoma

Radiation retinopathy
- Avastin may be effective at reducing retinopathy and stabilizing vision
- What about silicone oil? May reduce radiation retinopathy risk, but can cause other issues

Another example of RR

Radiation retinopathy
- Recent study by Mashayekhi, et al (Ophthalmology 2015; 1023-1029)
- Uveal melanomas often associated with subclinical macular edema before radiation
- Size dependent
- May not be direct radiation damage

Macular edema and other radiation retinopathy may be, at least in part, due to the release of VEGF, etc. from the tumor and surrounding retina
**Possible intervention**

- New research by Dr. Harbour indicates that a certain class of seizure drugs...HDAC inhibitors...may help.
- Cancer cells that have metastasized from the eye to other sites are inhibited and made less aggressive by these drugs. May be able to keep disease "at bay" for an extended period.

**More genetics....**

- 80% of uveal melanoma patients have mutations in either GNA11 or GNAQ.
- But............this mutation alone does not result in melanoma formation. Must have mutation plus other factors (as of now not known).

**Iris Melanomas**

- Around 5% of all uveal tumors.
- Located inferiorly secondary to sun exposure.
- Only metastasize in about 8% of cases after 15 years.
- Found mostly in light colored irides (therefore Caucasians).
- Can have satellite lesions.
- Can seed tumor cells in to the TM causing elevated IOP.
- May be melanotic or amelanotic.
- Can irradiate or surgically excise.

**Differential diagnoses**

- Neurolemmoma
- Xanthogranuloma
- Nevus
- Iris cyst
- Lisch nodule
- Melanocytoma
- Be suspicious if............
- > 3mm
- Increased IOP
- Distorted pupil
- Rapid growth
- Secondary cataract

**Amelanotic Iris Melanoma**

- Another iris melanoma
Melanocytomas

- Jet black lesion consisting of melanocytes
- Most often on ONH, but can rarely affect the conjunctiva or uveal tract
- Usually involves less than half of the disc but may cover the entire ONH
- Can have concomitant juxtapapillary choroidal nevus

Melanocytoma

- Very little potential for malignant transformation
- Very slow growing
- Usually little or no effect on vision but can cause VF defects including an enlarged blind spot
- May also cause an APD

Differential diagnoses

- Malignant melanoma
- Juxtapapillary choroidal nevus
- Optic disc meningioma

Melanocytomas

- Malignant melanoma
- Juxtapapillary choroidal nevus
- Optic disc meningioma
Multiple CHRPE / Bear tracks

A ticket for……….. Colonoscopy or not?

Familial Adenomatous Polyposis

- Studies vary 1 / 7000 people to 1 / 31,000 people
- Associated with RPE hypertrophy
- Colon polyps, up to thousands of them, with essentially a 100% chance of malignancy by age 40

Gardner’s Syndrome

- FAP
- Osteomas of the jaw
- Soft tissue benign tumors
- Dental abnormalities

What’s this? CIN

Or this? Melanocytoma

How about this? Osteoma

Photo Courtesy Dr. Mark Dunbar

Or this one? Syphilitic chorioretinitis

WHAT ABOUT PRIMARY ACQUIRED MELANOSIS?
Retinoblastoma
- Malignant, congenital tumor. Most common primary ocular tumor
- Derived from retinoblasts
- Most common intraocular tumor in infants / children
- 70% unilateral
- 1/15,000 children
- 200-300 US cases/yr
- No racial or sexual predilection
- Two types......
  1) Inherited (AD), Less than 10% of cases, Frequently multifocal and bilateral
  2) Sporadic. Usually unilateral
- Can metastasize and be fatal if detected too late
- Survival rate 90+% if detected early (typical age of diagnosis is around 18 months)
- LEUKOCORIA
- Strabismus
- Poor VA
- Involvement of ONH is ominous
- Many treatment options depending on multiple factors
- IV chemo?

Genetics
- RB survivor with inherited type: 50% chance of transmitting to their children
- Healthy parents: one child with RB; 6% chance of another; two or more children with RB; 50% of another

Leukocoria differentials
- Retinoblastoma
- Coats disease
- Toxocariasis
- Toxoplasmosis
- Congenital cataract
- PHPV (retrolental fibroplasia)
- coloboma

Coloboma

Retinoblastoma

Photo courtesy Dr. Dan Neely
Retinoblastoma

Photo courtesy Dr. Dan Nealy

The End!