Ocular Surface Oncology and Updates

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PENNINGTON EYE CLINIC

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Overview

- Ocular surface anatomy
- Classification of ocular surface tumours
- Focus on 2 most common ocular surface malignancies
  - OSSN
  - Conjunctival melanoma
- Uveal melanoma updates

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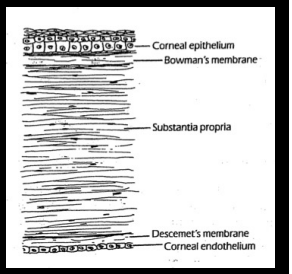
Corneal Layers

1. Corneal epithelium
   - Stratified squamous, non-keratinizing
   - 5-6 layers
2. Bowman's membrane
3. Stroma
4. Descemet's membrane
5. Endothelium



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Corneal Tumours

- Epithelial tumours of the cornea are very rare
  - Usually the result of involvement of the cornea in conjunctival tumours
- Corneal stromal tumours
  - Almost non-existent

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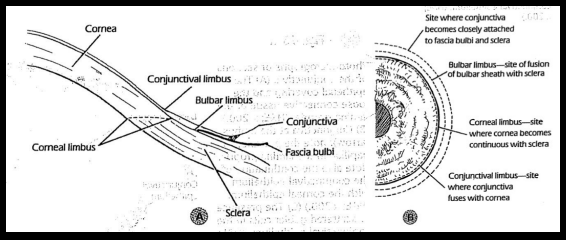
Conjunctival Anatomy



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Conjunctival Layers

- Epithelium
- Stroma
  - Superficial lymphoid layer
  - Deep fibrous layer

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Conjunctival Layers

- Epithelium
  - 2-5 layers
  - Stratified squamous, non-keratinizing epithelium
    - Marginal and limbal zones
  - Stratified columnar epithelium
    - Fornix
  - Cuboidal epithelium
    - Bulbar and tarsal conjunctiva
    - Can secrete mucin
  - Goblet cells
    - Specialised cells to secrete mucin
    - Present in the middle and superficial layers of epithelium
    - Most numerous in the lower fornix and close to plica
  - Melanocytes
    - Scattered in the basal layer of the epithelium

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Conjunctival Layers

- Stroma
  - Superficial lymphoid layer
  - Deep fibrous layer

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Conjunctival Layers

- Stroma
  - Superficial lymphoid layer
    - Thicker over the fornix
    - Thinner over palpebral conjunctiva and bulbar conjunctiva
    - Contains:
      - Collagenous and elastic tissue
      - Mucosal associated lymphoid tissue (lymphocytes, plasma cells, mast cells, neutrophils)
  - Deep fibrous layer

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Conjunctival Layers

- Stroma
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    - Contains:
      - Collagenous and elastic tissue
      - Mucosal associated lymphoid tissue (lymphocytes, plasma cells, mast cells, neutrophils)
  - Deep fibrous layer
    - Vessels (arteries, veins, lymphatics)
    - Nerves
    - Accessory lacrimal glands of Krause and Wolfring

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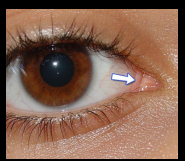
Specialized Regions

- Plica Semilunaris
  - Vertical fold of conjunctiva lateral to caruncle
  - Contains many goblet cells
  - May contain nonstriated muscle fibers and fatty tissue
- Caruncle
  - Fleshy prominence located in the medial canthus
  - Contains both conjunctival and cutaneous structures
  - Non-keratinized stratified squamous epithelium
  - Numerous goblet cells, sebaceous glands, sweat glands, accessory lacrimal glands, hair follicles
  - Tumours of the caruncle can be both mucosal and cutaneous origin



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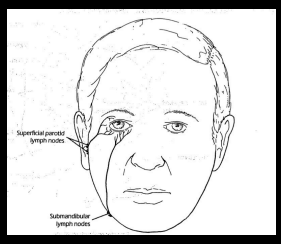
Lymphatic Drainage

- Lateral conjunctiva
  - Superficial parotid lymph nodes
- Medial conjunctiva
  - Submandibular lymph nodes



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Classification of Conjunctival Tumours

Location	Type of conjunctival tumours
Epidermal	Non-melanocytic
	Melanocytic
Stromal	Vascular
	Neural
	Myxoid
	Lipomatous
	Melanocytic
	Fibrous tissue
	Histiocytic
	Myogenic
	Lymphoproliferative

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Location	Types	Subtypes	
Epidermal	Non-melanocytic	Benign	Squamous papilloma
			Keratotic plaque
			Keratoacanthoma
			Inverted follicular keratosis
			Oncocytoma
			Dacryoadenoma
		Premalignant and malignant	Actinic (solar) keratosis
			Conjunctival intraepithelial neoplasia (CIN)
			Squamous cell carcinoma
			Mucoepidermoid carcinoma
			Sebaceous gland carcinoma (pagetoid spread)
			Basal cell carcinoma
	Melanocytic	Benign	Naevus (junctional, compound, Spitz, Blue)
			PAM without atypia
			Congenital melanosis
			Complexion associated melanosis
		Premalignant and malignant	PAM with atypia
			Conjunctival melanoma

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Location	Types	Subtypes
Stroma	Vascular	Capillary haemangioma
		Varix
		Haemangiopericytoma
		Kaposi's sarcoma
		Cavernous haemangioma
		Racemose angioma
		Lymphangiectasia
		Lymphangioma
		Pyogenic granuloma
	Fibrous	Nodular fasciitis
		Benign fibrous histiocytoma
		Fibroma
		Malignant fibrous histocytoma
	Neural	Neurofibroma
		Schwannoma (neurilemmoma)
		Granular cell tumour
	Histiocytic	Xanthoma
		Reticulohistiocytoma
		Juvenile xanthogranuloma

Location	Types	Subtypes
Stroma	Myxoid	Myxoma
	Lipomatous	Lipoma
		Liposarcoma
		Herniated orbital fat
	Lymphoproliferative	Benign reactive lymphoid hyperplasia
		Leukemic infiltrates
		Lymphoma

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Conjunctival Tumors in 5002 Cases. Comparative Analysis of Benign Versus Malignant Counterparts. The 2016 James D. Allen Lecture

CAROL L. SHIELDS, ADEL E. ALSET, NINA S. BOAL, MAIRGHREAD G. CASEY, AUSTEN N. KNAPP, JORDAN A. SUGARMAN, MARISA A. SCHOEN, PHILLIP S. GORDON, ALEXZANDRA M. DOUGLASS, KAREEM SIOUFI, EMIL A.T. SAY, AND JERRY A. SHIELDS

Tumour type	%
Naevus	23
OSSN (SCC, CIN)	14
Melanoma	12
PAM	12
Lymphoma	7

Am J Ophthalmol 2017;173:106–133

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Focus on

- OSSN
- Conjunctival Melanoma

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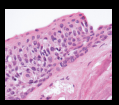
OSSN

- Ocular Surface Squamous Neoplasia (OSSN)
- Spectrum of pre-malignant and malignant epithelial lesions of the conjunctiva and cornea
- Includes:
  - Conjunctival intraepithelial neoplasia (CIN)
    - Mild
    - Moderate
    - Severe (carcinoma in-situ)
  - Invasive squamous cell carcinoma (SCC)
- Only used clinically where invasive nature on histology cannot be determined



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OSSN

- Incidence
  - 0.3 per million (US)
  - 1.3 per million (Uganda)
  - 19 per million (Australia)
- 5x higher in males and whites
- Two main patterns of presentation:
  - Older white male population – developed countries (UVB as primary risk)
  - Younger female – developing countries (HIV and HPV more prevalent)

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OSSN – Risk Factors

- Most important:
  - UV light exposure
- Other risk factors:
  - Pale skin, blue iris, propensity to sunburn
  - Significant sun exposure as a young child (>50% of time outdoors in first 6 years of life)
  - Proximity to equator (habitation within 30˚ of the equator)
  - Cigarette smoking
  - Human papilloma virus (HPV) infection (16 and 18 most common)
  - Immunosuppression
    - HIV
    - Xeroderma pigmentosum
    - Atopic disease
    - Iatrogenic (organ transplant, autoimmune diseases treatment)
  - Vitamin A deficiency
  - Exposure to petroleum products
  - Ocular surface injury

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OSSN – Clinical Features

- Usually in interpalpebral fissure zone
- Often begins at limbus
- Appearance:
  - Papilliform
  - Nodular or sessile
  - Gelatinous
  - Leukoplakic (keratinization caused by dyskeratosis)
  - Foamy infiltration of adjacent corneal epithelium
  - Epithelial thickening (frosted glass appearance)
  - Prominent nutrient feeder vessels

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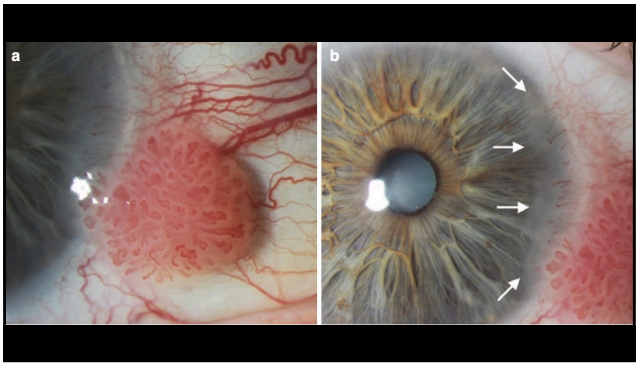

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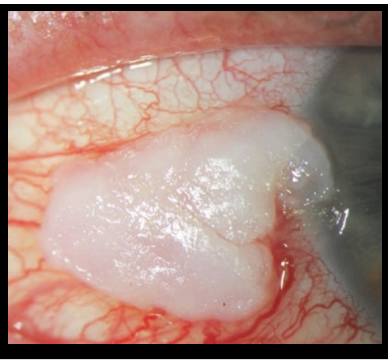

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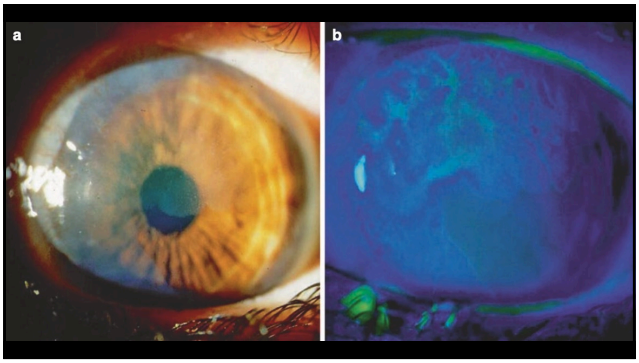

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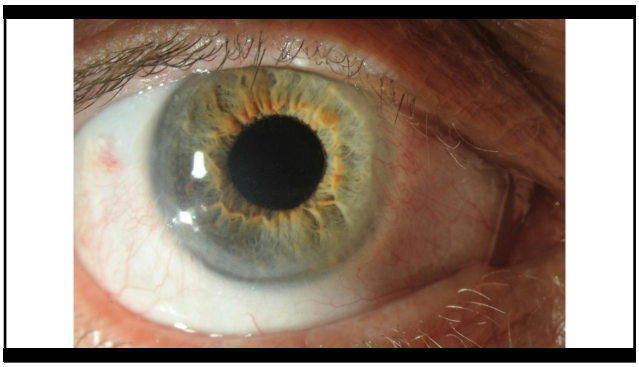

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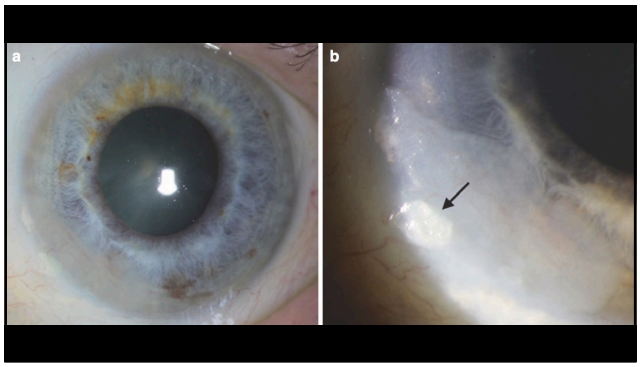

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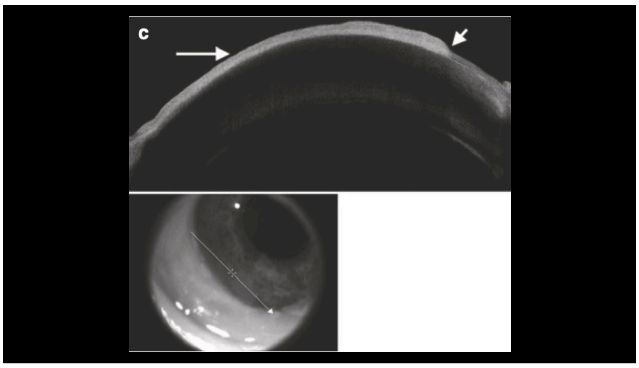

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Work-up of ocular surface tumours

- Establish risk factors
- Full slit lamp examination of ocular surface
  - Bulbar, palpebral, forniceal conjunctiva – evert eyelids!!
  - Caruncle
  - Fluorescein staining
  - ± gonio, dilated fundus exam
- Photograph – phone photography
- Palpate pre-auricular and submandibular lymph nodes

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Is Biopsy Necessary?

- Past 15 years – progressive shift to using topical chemotherapy as primary therapy for OSSN
  - Rationale that SCC is locally invasive disease
- Does histopathological diagnosis alter management of patients?

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Is Biopsy Necessary?

- Treatment of pre-malignant disease is different to invasive disease
  - Invasive SCC may require adjuvant radiotherapy
- Distinguishing premalignant from invasive disease based on clinical features alone by experienced clinicians can have an accuracy of only 40%.[1,2]
- There may be risk of misdiagnosis based on clinical features alone:
  - Misdiagnosis as OSSN as compared to other non-epithelial lesions can be as high as 10%.[3]
  - Amelanotic or minimally pigmented conjunctival melanoma – up to 30% of cases in some series
  - Certain types of ocular surface carcinomas are more aggressive (mucoepidermoid, spindle cell, Merkel cell, sebaceous ca)

1. Lee GA, Hirst LW. Ocular surface squamous neoplasia. Surv Ophthalmol. 1995;39(6):429-50.
2. Kao AA, Galor A, Karp CL, Abdelaziz A, Feuer WJ, Dubovy SR. Clinicopathologic correlation of ocular surface squamous neoplasms at Bascom Palmer Eye Institute: 2001 to 2010. Ophthalmology. 2012;119(9):1775-6. https://doi.org/10.1016/j.ophtha.2012.02.049.
3. Rudkin AK, Dodd T, Muecke JS. The differential diagnosis of localised amelanotic limbal lesions: a review of 162 consecutive excisions. Br J Ophthal- mol. 2011;95(3):350-4. https://doi.org/10.1136/bjo.2009.172908

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Is Biopsy Necessary?

- Full-thickness biopsy is still required for differentiating premalignant from invasive disease, aggressive variants and masquerades
- Differentiation of these types affects management and patient outcome

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Management of OSSN

- Full-thickness tissue biopsy
  - Excision biopsy if less than 5 clock hours limbal involvement
  - 'No-touch' technique
  - Wide margin (2-3mm)
  - Alcohol epitheliectomy if corneal involvement
  - Double-freeze thaw cryotherapy
- Closure
  - Direct closure
  - Amniotic membrane graft

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Management of OSSN

- Topical chemotherapy

	Mitomycin C	5-Fluorouracil	Interferon α2b
Dose	0.02% - 0.04% QID 1 week Then 1-3 weeks off 3-4 cycles Week off (flarex and poly gel)	1% QID for 1 week Then 3 weeks off 4 cycles	1 million IU/ml QID 3 million IU/0.5ml SC twice/week 3-6 months
Storage	Keep refrigerated	Keep room temperature	Keep refrigerated
Side-effects	Pain, limbal stem cell failure, punctal stenosis	Pain, epitheliopathy, hyperemia	Irritation, conjunctivitis, flu-like symptoms
Efficacy as primary treatment	76-100% resolution (primary) 0-35% recurrence	82-100% resolution 7-43% recurrence	82-100% resolution 0-9% recurrence

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Management of OSSN

- Recurrent or refractory OSSN
  - Cidofovir 0.25% 3x/day for 4-9 weeks
  - 83% resolution of refractory OSSN
- Novel treatments
  - EGFR inhibitors
  - Checkpoint inhibitors

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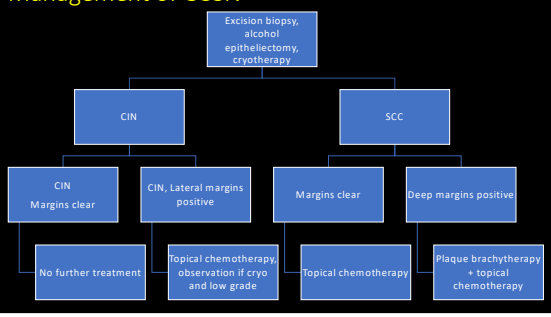
Management of OSSN



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Conjunctival Melanoma

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Conjunctival Melanoma

- Annual incidence
  - 0.3 – 0.5 cases per million in Western populations
  - 300% increase over 3 decades
- Origin:
  - 70% arise from pre-existing PAM
  - 20% from naevi
  - 10% de novo
- No sex predilection
- Presentation in 60s

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Conjunctival Melanoma

- Risk factors:
  - Whites, rare in Asian/Pacific Islanders
  - Older age
  - Pre-existing lesion (most well-established risk factor)
    - PAM and conjunctival naevi
  - UV radiation is suggested but not conclusively linked (unlike cutaneous melanoma)
  - No significant association with cutaneous melanoma, dysplastic naevus syndrome, or ocular/oculodermal melanocytosis

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Conjunctival Melanoma

- Clinical Features:
  - Vascularized lesion
  - Nodular, diffuse or mixed
  - Can be deeply pigmented, grey or amelanotic (fish flesh)
  - Common in the limbus, also palpebral, fornix, caruncle
  - Feeder vessel
  - Does not have surface keratinization
  - Haemorrhagic areas
  - Usually only unilateral

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Conjunctival Melanoma

- Key points for differentiating:
  - Conjunctival naevi
    - Pigmentation at the palpebral conjunctiva and fornix = excision
    - Most conjunctival naevi noticed in childhood and adolescence
      - Newly-elevated pigmented conjunctival lesion in adulthood = excise
      - Enlarging pigmented conjunctival lesion from childhood = suspect
    - Conjunctival naevi commonly associated with cysts
  - PAM
    - Placoid thickening within area of PAM
    - Nodules in area of PAM

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Conjunctival Melanoma

- Estimated mortality
  - 13-38% at 10 years in adult studies
  - Overall mortality 25% (Danish study)
- Local recurrence
  - 19% at 5 years
  - 37% at 10 years
  - Factors associated with lower recurrence rate:
    - Smaller extent of initial disease
    - No touch surgical technique
    - Adjunctive radiotherapy

Jain P, Finger PT, Fili M, et al. Conjunctival melanoma treatment outcomes in 288 patients: a multicentre international data-sharing study. *Br J Ophthalmol*. September 2020. doi:10.1136/bjophthalmol-2020-316293.

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Conjunctival Melanoma

- Staging examinations:
  - Full slit lamp examination
  - Lymph node examination (pre-auricular, submandibular, cervical)
  - US/CT head and neck lymph nodes
  - Refer medical oncologist
- Management:
  - Body of tumour
    - Excision biopsy with 4mm margins, alcohol epitheliectomy, cryotherapy
    - No touch technique
  - Roots of tumour
    - Adjunctive radiotherapy (plaque, strontium, proton beam)
  - Seeds of tumour
    - Topical mitomycin C 0.04% for 3 cycles
    - IFN-a2b (limited data)

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Conjunctival Melanoma

- Surveillance:
  - Q4/12 follow-ups lifelong
  - Q6/12 US head and neck LNs for first 5 years, then annually for life

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Conjunctival Melanoma

- Topical chemotherapy
  - MMC 0.04%
    - QID 1 week on 1 week off for 3 cycles is the most widely used
  - Interferon a2b
    - 1 million IU/ml, 5x/day for 6 weeks x 6 cycles = also used with good efficacy
  - 5-FU
    - Has been used but less effective and less well studied

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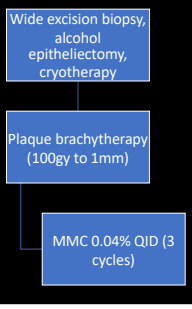
Management of Conjunctival Melanoma



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Choroidal Melanoma

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Choroidal Melanoma

- Suspicious choroidal naevi (TFSOMDim and MOLES)
- Light activated therapy (AU-011)
- Prognostication
- Metastatic uveal melanoma treatment (IMCgp100/Tebentafusp)

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- TFSOM "To Find Small Ocular Melanoma"
  - Shields CL, MD JAS, MD HK, De Potter MD P, PhD JRC. Risk Factors for Growth and Metastasis of Small Choroidal Melanocytic Lesions. *Ophthalmology*. 1995;102(9):1351-1361.
- TFSOMUHHD "To Find Small Ocular Melanoma Using Helpful Hints Daily"
  - Shields CL, Furuta M, Berman EL, et al. Choroidal nevus transformation into melanoma: analysis of 2514 consecutive cases. *Arch Ophthalmol*. 2009;127(8):981-987.

Risk factors	Combination of risk factors	Risk (%)
Thickness >2.0 mm	None present	5
Posterior margin touching the optic disc	Any one present	36
Presence of visual symptoms	Any two present	45
Presence of orange pigment	Any three present	50
Presence of subretinal fluid	Any four present	51
	All present	56

0 risk factors = monitor yearly
1-2 risk factors = monitor 4-6 monthly
≥3 risk factors = refer ocular oncology for discussion of treatment

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CHOROIDAL NEVUS IMAGING FEATURES IN 3,806 CASES AND RISK FACTORS FOR TRANSFORMATION INTO MELANOMA IN 2,355 CASES

The 2020 Taylor R. Smith and Victor T. Curtin Lecture

CAROL L. SHIELDS, MD, LAUREN A. DALVIN, MD, DAVID ANCONA-LEZAMA, MD, MICHAEL D. YU, BS, MAURA DI NICOLA, MD, BASIL K. WILLIAMS, Jr., MD, J. ANTONIO LUCIO-ALVAREZ, MD, SU MAE ANG, BS, SEAN MALONEY, BS, R. JOEL WELCH, MD, JERRY A. SHIELDS, MD

- TFSOMDim
  - To Find Small Ocular Melanoma Doing IMaging
    - Thickness = >2mm on US
    - Fluid = SRF on OCT
    - Symptoms = Snellen acuity ≤6/15
    - Orange = lipofuscin on AF imaging
    - Melanoma hollowness = internal acoustic hollowness on US
    - Diameter = >5mm on photography

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MOLES scoring criteria

cancers

Article

The MOLES System for Planning Management of Melanocytic Choroidal Tumors: Is It Safe?

Risk Factor	Severity	Score
Mushroom Shape	Absent	0
	Unsure/Early growth through RPE	1
	Present	2
Orange Pigment	Absent	0
	Unsure/Trace (i.e., Dusting)	1
	Confluent clumps	2
Large Size *	Thickness & Diameter	
	Thickness < 1.0 mm ('flat/minimal thickening') and diameter < 3DD	0
	Thickness = 1.0–2.0 mm ('subtle dome shape') and/or diameter = 3–4DD	1
	Thickness > 2.0 mm ('significant thickening') and/or diameter > 4DD	2
Enlargement	None (or lesion not documented or mentioned to patient previously)	0
	Unsure (i.e. Poor image quality)	1
	Definite (confirmed with sequential imaging)	2
Subretinal Fluid **	Absent	0
	Trace (if minimal and detected only with OCT)	1
	Definite (if seen without OCT)	2
	Total Score	

DD = disc diameter (= 1.5 mm); * ignore thickness if this cannot be measured; ** assume SRF if unexplained visual loss; MOLES = Mushroom, Orange pigment, Large size, Enlargement, and Subretinal fluid; RPE = retinal pigment epithelium; SRF = sub-retinal fluid; OCT = optical coherence tomography.

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MOLES scoring criteria

cancers

Article

The MOLES System for Planning Management of Melanocytic Choroidal Tumors: Is It Safe?

MOLES Score	Suggested Management
0 = Common Nevus	**Monitoring in community** with color photography every 1–2 years.
1 = Low-Risk Nevus 2 = High-Risk Nevus	**Non-urgent referral** for specialist investigation comprising wide-field photography, autofluorescence imaging, optical coherence tomography and, in selected cases, ultrasonography. Subsequent surveillance to be undertaken at a specialist clinic or in the community according to risk of malignancy.
3 = Probable Melanoma	**Urgent referral** to ophthalmologist with urgent onward referral to ocular oncologist if suspicion of malignancy is confirmed.

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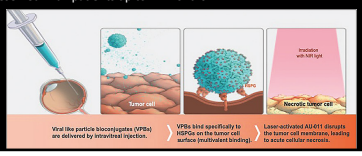
Uveal Melanoma – Targeted Treatments

- AU-011 (Aura Biosciences)
  - Synthetic recombinantly derived viral-like particles (VLP)
  - Binds selectively to uveal melanoma cells
  - Upon activation with 689nm diode laser, selectively destroys the cell membranes of malignant cells
- 2 year interim Phase 2 results – small to medium choroidal melanoma
  - Tumour control rate 92%
  - Vision preserved in all patients up to 24 months



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Uveal Melanoma - Prognostication

- Evolution
  - Tumour clinical and histopathologic features
    - Tumour location, dimensions, histopathologic cell type, vascular mimicry, infiltrating lymphocytes etc.
  - AJCC classification
    - Age, CB involvement, extraocular extension, tumour size
  - Cytogenetic and gene expression profiling
    - Ch 3, Ch 6, Ch 8q, Ch 8p
    - GEP Class 1a, 1b, 2
  - The Cancer Genome Atlas (TCGA) classification

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Uveal Melanoma - Prognostication

- The Cancer Genome Atlas (TCGA)
  - Initiated in 2005 to comprehensively explore genetic mutations found in human cancer
  - Uveal melanoma cohort found 4 molecularly distinct and clinically relevant subgroups based on alterations in chromosome 3 and 8

Table 4: Genetic features and outcome of uveal melanoma in 658 patients based on The Cancer Genome Atlas (TCGA) Classification of A, B, C, & D

	The Cancer Genome Atlas (TCGA) Class				
	A	B	C	D	*P*
Mutational profile					
Chromosome 3	Disomy 3	Disomy 3	Monosomy 3	Monosomy 3	NA
Chromosome 8	Disomy 8q	8q gain	8q gain	8q gains (multiple)	NA
Prognosis per TCGA[19,20]					
Estimated outcome	Favorable	Late metastases	Unfavorable	Unfavorable	NA
Prognosis per Wills Eye Hospital series[21] (*n*=658)					
Number of patients (%)	342 (52%)	91 (14%)	118 (18%)	107 (16%)	
5-year cumulative rate for distant metastasis	4%	20%	33%	63%	*P*<0.001

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JAMA Ophthalmology | Original Investigation
Survival Rates in Patients After Treatment for Metastasis From Uveal Melanoma
Anne Marie Lane, MPH; Ivana K. Kim, MD; Evangelos S. Gragoudas, MD
JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2018.2466
Published online June 28, 2018.
CONCLUSIONS AND RELEVANCE These findings suggest that advances in treatments that lead to clinically meaningful improvements in survival times have not been realized. Similar survival rates in patients who were treated for metastasis were observed in this recent analysis compared with our earlier study. Adjuvant therapies that are initiated at the time of melanoma diagnosis may be the most effective way to prolong survival.

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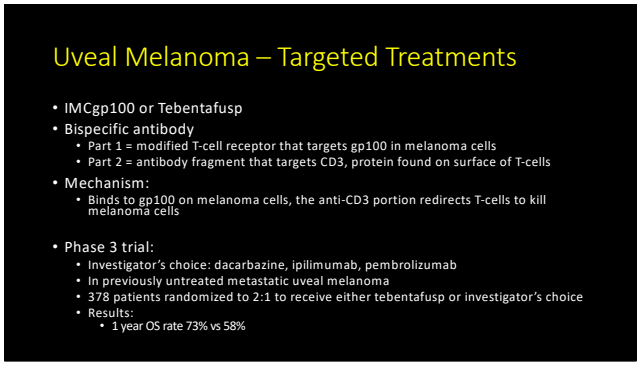
Uveal Melanoma – Targeted Treatments
• IMCgp100 or Tebentafusp
• Bispecific antibody
• Part 1 = modified T-cell receptor that targets gp100 in melanoma cells
• Part 2 = antibody fragment that targets CD3, protein found on surface of T-cells
• Mechanism:
• Binds to gp100 on melanoma cells, the anti-CD3 portion redirects T-cells to kill melanoma cells
• Phase 3 trial:
• Investigator's choice: dacarbazine, ipilimumab, pembrolizumab
• In previously untreated metastatic uveal melanoma
• 378 patients randomized to 2:1 to receive either tebentafusp or investigator's choice
• Results:
• 1 year OS rate 73% vs 58%

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Thank you!
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