Cancer Association of South Africa (CANSA)

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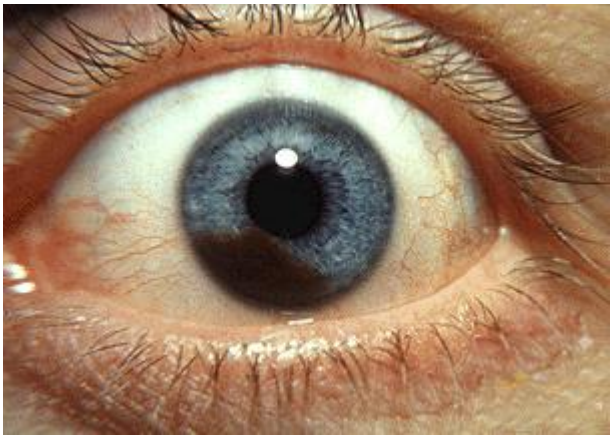
Fact Sheet on Ocular Melanoma

Introduction

Melanoma is a type of cancer that develops in the cells that produce melanin — the pigment that gives your skin its colour. One's eyes also have melanin-producing cells and can develop melanoma. Eye melanoma is also called ocular melanoma.



[Picture Credit: Uveal Melanoma]

Ocular melanoma is the most common primary cancer of the eye in adults. It occurs most often in lightly pigmented individuals with a median age of 55 years. However, it can occur in all races and at any age.

Called "OM" for short, ocular melanoma is a malignant tumour that can grow and spread to other parts of the body - this process, known as metastasis, is often fatal and occurs in about half of all cases. Although produced from the same cells in the body, called melanocytes, OM is different from skin (or cutaneous) melanoma and is not related to sun exposure. Ocular Melanoma is the second most common type of melanoma after cutaneous and represents about 5% of all melanomas.

Ocular Melanoma

Ocular melanoma (melanoma in or around the eye) is a type of cancer that develops in the cells that produce pigment. Pigment is the substance that gives colour to one's skin, hair and eyes. Just as one can develop melanoma on one's skin, one can also develop it inside one's eye or on one's conjunctiva. Although it is the most common eye cancer in adults, ocular melanoma is very rare.

Ocular melanomas usually begin in the middle of the three layers of the eye. The outer layer of the eye is the sclera. The innermost layer is the retina. The middle layer between the sclera and retina is called the uvea.

Rarely, eye melanoma can also occur on the conjunctiva.

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Because most eye melanomas form in the part of the eye one cannot see when looking in a mirror, they can be difficult to detect. Also, eye melanoma typically does not cause early signs or symptoms. That is why it is so important to see an ophthalmologist regularly.

Patel, D.R. & Patel, B C. 2021.
"Melanoma is a malignant, overproliferation of melanocytes. Ocular melanoma is the second most common type of melanoma after cutaneous and is the most common primary intraocular malignant tumor in adults. The prognosis of uveal melanoma has remained unchanged over the past few decades. The systemic prognosis depends on the size and other characteristics of the lesion. It is not affected by the choice of local treatment. This suggests dissemination at an early stage. Ocular melanoma tends to spread hematogenously, which almost always involves the liver."

Types of ocular melanoma
The uvea contains three parts:

- Iris - the coloured part in the front of the eye
- Ciliary body - the part that releases fluid into your eye and changes the shape of the lens to help your eye focus
- Choroid - the part that contains blood vessels to nourish your eye

Cancer can form in each of these three parts. It's most likely to grow in the choroid, followed by the ciliary body and then the iris. Some people have cancer in more than one of these three areas at the same time.

Melanoma of the iris is the least serious of the three types. Cancers of the ciliary body may be hardest to treat. When cancer is in the ciliary body, it can push the lens of the eye out of place and blur one's vision.

Johansson, P.A., Nathan, V., Bourke, L.M., Palmer, J.M., Zhang, T., Symmons, J., Howlie, M., Patch, A.M., Read, J., Holland, E.A., Schmid, H., Warrier, S., Glasson, W., Höiom, V., Wadt, K., Jönsson, G., Olsson, H., Ingvar, C., Mann, G., Brown, K.M., Hayward, N.K. & Pritchard, A.L. 2019.
"Germline mutations of BRCA1 and BRCA2 predispose individuals to a high risk of breast and ovarian cancer, and elevated risk of other cancers, including those of the pancreas and prostate. BRCA2 mutation carriers may have increased risk of uveal melanoma (UM) and cutaneous melanoma (CM), but associations with these cancers in BRCA1 mutation carriers have been mixed. Here, we further assessed whether UM and CM are associated with BRCA1 or BRCA2 by assessing the presence, segregation and reported/predicted pathogenicity of rare germline mutations (variant allele frequency < 0.01) in families with multiple members affected by these cancers. Whole-genome or exome sequencing was performed on 160 CM and/or UM families from Australia, the Netherlands, Denmark and Sweden. Between one and five cases were sequenced from each family, totalling 307 individuals. Sanger sequencing was performed to validate BRCA1 and BRCA2 germline variants and to assess carrier status in other available family members. A nonsense and a frameshift mutation were identified in BRCA1, both resulting in premature truncation of the protein (the first at p.Q516 and the second at codon 91, after the introduction of seven amino acids due to a frameshift deletion). These variants co-segregated with CM in individuals who consented for testing and were present in individuals with pancreatic, prostate and breast cancer in the respective families. In addition, 33 rare missense mutations (variant allele frequency ranging from 0.00782 to 0.000001 in the aggregated ExAC data) were identified in 34 families. Examining the previously reported evidence of functional consequence of these variants revealed all had been classified as either benign or of unknown consequence. Seeking further evidence of an association between BRCA1 variants and melanoma, we examined two whole-genome/exome sequenced collections of sporadic CM patients (total N = 763). We identified one individual with a deleterious BRCA1 variant, however,

this allele was lost (with the wild-type allele remaining) in the corresponding CM, indicating that defective BRCA1 was not a driver of tumorigenesis in this instance. Although this is the first time that deleterious BRCA1 mutations have been described in high-density CM families, we conclude that there is an insufficient burden of evidence to state that the increased familial CM or UM susceptibility is because of these variants. In addition, in conjunction with other studies, we conclude that the previously described association between BRCA2 mutations and UM susceptibility represents a rare source of increased risk."

Risk Factors for Ocular Melanoma (OM)

Doctors do not know exactly what causes ocular melanoma. OM tumours arise from the pigment cells (melanocytes) that give colour to the eye. Formation of these tumours is quite rare and, as for many other forms of cancer, the exact cause is unknown. It is known that exposure to ultraviolet (UV) rays (either from the sun or sunbeds) increases the risk of developing melanoma of the skin. People whose skin burns easily are most at risk – people with fair skin, fair or red hair and blue eyes. However, there is no conclusive evidence linking UV exposure and OM.

Incidence of Ocular Melanoma in South Africa

The South African National Cancer Registry (2017) does not provide any information regarding the incidence of Ocular Melanoma.

Signs and Symptoms of Ocular Melanoma

Eye melanoma may not cause signs and symptoms. When they do occur, signs and symptoms of eye melanoma may include:

- A sensation of flashes or specks of dust in one's vision (floaters)
- A growing dark spot on the iris
- A change in the shape of the dark circle (pupil) at the centre of one's eye
- Poor or blurry vision in one eye
- Loss of peripheral vision

Make an appointment with an optometrist or doctor if any signs or symptoms appear that may be worrisome. Sudden changes in one's vision signal an emergency, so seek immediate care in those situations.

Diagnosis of Ocular Melanoma

Doctors often notice a melanoma during a routine eye exam because the tumours usually are darker than the area around them or leak fluid.

To diagnose eye melanoma, the doctor may recommend:

- Eye examination. A doctor will examine the outside of the eye, looking for enlarged blood vessels that can indicate a tumour inside the eye. Then, with the help of instruments, the doctor will look inside the eye

One method, called binocular indirect ophthalmoscopy, uses lenses and a bright light mounted on the examiner's forehead — a bit like a miner's lamp. Another method, called slit-lamp biomicroscopy, uses lenses and a microscope that produces an intense beam of light to illuminate the interior of the eye

- Eye ultrasound. An eye ultrasound uses high-frequency sound waves from a hand-held, wandlike apparatus called a transducer to produce images of the eye. The transducer is placed on the closed eyelid or on the front surface of the eye.

- Imaging of the blood vessels in and around the tumour (angiogram). During an angiogram of the eye, a coloured dye is injected into a vein in the arm. The dye travels to the blood vessels in the eye.
  A camera with special filters to detect the dye takes flash pictures every few seconds for several minutes.

- Optical coherence tomography. The imaging test creates pictures of portions of the uveal tract and retina.

- Removing a sample of suspicious tissue for testing. In some cases, the doctor may recommend a procedure to remove a sample of tissue (biopsy) from the eye.
  To remove the sample, a thin needle is inserted into the eye and used to extract suspicious tissue. The tissue is tested in a laboratory to determine whether it contains eye melanoma cells.

An eye biopsy is not usually necessary to diagnose eye melanoma.

Garcia-Arumi Fuste, C., Peralta Iturburu, F. & Garcia-Arumi, J. 2019.
PURPOSE: To describe the imaging features of choroidal nevus and melanoma using optical coherence tomography angiography, and evaluate the ability of this technique to establish the differential diagnosis based on the display of the tumor's intrinsic vasculature.
METHODS: Comparative analysis of optical coherence tomography angiography findings in consecutive patients diagnosed with choroidal nevus or choroidal melanoma following a complete ophthalmic evaluation, including best-corrected visual acuity and several imaging studies: color fundus photography, B-scan ultrasound, spectral-domain optical coherence tomography, and optical coherence tomography angiography. Optical coherence tomography angiography was used to investigate qualitative differences in the tumor vasculature.
RESULTS: Thirty-six eyes (18 cases of choroidal nevus and 18 cases of choroidal melanoma) from 36 consecutive patients were included in the study. Only cases located posterior to equator were included to enable performance of all tests. On optical coherence tomography angiography, choroidal nevus showed well-delimited margins (78%), hyperreflective choroid capillary vasculature (83%), fewer avascular areas (17%), and neovascular membrane in one case (6%). Choroidal melanoma showed imprecise margins (72%), hyporeflective choroidal capillary vasculature (72%), multiple avascular areas (78%), and choroidal vascular changes (e.g. thick vascular networks or vascular loops; 45%).
CONCLUSION: Optical coherence tomography angiography can provide useful information for assessing and differentiating between choroidal nevi and small melanomas. Significant differences between these conditions were found for the pattern of reflectivity, and presence/absence of avascular zones and vascular anomalies, which could be helpful for supporting the diagnosis.

Treatment of Ocular Melanoma
If diagnosed with ocular melanoma, treatment options may vary.

Treatment will depend on:

- the location and size of the melanoma
- the person's general health

Generally, treatment options fall into two categories: radiation and surgery.

Ocular melanoma radiation - In radiation therapy, various types of radiation are used to kill the melanoma or keep it from growing.

The most common type of radiation therapy used for ocular melanoma is called plaque radiation therapy. Radioactive seeds are attached to a disk, called a plaque, and placed directly on the wall of the eye next to the tumour. The plaque, which looks like a tiny bottle cap, is often made of gold. This helps protect nearby tissues from damage from the radiation directed at the tumour. Temporary stitches hold the plaque in place for four or five days, before it is removed.

Radiation therapy can also be delivered by a machine. This machine directs a fine beam of radioactive particles to the affected eye. This type of radiation therapy is often done over the course of several days.

Ocular melanoma surgery - Depending on the size and location of the melanoma, surgery may be recommended. The surgery may involve removing the tumour and some of the healthy tissue of the eye surrounding it.

For larger tumours, tumours that cause eye pain, and for tumours involving the optic nerve, the surgery may involve removing the entire eye (enucleation). After the eye is removed, an implant is put in its place and attached to the eye muscles, so that the implant can move. Once a person is healed from the surgery, he/she will be fitted with an artificial eye (prosthesis). It will be custom painted to match the existing eye. Both radiation and surgery can damage the vision in one's eye.

Conjunctival melanoma treatment - For melanoma on the surface of the eye, treatment can include chemotherapy eye drops, freezing treatment, and radiation.

One should talk to one's ophthalmologist about how treatment may affect vision. He or she can also explain the options available to help with any vision loss.

Weersink, R.A., Patterson, S., Ballantyne, H., Di Tomasso, A., Borg, J., Vitkin, A., Rink, A. & Beiki-Ardakani, A. 2019.
PURPOSE: To develop a treatment planning platform for episcleral Collaborative Ocular Melanoma Study plaque therapy in an established treatment planning software and to improve an existing quality assurance (QA) process for nonuniformly loaded plaques that measures air kerma strengths (AKSs) and loading profile.
MATERIALS AND METHODS: Treatment planning is performed in Pinnacle using scripts that let the planner choose plaque size and notching. Scripts load seed positions for each plaque and five source groups corresponding to available stock seeds that can be placed into each seed position. Contours are loaded that display the model eye and the plaque itself. Plaque QA is performed using a modification of our previous pinhole apparatus by replacing x-ray film exposure with an optical camera and scintillating film system. The captured image is processed to remove background and to correct the intensity of seeds on the plaque periphery. Measured total optical counts provide an estimate of total plaque AKS.
RESULTS: Treatment planning of eye plaques using Pinnacle, in conjunction with our stock inventory of seeds, is established as standard practice at our center. Planned plaques can vary from uniformly loaded to

asymmetrically loaded notched plaques. Using the optical camera system for assessment of the seed loadings has decreased QA time from 40 min/plaque to 10 min/plaque. Total AKS of each plaque can be measured using the optical camera with an accuracy of 10%.
CONCLUSIONS: Treatment planning is performed on a Health Canada-approved software that accommodates nonuniform plaque loading. Optical imaging of the plaque provides absolute total AKS and the relative seed arrangement in the plaque.

Piperno-Neumann, S., Piulats, J.M., Goebeler, M., Galloway, I., Lugowska, I., Becker, J.C., Vihinen, P., Van Calster, J., Hadjistilianou, T., Proença, R., Caminal, J.M., Rogasik, M., Blay, J.Y. & Kapiteijn, E. 2019.
"Uveal melanoma (UM) is the most frequent primary ocular cancer in adults, accounting for 5% of all melanomas. Despite effective treatments for the primary tumour, up to 50% of UM patients will develop metastasis, leading to a very poor prognosis and a median overall survival of 6 to 12 months, with no major improvements in the last 30 years. There is no standard oncological treatment available for metastatic UM patients, and BRAF/MEK and immune checkpoint inhibitors show disappointing results when compared to cutaneous melanoma (CM). Recent advances in biology, however, identified specific gene and chromosome alterations, potentially permitting an actively tailored surveillance strategy, and dedicated clinical studies. Being a rare cancer, UM patients have to overcome issues such as identifying referral centres, having access to information, and partnering with oncologists for specific management strategies and research priorities. Here, we describe how the EUropean Rare Adult solid CAacer Network (EURACAN) will help in addressing these challenges and accelerating international collaborations to enhance the development of innovative treatments in UM."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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