PRIMEVIEW

UVEAL MELANOMA

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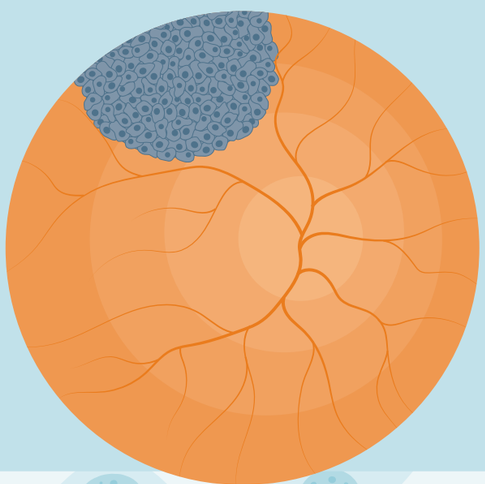
Uveal melanoma (UM) is the most common primary intraocular malignancy in adults. UM arises from melanocytes in the uvea, which comprises the pigmented tissues of the iris, ciliary body and choroid.

DIAGNOSIS

Although symptoms of UM include blurred or distorted vision, visual field loss or photopsia (seeing flashes of light), many patients with UM are asymptomatic and only diagnosed during routine eye tests. Imaging of the eye, using methods such as slit lamp biomicroscopy, ultrasonography and angiography, is required to completely visualize the eye and assess the size of the lesions. Biopsy can help with prognostication and can establish a diagnosis when conditions that mimic UM are suspected, such as other malignancies or benign retinal pigment epithelial tumours. As with other cancers, staging is made according to the tumour–node–metastases categories as defined by the American Joint Committee on Cancer.



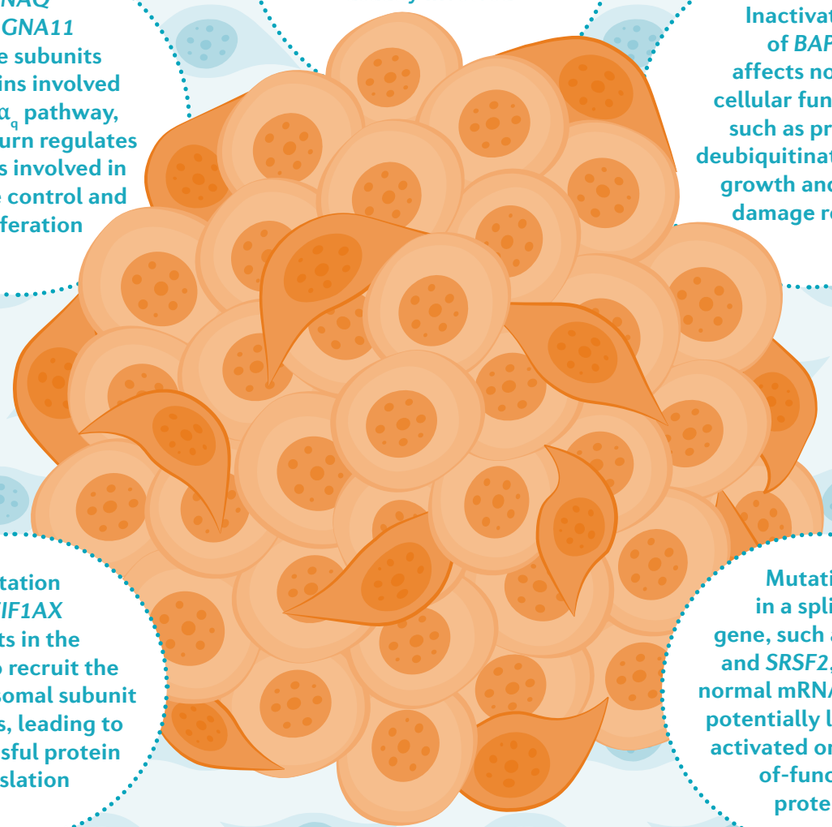
Factors linked to metastasis include a large tumour size, ciliary body involvement, extrascleral extension, epithelioid cell type, chromosome 3 loss, mutations in *BAP1* and the splice genes, and a class 2 gene expression profile

MECHANISMS

Although the order of molecular events that lead to the development of UM is unknown, $G\alpha_q$ pathway alteration and a BSE event — standing for *BAP1*, splice and *EIF1AX* mutations — are usually involved

GNAQ and *GNA11* encode subunits of proteins involved in the $G\alpha_q$ pathway, which in turn regulates pathways involved in cell cycle control and proliferation

Inactivation of *BAP1* affects normal cellular functions, such as protein deubiquitination, cell growth and DNA damage repair



Mutation in *EIF1AX* results in the failure to recruit the small ribosomal subunit to mRNAs, leading to unsuccessful protein translation

Mutations in a splicing gene, such as *SF3B1* and *SRSF2*, disrupt normal mRNA splicing, potentially leading to activated or change-of-function proteins

QUALITY OF LIFE

Patients can experience ocular discomfort, visual field loss, anxiety, depression and/or loss of wellbeing. Patient counselling, treatment selection and psychological support should address these issues but are currently untested. Despite treatment of the primary tumour, ~50% of patients with UM will develop metastatic disease, predominantly to the liver; 15-year disease-related mortality of UM is as high as 45%.

The roles of the different melanin types in early malignant transformation are under investigation

MANAGEMENT

As UMs are rare (incidence of <1 to >9 per million population per year), no standardized care pathway has been determined. Tumour size, location within the eye and whether retinal detachment, vitreous haemorrhage and retinal invasion have occurred can influence the treatment strategy. Patient age and general health, status of the other eye and patient preference are also important considerations. Radiotherapy is the most common eye-conserving therapy; treatable adverse effects include cataract. Enucleation (removal of the eye) is indicated for large UMs and UMs that affect the optic nerve. Specialized centres can offer local resection and laser treatment that aim to conserve the eye and vision. As there is no standard treatment for the prevention or treatment of metastases, clinical trial participation is encouraged.

OUTLOOK

Metastatic UMs have low responsiveness to immune-checkpoint inhibition; improved understanding of interactions between tumour cells and their immune-privileged microenvironment will hopefully overcome this hurdle. Advances in ocular imaging are improving early detection; however, differentiation of small UMs from naevi and other benign lesions continues to be a problem. Applying artificial intelligence to ocular imaging may overcome these challenges, as is already being demonstrated in other diseases. Liquid biopsies may also help diagnose malignancy or detect metastases early.

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