Contenu

Key points

Uveal melanoma

Melanoma of the eye is the most common eye cancer in adults with between 500 and 600 new cases diagnosed each year in France. It can cause serious vision impairment and in 50% of cases death.

Uveal melanoma is very different to skin melanoma which is the most common melanoma. However it can occur in the mucous membranes or the eye. Like our skin our eyes contain melanocytes which are the cells responsible for producing melanin, a pigment that protects from the sun's rays. In the eye they are located in the uvea.

In its posterior part, this tissue includes the choroid which covers the retina. In its anterior part it consists of the ciliary body and the iris.

In the large majority of cases the melanoma appears in the choroid. The ciliary body is rarely the seat of this tumor and the iris even less often. Iris melanomas, another eye cancer, are associated with a better prognosis than those that occur in the ciliary body and the choroid.

Uveal melanoma can occur de novo or by degeneration of a choroidal nevus. This is why patients who have a large choroidal nevus usually benefit from regular monitoring of the fundus.

Uveal melanoma is a tumor that develops and can invade surrounding tissues. It can spread using blood vessels to reach distant organs. This is metastasis. Up to 50% of uveal melanoma patients develop metastases most commonly in the liver. Uveal melanoma metastases remain very difficult and are often impossible to treat.

The French National Cancer Institute (INCa) has put in place a network of centers specialized in uveal melanoma named Melachonat. Clinicians collaborate by web conference and have common protocols. They organize regular meetings to harmonize treatment throughout France.

Discovering uveal melanoma

Melanoma of the eye can be discovered during a routine fundus exam or following recent vision impairment: decreased visual acuity, spots in the visual field (scotoma), lightning flashes, amputation of the visual field (retinal detachment).

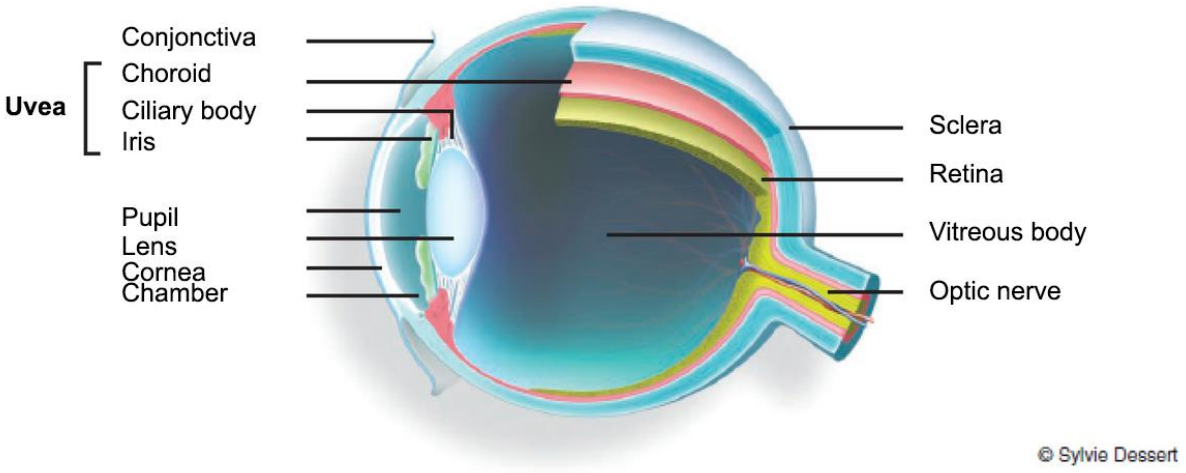
Treatment

Treatment for uveal melanoma is generally surgery, radiotherapy or a combination of both.

There are several concerns when treating uveal melanoma including the preservation of sight. Preventing the spread of the tumor to other parts of the body is another big concern.

Comprehensive care, monitoring during and after treatment

The eye



The eye is made up of 3 layers. The outside of the eyeball is a hard, fibrous, white layer called the sclera that blends into the clear cornea. Inside, there is another layer called the uvea. It's rich in blood vessels.

The uveal traditionally has 3 zones which are, from the front to the back :

- Iris
- Ciliary body
- Choroid

These 3 zones are the site of numerous eye cancers.

The colored part of the eye includes the iris and the pupil which reacts to light. The innermost layer of the eyeball is the retina. The retina is made up of cells that react to light. They communicate with the optic nerve and finally the brain allowing us to see.

Risk factors

Little is known about possibile environmental risk factors for this tumor which occurs most often in people – men or women – between 50 and 70 years old. The incidence of this cancer seems to be higher:

- In people with blue, green or grey eyes who are 2 to 3 times more likely to be affected that people with brown eyes
- In Nordic countries
- Men (4.9 million vs 3.7 million women)
- In people with a lot of moles (some may be inside the eye)

Numerous observation studies have tried to establish a link between the risk of uveal melanoma and sun exposure. To date only weak reports or contradictory results have been

found.

Symptoms

The tumor has often been developing for a while before the first symptoms appear. Uveal melanoma develops within the eyeball and, as such, is not externally visible. In a third of cases uveal melanoma is detected during a routine ophthalmological exam usually without the patient having mentioned any symptoms.

However there are early warning signs. Knowing them makes it possible to locate them and consult quickly. In general they are caused by a partial detachment of the retina. The diagnosis is confirmed by ultrasound.

- The presence of a benign pigment lesion, a nevus, which may become malignant. People who have a large choroidal nevus usually benefit from regular fundus monitoring.
- A decrease in visual acuity
- A spot in the visual field (scotoma)
- Flashes or phosphenes which always repeat in the same place in the same eye
- Changing appearance of the eye for example:
    - A bump or a spot on or near the iris
    - Swelling of one eye
    - A raised pale mass on the surface of the eye (iris) which grows with time
    - A change of the dark sport on the colored part of the eye (the iris) which grows with time
- Pain in or around the eye (a rare symptom unless the cancer has spread outside of the eye or has caused pressure inside the eye [intraocular pressure] to become too high)
- Loss of peripheral vision – we can see clearly what is in front of us but not on the sides
- Irritation of the eye, red eyes or chronic inflammation of the conjunctiva (conjunctivitis)

Eye cancer is rare. Lots of ocular conditions can bring on similar symptoms to those described here. Nevertheless symptoms should always be reported to a clinician – early diagnosis is very important for successful treatment.

Diagnosis

When a person presents symptoms or an anomaly is detected during a screening a certain number of exams must be carried out to establish a diagnosis. Any suspicion of cancer diagnosis warrants expert advice without delay.

How is a cancer diagnosis established?

An in-depth exam by an experienced clinician is still the most important diagnostic method for uveal melanoma detection. The diagnosis is largely based on a fundus exam following pupil dilation which can be carried out by an ophthalmologist. An ultrasound of the eye also allows the confirmation of the diagnosis and the measurement of the tumor.

It’s difficult to distinguish between a small uveal melanoma and a nevus. Routine exams of the nevus are important to observe whether it is growing.

Clinical results that help to identify uveal melanoma are:

- A lesion thickness greater than 2mm
- Sub retinal fluid
- Signs and visual symptoms
- A surface of the orange pigmented tumor
- A tumor margin that affects the optical disc

There are multiple important tests for the diagnosis of uveal melanoma such as:

- Eye exam
- Eye ultrasound
- Angiogram or fluorescein angiogram : this examination allows you to look at blood vessels with a dye. It’s not essential but sometimes useful for small lesions where there is a diagnostic doubt with a nevus.
- Biopsy: this is a rarely used test as the tests mentioned above are usually accurate in the diagnosis however this test is important to know the stage of the tumor and to determine the risk of metastasis during sample genetic tests as below
- Cytogenetic test (testing genetic cell information): it helps inform the doctor of the possibilities of the return or the spread of the cancer. At present tumor genetics do not directly affect the treatment of the eye tumor but this information is crucial to determine the risk of recurrence in the future. It should be noted that uveal melanoma is very different to cutaneous melanoma and does not show melanoma-associated skin mutations (BRAF, NRAS and C-KIT). The main mutations detected in uveal melanoma are BAP1, EIF1AX, GNA11, GNAQ and SF3B1.
- Genetic analyses can essentially show a monosomy of chromosome 3 or an addition of 8q. The presence of these abnormalities is mainly found in tumors that have a greater metastatic risk.

If an ophthalmologist suspects a uveal melanoma, an eye cancer specialist should be informed.

What are the additional examinations ?

An extension assessment is necessary to search for distant metastases especially in the liver.

In the case of tumor dissemination the metastasis is often located in the liver. Regular monitoring by hepatic ultrasound or liver MRIs are recommended. This allows early diagnosis of possible hepatic lesions for better management.

Treatment

Treatment for uveal melanoma is mainly surgery, radiotherapy or a combination of the two. When planning treatment the following aspects should be taken into consideration:

- Tumor diameter
- Localization of the tumor in the eye
- Possible extension of the tumor beyond the sclera (white of the eye)
- Histological analysis (if available)
- General health and fitness

One of the major concerns is the preservation of eyesight. Preventing the tumor spreading to other parts of the part is another concern. A positive result with initial treatment is very important but this doesn't mean that the cancer hasn't spread.

Uveal melanoma spreads by blood vessels and there is currently no way to test for this spread apart from a risk assessment of the primary tumor cells by genetic testing and monitoring of modifications elsewhere in particular in the liver.

Protontherapy

Conservative treatments that destroy or remove the tumor by keeping the eyeball are mainly based on proton therapy and brachytherapy.

Protontherapy which uses a proton beam with very precise ballistics is ideal for treating tumors located near health organs as is the case with uveal melanoma as it reduces their irradiation. It is mainly proposed for posterior tumors and straddles the equator of the eye.

This treatment requires firstly a hospitalization and a surgical intervention during which the surgeon will identify the tumor and place tantalum clips to guide the proton beam. Fine needle aspiration is performed during the procedure whenever possible to better characterize the tumor biologically.

This therapy helps to conserve the eyeball but unfortunately, in 90% of cases, not always the vision. It also allows local control of the tumor in 95% of cases and the risk of local recurrence, less than 5% at ten years, remains very low.

Endoresection

Endoresection (surgical removal of scar tumor tissue) is sometimes performed after proton therapy to avoid complications particularly neovascular glaucoma.

Bracytherapy

Brachytherapy is used to treat small tumors situated in the anterior part of the eye while protecting the eyelids and the lacrimal gland.

Doctors place a gold disc with a diameter of 12mm to 20mm, directly at the level of the tumor in which radioactive iodine grains are incorporated (iodine 125). Local control of the tumor is obtained in 95% of cases.

Prolonged monitoring of the ocular scar is essential. Complications (cataract, glaucoma, radiation retinopathy) are possible and require ophthalmological management.

Metastatic management

Rarely present at the initial diagnosis metastases are detected in 30% to 50% of patients sometimes occurring 10 years after the local treatment of the eye tumor. The eye doesn't have a lymphatic system so tumor cells are disseminated via the blood system. In 90% of cases metastases appear in the liver first (in close to 80% of cases only the liver is affected) and, much rarer, in the bones, lungs sub cutaneous tissues and other organs. Patients having had a uveal melanoma are monitored every six months by hepatic ultrasound to detect the occurrence of metastases. Some patients having had a high risk tumor are monitored by MRI.

Only the complete surgical removal of metastases seems to benefit the patient but this is only practicable in 20% of cases. Chemotherapies that are currently available haven't shown a marked efficiency for the treatment of metastases. Otherwise research protocols and some targeted therapy combinations seem promising. Anti-PD1s which are very active in melanoma are only active in 5% of uveal melanoma patients.

Surgery

Surgical removal of the tumor

Surgical removal of the tumor while conserving the eyeball is only possible for tumors with a narrow implantation. This intervention requires a deep anesthesia is only possible for patients in perfect health. It can be carried out by transclerally before radiotherapy or intraocularly generally after proton beam radiation. In this case the removal of already radiated tumor tissue avoids complications such as glaucoma and allows the conservation of the eyeball. If this treatment is recommended for you, the ophthalmologist and the anesthetist will give you all the necessary information.

Enucleation

Removal of the tumor while conserving the eyeball is only possible for some tumors. If the tumor is too big, in the case of recurrence or major complications of conservative treatment, surgical removal of the eye may be considered.

Doctors then install an implant consisting of a coral ball on which are grafted the muscles of the eye. This makes it possible to implant a mobile prosthesis with a satisfactory aesthetic result.

Immediate complications such as hematoma, infection or rejection of the coral are still possible even if in the majority of cases the follow-up is simple. Usually a swelling of the orbit and the eyelids linked to the hematoma can form just after the operation. Post-operative pain is common on the day of the operation. You should report this to the nurse who will give you analgesics prescribed by the anesthesiologist. This discomfort usually disappears after a few days.

Evolution and prognosis

Prognosis depends mainly on the size of the tumor as well as its genetic characteristics. Local treatment can control the tumor in more than 95% of cases. Prolonged monitoring of the ocular scar is essential.

Monitoring

Patients that have had an eye melanoma are monitored every six months by hepatic ultrasound to detect the eventual occurrence of metastases. Patients with a high risk tumor are monitored by MRI. This monitoring is decided during Multidisciplinary coordination meetings (RCP).

In the cases of metastasis surgery can be proposed. Otherwise research protocols and some targeted therapy combinations seem promising. Anti-PD1s which are very active in melanoma are only active in 5% of patients with uveal melanoma. Any decision must be validated by a specialist in uveal melanoma.

Follow-up

As there are controversial results on the different methods available for screening for the apparition of metastatic disease it's important that an individual plan is decided in collaboration with the clinician.

If the tumor is removed from the eye (surgical treatment) or if the patient has had a biopsy more information can be obtained from the tumor tissue to affirm:

- The type of tumor cells that are present
- The tumor cell cycle and division activity
- The genetic profile of tumor cells

The importance of a tumor biopsy is the identification of a high risk group which allows the determination of the frequency of liver analyses. Collection of all clinical information with auxiliary diagnostic examinations (obtained by tissue biopsy) is crucial for global risk assessment.

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Dr Marc-Henri Stern, team leader, Institut Curie

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Links / useful resources

Orphanet
National Choroid Melanoma Network