Primary posterior segment uveal melanoma: French MELACHONAT Network Clinical Practice Guidelines for diagnosis and local/locoregional management

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INCIDENCE AND EPIDEMIOLOGY

The annual incidence of uveal melanoma varies globally, partially owing to its more common occurrence in non-Hispanic white individuals when compared with Hispanic, Asian or Black individuals[1]. In Europe, the age-standardized incidence of the disease increases from south to north, with <2 cases per million persons in Spain and southern Italy and >8 per million in Norway and Denmark[2]. The age-adjusted incidence is 5.09 cases per million individuals in Europe, 5.2 in the USA and 7.6 per million in Australia[3–5].

Unlike in cutaneous melanoma, however, ultraviolet light is not implicated in the pathogenesis of uveal melanoma[6,7], with the exception of iris melanomas, which arise from a region of the eye exposed to sunlight[8]. Nevertheless, shared risk factors exist, including the presence of common and atypical cutaneous naevi, family history of cutaneous melanoma, choroidal naevi, secondhand cigarette smoke exposure, fair skin color, a propensity to sunburn, light eye color and iris naevi[9,10], suggesting that one or more genomic determinants of cutaneous pigmentation, such as select polymorphisms of *MC1R* might increase the risk of melanocyte transformation independent of pigmentary pathways[11]. Additional shared risk factors include occupational exposures associated with cooking and welding[9]; however, the precise nature of the causative agent, whether it be ultraviolet or other non-ionizing radiation, fumes (which can contain carcinogens) or radioactive materials, is not known. The presence of ocular or oculodermal melanocytosis (a congenital condition characterized by hyperpigmentation of the uveal tract, sclera and episcleral, also termed 'Ota naevus'), or of a melanocytoma (typically benign pigmented tumors of the optic nerve and uveal tract), has been observed in patients diagnosed with uveal melanoma[12,13]. Individuals with oculodermal melanocytosis have an estimated lifetime risk of developing uveal melanoma of 1 in 400 (0.25%)[14], whereas malignant transformation of melanocytomas is estimated to occur in 1–2% of affected individuals[12]. Between 2% and 5% of uveal melanomas are considered to be familial[15], most commonly associated with germline pathogenic variants of the tumor-suppressor gene *BAP1*[16]. The point prevalence of uveal melanoma in individuals with germline *BAP1* mutations has been estimated to be 2.8%, with a lower median age at diagnosis in these individuals (50 years) than in an unselected population (63 years)[16]. Deleterious germline variants of *PALB2*[15], *MLH1*[15], *SMARCE1*[15], *NF1*[17] and *MBD4*[18,19] are also implicated as susceptibility genes. However, due to the rarity of the disease in the general population, no population screening takes place.

Recommendations

- Population screening is not recommended [IV, E].
- Annual dilated eye fundus is recommended in case of a choroidal nevus, an ocular or oculodermal melanocytosis, or a melanocytoma [IV, B].
- Annual dilated eye fundus is recommended in case of germline pathogenic variants of *BAP1* and *MBD4* [IV, B].

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

These guidelines apply to posterior segment uveal, namely choroidal, ciliary body, or cilio-choroidal melanoma (representing ~90% of uveal melanomas). Guidelines specific to iris melanomas (~10% of uveal melanomas) will be developed in a separate document. For simplicity, posterior segment uveal melanoma will be referred to as uveal melanoma.

Symptoms

Up to 31% of patients are diagnosed incidentally during routine eye examination, with the remainder presenting with changes in vision or non-specific other ocular symptoms; approximately 8% are diagnosed after evolution of a previously identified choroidal naevus under surveillance at regular intervals.[20,21]

Clinical diagnosis

The diagnosis of uveal melanoma is clinical. It is achieved by recognizing classic tumor features, using eye slit lamp biomicroscopy and indirect ophthalmoscopy, combined with the results of a wide range of imaging diagnostic tests.[22–24] All patients undergo digital slit lamp biomicroscopy and wide-field fundus photography to determine tumor location, configuration, pigmentation, vascularity, discreteness of margins, distances from the foveola and optic disc, involvement of ciliary body and iridocorneal angle, and anteriorly located extrascleral extension. These methods also identify secondary features such as episcleral sentinel vessels, cataract, subretinal fluid or orange pigment on the tumor, intravitreal hemorrhage, elevated intraocular pressure, rubeosis iridis, completed by optical coherence tomography (OCT) and autofluorescence photography when available.

Multimodal imaging

Ocular ultrasonography (US) and ultrasound biomicroscopy (UBM) (for anteriorly located lesions) are essential to determine the dimensions of a uveal melanoma, according to its location in the eye. There are two types of ocular US: A-scan for internal reflectivity and B-scan to estimate echodensity properties, and dimensions. With A-scan US, a uveal melanoma shows medium to low internal reflectivity, demonstrating a high peak on the tumor apex, then a gradual decrease in reflectivity as the sound wave travels through the mass. With B-scan US, uveal melanoma shows a dome, mushroom or flat surface configuration.[25] Additional features of a B-scan include acoustic hollowness and choroidal excavation. In a few patients, ultrasonography can disclose orbital extension of the tumor where the tumor grows through the sclera, usually via an emissary canal,

possible even in small tumors.[26,27] The presence of intrinsic vascular pulsations on B-scan is strongly suggestive of a solid tumor rather than subretinal hemorrhage, a differential diagnosis. In eyes with opaque media from cataract or vitreous hemorrhage, the tumor may not be visualized by indirect ophthalmoscopy; instead, the ultrasound waves can be transmitted through the opacification to image the posterior segment of the eye.[28] In some instances, ultrasonography might reveal one or more cavities within the mass, suggestive of cavitary uveal melanoma.[29]

Fluorescein angiography and indocyanine angiography can be used to differentiate uveal melanoma from other tumors, particularly in case of achromic tumors, or to identify the origin of subretinal fluid (pin points or choroidal neovascularization).[30]

Autofluorescence photography can be used to detect lipofuscin ('orange pigment') in the retinal pigment epithelium that can be seen by indirect ophthalmoscopy, which can be useful in the early diagnosis of small uveal melanoma that often have overlying lipofuscin and give rise to geographic hyperautofluorescence.[31]

OCT is valuable for early detection of uveal melanoma, especially when considering factors for distinguishing a choroidal naevus from a uveal melanoma.[31]

Magnetic Resonance Imaging (MRI) may be valuable for imaging a uveal melanoma or orbital extension, particularly with large tumors and/or ciliary body tumors, and MRI can detect extrascleral extension of tumor.[32–34] MRI has high resolution and uveal melanomas show a fairly typical pattern on T1-weighted images, demonstrating a bright signal relative to the vitreous compared with T2-weighted images, which provide a low (dark) tumor signal compared with the vitreous.[35] Uveal melanomas show bright enhancement with gadolinium, a feature that differentiates the solid tumor from vitreous or a subretinal hemorrhage.

<u>Terminology</u>
There is a lack of universal size criteria/definition for distinguish small, medium and large melanoma, or a small melanoma with a naevus.[36] As the vast majority of uveal melanomas are treated without histological confirmation, the diagnosis of uveal melanoma is based on a combination of clinical and multimodal imaging evidence.

Recommendations for diagnosis and staging

- In the absence of histological evidence, small lesions can be classified as nevi, indeterminate melanocytic tumors or uveal melanomas, depending on their clinical features and progression [II, B].
- Progression of small melanoma before treatment is defined by an increase in thickness or basal diameter confirmed by at least one repeated measurement [II, B].

- Choroidal and ciliary body melanomas can be labelled in small, medium or large lesion, according to their size:

- Small melanoma with a (tumor-based) thickness ≥0.5 mm and ≤2.5 mm on ultrasound B-scan and largest basal diameter ≤10.0 mm on color fundus photography
- Medium melanoma with a (tumor-based) thickness ≥2.5 mm and <7 mm on ultrasound B-scan and largest basal diameter <15.0 on B-scan
- Large melanoma with a (tumor-based) thickness ≥ 7.0 mm on ultrasound B-scan and largest basal diameter ≥ 15 mm on B-scan

- Clinical staging should be performed according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM (tumor–node–metastasis) staging system (AJCC8) [II, A].

- Biopsy: a transscleral or transvitreal biopsy should be performed only in case of diagnosis uncertainty, for cytological and if possible cytogenetic characterization.

Molecular characterization

Somatic genetic alterations in the tumor are important for followup since presence of chromosome 3 deletion (partial/total) or chromosome 8q gain (partial/total) on one side, or both alterations, induce a middle or high risk to develop systemic metastases, respectively (80% of which will initially develop in the liver).

Tumor samples will be systematically sent for somatic genetic analysis, ideally through next-generation sequencing using a dedicated panel, in case of enucleation. In case of conservative treatment, a transscleral of transvitreal fine-needle aspiration biopsy should be performed whenever possible. Knowledge of the cytogenetic characteristics will be useful to intensify hepatic screening (by liver MRI instead of ultrasound) and to select candidate patients for ongoing/upcoming adjuvant clinical trials.

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

All indications of local/locoregional treatments are made during a multidisciplinary tumor board meeting associating ophtalmologists specialized in ocular oncology, radiation oncologists, and pathologists.

- Indications for proton therapy

Tumors of diameter <20-22 mm, and thickness ≤ 10-11 mm are eligible to proton beam therapy. Proton beam therapy requires a surgical positioning of tantalum clips, and a treatment plan designed by radiation physicists/oncologists and ophthalmologists expert in ocular oncology. The recommended dose is 60 Grays (Cobalt equivalents) in 4 fractions, over 4 consecutive days.

- Indications for Iodine-125 brachytherapy

Tumors located anteriorly in the superior temporal quadrant, may be eligible to Iodine-125 brachytherapy, according to local protocols. Tumors must be of thickness ≤ 10 mm

and of diameter ≤16 mm. Certain centers use Rhutenium-106 brachytherapy, which is not to date available in France, and is limited to uveal melanomas of thickness ≤6 mm. The recommended dose is 90 Grays (Cobalt equivalents) at the apex.

- Indications for enucleation

Tumors of diameter > 20-22 mm, or thickness > 10-11 mm are eligible to enucleation, given the elevated risk of massive toxic tumor syndrome (tumor lysis syndrome), total retinal detachment, massive retinal ischemia and neovascular glaucoma that may ultimately require secondary enucleation.

- Particular cases:
  - Metastatic disease at diagnosis: locoregional treatment of the primary uveal melanoma is still recommended because tumor growth will produce pain and visual impairment, independently of the efficacy of the systemic therapy.
  - Extrascleral exteriorization at diagnosis: if identified by initial evaluation, imaging (ultrasound or MRI) or during clip positioning, it may be included in the protontherapy treatment plan or in the brachytherapy field. If enucleation is performed, or if identified during histopathological examination of the eye, adjuvant photon radiotherapy of the orbital cavity will be necessary, based on a case-by-case evaluation during the multidisciplinary tumor board meeting. If anteriorly located and small, adjuvant radiotherapy may be waived if a conjunctival flap can be preserved overlying the exteriorization area.
  - Intravitreal hemorrhage: concomitant vitrectomy and tantalum clip positioning may be necessary, using appropriate safety measures such as trocars and cryoapplication of sclerotomies .

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