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SPECIAL ARTICLE

Uveal melanoma: ESMO—EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up†

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INTRODUCTION

Uveal melanoma (UM) is associated with specific challenges due to its rare incidence. Optimal management of the disease requires multidisciplinary collaboration and coordination for the diagnosis, treatment, follow-up and support of patients at all stages and clearly established referral pathways.[1] All patients should have access to centres with dedicated expertise in primary and metastatic UM either nationally or through cross-border access agreements, using the potential of the existing and forthcoming European Reference Networks as outlined in Europe's Beating Cancer Plan, the ambition of the European Union (EU) Cancer Mission and the establishment and connection of Comprehensive Cancer Care Infrastructures in the EU.[1-3]

INCIDENCE AND EPIDEMIOLOGY

UM is the most common primary intraocular malignancy in adults. Unlike cutaneous melanoma, the incidence of UM has remained stable over time and is not linked to ultraviolet light exposure, except iris melanoma.[4,5]

In a recent study, incidence that correlated with latitude was expressed as a north-to-south decreasing gradient, ranging from $\geq$8.0 cases per million person-years in Northern/Western Europe and Oceania, to 2.0-7.9 in North America, Eastern Europe and Southern Europe and $<$2.0 in South America, Asia and Africa.[6]

UM affects non-Hispanic white patients 18 times more frequently than black patients and 15 times more than

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Asian patients.[7] Grey/blue-eyed coloured irises are at higher risk than brown-eyed coloured irises.[7]

UM occurs in patients of all ages; 1% of cases affect the paediatric population.[8] Incidence increases with age, rising to >20 cases per million by the age of 70.[9]

UM typically occurs sporadically but it is also known to be associated with oculo-dermal melanocytosis,[10] familial atypical mole and melanoma syndrome, neurofibromatosis type 1 and Li-Fraumeni syndrome.[4] About 2%-5% of UMs are considered familial and are mainly associated with germline mutations in the tumour-suppressor gene *BAP1* and less frequently with an *MBD4* pathologic variant.

Germline mutations in *BAP1* have been identified as being responsible for the *BAP1* tumour predisposition syndrome (*BAP1*-TPDS), which is associated with UM, mesothelioma, cutaneous melanoma and renal cell carcinoma.[11] Patients with atypical presentations such as bilateral UM, early age of onset (<40 years) and familial inheritance patterns (≥2 *BAP1*-TPDS-associated tumours) can benefit from genetic counselling or undergoing germline *BAP1* or *MBD4* mutation analysis to detect pathogenic variants.[12,13]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

UM diagnosis is based on clinical examination by ophthalmoscopy, fundus photography and conventional ocular ultrasound (US) in patients presenting with blurred vision or other visual symptoms; however, 13%-30% are diagnosed during routine eye examinations. UM appears as a pigmented or achromic mass arising from the choroid (90%), the ciliary body (6%) or the iris (4%)[4] and is composed of a variable proportion of spindle and/or epithelioid cells. Epithelioid cell type, a high number of mitoses, extrascleral extension, presence of extravascular matrix patterns and ciliary body invasion have all been associated with poor prognosis.[14] See Supplementary Material Section 1, available at https://doi.org/10.1016/j.esmoop.2026.106888 for more information on spindle and/or epithelioid cells, symptoms suggesting UM and clinical evaluation and examination for suspected UM.

Molecular testing of UM can be carried out on tissue samples of varying sizes, from fine-needle aspiration (FNA) biopsies to local resections, larger enucleations or orbital exenterations. Biopsies should be discussed with patients who will likely benefit from conservative treatment to highlight the risks (e.g. potential complications such as haemorrhage, tumour seeding[15]), the balance of insufficient sampling for analysis and the expected benefit of the procedure (i.e. personal genomic risk and tailored surveillance adapted to the risk). A summary of the pros and cons of intraocular biopsies is shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.106888.

Harvesting tumour material surplus for diagnostics and prognostication should be discussed with the patient for molecular and genetic research programmes that could provide validated prognostic and predictive factors (such as liquid biopsies) and new therapeutic options in the future.

Mutations can be analysed using conventional or next-generation sequencing (NGS) platforms. The latter have enabled bespoke-designed NGS prognostic assays for UM, incorporating analyses of relevant copy number variants and mutations[16-18] as well as epigenetic changes.[19]

The UM microenvironment is characterised by high levels of tumour-promoting M2 macrophages, few active cytotoxic T cells and low programmed death-ligand 1 (PD-L1) expression.[20,21] Melanocytic markers such as Melan-A, S100 and human melanoma black (HMB45) help to confirm diagnosis, whereas loss of nuclear BRCA1-associated protein 1 (BAP1) expression is associated with *BAP1* mutations, monosomy 3 and poor prognosis.[22] Human leukocyte antigen (HLA) testing in peripheral blood to identify the presence of the HLA-A*02:01 allele should be considered at diagnosis of high-risk patients to determine eligibility for tebentafusp in the metastatic setting[23] and for the ATOM phase III trial in the adjuvant setting (NCT06246149).

Recommendations

- Biopsy is not mandatory for typical UM diagnosis, which is well characterised by ophthalmoscopy, fundus photography and conventional ocular US [II, D].
- Ciliary body melanoma should be imaged with high-frequency US biomicroscopy for ciliary body location [II, A] (see Supplementary Material Section 1, available at https://doi.org/10.1016/j.esmoop.2026.106888).
- A biopsy is recommended if the clinical diagnosis is uncertain and if it has been discussed with the patient due to the potential risks of the procedure and the uncertainty of a conclusive result [II, A].
- If technically feasible regarding size and localisation, FNA biopsies should be discussed for prognostication via transcleral or transvitreal routes [III, B].
- HLA-A*02:01 peripheral blood testing is mandatory in the metastatic setting [I, A] but can also be considered in the localised setting to facilitate access to adjuvant clinical trials [V, B].
- Routine peripheral blood examination for standard-of-care tests cannot be recommended, as current evidence does not support that it affects diagnosis of metastatic disease or survival [III, D].
- Liquid biopsy testing is considered experimental and for research use only and cannot be recommended at this time [III, D].

STAGING AND RISK ASSESSMENT

An algorithm for staging and risk assessment of suspected or confirmed UM is shown in Figure 1.

UM should be staged according to the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2026.106888).[24] The AJCC Cancer Staging Manual is an anatomy-based system; tumour diameter and thickness, ciliary body involvement and extraocular

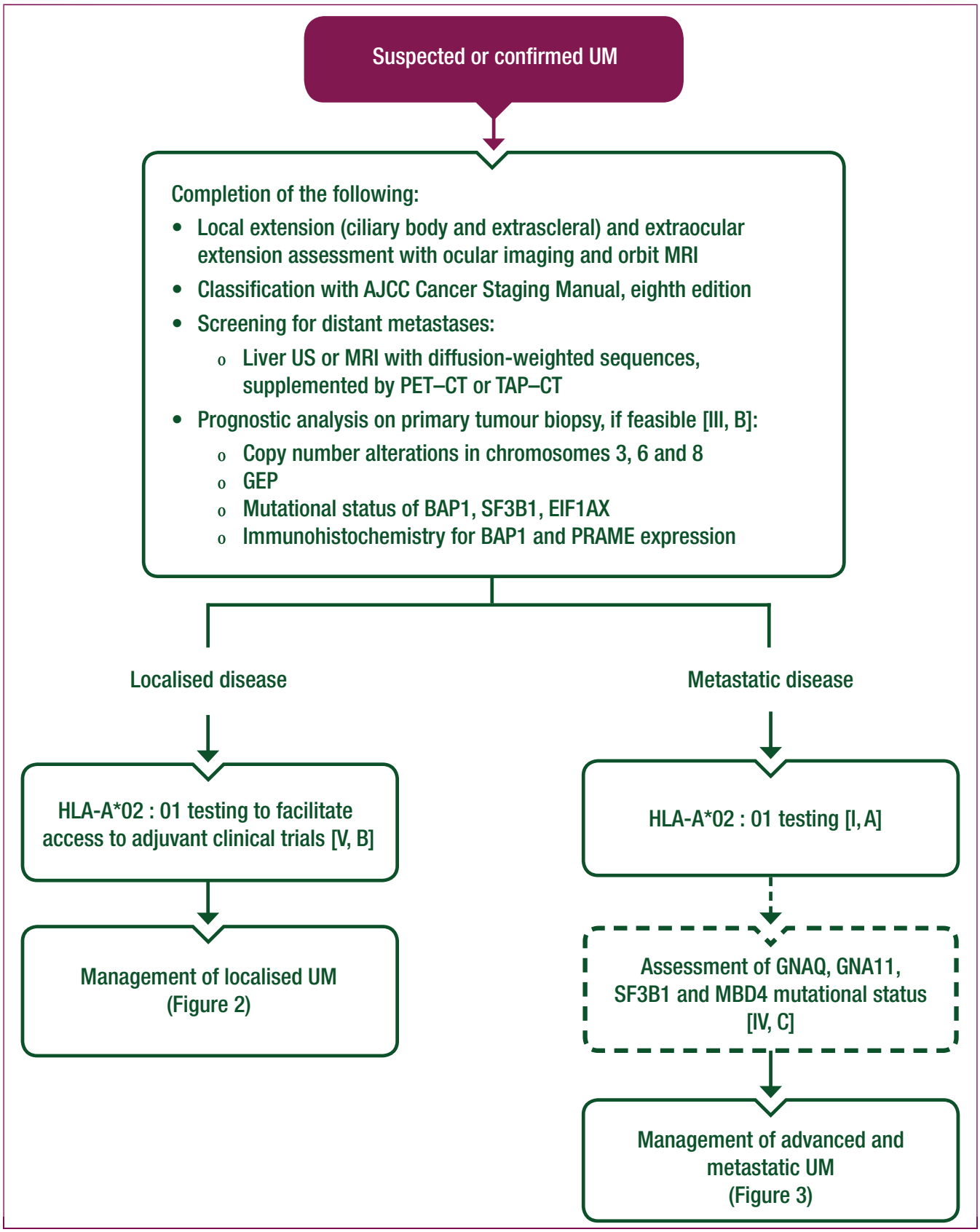

Figure 1. Staging and risk assessment of suspected or confirmed UM.
Purple: algorithm title; white: other aspects of management and non-treatment aspects; dashed lines: optional branches, colour used as described in the categories above.
AJCC, American Joint Committee on Cancer; BAP1, BRCA1-associated protein 1; CT, computed tomography; GEP, gene expression profiling; HLA, human leukocyte antigen; MRI, magnetic resonance imaging; PET, positron emission tomography; PRAME, preferentially expressed antigen in melanoma; TAP, thoraco-abdomino-pelvic; UM, uveal melanoma; US, ultrasound.

extension are factors associated with the risk of metastasis at 10 years from 5% for stage I to 40% for stage III.

Findings suggest that the AJCC Cancer Staging Manual may be improved when other important prognostic parameters are included (e.g. cytogenetic, molecular genetic or epigenetic alterations).[25-27]

The 'Liverpool Uveal Melanoma Prognosticator Online' tool is used for prognostication in several centres worldwide.[28] It generates an all-cause mortality curve according to age, sex, AJCC Cancer Staging Manual size category, melanoma cell type, closed connective tissue loops, mitotic count and chromosome 3 loss and, more recently, gain of chromosome 8q.[29]

Molecular prognostication

The genomic landscape of UM is characterised by a low tumour mutational burden and chromosomal copy number alterations, including chromosomes 3, 6 and 8, which are associated with prognostic significance.[30] Aneuploidies, including monosomy 3, 6q loss and 8q gain, have been associated with shorter survival.[30] Driver mutations include early mutually exclusive mutations in *GNAQ* or *GNA11* in 43% and 49% of patients, respectively,[31] leading to downstream activation of the mitogen-activated protein kinase, the phosphatidylinositol 3-kinase and the yes-associated protein pathways.[32,33] Activating mutations rarely involve *CYSLTR2* and *PCLB4*, but when they occur, they are early events in UM development, as seen in choroidal nevi.[34] Biallelic *BAP1* inactivation is associated with high risk of metastasis.[35] Change-of-function *SF3B1* mutations are associated with late metastasis.[36] Mutations in *EIF1AX* are associated with a better prognosis.[36] Mutations in *MBD4* lead to a hypermutator phenotype, which has been correlated with improved response to immune checkpoint inhibitor (ICI) therapy.[37] Expression of PRAME (preferentially expressed antigen of melanoma) is associated with a higher risk of metastases.[38]

The most commonly used prognostic tests are FISH, multiplex ligation-dependent probe amplification, microsatellite analysis, single-nucleotide polymorphism array, array comparative genomic hybridisation, targeted NGS and a 12-gene PCR assay based on gene expression profiling (GEP).[39] In general, three prognostic groups are defined.[4]

A low risk of metastasis is associated with tumours that have normal chromosomes 3 and 8; these tumours often display 6p gain. They are typically classified as GEP class 1 and lack PRAME expression.[35,38-40] These tumours may harbour an *EIF1AX* mutation.

Late but infrequent metastatic spread is associated with normal chromosome 3, one or more extra copies of (partial) chromosome 8, GEP class 1 status and with PRAME expression. These tumours may have an *SF3B1* mutation.[36]

A high risk of metastasis is associated with loss of one copy of chromosome 3 or isodisomy of this chromosome, polysomy of chromosome 8q, a GEP class 2 profile and inactivating mutations or deletions of the *BAP1* gene located on chromosome 3.[30]

Due to the limited comparative analyses between these different molecular testing techniques, no statement can be made about the superiority of one technique over another.

Recommendations

- Local extension (ciliary body and extrascleral) and extra ocular extension should be assessed with ocular imaging and orbit magnetic resonance imaging (MRI).
- UM should be staged according to the eighth edition of the AJCC Cancer Staging Manual.
- Patients should be screened for distant metastases [liver US or MRI with diffusion-weighted sequences, supplemented by positron emission tomography (PET)—computed tomography (CT) or thoraco-abdomino-pelvic CT for extrahepatic extension].
- If sufficient tumour material is available, the molecular work-up of primary UM could include copy number assessment in chromosomes 3, 6 and 8, GEP, mutational status of *BAP1*, *SF3B1*, *EIF1AX*, and immunohistochemistry for BAP1 and PRAME expression [III, B].
- Assessment of mutational status of *GNAQ, GNA11, SF3B1* and *MBD4* may be recommended in the metastatic setting as results may impact treatment decisions [IV, C].

MANAGEMENT OF LOCALISED PRIMARY UM

Most UMs are localised at diagnosis, with <2% presenting with detectable metastases.[41] Although local therapy is effective for local control in >90% of cases, up to 50% of patients will develop metastases, mainly in the liver (90%).[41-43]

The choice of treatment depends on tumour size and location, extraocular extension, patient preferences and availability of radiotherapy (RT) oncology facilities. A proposed algorithm for the management of localised primary UM is shown in Figure 2.

Local treatment

Enucleation

A tumour with an extensive extraocular extension or that replaces >50% of the globe or leads to a blind and/or painful eye should be treated with enucleation or exenteration (30% of patients). See Supplementary Section 2, available at https://doi.org/10.1016/j.esmoop.2026.106888 for prosthetics.

Resection

To preserve the eye and vision, conservative resection techniques have been developed for small iris or ciliary body tumours. These approaches are technically more demanding than enucleation and are associated with complications, including bleeding, retinal detachment and ocular hypertension, which may require additional salvage surgery.[44] In a selection of cases, local resection of the tumour is a viable option.[45]

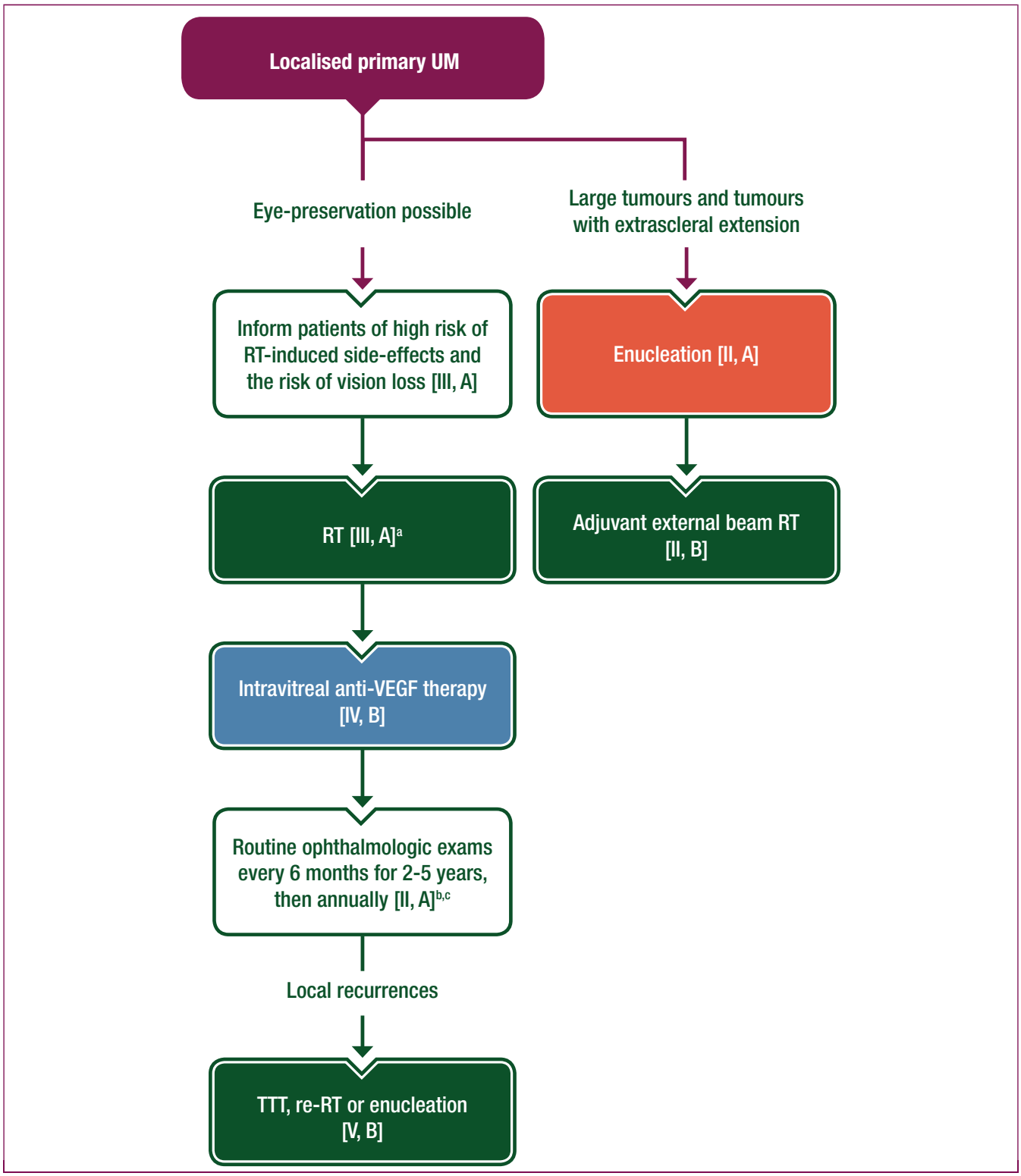

Figure 2. Management of localised primary UM.
Purple: algorithm title; orange: surgery; dark green: radiotherapy; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
PBR, proton beam radiotherapy; RT, radiotherapy; SRT, stereotactic radiotherapy; TTT, transpupillary thermotherapy; UM, uveal melanoma; US, ultrasound; VEGF, vascular endothelial growth factor.
[a]Brachytherapy or PBR can be used as both are associated with excellent results in terms of local control [III, A]. SRT is an alternative with more limited prospective validation [IV, B].
[b]In cases where tumour stability is uncertain, the interval between follow-up visits should be shortened to help confirm whether the tumour remains stable or requires additional intervention [II, A].
[c]Colour photography can be used as it effectively detects almost all local recurrences [II, B]. If the tumour is not fully visible, ophthalmic US can be a valuable tool [II, A].

RT

Several RT techniques are established in the management of UM, each with unique characteristics and clinical applications. Plaque brachytherapy and proton beam RT (PBR) are commonly used RT modalities for primary tumours, particularly thin ones (<2.5 mm thick) with the largest diameters ranging 5-18 mm.[46,47] See Supplementary Section 2, available at https://doi.org/10.1016/j.esmoop.2026.106888 for more information on PBR versus brachytherapy.

Brachytherapy. Plaque brachytherapy allows for eye function preservation, particularly in small- to medium-sized tumours. This technique is generally more widely available and less expensive than PBR and usually involves a shorter treatment course. The COMS phase III trial for patients with small-to-medium UM achieved similar 10-year overall survival (OS) with enucleation and brachytherapy and reported an average local failure rate of 9.5% after brachytherapy.[48] Brachytherapy demonstrates favourable 5-year local tumour control (LTC), with a reported median actuarial 5-year LTC rate of 91%.[49] Subgroup analysis by radionuclide indicates a median 5-year LTC of 86% for ruthenium-106 and 93% for iodine-125.[49]

PBR. PBR is often indicated for larger tumours or those located close to critical structures within the eye. This technique can be beneficial when brachytherapy is not feasible due to tumour size or proximity to sensitive ocular features. Compared with iodine-125 brachytherapy, it offers similar or higher rates of LTC and similar or lower rates of enucleation, with most recurrences occurring within the first 4-5 years and a median recurrence time <2 years.[50] A recent systematic review and meta-analysis reported a 5-year LTC rate of 94% for PBR in the management of choroidal melanoma.[51] PBR is often more costly and less accessible, as proton therapy centres are less common.

Stereotactic RT. Stereotactic RT (SRT), including hypofractionated techniques, is only suitable if brachytherapy or PBR are unavailable. SRT has become an alternative for tumours thicker than 2-3 mm and with a basal diameter of ≤15 mm.[52] Limited prospective studies are available; a recent systematic review reported a 5-year LTC rate of 90% for fractionated SRT and 89% for stereotactic radiosurgery.[53] SRT appears to be effective for LTC, but with a higher incidence of complications, including vitreous haemorrhage, compared with other techniques.[54]

Follow-up after local treatment

Complications of local RT

Any type of RT can lead to posterior complications such as maculopathy, optic neuropathy, neovascular glaucoma and retinopathy, which can have an impact on vision and eye preservation.[55] In the anterior segment of the eye, cataract and dry eye are the most common side-effects. Signs of RT-induced maculopathy on fundus examination are detected in ≤66.5% of cases within 3 years of PBR.[55] RT-induced maculopathy and neuropathy are associated with a high risk of vision loss; several predictive factors have been identified (see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.106888). Neovascular glaucoma is a severe form attributed to new blood vessels obstructing the aqueous humour outflow secondary to posterior segment ischaemia. The vascular endothelial growth factor (VEGF) plays a major part in mediating active intraocular neovascularisation in patients with ischaemic retinal diseases (see Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2026.106888). Several studies have reported on the efficacy of intravitreal anti-VEGF agents for the management of RT-induced maculopathy; injections, given every 2 months for the first year and every 3 months for the second year, slow down vision loss and anatomical degradation for ≤18 months in RT-induced maculopathy following PBR.[56]

Ophthalmological follow-up

After RT or surgery for primary UM, ophthalmological follow-up is critical to detect recurrence, manage RT complications and provide vision support.[48] The 5-year local recurrence rate is 7.3%, but a literature review found a wide range of local recurrence rates ranging 0%-55.6%,[24,57] depending on tumour location and treatment type. Patients should be monitored every 6 months for the first 2-5 years, then transition to annual visits, depending on tumour response and individual patient factors. The interval between follow-up visits may be shortened to allow for a period of closer monitoring to assess tumour stability. With a clear view of the fundus, colour photography detects 98% of local recurrences. If the entire tumour is not visible with colour photography, it can be adequately visualised with ocular US. Except for rare familial syndromes, the risk of contralateral UM is extremely low.

Management of local recurrences

The treatment approach depends on the extent and location of the recurrence and remains a case-by-case decision. Treatment options include laser ablation, RT or enucleation. Transpupillary thermotherapy (TTT) may be suitable for small intraocular marginal recurrences.[58,59] High local control rates with globe-sparing methods such as PBR and plaque brachytherapy have also been described.[59,60]

Patients with an extraocular recurrence require orbital and brain imaging (MRI) to assess regional extent and body staging to assess metastatic disease. Extraocular involvement requires surgical resection, possibly combined with RT and/or cryotherapy. Surgical options include enucleation, partial orbital resection or exenteration. RT with plaque brachytherapy or PBR alone may also be offered. Some patients, however, require enucleation due to tumour regrowth or complications.

In patients with prior enucleation and orbital recurrence, management may include surgical resection or cryotherapy, along with RT (particle or photon beam).

Retrospective studies suggest similar metastasis-free survival (MFS) and OS between PBR and enucleation, but the local control rate was reduced to 31% in patients retreated with PBR for local recurrences, suggestive of radioresistance.[61]

Adjuvant treatment

Adjuvant RT

There are no randomised trials comparing the effectiveness of adjuvant RT with no RT for patients with UM. Adjuvant RT is only suitable for macroscopic extraocular tumour extension (>5 mm) at the time of enucleation or if gross orbital disease is suspected.[62,63] Cases with limited extraocular extension (<5 mm) and complete excision from the orbital contents can be safely observed without adjuvant RT.[62]

Adjuvant systemic treatment

Despite successful ocular treatment, up to 50% of patients, depending on stage and genomic alterations, will develop metastatic disease, mainly in the liver.

In the adjuvant setting, randomised phase III trials are sparse due to the rarity of UM. The largest study to date, FOTEADJ, compared adjuvant fotemustine and surveillance in 244 patients before being terminated early due to evidence of futility. With a median follow-up of 3 years, there was no difference in 3-year MFS or OS.[64] Nevertheless, the study showed the feasibility of real-time genomic analysis and paved the way for future adjuvant studies. Compared with historical controls, a single-arm study of crizotinib in 34 patients with high-risk UM failed to show improved MFS,[65] whereas nivolumab—ipilimumab improved MFS in a trial of 50 patients (44% discontinued treatment due to toxicity).[66] An ongoing randomised phase II trial on sunitinib versus valproic acid given for 6 months has so far shown 2-year OS of 95.6% and 90.7%, respectively, in high-risk patients.[67] A multicentre phase II trial is investigating the protein kinase C inhibitor, darovasertib, in the neoadjuvant and adjuvant setting (NCT05907954).[68]

The ATOM trial, a randomised phase III study of tebentafusp as monotherapy versus surveillance in the adjuvant setting for patients with high risk of metastasis, is currently recruiting (NCT06246149).

Recommendations

Local treatment

- If eye-preserving techniques are possible, RT options should be preferred over endo- and transscleral resections [I, B].
- Enucleation should be limited to large tumours and tumours with extrascleral extension [II, A].

RT

- Patients should be informed of the high risk of RT-induced side-effects and the risk of vision loss [III, A].
- RT is recommended [III, A].
  - Brachytherapy or PBR can be used as both are associated with excellent results in terms of local control [III, A].
  - SRT is an alternative with limited prospective validation [IV, B].
- It is recommended that brachytherapy dose values be interpreted with caution, as they vary by applicator type (Ru-106 versus I-125), and the lack of international dosimetry standards limits the comparability of published data [V, B].
- The recommended total doses of PBR are 60 Gy in four fractions, or 50 or 70 Gy in five fractions [III, A].
- The recommended proton treatment modalities are a therapeutic sitting position facing a fixed horizontal proton line and using a passive delivery beam [III, A].
- The inclusion of patients in controlled studies for follow-up after RT is recommended [IV, A].

Follow-up after local treatment

- Intravitreal anti-VEGF therapy is recommended to prevent the formation of intraocular neovascularisation [IV, B].
- Patients should receive routine ophthalmologic examinations every 6 months for 2-5 years, then annually to allow for timely detection of any recurrences or complications [II, A].
- In cases where tumour stability is uncertain, the interval between follow-up visits should be shortened to help confirm whether the tumour remains stable or requires additional intervention [II, A].
- Colour photography can be used as it effectively detects almost all local recurrences [II, B]. If the tumour is not fully visible, ophthalmic US is recommended as a valuable tool [II, A].

Management of local recurrences

- There is no current standard treatment of local recurrence. TTT, re-RT or enucleation can all be recommended as feasible and effective treatment options, depending on the extent and location of the recurrence [V, B].

Adjuvant treatment

- For patients with a high risk of local recurrence (i.e. positive margins after enucleation or extraocular tumour extension), adjuvant external beam RT can be recommended [II, B].
- Patients with a genomic and/or clinical high risk of metastasis should be offered an adjuvant clinical trial, if available [II, A].

MANAGEMENT OF METASTATIC UM

UM is characterised by early seeding and years of dormancy of micrometastases; the liver constitutes a specific niche, as numerous molecules like chemokine ligand 12 and

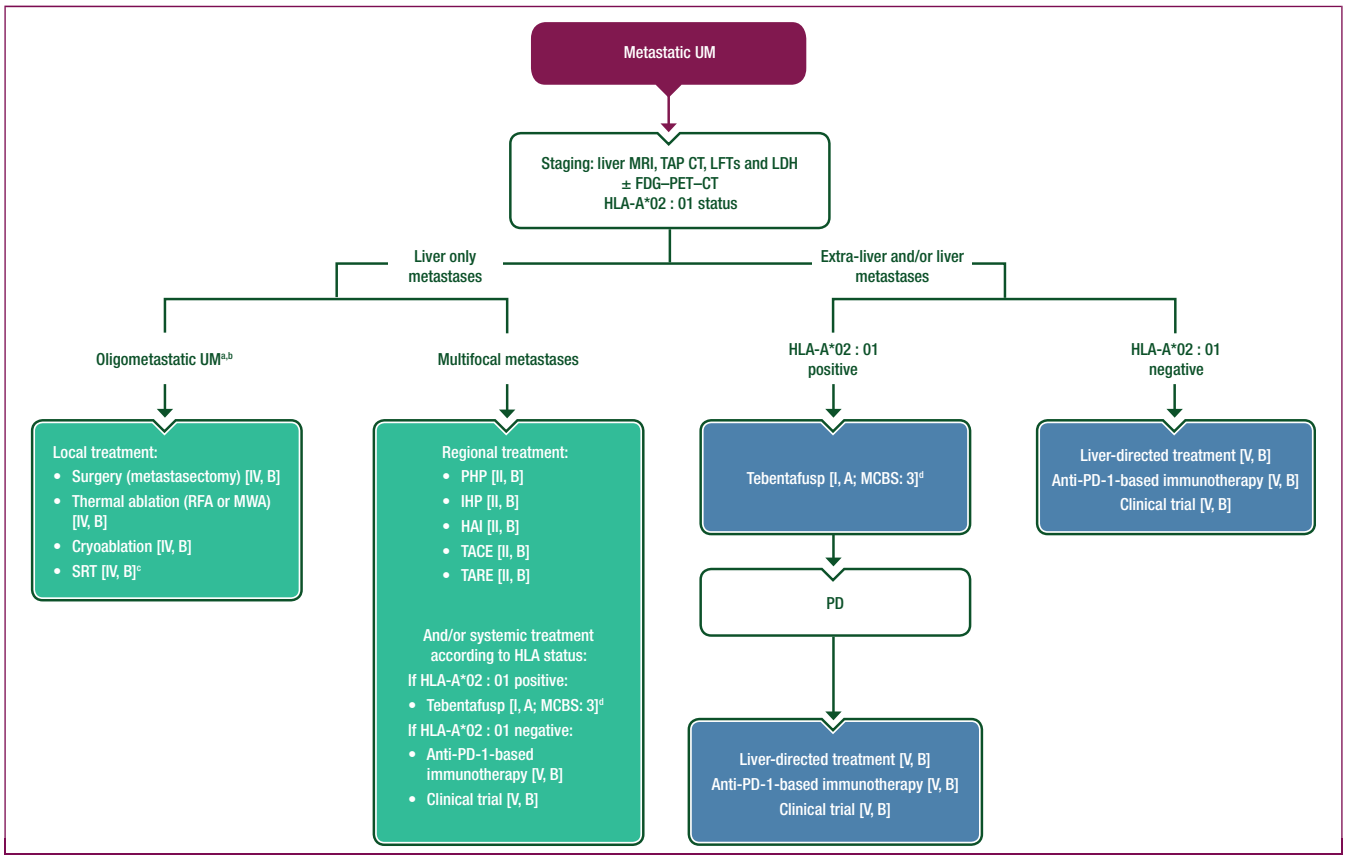

Figure 3. Management of metastatic UM.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
CT, computed tomography; EMA, European Medicine Agency; FDA, Food and Drug Administration; FDG, fluorodeoxyglucose; HAI, hepatic arterial infusion; HLA, human leukocyte antigen; IHP, isolated hepatic perfusion; LDH, lactate dehydrogenase; LFT, liver function test; MCBS, Magnitude of Clinical Benefit Scale; MRI, magnetic resonance imaging; MWA, microwave ablation; PD, progressive disease; PD-1, programmed cell death protein 1; PET, positron emission tomography; PHP, percutaneous hepatic perfusion; RFA, radiofrequency ablation; SRT, stereotactic radiotherapy; TACE, transarterial chemoembolisation; TAP, thoraco-abdomino-pelvic; TARE, transarterial radioembolisation; UM, uveal melanoma.
[a]The risk—benefit ratio or liver-directed strategies should be weighed in a multidisciplinary tumour board [IV, B].
[b]Discuss tebentafusp before localised liver-directed treatment.
[c]Alternative in patients not eligible for surgery or thermal ablation.
[d]ESMO-MCBS v2.0[130] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

chemokine receptor 4 (CXCL12/CXCR4) are involved in UM liver homing.[69] Extrahepatic metastases, involving lung, bone and soft tissue, are less common; brain metastases are rare.[70] Staging of metastatic disease is based on total body CT scan and liver MRI; brain imaging is not required in the absence of central nervous system symptoms; the usefulness of fluorodeoxyglucose (FDG)—PET—CT is still debated.

Different staging systems predict survival after metastatic disease appears, based on tumour burden, liver function tests, World Health Organization performance status (PS) and metastasis-free interval.[71-73]

A proposed algorithm for the management of metastatic UM is shown in Figure 3. Therapeutic options should be discussed at an oncology or molecular tumour board (MTB) in reference centres with expertise in UM. The MTB should at minimum include ophthalmologists (optionally), pathologists, interventional radiologists, liver surgeons, radiation and medical oncologists.

Patients should be referred for the recommendation of first-line locoregional or systemic treatment and discussion of UM clinical trials. National networks and patient advocacy groups may help facilitate patient access to expert centres and organise local patient care.

A greater knowledge of UM genetics and immunology, which differs deeply from cutaneous melanoma, and international networks devoted to rare cancers, such as the European Reference Network for Rare Adult Solid Cancers (EURACAN) and the Melanoma Patient European Network (MPNE), should make it possible to increase the number of trials dedicated to UM.[1]

Liver-directed therapies

Local treatments

Surgery. There is a lack of prospective comparative studies that define the role of surgery in patients with UM liver metastases (UMLMs). Retrospective cohorts have reported a

median OS of 14-29 months after surgery of UMLMs.[74] Patients with oligometastatic disease may be potentially cured by surgery, but the decision to operate should be carefully weighed against the risk of complications and disease recurrence by an MTB. Perioperative mortality and morbidity rates after surgery of UMLMs are ∼2% and ∼14%, respectively.[74,75] Median progression-free survival (PFS) and OS after resection with curative intent are 12 months and 26 months, respectively, with reported 5-year survival rates of ∼35% in highly selected patients.[75]

Patients with a good general condition and a limited extent of accessible metastases should be offered a local treatment, either alone or in combination with systemic treatment.

Surgery with curative intent (R0 resection) is the treatment of choice when the disease-free interval from primary tumour diagnosis to liver metastases is >24 months, and the number of metastases is ≤4 in the absence of miliary disease.[76] Most patients with UMLMs have multifocal and small metastases. Around 10% of the patients are eligible for local therapy.[75] To reduce the risk of futile surgery, preoperative MRI and exploratory laparoscopy are recommended before or at the time of planned resection.

Thermal ablation. Compared with liver resection, cryoablation, microwave or radiofrequency ablation is associated with lower complication rates, lower costs, shorter hospital stays and faster patient recovery. SRT with MRI guidance may also be an option to treat oligometastatic liver disease with a limited extent. A retrospective study comparing resection and percutaneous ablation in 57 and 15 patients, respectively, found no difference in median OS (27 months versus 28 months).[77]

Regional treatments

Patients with liver-dominant disease and a good general condition can be considered for regional treatment at any line of metastatic recurrence. Findings from two meta-analyses of individual-level data from patients enrolled in trials or from real-life series before tebentafusp show that hepatic arterial-based therapies prolong PFS and OS compared with systemic therapy.[78,79]

Hepatic perfusion. Percutaneous hepatic perfusion (PHP) is a drug—device combination that allows delivery of high doses of chemotherapy (ChT) to the liver with limited systemic toxicity.[80] PHP with melphalan (M-PHP) was randomly compared with best alternative care (BAC) in 93 patients with unresectable liver metastases from ocular ($n = 83$) or cutaneous ($n = 10$) melanoma.[81] Hepatic PFS and overall PFS improved in patients treated with M-PHP compared with BAC: 7.0 versus 1.6 months and 5.4 versus 1.6 months, respectively. No OS benefit was observed, which may be explained by the 57% crossover rate and the high proportion of patients with extrahepatic disease.[81] The FOCUS trial comparing M-PHP with BAC was initiated as a randomised phase III trial, but later amended to a single-arm study (of M-PHP), due to enrolment limitations; as a result, the efficacy analyses were underpowered and thus exploratory.[82] Eighty-five patients were randomised: 43 were assigned to M-PHP and 42 to BAC.[82] Median PFS and OS were 9.1 and 18.5 months, respectively, among patients treated with M-PHP compared with 3.3 and 14.5 months, respectively, among patients treated with BAC.[82] Serious adverse events (AEs) occurred in 51.2% of the M-PHP group versus 21.9% in the BAC group.[82] In the treated population, overall response rate (ORR) was 27.5% in the M-PHP population and 9.4% in the BAC population, respectively.[82]

The melphalan for Injection/Hepatic Delivery System, recently approved by the Food and Drug Administration (FDA), may be considered an option in patients with HLA-A*02:01-negative UMLMs and limited tumour burden. The expected benefit should be weighed against the risk of AEs (haematological complications mostly), but serious cardiovascular and thromboembolic complications may occasionally occur.[83]

Isolated hepatic perfusion (IHP) is the surgical counterpart of PHP.[84] The efficacy of IHP is similar to PHP, but IHP is non-repeatable and is associated with higher morbidity and mortality rates.[85] In the randomised SCANDIUM phase III trial of 93 patients with untreated UMLMs with no extrahepatic disease and ≤50% liver involvement, 87 patients received either IHP or BAC. Median PFS was 7.4 months versus 3.3 months, and the median hepatic PFS was 9.1 months versus 3.3 months, both favouring the IHP arm.[85] There were 11 treatment-related AEs (TRAEs) and one treatment-related death in the IHP arm.[85] The primary endpoint of OS at 24 months was 46.5% in the IHP group versus 29.5% in the BAC group, and median OS was 21.7 months versus 17.6 months, respectively; neither was statistically significant.[86]

Hepatic arterial infusion. In hepatic arterial infusion (HAI), also known as intra-arterial or transarterial ChT, ChT is administered through a catheter placed in the hepatic artery. Many cytotoxic agents have been tested, with fotemustine being the most active. The ORR range is 0%-40% and the median OS 2.9-21 months.[74] A randomised phase III trial in 171 patients with metastases limited to the liver, compared HAI with fotemustine with intravenous treatment.[87] HAI resulted in a significant, yet marginal, improvement in PFS (4.5 versus 3.5 months) and no difference in OS (median 14.6 versus 13.8 months).[87]

Transarterial chemoembolisation. Transarterial chemoembolisation (TACE) combines the transarterial local administration of ChT with embolisation of tumour-feeding arteries. Studies investigating TACE in patients with UMLMs are limited to retrospective and small phase II trials and vary widely in the type of cytotoxic drugs and embolic agents used, the number of procedures per patient and patient selection criteria. The larger studies reported ORRs of 14%-46%, median PFS of 3-8 months and median OS of 5-29 months.[74]

Transarterial radioembolisation. In transarterial radioembolisation (TARE), microspheres labelled with yttrium-90 or holmium-166 have been studied in retrospective and small prospective series; median PFS was 5.4 months and

median OS was 12.3 months.[88] The largest prospective study included 48 patients who were treatment-naive or had progressed after immunoembolisation with a hepatic tumour load of <50%.[89] Median OS was 18.5 months in treatment-naive patients and 19.2 months in patients who had failed prior immunoembolisation.[89]

Low-grade AEs are common after TARE, including abdominal pain, fatigue and nausea and/or vomiting. Severe complications are rare but may include gastrointestinal RT ulcer or liver failure.[88]

Systemic treatments

In 2021, tebentafusp demonstrated OS benefit in the HLA-A*02:01-positive first-line population;[23] the first time a systemic treatment showed a survival benefit in metastatic UM.

Few prospective studies have been published on this rare cancer, especially randomised controlled trials.[90] According to findings from a literature review, systemic treatment of metastatic UM was associated with low response rates (<10%), low median PFS (1.8-7.2 months) and OS (5.2-19.0 months).[91] Two meta-analyses have provided benchmarks for future studies.

The first meta-analysis, based on individual data from 912 patients who participated in one of 29 prospective clinical trials published between 2000 and 2016, reported a median PFS of 3.3 months and a 6-month PFS rate of 27%.[78] The median OS was 10.2 months and the 1-year OS rate was 43%. Elevated lactate dehydrogenase and alkaline phosphatase levels were the most significant prognostic factors for 6-month PFS and 1-year OS rates in a multivariate analysis. Liver-directed treatments were associated with significantly longer PFS and OS than other treatment modalities in this selected patient population.

The second meta-analysis, based on patient-level survival data for 2494 patients from 78 studies published between 1980 and 2017, reported a median OS of 1.07 years across all treatment modalities.[79] Most of the data came from small retrospective patient series and were subject to heterogeneity in terms of PS, number of lines of treatment, tumour burden and liver function.

ChT. Response rates are low (<10%) regardless of the cytotoxic agent tested and whether it was used as monotherapy or in combination. Drugs evaluated in this setting include dacarbazine, temozolomide, treosulfan, cisplatin and fotemustine,[92] with no demonstrated OS benefit over best supportive care.

Targeted agents. An interim analysis of a phase II trial (NCT03947385) evaluating darovasertib in combination with the mesenchymal-epithelial transition factor (c-MET) inhibitor crizotinib showed ORR of 31% in the first 35 assessable patients.[93] For more information on targeted therapies, see Supplementary Material Section 3, available at https://doi.org/10.1016/j.esmoop.2026.106888.

Immunotherapy. Patients with metastatic UM have been excluded from most trials evaluating ICIs in cutaneous melanoma.

In the absence of a standard of care, and because of the lack of available clinical trials, many patients with metastatic UM have received cytotoxic T-lymphocyte-associated antigen 4 inhibitors (ipilimumab, tremelimumab) or programmed cell death protein 1 (PD-1)/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab) alone or in combination, and at different dose schedules with liver-directed therapy or ChT, mostly in retrospective series.[94]

Although the safety profile of PD-1 inhibitors was better in UM compared with cutaneous melanoma, efficacy was comparatively disappointing, showing <5% ORR, median PFS of 3 months and 1-year OS ∼50%, likely due to low tumour mutational burden, poor antigen processing and presentation and the immune-suppressive tumour microenvironment in UM.[78,79] *MBD4*-deficient tumours may be sensitive to ICIs, making *MBD4* a potential predictive marker for response to ICIs in the 2% of germline *MBD4*-deficient patients with UM.[37]

In two phase II studies in 52 and 33 patients, respectively, nivolumab—ipilimumab was associated with ORR of 11% and 18%, median PFS of 3 and 5.5 months and median OS of 12 and 19 months, respectively, after a median follow-up of ∼13 months.[95,96] In the subgroup of 64 patients with metastatic UM from CheckMate 401, ORR was 9% and median OS was 15 months; nivolumab—ipilimumab was associated with 64% grade 3-4 TRAEs, leading to discontinuation in 30% of patients.[97]

Autologous T cells can be modified to target PRAME or antigens expressed across different tumour types, such as GD2; trials are ongoing in patients with UM (NCT02743611, NCT03635632). Peptide vaccines using dendritic cells are currently being investigated as single-agent therapy in a phase I trial that includes a UM cohort (NCT04335890).[98]

A randomised phase III trial compared tebentafusp, a T-cell receptor—bispecific molecule that targets glycoprotein 100 and cluster of differentiation 3, with investigator's choice (single-agent pembrolizumab, ipilimumab or dacarbazine) in 378 HLA-A*02:01-positive, previously untreated patients with metastatic UM.[23] Tebentafusp significantly improved OS (hazard ratio 0.51) despite a lack of improvement in PFS, with manageable toxicity. The median OS was 21.7 months with tebentafusp versus 16.9 months with investigator's choice. There was a survival benefit in patients treated with tebentafusp, with disease progression as best response compared with the control arm. In a recent update with a minimum follow-up of 36 months, the OS benefit of tebentafusp was confirmed (27% versus 18% with investigator's choice) and was associated with the reduction of circulating tumour DNA (ctDNA) from baseline, including total clearance.[99] Survival benefit was confirmed in real-life cohorts of patients with metastatic UM treated with tebentafusp.[100-102]

Tebentafusp has been approved by the FDA and the European Medicines Agency (EMA) as first-line systemic treatment in HLA-A*02:01-positive patients with metastatic UM. Evaluation as part of combination therapy in the metastatic setting in patients with molecularly relapsed disease (NCT05315258) and as adjuvant

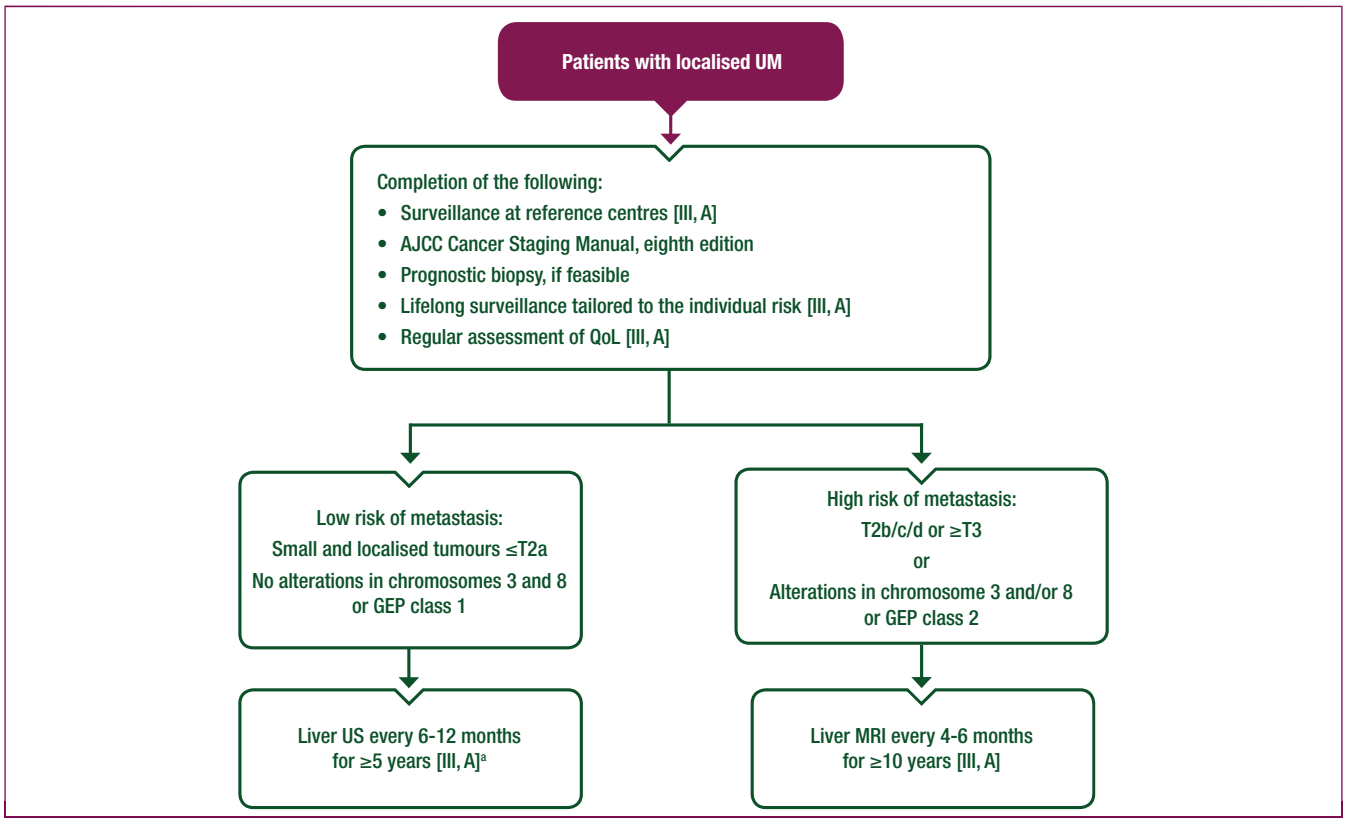

Figure 4. Risk-adapted surveillance in localised UM.
Purple: algorithm title; white: other aspects of management and non-treatment aspects.
AJCC, American Joint Committee on Cancer; GEP, gene expression profiling; MRI, magnetic resonance imaging; QoL, quality of life; US, ultrasound; UM, uveal melanoma.
[a]Liver MRI should be scheduled if any suspicious finding is detected [III, A].

treatment in high-risk patients (NCT06246149) are the next steps in the development of this practice-changing new class of therapy for UM. There is no consensus on first-line systemic therapy in HLA-A*02:01-negative patients with metastatic UM.

In the absence of randomised comparative studies, indirect comparisons of ICIs with tebentafusp in first-line metastatic UM have been conducted.[103] A propensity score analysis of two studies showed an OS benefit for tebentafusp versus nivolumab—ipilimumab (1-year OS rate of 73% versus 50%, respectively), independent of HLA status, and no significant difference in survival between pembrolizumab and nivolumab—ipilimumab (median OS and 1-year OS rate of 16.9 months and 60% versus 14.2 months and 52%, respectively).[103] Toxicity rates were higher with nivolumab—ipilimumab compared with pembrolizumab (23% versus 2%-5% treatment-related discontinuations and two versus no treatment-related deaths).[103] These results were confirmed in a population-level, match-adjusted indirect comparison of pooled patients treated with combined ICI or tebentafusp.[104]

Given the lack of a clear survival advantage in metastatic UM associated with nivolumab—ipilimumab versus pembrolizumab and the increased toxicity associated with the former, only selected patients fit enough for the combination and with predominant extrahepatic disease should be considered for the combination immunotherapy.[103]

IMC-F106C brenetafusp is a new bispecific molecule targeting PRAME and is currently being tested as a single agent and in combination with ICI (NCT04262466). Preliminary results showed durable objective responses by Response Evaluation Criteria in Solid Tumors (RECIST) and ctDNA responses in multiple tumour types, including metastatic UM.[105]

Palliative and supportive care

Early integration of palliative care is internationally recommended to facilitate the transition from curative to palliative care and to individualise the intensity of care for patients with cancer.[106] It may include psychological support, nutrition and palliative care support. This multidisciplinary strategy has demonstrated an improvement in quality of life (QoL) and survival in patients with advanced lung cancer.[107] In a review of seven randomised trials conducted in highly symptomatic patients with cancer, the early integration of palliative care improved QoL and symptom intensity but showed no difference in OS.[108]

Patients with metastatic UM develop late symptoms leading to rapid deterioration in the liver and overall QoL before death. The difference between a normal life in good health and the receipt of a short-term poor prognosis is a complex situation for patients, families and health care teams. An ongoing randomised, multicentre, phase III French study is investigating whether the early introduction

of supportive care has a positive impact on patients.[109] The study, which includes communication skills training for health care professionals and regular follow-up of patients' needs for any type of psychological, existential or physical symptoms, will enrol 162 patients with metastatic UM.[109]

Recommendations

Liver-directed treatment

- Patients with oligometastatic UM with metastases confined to the liver can be considered for surgical resection and/or local liver-directed therapies (thermal ablation with radiofrequency, cryoablation or microwave ablation) [IV, B]. SRT could be an alternative in patients not eligible for surgery or thermal ablation [IV, B].
  - The risk—benefit ratio of liver-directed strategies should be weighed in a multidisciplinary tumour board [IV, B].
- Preoperative MRI can be recommended as well as laparoscopy before or at the time of planned resection [IV, B].
- Patients with multifocal liver metastases confined to the liver should be considered for regional liver-directed therapies (PHP or IHP) [II, B].

Systemic treatment

- For HLA-A*02:01-positive patients, tebentafusp should be standard of care in the first-line metastatic setting unless liver-directed treatment modalities are required first for tumour debulking [I, A; ESMO-Magnitude of Clinical Benefit (ESMO-MCBS) v2.0 score: 3].
  - If these patients progress, liver-directed treatment modalities, anti-PD-1-based immunotherapies and clinical trial enrolment are the preferred therapeutic options [V, B].
- For HLA-A*02:01-negative patients, in the absence of a standard of care and depending on local resources, liver-directed therapies (PHP and IHP), anti-PD-1-based immunotherapies and clinical trial enrolment are the preferred therapeutic options [V, B].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

There is no consensus regarding the optimal methods of monitoring patients for the appearance of metastases after treatment of the ocular tumour.[110] There is no prospective evidence that imaging surveillance impacts the outcomes of patients with UM.[111,112]

Liver function tests have a low sensitivity and do not help detect early metastasis.[113] Hepatic US has a sensitivity of 96% in detecting liver metastasis from UM but the positive predictive value (PPV) is only 45%.[114,115] Gadolinium-enhanced liver MRI with diffusion-weighted sequences has demonstrated sensitivity of nearly 100% and specificity of 80%-99%, with a better ability to detect small lesions compared with US.[112,116,117] Few data exist on using FDG—PET—CT in systematic screening for metastasis. In case of suspected or proven liver metastases, FDG—PET—CT has a varying sensitivity of 41%-88%, which drops to 11% for small lesions detected by MRI,[116,118] and a PPV range of 88%-100%.[116,119] FDG—PET—CT may detect extrahepatic lesions but PPV is uncertain due to the high frequency of detection of a second cancer and/or concurrent benign lesions.[120,121] MRI outweighs PET—CT for detecting small liver metastases; PET—CT has been shown to miss 65% of liver lesions.[122]

Depending on local expertise and access to imaging modalities, clinical and genetic prognostic factors should be incorporated into the choice of surveillance methods. This may be challenging, as not all centres carry out molecular genetic testing, and some only do so on enucleation samples. The occurrence of late metastases in patients with specific risk profiles encourages a surveillance agenda tailored to chromosomal aberrations (see Figure 4).[123-125] An optimal surveillance scheme is yet to be established and is likely to be influenced by new knowledge on genetics and additional therapies.

Prognostication and surveillance should be led by a specialist MTB with UM expertise in ophthalmology, liver imaging, surgery, medical oncology and supportive care.[125]

All patients, regardless of their risk, should undergo a comprehensive assessment to evaluate the potential risks and benefits of entering into a surveillance programme. The discussion should include the emotional and organisational impact of this surveillance strategy as well as its frequency and duration.

QoL is affected by specific concerns, including recurrence and loss of the eye or visual impairment. These need to be considered by ophthalmologists and oncologists, who should provide appropriate care, including psychological support, as depressive symptoms are common after ocular tumour treatment.[126,127] The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire—Ophthalmic Cancer (QLQ-OPT30), has been developed to measure QoL in patients with UM.[128] Other studies focused on patient preference (NCT05377957) and information needs (NCT06073548) are recruiting.

Metastatic disease

Metastatic disease remains an area of high unmet need and requires ambitious research collaborations. Patients should have access to experimental treatments, including precision diagnostics and medicine and early-phase clinical trials for solid tumours. Particular attention should be paid to early access and/or compassionate use programmes and cross-border access to clinical trials with established reimbursement mechanisms to reduce the existing inequalities in access to innovative therapies. Research ranging from fundamental to translational to clinical, as well as implementation, is needed. The community should therefore strengthen its collaboration at the European level and beyond, with effective and harmonised structures for registries, biobanking and data exchange. Programmes for drug repurposing and open drug development should be explored.

Patient education and participation

Patient education should be evidence-based, verifiable and accessible to enable patients to seek the right information to improve communication with their health care team.[129]

Patient communities and organisations offer valuable support and information to patients, clinicians and other stakeholders, often identifying new developments and challenges through their broad networks (see Supplementary Section 4, available at https://doi.org/10.1016/j.esmoop.2026.106888). As most medical information is only available in English, they can also play an important role in disseminating information in local languages and reaching remote patient populations.

Recommendations

- Surveillance strategies should be managed at reference centres [III, A]. This should include input from ophthalmology, molecular genetics, liver imaging, oncology and supportive care to ensure patients receive comprehensive care specific to their risk profile [III, A].
- Genetic and clinical factors should be used to guide surveillance, as there is no standard approach to detecting metastases in patients with UM [III, A].
- Regular assessment of QoL, including the use of specific UM-related tools such as the EORTC QLQ-OPT30, is recommended to identify psychological support needs and ensure that patients receive holistic care tailored to their experiences and preferences [III, A].
- In low-risk patients, liver US every 6-12 months for $\geq$5 years is recommended; liver MRI should be scheduled if any suspicious finding is detected [III, A].
- In high-risk patients, liver MRI is recommended every 4-6 months for $\geq$10 years [III, A].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/guidelines/esmo-guidelines-methodology). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. ESMO-MCBS v2.0[130] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/guidelines/esmo-mcbs). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The ESMO-MCBS scores and corresponding scorecard links included in this CPG are correct at the time of publication. For the most up-to-date scores, please refer to the scorecard links in Supplementary Table S5 (available at https://doi.org/10.1016/j.esmoop.2026.106888). The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2026.106888.[131] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Guideline Updates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/melanoma-and-skin-cancers.

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