



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma: Uveal

Version 1.2025 — February 11, 2025

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Melanoma: Uveal

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Melanoma: Uveal

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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Melanoma: Uveal

Updates in Version 1.2025 of the NCCN Guidelines for Melanoma: Uveal from Version 1.2024 include:

UM-4

- Risk of Distant Metastasis
 - ▶ Low risk; 1st bullet revised: Class 1A or Class 1 PRAME (-)
 - ▶ Medium risk; 1st bullet revised: Class 1B or Class 1 PRAME (+)
- Footnote dd revised: Gene expression profile (GEP) class had a stronger independent association with metastasis than any other prognostic factor (P < .0001) (Onken MD, et al. Ophthalmology 2012;119:1596-1603). ~~Elevated expression of PRAME (PRAME+) could be a risk modifier for metastasis in patients with either Class 1 or Class 2 uveal melanoma.~~ PRAME expression is a marker for metastasis in Class 1 uveal melanoma tumors, and in Class 2 patients with PRAME expression may be associated with a shorter time to metastasis (Field MG, et al. Oncotarget 2016;7:59209-59219 Harbour JW, et al. J Clin Oncol 2024;42:3319-3329).
- Footnote ff revised: The most frequent site of metastasis is the liver; other sites include lungs, skin/soft tissue, and bones. For patients who elect to have surveillance imaging, options include: contrast-enhanced MRI (*most sensitive*), CT abdomen ± pelvis, or abdominal ultrasound of the liver, with modality preference determined by expertise at the treating institution. ~~Additional imaging modalities may include chest/abdomen/pelvis CT with contrast, or chest x-ray~~ Chest imaging can be done with CT chest without contrast, or chest x-ray.

UM-6

- After Workup, pathway bifurcations revised
 - ▶ Isolated liver metastases changed to *Hepatic-dominant disease*
 - ▶ Non-isolated liver metastases changed to *Non-hepatic-dominant disease*

UM-6A

- Footnote nn is new: The bulk of overall metastatic disease is confined to the liver.

UMSYS-1

- The following footnotes are new:
 - ▶ Footnote g: Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
 - ▶ Footnote h: Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.



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CLINICAL PRESENTATION^a

- Suspicious pigmented uveal tumor of ciliary body and/or choroid^b
 - ▶ Symptoms may include:
 - ◊ Vision loss
 - ◊ Vision changes (eg, blurred vision, photopsia, floaters, metamorphopsia)
 - ▶ May be asymptomatic
 - ▶ Assess risk factors for developing uveal melanoma^c

WORKUP AND DIAGNOSIS

- Clinical evaluation, including:
 - ▶ History and physical (H&P), including personal/family history of prior or current cancers (outside the eye)^b
 - ▶ Comprehensive eye exam: Examine the front and back of eye (biomicroscopy)
 - ◊ Perform dilated fundus exam (indirect ophthalmoscopy)
 - ◊ Measure visual acuity
 - ◊ Measure and document location and size of the tumor (diameter, thickness), distance from disc and fovea, and ciliary body involvement
 - ◊ Assess and document if present:
 - Subretinal fluid
 - Orange pigment
- Additional testing options include, but are not limited to:
 - ▶ Color fundus photography
 - ▶ Ocular ultrasound (including ultrasound biomicroscopy for anterior uveal or ciliary body lesion)
 - ▶ Autofluorescence of the ocular fundus
 - ▶ Optical coherence tomography
 - ▶ Retinal fluorescein angiography of the ocular fundus
 - ▶ Transillumination
 - ▶ MRI (with and without IV contrast) as clinically indicated to confirm diagnosis
- Consider biopsy if needed to confirm diagnosis^d or for prognostic analysis for risk stratification^e

CLINICAL STAGING

Diagnosis uncertain (especially for small tumors) and/or <3 risk factors for growth^f

- Observe and re-evaluate for growth or features of malignancy^g
 - ▶ Every 2–6 months^h as clinically indicated
 - ▶ Then close follow-up for 5 years^h
 - ▶ Then annually thereafter

Uveal melanoma (per clinical diagnostic criteria)

See Workup and Staging for uveal melanoma ([UM-2](#))

^a Referral to centers with expertise in the management of uveal melanoma is recommended.

^b This guideline does not include the management of iris melanoma.

^c [Risk Factors for Development of Uveal Melanoma \(UM-A\)](#).

^d Biopsy is usually not necessary for initial diagnosis of uveal melanoma and selection of first-line treatment, but may be useful in cases of uncertainty regarding diagnosis, such as for amelanotic tumors, or retinal detachment.

^e Biopsy of the primary tumor may provide additional prognostic information that can help inform frequency of follow-up and may be needed for eligibility for clinical trials. Biopsy is typically performed before the tumor is irradiated and can often be performed at the time of primary treatment depending on the procedure modality. If biopsy is performed, molecular/chromosomal testing for prognostication is preferred over cytology alone. The risks/benefits of biopsy for prognostic analysis should be carefully considered and discussed.

^f Risk factors for growth of small melanocytic tumors: presence of symptoms, tumor thickness >2 mm, tumor diameter >5 mm, presence of subretinal fluid and orange pigment, tumor margin within 3 mm of optic disc, and ultrasound hollowness. Documented growth may indicate progression to uveal melanoma ([UM-2](#)).

^g The recommendation to "observe and re-evaluate" consists of tests listed under "Workup and Diagnosis" that would help to clarify if there is progression and determine the natural history of the indeterminate lesion.

^h Frequency of evaluation should depend on index of suspicion, patient age, and medical frailty.

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WORKUP AND STAGING

- Ocular imaging if not previously done:
 - ▶ If large tumor, close to nerve or suspicion of extraocular involvement, MRI of orbit with and without IV contrastⁱ
- Consider biopsy of primary tumor for prognostic analysis^e
- Assess and document, if present:
 - ▶ Ciliary body involvement
 - ▶ Extraocular extension
- Extraocular imaging:
 - ▶ Baseline imaging to screen for distant diseaseⁱ

TUMOR SIZE

Largest diameter 5–19 mm^j
and thickness <2.5 mm

Largest diameter ≤19 mm^j
and thickness 2.5–10 mm

Largest diameter >19 mm^j
(any thickness)
or Thickness >10 mm (any
diameter)
or Thickness >8 mm with
optic nerve involvement
(any diameter)

Metastasis^k

PRIMARY TREATMENT^l

Options:

- Regular ophthalmologic follow-up in select patients^m
- Brachytherapy plaque^{n,o,p}
- Particle beam radiation^{n,p}
- Other options in highly select patients^{q,r}

Options:

- Brachytherapy plaque^{n,o,p,s}
- Particle beam radiation^{n,p,s}
- Enucleation^{t,u}

Options:

- Radiation therapy (RT)ⁿ
- Particle beam radiation^{n,p,s}
- Stereotactic radiosurgery (SRS)ⁿ
- Enucleation^{t,u}

Additional
Primary
Treatment
[\(UM-3\)](#)

[UM-6](#)

^l Clinical decisions should be informed by a variety of case-specific factors (eg, patient characteristics and preferences like age, status of the other eye, disease characteristics, and medical history), such that for some patients the best clinical approach may be other than one of the listed options, including clinical observation in select patients.

Note: All recommendations are category 2A unless otherwise indicated.

[Additional footnotes on UM-2A](#)



FOOTNOTES FOR [UM-2](#)

- ^e Biopsy of the primary tumor may provide additional prognostic information that can help inform frequency of follow-up and may be needed for eligibility for clinical trials. Biopsy is typically performed before the tumor is irradiated and can often be performed at the time of primary treatment depending on the procedure modality. If biopsy is performed, molecular/chromosomal testing for prognostication is preferred over cytology alone. The risks/benefits of biopsy for prognostic analysis should be carefully considered and discussed.
- ⁱ The most frequent site of metastasis is the liver; other sites include lungs, skin/soft tissue, and bones. At minimum, all patients should have contrast-enhanced MR or ultrasound of the liver, with modality preference determined by expertise at the treating institution. Additional imaging modalities may include chest/abdomen/pelvis CT with and without contrast. Scans should be performed with IV contrast unless contraindicated.
- ^j The cutoff for largest basal diameter depends on the dimensions of the largest brachytherapy plaque available, so may depend on the type of plaque and isotope selected if brachytherapy is used.
- ^k Patients may be considered for palliative local therapy to the primary tumor in the setting of metastatic disease. Patients who present with advanced metastatic disease and limited life expectancy may elect to have no treatment to their primary tumor.
- ^m For patients who meet the criteria for observation, regular ophthalmologic follow-up is recommended to re-evaluate for growth.
- ⁿ [Principles of Radiation Therapy \(UM-B\).](#)
- ^o [The plaque should cover the tumor with a \$\geq 2\$ mm circumferential margin. The exception is for tumors near the optic nerve where it may be impossible to achieve adequate coverage of the margins. The largest commercially available brachytherapy plaque is 23 mm in diameter; thus, plaque brachytherapy is recommended only for tumors with largest basal diameter \$\leq 19\$ mm and can be considered for select cases with tumors \$>10\$ mm in height.](#)
- ^p Brachytherapy with scleral patch graft or particle beam radiation for cases with limited extraocular extension.
- ^q Consider laser treatment or enucleation (per patient preference) for patients who are not good candidates for brachytherapy or particle beam radiation.
- ^r For small ciliary body tumors (less than 3 clock hours), surgical excision may be considered.
- ^s Consider additional treatment with resection, laser ablation, transpupillary thermotherapy, or cryotherapy if concerned that adequate response was not achieved from initial radiation.
- ^t While there is a trend toward avoiding enucleation, it is recommended for patients with neovascular glaucoma, tumor replacing $>50\%$ of globe, or blind, painful eyes. Consider enucleation in cases of extensive extraocular extension.
- ^u Pathologic evaluation should follow the uveal melanoma synoptic report recommendations by the College of American Pathologists.
Available at: <https://documents.cap.org/protocols/cp-uveal-melanoma-17protocol-4000.pdfv>

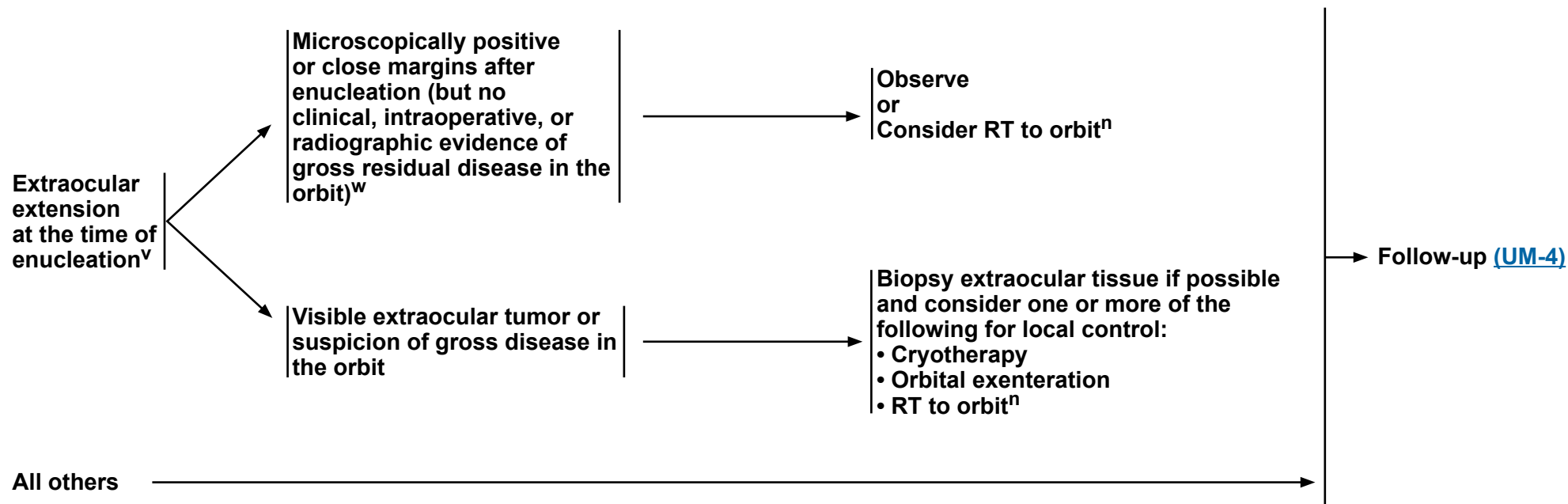
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ADDITIONAL PRIMARY TREATMENT



ⁿ [Principles of Radiation Therapy \(UM-B\)](#).

^v This is a relatively rare occurrence; data are limited for these recommendations.

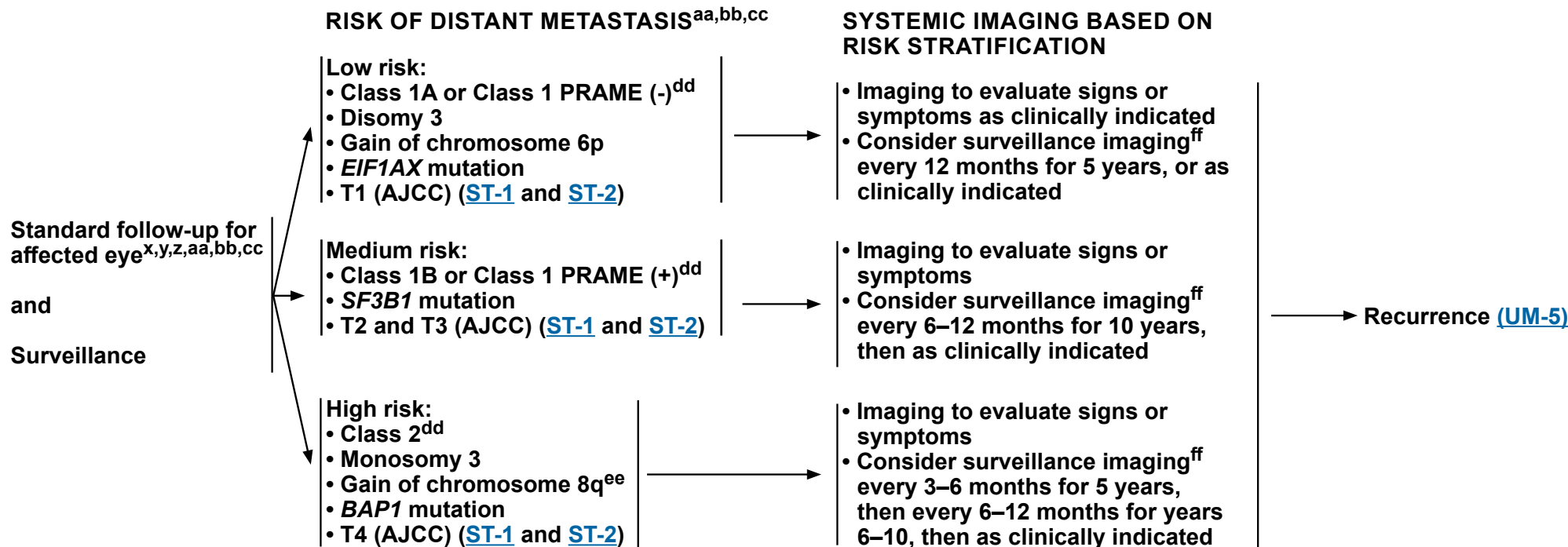
^w Consider orbital biopsy if clinically appropriate.

Note: All recommendations are category 2A unless otherwise indicated.



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^{bb} Risk stratification to determine the frequency of follow-up should be based on the highest risk factor present.

^x The affected eye should be imaged with color fundus photography and ultrasonography every 3–6 months for 3–5 years, then every 6–12 months thereafter, if stable. Serial orbital MRI may be used as clinically indicated. The frequency of follow-up should depend on the size and location (eg, juxtapapillary location, ciliary body involvement) of the tumor at presentation. Radiation-related retinopathy and other treatment-related complications may occur at any time following treatment.

^y The contralateral eye is not at increased risk of uveal melanoma, and should be followed with routine ophthalmologic care including routine eye protection for the remaining eye (eg, polycarbonate glasses).

^z Liver function tests (LFTs) may be considered as part of follow-up, although some studies showed poor sensitivity for early detection of liver metastases.

^{aa} If biopsy is not performed, then follow medium- or high-risk pathways depending on whether any high-risk features are present.

^{cc} Additional risk factors for recurrence: juxtapapillary location and ciliary body involvement.

^{dd} Gene expression profile (GEP) class had a stronger independent association with metastasis than any other prognostic factor ($P < .0001$) (Onken MD, et al. Ophthalmology 2012;119:1596-1603). PRAME expression is a marker for metastasis in Class 1 uveal melanoma tumors, and in Class 2 patients with PRAME expression may be associated with a shorter time to metastasis (Harbour JW, et al. J Clin Oncol 2024;42:3319-3329).

^{ee} 8q gain, especially when numerous copies are found, portends greater risk for metastasis.

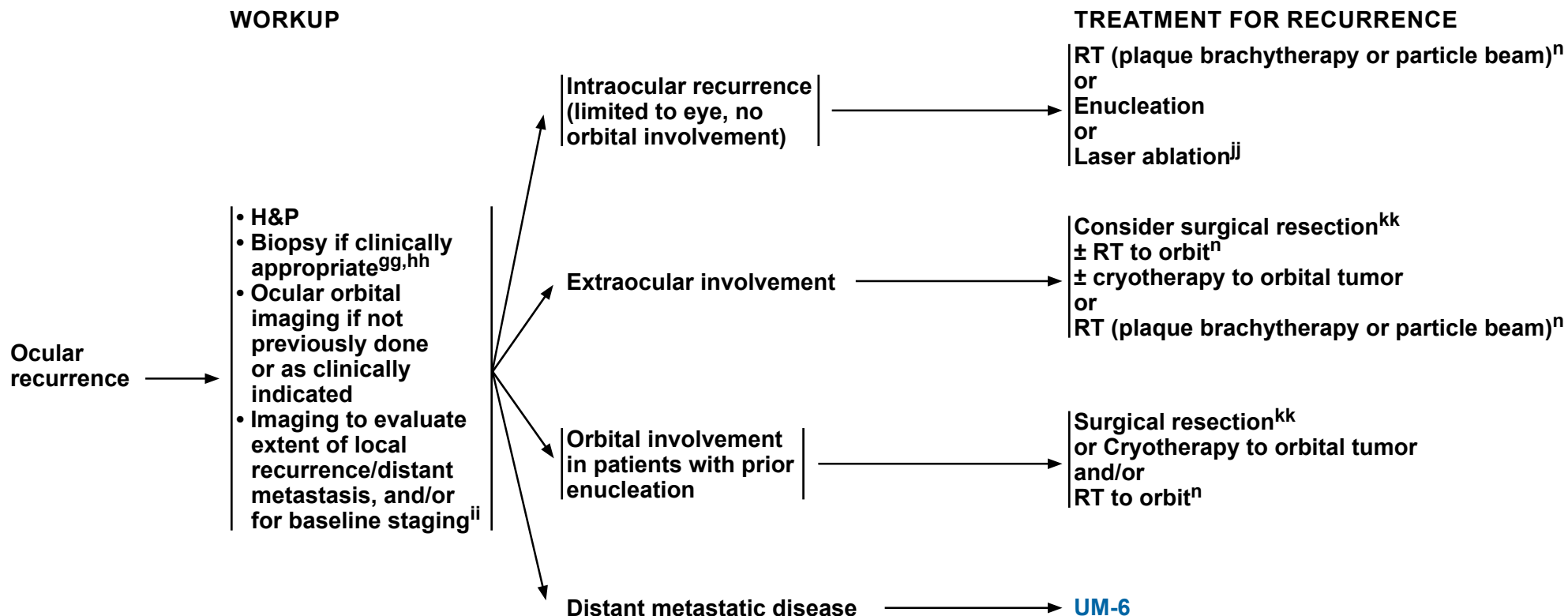
^{ff} The most frequent site of metastasis is the liver; other sites include lungs, skin/soft tissue, and bones. For patients who elect to have surveillance imaging, options include: contrast-enhanced MRI (most sensitive), CT abdomen ± pelvis, or abdominal ultrasound, with modality preference determined by expertise at the treating institution. Chest imaging can be done with CT chest without contrast, or chest x-ray.

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ⁿ [Principles of Radiation Therapy \(UM-B\)](#).

^{gg} Extraocular recurrence or metastasis should be confirmed histologically whenever possible or if clinically indicated. Biopsy techniques may include core needle biopsy, if possible, or otherwise fine-needle aspiration (FNA). Consider genetic testing if it might affect treatment options.

^{hh} Intraocular recurrence can often be diagnosed and managed without a biopsy. Additional prognostic FNA biopsy may be valuable.

ⁱⁱ The most frequent site of metastasis is the liver; other sites include lungs, skin/soft tissue, and bones. Modalities of choice for detection of metastasis are CT chest/abdomen/pelvis with IV iodinated contrast, CT chest with or without IV contrast, and MRI abdomen with IV gadolinium-based contrast or whole-body FDG-PET/CT. In select patients with renal failure and/or iodinated contrast allergy, MR abdomen with gadolinium-based contrast is the preferred imaging study over CT. If no IV contrast can be administered, MR without contrast is superior to non-enhanced CT. Ultrasound evaluation of the liver can be used in select patients; however, it has limited value given its operator-dependent nature, limited sensitivity in patients with obesity, and lack of specificity. Brain MRI with IV contrast may be performed if neurologic symptoms are present, but routine central nervous system (CNS) imaging is not recommended. Abdominal imaging should be performed with IV contrast unless contraindicated.

^{jj} For small recurrences in patients who cannot undergo RT or surgery, transpupillary thermotherapy is recommended.

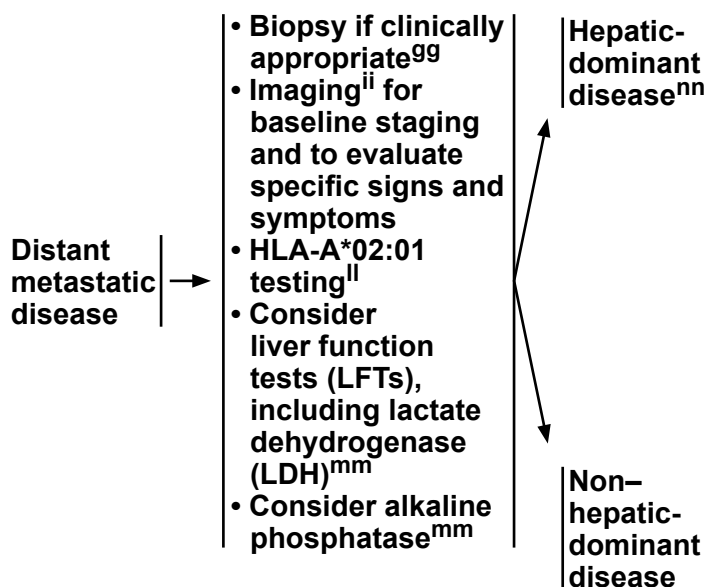
^{kk} Surgical resection may potentially include partial orbital tumor resection, enucleation, or exenteration.

Note: All recommendations are category 2A unless otherwise indicated.

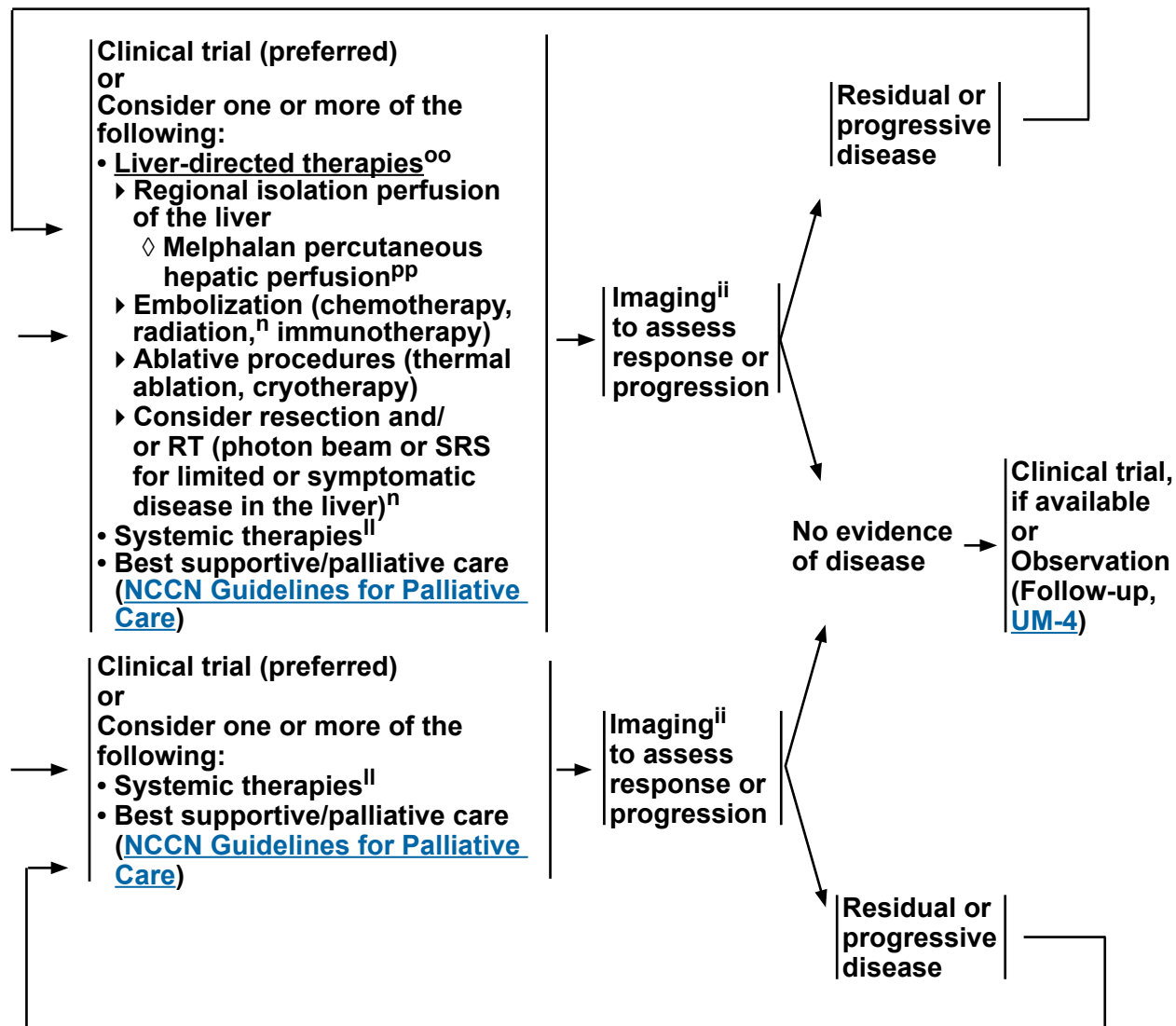
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WORKUP



TREATMENT OF METASTATIC DISEASE



[Footnotes on UM-6A](#)

Note: All recommendations are category 2A unless otherwise indicated.



FOOTNOTES FOR [UM-6](#)

ⁿ [Principles of Radiation Therapy \(UM-B\)](#).

⁹⁹ Extraocular recurrence or metastasis should be confirmed histologically whenever possible or if clinically indicated. Biopsy techniques may include core needle biopsy, if possible, or otherwise FNA. Consider genetic testing if it might affect treatment options.

ⁱⁱ The most frequent site of metastasis is the liver; other sites include lungs, skin/soft tissue, and bones. Modalities of choice for detection of metastasis are CT chest/abdomen/pelvis with IV iodinated contrast, CT chest with or without IV contrast, and MRI abdomen with IV gadolinium-based contrast or whole-body FDG-PET/CT. In select patients with renal failure and/or iodinated contrast allergy, MR abdomen with gadolinium-based contrast is the preferred imaging study over CT. If no IV contrast can be administered, MR without contrast is superior to non-enhanced CT. Ultrasound evaluation of the liver can be used in select patients; however, it has limited value given its operator-dependent nature, limited sensitivity in patients with obesity, and lack of specificity. Brain MRI with IV contrast may be performed if neurologic symptoms are present, but routine CNS imaging is not recommended. Abdominal imaging should be performed with IV contrast unless contraindicated..

^{ll} A phase III randomized trial was conducted in previously untreated HLA-A*02:01-positive, metastatic uveal melanoma. Patients were randomized to receive tebentafusp-tebn (a bispecific protein) or investigator's choice of either pembrolizumab, ipilimumab, or dacarbazine. Treatment with tebentafusp-tebn resulted in longer overall survival (OS) compared to control therapy. Agents that are effective for metastatic cutaneous melanoma may be used as first-line therapy for HLA-A*02:01-negative disease and after disease progression with first-line use of tebentafusp-tebn for HLA-A*02:01-positive disease. If disease is confined to the liver, regional therapies such as chemoembolization, radioembolization, or immunoembolization should be considered. Since tebentafusp-tebn response rates are low, symptomatic patients may be better palliated by liver-directed treatment first or their disease may respond better to ipilimumab/nivolumab. See [Systemic Therapy for Metastatic or Unresectable Disease \(UMSYS-1\)](#).

^{mm} LDH and alkaline phosphatase may assist in determining prognosis in the setting of uveal melanoma (Khoja L, et al. Ann Oncol 2019;30:1370-1380).

ⁿⁿ The bulk of overall metastatic disease is confined to the liver.

^{oo} Liver-directed therapies have efficacy largely in hepatic-dominant metastatic uveal melanoma and are thus recommended only in this setting.

^{pp} Melphalan percutaneous hepatic perfusion was tested in patients with hepatic-dominant metastatic uveal melanoma with <50% liver involvement and was associated with a 36.6% response rate in a 91-patient phase II trial, and with improved response rate (36.3% vs. 12.5%) and median PFS (9 vs. 3.1 months) compared with best alternative care in a phase III trial (n = 123 treated). Median OS was similar (19.3 vs. 14.5 months, *P* = .14). Overnight stay in intensive care unit is recommended for hemodynamic monitoring; this therapy is recommended only at experienced centers. Prescribing information is available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/201848s000lbl.pdf. (Hughes MS, et al. Ann Surg Oncol 2016;23:1309-1319; Olofsson Bagge R, et al. J Clin Oncol 2023;41:3042-3050)

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE^{a,b}

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none">• When available and clinically appropriate, enrollment in a clinical trial is recommended.• Tebentafusp-tebn in patients who are HLA-A*02:01-positive (category 1)^c• Immune checkpoint inhibitors^{d,e}<ul style="list-style-type: none">▶ Nivolumab/ipilimumab^{f,g}	<ul style="list-style-type: none">Immune checkpoint inhibitors^{d,e}<ul style="list-style-type: none">• Ipilimumab• Anti-PD-1 monotherapy<ul style="list-style-type: none">▶ Pembrolizumab▶ Nivolumab^h	<ul style="list-style-type: none">Consider one or more of the following options:• Cytotoxic regimens<ul style="list-style-type: none">▶ Dacarbazine▶ Temozolomide▶ Paclitaxel▶ Albumin-bound paclitaxel▶ Carboplatin/paclitaxel• Targeted therapy^{i,j}<ul style="list-style-type: none">▶ Trametinib

^a The order of listed systemic therapies in a given section does not reflect order of preference. The choice of treatment is based on evaluation of the individual patient, which includes patient characteristics, disease presentation, health system resources/experience, and patient preference.

^b Referral to centers with expertise in the management of uveal melanoma is recommended.

^c A phase III randomized trial was conducted in previously untreated HLA-A*02:01-positive, metastatic uveal melanoma. Patients were randomized to receive tebentafusp-tebn (a bispecific protein) or investigator's choice of either pembrolizumab, ipilimumab, or dacarbazine. Treatment with tebentafusp-tebn resulted in longer OS compared to control therapy. Agents that are effective for metastatic cutaneous melanoma may be used as first-line therapy for HLA-A*02:01-negative disease and after disease progression with first-line use of tebentafusp-tebn for HLA-A*02:01-positive disease. If disease is confined to the liver, regional therapies such as chemoembolization, radioembolization, or immunoembolization should be considered. Since tebentafusp-tebn response rates are low, symptomatic patients may be better palliated by liver-directed treatment first ([UM-6](#)) or their disease may respond better to ipilimumab/nivolumab.

^d Immune checkpoint inhibitors have inferior activity in uveal melanoma compared with cutaneous melanoma, though may still produce durable benefit in a minority of patients. Small prospective or retrospective studies have shown response rates of 0%–5% for anti-programmed cell death protein 1 (PD-1) or ipilimumab monotherapy, and 5%–20% for nivolumab 1 mg/kg and ipilimumab 3 mg/kg. No prospective studies have demonstrated differences in OS between immune checkpoint inhibitor regimens.

^e [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

^f Studies of nivolumab/ipilimumab have used a dose of nivolumab 1 mg/kg and ipilimumab 3 mg/kg; it is unknown whether other dosing regimens (ie, nivolumab 3 mg/kg and ipilimumab 1 mg/kg) are equally effective in uveal melanoma.

^g Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

^h Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

ⁱ See Management of Toxicities Associated with Targeted and Immune Therapies in the [NCCN Guidelines for Melanoma: Cutaneous](#).

^j The listed systemic therapy options do not cover *BRAF*- or *KIT*-mutated tumors. In general, uveal melanomas rarely have *BRAF* or *KIT* mutations.

Note: All recommendations are category 2A unless otherwise indicated.

References



SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

REFERENCES

Immunotherapy

Tebentafusp-tebn for HLA A*02:01-positive tumors

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Note: All recommendations are category 2A unless otherwise indicated.



NCCN Guidelines Version 1.2025

Melanoma: Uveal

RISK FACTORS FOR DEVELOPMENT OF UVEAL MELANOMA

- Patients with the following risk factors are at increased risk of developing uveal melanoma:
 - Choroidal nevi^a
 - Ocular/oculodermal melanocytosis (hyperpigmentation of episclera, uvea, and skin)
 - Familial uveal melanoma (eg, germline mutations in *BAP1*, *PALB-2*, or *MBD4*)¹⁻⁷
 - Light skin color, propensity to sunburn, and/or light eye (iris) color⁸
 - Strong personal or family history of cancer^b
 - Occupational history of welding⁹
- The presence of cutaneous melanoma does not increase the risk of uveal melanoma. Among patients with cutaneous melanoma, routine screening for uveal melanoma is not required.

^a Risk factors for growth of small melanocytic tumors: presence of symptoms, tumor thickness >2 mm, tumor diameter >5 mm, presence of subretinal fluid and orange pigment, tumor margin within 3 mm of optic disc, and ultrasound hollowness. Documented growth may indicate progression to uveal melanoma ([UM-2](#)).

^b Evaluate for evidence of hereditary syndrome and refer for genetic counseling and testing if indicated:

- Early age of diagnosis (<30 years of age)
- History of other primary cancers in the patient
- Family or personal history of other cancers known to be associated with a hereditary syndrome:
- *BRCA*, *PALB2*: breast, ovarian, or pancreatic cancers
- *BAP1*: Mesothelioma, cutaneous melanoma, renal cell carcinoma, basal cell carcinoma, hepatocellular carcinoma, cholangiocarcinoma, or meningioma¹

Note: All recommendations are category 2A unless otherwise indicated.

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Melanoma: Uveal

RISK FACTORS FOR DEVELOPMENT OF UVEAL MELANOMA REFERENCES

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Note: All recommendations are category 2A unless otherwise indicated.



NCCN Guidelines Version 1.2025

Melanoma: Uveal

PRINCIPLES OF RADIATION THERAPY

Plaque Brachytherapy

• Treatment Information

- ▶ Plaque brachytherapy is a common form of definitive radiotherapy for the primary tumor.¹ A prospective trial found no difference in cause-specific survival among patients with tumors 2.5–10 mm in apical height (2.5–8 mm if peripapillary) and ≤16 mm in maximum basal diameter randomized to plaque brachytherapy or enucleation.²
- ▶ Plaque brachytherapy is appropriate for patients with tumors ≤19 mm^a in largest basal diameter and ≤10 mm in thickness. It may be used selectively in patients with larger tumors.
- ▶ Plaque brachytherapy is appropriate as an upfront therapy after initial diagnosis, or after local recurrence following a prior local therapy.
- ▶ Plaque brachytherapy should be performed by an experienced multidisciplinary team including an ophthalmic oncologist, radiation oncologist, and brachytherapy physicist.³
- ▶ Tumor localization for brachytherapy may be performed using indirect ophthalmoscopy, transillumination, light pipe diathermy, and/or ultrasound (intraoperative and/or preoperative).⁴ MRI or CT may be used for preoperative planning.
- ▶ Round or custom plaques are most commonly used. Custom plaques, such as notched plaques, are commonly used for tumors in specific locations (peripapillary).

• Treatment Dosing Information

- ▶ Using iodine-125 Collaborative Ocular Melanoma Study (COMS) plaques, 85 Gy should be prescribed to the tumor apex at low dose-rate (≥0.6 Gy/h). Dose adjustments may need to be made for non-COMS plaques.⁵⁻⁷ The plaque margin on the tumor border should be ≥2 mm when feasible (diameter of plaque ≥4 mm larger than largest basal diameter of tumor). The exception is for tumors near the optic nerve where it may be impossible to achieve adequate coverage of the margins. The largest commercially available brachytherapy plaque is 23 mm^a in diameter; thus, plaque brachytherapy is recommended only for tumors with largest basal diameter ≤19 mm.
- ▶ Using other radioisotopes (eg, ruthenium-106, palladium-103, strontium-90, cobalt-60, cesium-131), or non-COMS iodine-125 plaques, 60–100 Gy may be prescribed at low dose-rate to the tumor apex; alternatively, a minimum dose may be prescribed to the tumor base. The plaque margin on the tumor border may vary for other radioisotopes.

^a The cutoff for largest basal diameter depends on the dimensions of the largest brachytherapy plaque available, so may depend on the type of plaque and isotope selected if brachytherapy is used.

Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines Version 1.2025

Melanoma: Uveal

PRINCIPLES OF RADIATION THERAPY

Particle Beam Therapy

• Treatment Dosing Information

- ▶ Particle beam therapy is a common form of definitive radiotherapy for the primary tumor.¹ A prospective trial found no difference in cause-specific survival among patients with tumors ≤15 mm in maximum basal diameter and ≤11 mm in apical height randomized to plaque brachytherapy or particle beam therapy.⁸
- ▶ Particle beam therapy is appropriate as upfront therapy after initial diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence.
- ▶ Particle beam therapy should be performed by an experienced multidisciplinary team including an ophthalmic oncologist, radiation oncologist, and particle beam physicist.⁹
- ▶ Tumor localization for particle beam therapy may be performed using indirect ophthalmoscopy, transillumination, and/or ultrasound (intraoperative and/or preoperative), MRI, and/or CT.
- ▶ For intraocular tumors:
 - ◊ Using protons, 50–70 cobalt Gray equivalent (CGyE) in 4–5 fractions should be prescribed to encompass the planning target volume surrounding the tumor.^{9-11,b}
 - ◊ Using carbon ions, 60–85 CGyE in 5 fractions should be prescribed to encompass the planning target volume surrounding the tumor.¹²
 - ◊ Fiducial markers (tantalum clips) are encouraged to permit eye and tumor position verification for image-guided radiotherapy delivery.
 - ◊ Volumetric planning in 3 dimensions (with or without CT and/or MRI) is encouraged to maximize radiation delivery to tumor and minimize radiation delivery to organs and tissues at risk of injury from radiation.

Proton Beam Therapy

- Tumor localization for proton beam therapy may be performed by indirect ophthalmoscopy, transillumination, and/or ultrasound (intraoperative or postoperative but before proton beam), x-ray, MRI, and/or CT.¹³

^b The prospective trial showing no difference in local control for 50 CGyE and 70 CGyE in 5 fractions was for tumors <15 mm in diameter and <5 mm in height and near the optic disc or macula (within 4 disc diameters of either structure) (Gragoudas ES, Lane AM, Regan S, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. Arch Ophthalmol 2000;118:773-778).

Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines Version 1.2025

Melanoma: Uveal

PRINCIPLES OF RADIATION THERAPY

Stereotactic Radiosurgery (SRS)

• Treatment Information

- ▶ SRS is the least often used form of definitive radiotherapy for the treatment of primary or recurrent intraocular tumors.^{14,15}
- ▶ Few prospective studies have assessed the efficacy and safety of radiosurgery.^{16,17}
- ▶ Tumor localization, fiducial marker use, and planning for SRS are generally consistent with particle beam therapy approaches.

• Treatment Dosing Information

- ▶ Using fractionated SRS: 45–70 Gy in 2–5 fractions should be prescribed.
- ▶ Using single-fraction SRS: 18–45 Gy in 1 fraction should be prescribed.

Photon Beam Radiotherapy

• Treatment/Dosing Information

- ▶ Photon beam radiotherapy is a preferred option as an adjuvant to surgery for orbital involvement.
 - ◊ Adjuvant radiotherapy can be used in patients at risk for local recurrence (margin-positive enucleation or exenteration) or regional recurrence (resected regional metastases).
 - Adjuvant RT Dosing
 - A dose of 20–30 Gy in 5 fractions should be prescribed to the clinical target volume at risk for recurrence^{18,19} using intensity-modulated RT (IMRT) with image guidance.
- ▶ For symptom palliation, photon beam radiotherapy can be used for treatment of distant metastases at risk for causing symptoms or for palliation of symptomatic distant metastases.
 - RT Dosing for Distant Metastases
 - Doses of 8–30 Gy in 1–10 fractions should be prescribed to the appropriate target volume²⁰ using appropriate 3D or IMRT techniques with or without image guidance.
 - For ablative therapy of oligometastases, doses of 16–24 Gy/1 fraction or 24–60 Gy/2–8 fractions should be prescribed to the appropriate target volume using appropriate stereotactic body RT (SBRT) techniques with image guidance.^{21–24}

Radioembolization

- Selective internal RT for patients with liver metastases using yttrium-90 has been reported in retrospective studies and in one prospective study.^{25,26}
- Further study is required to determine the appropriate patients for and risks and benefits of this approach.

[References](#)

Note: All recommendations are category 2A unless otherwise indicated.



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Note: All recommendations are category 2A unless otherwise indicated.



NCCN Guidelines Version 1.2025

Melanoma: Uveal

American Joint Committee on Cancer (AJCC) Definitions of TNM for Choroidal and Ciliary Melanoma (8th ed., 2017)

Table 1. Definitions for T, N, M **Choroidal and Ciliary Body Melanomas**

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor size category 1
T1a	Tumor size category 1 without ciliary body involvement and extraocular extension
T1b	Tumor size category 1 with ciliary body involvement
T1c	Tumor size category 1 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
T1d	Tumor size category 1 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T2	Tumor size category 2
T2a	Tumor size category 2 without ciliary body involvement and extraocular extension
T2b	Tumor size category 2 with ciliary body involvement
T2c	Tumor size category 2 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
T2d	Tumor size category 2 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T3	Tumor size category 3
T3a	Tumor size category 3 without ciliary body involvement and extraocular extension
T3b	Tumor size category 3 with ciliary body involvement
T3c	Tumor size category 3 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
T3d	Tumor size category 3 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T4	Tumor size category 4
T4a	Tumor size category 4 without ciliary body involvement and extraocular extension
T4b	Tumor size category 4 with ciliary body involvement
T4c	Tumor size category 4 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
T4d	Tumor size category 4 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T4e	Any tumor size category with extraocular extension >5 mm in largest diameter

Notes

1. Primary ciliary body and choroidal melanomas are classified according to the four tumor size categories defined in Figure 1. ([ST-3](#))
2. In clinical practice, the largest tumor basal diameter may be estimated in optic disc diameters (DD; average: 1 DD = 1.5 mm), and tumor thickness may be estimated in diopters (average: 2.5 diopters = 1 mm). Ultrasonography and fundus photography are used to provide more accurate measurements.
3. When histopathologic measurements are recorded after fixation, tumor diameter and thickness may be underestimated because of tissue shrinkage.

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Melanoma: Uveal

American Joint Committee on Cancer (AJCC) Definitions of TNM for Choroidal and Ciliary Melanoma (8th ed., 2017)

Table 1. Definitions for T, N, M (continued)

N Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node metastases or discrete tumor deposits in the orbit
N1a	Metastasis in one or more regional lymph node(s)
N1b	No regional lymph nodes are positive, but there are discrete tumor deposits in the orbit that are not contiguous to the eye (choroidal and ciliary body).

M Distant Metastasis

M0	No distant metastasis by clinical classification
M1	Distant metastasis
M1a	Largest diameter of the largest metastasis ≤3.0 cm
M1b	Largest diameter of the largest metastasis 3.1–8.0 cm
M1c	Largest diameter of the largest metastasis ≥8.1 cm

G Histologic Grade

GX	Grade cannot be assessed
G1	Spindle cell melanoma (>90% spindle cells)
G2	Mixed cell melanoma (>10% epithelioid cells and <90% spindle cells)
G3	Epithelioid cell melanoma (>90% epithelioid cells)

Note: Because of the lack of universal agreement regarding which proportion of epithelioid cells classifies a tumor as mixed or epithelioid, some ophthalmic pathologists currently combine grades 2 and 3 (non-spindle, ie, epithelioid cells detected) and contrast them with grade 1 (spindle, ie, no epithelioid cells detected).

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Table 2. AJCC Prognostic Stage Groups

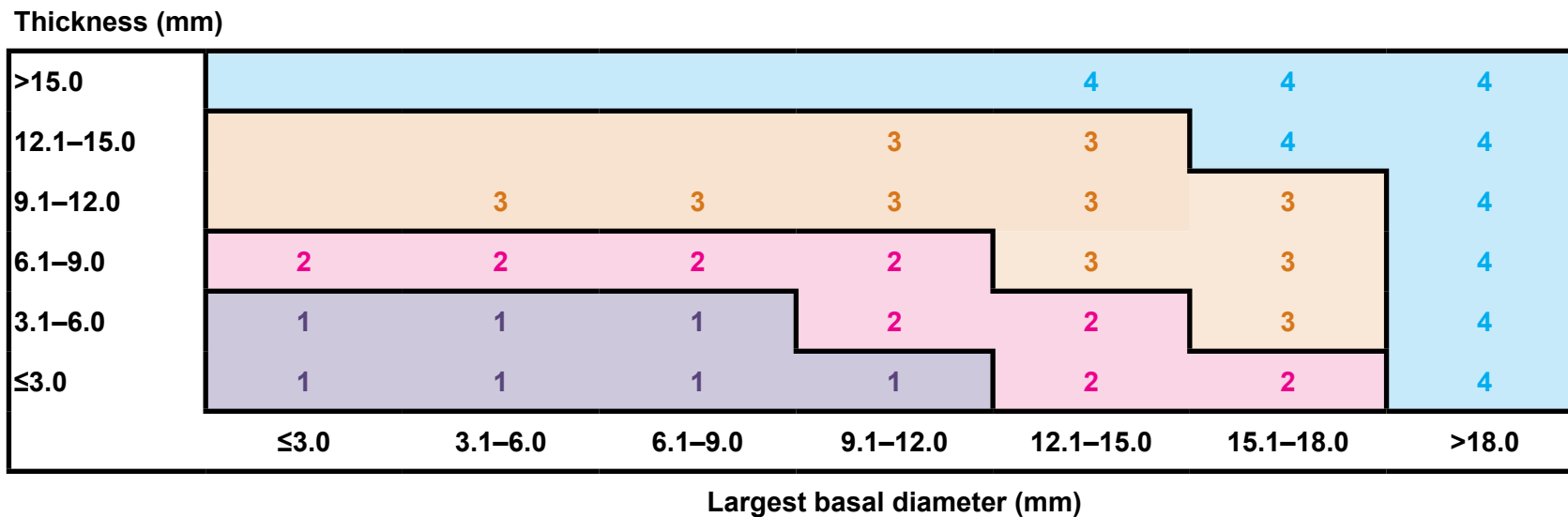
	T	N	M
Stage I	T1a	N0	M0
Stage IIA	T1b-d	N0	M0
	T2a	N0	M0
Stage IIB	T2b	N0	M0
	T3a	N0	M0
Stage IIIA	T2c-d	N0	M0
	T3b-c	N0	M0
	T4a	N0	M0
Stage IIIB	T3d	N0	M0
	T4b-c	N0	M0
Stage IIIC	T4d-e	N0	M0
Stage IV	Any T	N1	M0
	Any T	Any N	M1a-c



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Melanoma: Uveal

Figure 1: Classification of Ciliary Body and Choroid Uveal Melanoma Based on Thickness and Diameter



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ABBREVIATIONS

CGyE	cobalt Gray equivalent
COMS	Collaborative Ocular Melanoma Study
CNS	central nervous system
FDG	fluorodeoxyglucose
FNA	fine-needle aspiration
GEP	gene expression profiling
H&P	history and physical
IMRT	intensity-modulated radiation therapy
LDH	lactate dehydrogenase
LFT	liver function test
PD-1	programmed cell death protein 1
SBRT	stereotactic body radiation therapy
SRS	stereotactic radiosurgery



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Melanoma: Uveal

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.



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Melanoma: Uveal

Discussion

This discussion corresponds to the NCCN Guidelines for Melanoma: Uveal. Last updated: April 5th, 2022.

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Overview

Uveal melanoma is the most common type of primary intraocular malignancy in adults, with new cases occurring in 5 to 10 people per million per year.¹⁻⁹ Uveal melanomas can arise anywhere in the uveal tract, with less than 75% arising in the choroid, and the remainder arising in the iris or ciliary body.^{1,3,6,10,11}

The distribution of uveal melanoma by sex, race, and geography differs from that of cutaneous melanoma.^{1,3,12} Most uveal melanomas are localized at first presentation, and only a small percentage of cases present with metastases (<3%).^{6,12-16} Risk of metastasis varies by stage at presentation, with 5-year risk of metastasis ranging from 3% to 5% for stage I to 44% or greater for stage III.^{10,15} Large population-based analyses have reported disease-specific survival (DSS) between 70% to 81% at 5 years.^{2,5,6,12,14,15,17-20} For those with early-stage disease (stage I–II), 5-year DSS is 85% or better.^{15,17,20} For those with distant metastatic disease, most studies report estimated 5-year survival of less than 20%,^{15,17,21-24} which has not improved over the past few decades.²⁵

These NCCN Guidelines include recommendations for management of melanomas arising in the choroid or ciliary body. Recommendations for iris melanomas are not included in these guidelines, because iris melanomas are rare (3%–5% of uveal melanomas),^{3,10,11,26,27} have a low rate of systemic metastasis (~5% at 5 years compared with 15%–20% for ciliary body or choroidal melanomas),^{28, 10,29-32} have a better prognosis than other types of uveal melanoma,^{27,32} have a different AJCC staging system,³³ and have a different molecular signature.³⁴⁻³⁸ Treatments for iris melanoma may differ from other types of uveal melanoma due to these factors, as well as anatomic considerations, ease of resection,³⁹⁻⁴² and the negative effects of radiation to the iris.⁴³⁻⁴⁸ Moreover, patients with iris melanomas were excluded from many of the large randomized trials that inform treatment recommendations for uveal melanomas.^{16,49,50}

The patterns of presentation and prognosis for uveal melanoma are different from cutaneous melanoma. The AJCC Staging Manual 8th Edition includes separate staging systems for cutaneous, uveal, and conjunctival melanoma.³³ The staging system for uveal melanoma is further subdivided into separate T-staging for iris versus choroidal or ciliary body melanoma.³³ Each of these staging systems is based on survival data from large epidemiologic studies, with more data independently validating the staging system for melanoma of the choroid and ciliary body^{14,15,20} compared with the iris³¹ or conjunctiva.^{51,52}

Cutaneous, uveal, and conjunctival melanomas also have different molecular signatures.^{36,53-63} Whereas *BRAF*, *NRAS*, *KIT*, and *TERT* promoter mutations are extremely rare in uveal melanoma,^{36,53-56,62,64,65} they are more common in conjunctival and cutaneous melanomas.⁵⁷⁻⁶³ Molecular markers common in uveal melanomas that may have prognostic significance are not often found in conjunctival or cutaneous melanoma. These include chromosomal abnormalities (particularly chromosomes 3 and 8),^{14,66-70} and mutations in *GNAQ* or *GNA11* (>80% of uveal cases),^{36,53,68,71,72} *BAP1*,^{73,74} *SF3B1*, and *EIFAX*.^{38,75,76}



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Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Melanoma: Uveal, an electronic search of the PubMed database was performed to obtain key literature using the following search term: uveal melanoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.⁷⁷

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Risk Factors for Uveal Melanoma

Choroidal Nevi

Large population-based studies have found that choroidal nevi occur in 1.9% to 6.5% of the population, depending on the population studied.⁷⁸⁻⁸⁰ Choroidal nevi can transform into choroidal melanoma,^{81,82} and one study reported that of uveal melanomas diagnosed, 8% arose from a previously documented nevus.⁸¹ Others have argued that the fraction of uveal melanomas that arise from nevi may in fact be much higher, as many patients diagnosed with uveal melanoma have not had an ophthalmologic exam for many years.⁸³ The rate of transformation from nevi to uveal melanoma is an issue of much debate.^{79,84-90} Besides, choroidal nevi can be difficult to distinguish from choroidal melanoma, as there is evidence that many small lesions presumed to be nevi may actually be melanoma.^{91,92} Due to uncertainty regarding uveal melanoma diagnosis, studies have looked at the likelihood of lesion growth in patients with untreated melanocytic choroidal lesions ([Table 1](#)).^{93,86,87,94-100} Documented growth has been correlated with progression to uveal melanoma⁹⁴ and risk of metastasis,⁹⁴ even though some growing choroidal nevi do not undergo malignant transformation.^{86,93,97,98,101,102} It is important to note that for patients with small lesions presumed to be nevi or indeterminate, who are observed and treated upon evidence of transformation, the risk of metastasis and death is low.^{87,94,98} However, these risks increase with increasing baseline tumor size.⁸⁷ Patient characteristics that increase the likelihood of choroidal nevi growth or choroidal/ocular melanoma include Birt-Hogg-Dubé syndrome,^{103,104} myotonic dystrophy,¹⁰⁵⁻¹⁰⁷ and immunocompromise.^{108,109}

Ocular/Oculodermal Melanocytosis

The rate of ocular/oculodermal melanocytosis, which causes hyperpigmentation of the episclera, uvea, and skin, is much higher in patients with uveal melanoma than in the general population.¹¹⁰⁻¹¹⁵



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Familial Uveal Melanoma

Although only a small percentage of patients with uveal melanoma have at least one family member with uveal melanoma,^{116,117} this rate is higher than would be expected, given the very low incidence of uveal melanoma in the population as a whole.^{118,119} Having a family member with uveal melanoma is therefore considered a risk factor for melanoma. Studies of families with more than one member with uveal melanoma have shown that there are several family cancer syndromes associated with increased risk of uveal melanoma.

Certain *BAP1* germline mutations have been associated with predisposition for uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell carcinoma, and cholangiocarcinoma.^{74,119-129} Some families with *BAP1* tumor predisposition syndrome also tend to have atypical Spitz tumors, which are benign/precursor melanocytic lesions with distinctive clinical and pathologic features.^{119,123,126,130-132} In individuals with germline *BAP1* mutations associated with this syndrome, the risk of uveal melanoma is high (up to ~30%),^{126,132,133} uveal melanoma tends to develop at a younger age,^{125,132} primary lesions tend to be larger and involve the ciliary body,⁷⁴ and the disease has a more aggressive course.^{74,134} Some individuals with this syndrome develop more than one type of primary cancer,^{132,133,135} and there is a high likelihood of *BAP1*-associated cancers in first- or second-degree relatives.^{119,132}

Mutations in *PALB2* have been associated with increased risk for developing breast, ovarian, and pancreatic cancer. Pathogenic variants leading to biallelic inactivation of *PALB2* were identified in tumors of two patients with familial uveal melanoma.¹³⁶ This finding from a retrospective case series might warrant further investigation into *PALB2* as a uveal melanoma susceptibility gene.

MBD4 deleterious mutations have been identified in uveal melanoma tumors at increased incidence compared with the general population and

associated with high tumor mutational burden.^{137,138} Questions remain whether *MBD4* germline variants or somatic loss predisposes individuals to uveal melanoma.¹³⁹ How *MBD4* inactivation might affect immunotherapy response is also worth further investigation.^{137,140}

Based on case reports of uveal melanomas developing in patients with neurofibromatosis,¹⁴¹⁻¹⁴⁸ neurofibromatosis type 1 (NF-1) is thought to be a risk factor for uveal melanoma, although population statistics supporting this claim are lacking.¹⁴⁹

Other Potential Risk Factors

Patient characteristics associated with increased uveal melanoma risk are lighter skin and eye color and propensity to sunburn.¹⁵⁰⁻¹⁵³ Occupational history of welding and a dose-response relationship with job duration have also been associated with increased uveal melanoma risk.¹⁵⁴

In conclusion, the NCCN Panel recommends evaluation for evidence of hereditary syndrome and referral for genetic counseling and testing in case of: early age of diagnosis (<30 years of age), history of other primary cancers in the patient, or family or personal history of other cancers known to be associated with a hereditary syndrome.

The Relationship Between Uveal and Cutaneous Melanoma

Clinic-based studies (N < 250) evaluating the likelihood of finding concurrent cutaneous melanoma in patients with ocular melanoma suggest a relationship between these two cancers.¹⁵⁵⁻¹⁵⁸ Most large population-based studies reveal no relationship between preexisting cutaneous melanoma and the subsequent development of uveal melanoma.¹⁵⁹⁻¹⁶³ However, one SEER-based study revealed a potential relationship between these two cancers.¹⁶⁴ For patients who present with uveal melanoma as their first primary cancer, some population-based studies have shown increased risk of subsequent cutaneous melanoma,^{160-162,165} and others have not found the risk to be significantly



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higher than in the general population.^{163,166} Currently the NCCN Panel does not consider cutaneous melanoma to be a risk factor for uveal melanoma, and patients with cutaneous melanoma do not need more frequent ocular screening than the general population.

Diagnosis and Workup

Characteristics, Detection, and Differential Diagnosis

Uveal melanoma typically presents as a pigmented lesion.¹⁶⁷ One study of 8033 eyes with uveal melanoma found that the lesion was pigmented in 55%, nonpigmented in 15%, and 30% had a mixture of pigmented and nonpigmented areas.¹⁶⁸ Uveal melanoma most often presents as a dome-shaped tumor (75%), but approximately 20% present with a mushroom shape due to the rupture of Bruch's membrane and growth into the sub-retinal space.¹⁶⁸ A small number of cases present as a diffuse, flat, plateau-shaped tumor (6%) or have a multinodular tapioca appearance (<1%).¹⁶⁸ Subretinal fluid is present in the majority of cases (75%).¹⁶⁸

The majority of uveal melanomas are symptomatic at presentation,^{11,81,169,170} but studies have reported 13% to 30% of patients were asymptomatic at diagnosis (and are discovered by routine eye exam).^{11,81,167,170} The most common symptom is blurred vision; other common symptoms include visual field defect/loss, photopsia, irritation and pain, metamorphopsia, floaters, redness, and pressure.^{11,81,170}

Although current imaging techniques provide high accuracy of diagnosis of medium to large uveal melanomas,^{171,172} real-world studies have reported relatively high rates of delay in diagnosis and treatment (23%–37%) due to failure to detect these lesions in the initial ophthalmologic exam.^{11,81,170,173}

Surprisingly, the rate of delayed diagnosis is also high in symptomatic patients.^{11,81} Furthermore, conditions such as choroidal nevus, congenital hypertrophy of the retinal pigment epithelium (RPE), and choroidal hemangioma can be mistaken for uveal melanoma.^{174–177} Therefore, full dilation of the pupil and meticulous examination of the fundus in any patient presenting with symptoms is critical.⁸³

Ciliary body melanoma can be difficult to detect,¹¹ as it is often hidden behind the iris,¹⁷⁸ and symptoms often do not develop until the tumor is large.^{11,43,48,178} Ciliary body melanoma can cause lens tilting or



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displacement,^{48,178} cataract development,^{48,178,179} and elevated intraocular pressure,⁴⁸ and is often associated with dilated episcleral “sentinel” vessels.¹⁷⁸ Ciliary body melanomas usually present with a dome shape,^{48,178} but occasionally have a circumferential ring shape.^{178,180}

As described above, several risk factors have been identified that may increase the risk of uveal melanoma. When a pigmented lesion on the ciliary body or choroid is discovered, these factors should be evaluated, as they may inform the index of suspicion.

It is also important to rule out metastasis to the uvea from other cancers—either known cancers based on patient history or occult primary cancer. Among patients with metastases to the eye or orbit, the most common primary cancer diagnosis is breast cancer, followed by lung cancer, which together account for over half of the cases.¹⁸¹⁻¹⁸³ The remainder of uveal metastases can arise from cancers of the kidney, gastrointestinal (GI) tract, skin, prostate, thyroid, pancreas, and others.^{182,183}

Initial Workup of Suspicious Pigmented Uveal Lesion

Upon discovery of a suspicious pigmented lesion in the ciliary body or choroid, clinical evaluation should include a complete history and physical (H&P), including personal or family history of prior or current cancers (outside the eye), as this may help determine whether the lesion is primary uveal cancer or a metastasis from another primary cancer. A wide variety of imaging and clinical exam techniques have been tested for their utility in diagnosis and characterization of uveal melanoma. In most cases, the diagnosis of uveal melanoma and characterization for treatment planning (or follow-up) can be achieved based on comprehensive exam of the front and back of the eye including biomicroscopy and dilated fundus exam (indirect ophthalmoscopy).^{47,48,83,184} In some cases, additional imaging may be needed to confirm diagnosis or better characterize the tumor for treatment planning (or monitoring). Additional imaging options that may be

useful include color fundus photography, conventional ocular ultrasound (US), autofluorescence of the ocular fundus, optical coherence tomography (OCT), retinal fluorescein angiography of the ocular fundus, transillumination, and MRI.

Features that are essential to measure and document as part of workup include visual acuity (VA), location and size of the tumor (ie, diameter, thickness), distance from the tumor to the disc and to the fovea, ciliary body involvement, and subretinal fluid and orange pigment, if present.

Biopsy may be considered if needed to confirm diagnosis or for prognostic analysis for risk stratification. Biopsy is usually not necessary for initial diagnosis of uveal melanoma and selection of first-line treatment, but may be useful in cases of uncertainty regarding diagnosis, such as for amelanotic tumors or retinal detachment. Biopsy of the primary tumor may provide prognostic information that can help inform frequency of follow-up and may be needed for clinical trial eligibility. If biopsy is performed, molecular/chromosomal testing for prognostication is preferred over cytology alone. The risks/benefits of biopsy for prognostic analysis should be carefully considered and discussed.

Imaging Methods

Comprehensive Eye Exam (biomicroscopy)

Meticulous analysis of the fundus after full pupil dilation will allow detection of most choroidal melanomas,⁸³ and can be used to record many of the relevant features needed for diagnosis and treatment planning. Whereas ciliary body melanomas can be difficult to detect by this method, fundus exam with good indentation can sometimes help.⁴³

Color Fundus Photography

Color fundus photography is useful for documenting the clinical features of lesions, with the advantage of giving the most identical appearance to clinical examination.¹⁸⁵ Color fundus photography can be used to evaluate



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the borders of the lesion, and thereby record the location and shape; calculate lesion basal diameter and area; and be used to detect orange pigment, drusen, and halo.^{83,185-187} Areas of orange pigment seen by color fundus photography have been shown to correlate with those seen by fundus autofluorescence.^{186,187} It is important to note that color fundus photography alone is not sufficient for a differential diagnosis, and diagnostic accuracy based on color fundus photography has wide interobserver variation.¹⁸⁸

Ocular Ultrasound

In addition to comprehensive clinical ophthalmologic exam and color fundus photography, US of the eye (ocular echography) is one of the most useful tools for diagnosis of choroidal melanomas.^{47,189-191} In experienced hands, US in combination with complete ophthalmologic clinical exam results in a high level of diagnostic accuracy (>99%) for studies of medium to large uveal melanomas.^{171,172,192} Melanomas tend to exhibit low internal reflectivity as well as an intrinsic acoustic quiet zone on US,¹⁹¹ features that distinguish them from a variety of other intraocular conditions. US is particularly useful when a mass cannot be visually inspected due to opacity or pathology of structures in the anterior portion of the eye such as corneal scars, cataract, or blood in the vitreous.⁴⁷

US can help in the detection of ciliary body melanomas that may be missed by fundoscopy.¹⁹³ US is particularly useful for determining the thickness of the tumor,^{179,189} and has been shown to have a high level of accuracy compared with tumor height measurements based on histopathology of enucleated specimens.^{194,195} By facilitating measurement of tumor dimensions, US is useful for detecting lesion growth.^{178,190} US can also be used to detect extraocular extension,⁴⁷ which shows hyporefectivity on US.⁸³ There are two modes of US to evaluate the eye, A-mode and B-mode. Uveal melanomas show low reflectivity on both A-scan and B-scan ultrasonography, although other features differ.⁸³

A-Scan Ultrasonography

Uveal melanomas typically show low to medium internal reflectivity on A-mode US,^{43,47,178,190,196} which further decreases toward the sclera.^{47,83} Other A-scan US hallmarks specific to uveal melanoma are: 1) a regular internal structure with similar height of the inner tumor spikes or regular decrease in height (positive angle kappa sign); 2) solid consistency with no aftermovement of tumor spikes; and 3) echographic sign of vascularization with a fast, spontaneous, continuous, flickering vertical motion of single tumor spikes.^{43,196} In contrast, choroidal metastases from other types of cancer typically show an irregular structure on A-mode US,¹⁹⁶ hemangiomas show much higher reflectivity,^{47,190,196} and nevi and melanocytomas show higher reflectivity and more irregular structures than malignant melanoma.¹⁹⁶ Fresh choroidal hemorrhages may have similar structure and reflectivity as melanomas, but will show aftermovement following small eye movements.¹⁹⁶

B-Scan Ultrasonography

On B-scan US, posterior uveal melanomas appear as hyperchromic mass with lower reflectivity than the surrounding choroid, thus giving an acoustically hollow appearance.^{43,47,83,178} Posterior uveal melanomas, particularly the larger ones, show choroidal excavation and orbital shadowing on B-scan US.^{43,47,178,190} These features help confirm clinical diagnosis, and are distinct from hemangiomas or metastases to the eye, which typically show high reflectivity.^{178,197} However, some other lesions that may show choroidal excavation include: hemangiomas, long-standing nevi, and choroidal metastases.¹⁹² B-scan US is used for obtaining tumor dimensions, extent, and shape,^{43,190,197} and is useful for characterizing larger ciliary body tumors.⁴³ Extraocular extension can be observed by B-scan US as areas of hyporefectivity compared to normal orbital tissue.^{83,178}



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Autofluorescence of Ocular Fundus

Fundus autofluorescence has been proposed as a method to help in the diagnosis and characterization of uveal melanomas.^{179,186,198,199} Choroidal melanoma generally shows slight intrinsic hyperautofluorescence and the brightness increases with tumor pigmentation and disrupted RPE.^{200,201} Orange pigment is the most highly autofluorescent uveal melanoma feature.^{198,200-205} Drusen can also be detected by autofluorescence,²⁰⁴ and have increased, normal, or decreased autofluorescence.^{198,202,205} Fibrous metaplasia also shows elevated autofluorescence.^{201,202,204} Autofluorescence can be used to distinguish orange pigment from drusen in both pigmented and non-pigmented tumors.¹⁷⁸ Unlike uveal melanoma and choroidal nevi, melanocytomas show hypofluorescence.²⁰⁶ Comparative studies have shown that the autofluorescence pattern often matches that of orange pigment and hyperpigmentation seen by color fundus photography.^{47,187,202} Based on comparative studies, it is not clear that fundus autofluorescence increases the detection rate of orange pigment relative to standard ophthalmologic exam.²⁰⁷

Optical Coherence Tomography

OCT is another imaging method proposed for assisting diagnosis of uveal melanoma.^{47,179} Spectral domain OCT (SD-OCT) allows the detailed evaluation of the retina and RPE, changes in which are more common in choroidal melanoma versus choroidal nevi.^{47,198} OCT can help identify overlying retinal detachment or edema, even before clinically apparent.¹⁹⁸ OCT can detect subretinal and intraretinal fluid, subretinal lipofuscin, retinal epithelium atrophy and degeneration, shaggy photoreceptors, and structural loss of photoreceptors in the neurosensory retina.^{47,178,198,208,209} These features are more likely in choroidal melanoma than in choroidal nevi, although some features are more useful than others for differential diagnosis, especially in small lesions.^{47,208,210-212} Results differ across comparative studies regarding whether OCT is more sensitive than

standard ophthalmologic exam plus US for detecting subretinal fluid.^{207,212,213}

In OCT, the structure of the lesion differed between choroidal nevi, melanomas, hemangiomas, and metastases.²⁰⁹ Optical density ratio based on OCT can also be used to distinguish choroidal melanomas from choroidal metastases.²¹⁴ Enhanced depth imaging OCT (EDI-OCT) is particularly useful for detecting small lesions, and distinguishing small nevi from small choroidal melanoma.⁴³ OCT angiography (OCT-A) can be used to distinguish choroidal nevi from choroidal melanoma based on margin characteristics (well-delimited vs. imprecise), reflectivity of choroid capillary vasculature (hyper vs. hypo), and characteristics of lesion vasculature.^{215,216} Compared to US biomicroscopy, OCT provides better resolution of the anterior segment anatomy and margin, while the former provides better overall visualization and resolution of the posterior margin.²¹⁷

Retinal Fluorescein Angiography

Retinal fluorescein angiography can be used to characterize lesion vasculature, which can aid in diagnosis because choroidal melanomas may have intrinsic tumor circulation, sometimes called “double circulation,” in addition to normal choroidal vasculature.^{43,47,83,178,190,191,218} Observation of the tumor vasculature is helpful in distinguishing melanomas from choroidal nevi, hemorrhagic degeneration, or choroidal melanoma.^{47,83,219} After treatment with brachytherapy, fluorescein angiography is also useful for detection of complications such as radiation retinopathy.^{47,83}

Transillumination

Transillumination has been tested as a method for detecting and measuring uveal melanomas that may be difficult to detect or fully characterize by other techniques. Examples include large ciliary body melanomas,^{43,47,83} or tumors obscured by cataracts.²²⁰ Compared with tumor dimension measurements based on histology of enucleated eyes,



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transillumination tends to overestimate both the thickness and diameter of tumors, and is prone to shadowing artifacts.^{195,221} Therefore, it is only used if other methods have proven inadequate.

MRI

MRI is generally not needed for diagnosis and workup, but occasionally is necessary with features that may make other imaging methods difficult, such as secondary vitreous hemorrhage, extensive retinal detachment, or cataract.^{47,83} MRI may be useful in determining whether cataract is caused by an underlying ciliary body melanoma, and can help distinguish uveal melanomas from hemangiomas.⁴⁷ Uveal melanomas usually have high signal intensity in T1-weighted MRI images and low signal intensity in T2-weighted images.^{43,47,83,178} Although similar signal pattern can be caused by hemorrhage or necrosis,^{47,83} hemangiomas typically have hyperintense signal on T-weighted images and T2-weighted images are isointense with the vitreous.⁴⁷ MRI is useful for detecting and characterizing extraocular extension,^{47,83,178,189,222,223} and is also used for radiation therapy (RT) planning.^{83,178,189,224,225}

Features to Record

Visual Acuity

It is important to measure VA during workup, as many uveal melanomas can disturb vision, and changes in VA can be an indication of progression, response to treatment, or a side effect of certain treatments. VA or changes in VA can contribute to the differential diagnosis, as benign nevi rarely cause visual impairment,^{79,226} whereas malignancy does.^{11,81,90,99} In patients with uveal melanoma, VA in the affected eye tends to be worse than in the fellow eye.¹⁶ A baseline measure of VA is also important to determine effects of uveal melanoma treatment. RT can cause a decline in VA, although the effects are highly variable.²²⁷⁻²²⁹ Larger tumor size and tumor location near the optic disc are associated with greater loss of VA and higher rates of local complications.²³⁰⁻²³²

Size

Although size alone does not determine diagnosis, it can contribute to differential diagnosis, as uveal melanomas are generally larger than choroidal nevi, and size (thickness >2 mm, tumor diameter >5 mm) is predictive of growth in melanocytic lesions.^{97,99} For lesions thought to be nevi, or small lesions with uncertain diagnosis, accurate measurements of size are important for monitoring for growth, as rapid growth is a sign of likely malignancy.⁹⁴ Baseline tumor size is needed to determine the T stage of the tumor, which helps determine the prognostic risk category used to inform post-treatment surveillance. Tumor size is also important for selecting and planning treatment. For brachytherapy, selection of the appropriate size plaque is important to ensure that the lesion is fully covered, and alternative or additional treatment options need to be considered for tumors that exceed the size of the largest commercially available plaque. Selection of alternative treatment options (eg, particle beam RT, stereotactic radiosurgery [SRS], enucleation) should also depend on tumor size. Accurate measurements of size and shape of the tumor are also needed for monitoring response or progression after treatment.

Location, Distance from Disc and Fovea, Ciliary Body Involvement

Lesion location is one of the features that can contribute to diagnosis. Proximity to the optic disc is considered a diagnostic feature of uveal melanomas, as it is correlated with likelihood of growth in melanocytic choroidal lesions.^{93-95,97} Lesion location, including distance from disc and fovea, and ciliary body involvement, can impact imaging results, such as the ability to detect certain diagnostic features and accurately discern borders for measurement of tumor size. In some cases, color fundus photography, US, and complete clinical exam may not be sufficient for detection and/or characterization of ciliary body involvement; this is a feature that may require additional imaging approaches.¹⁸⁴ Lesion location can help explain visual symptoms and may impact the efficacy and safety



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of specific treatments. Ciliary body involvement is one of the elements that determines the T stage of the tumor and prognostic risk category used to inform post-treatment follow-up surveillance.

Subretinal Fluid

Subretinal fluid is a feature that supports the diagnosis of uveal melanoma, as it is rare in benign choroidal nevi,^{88,102} and has been shown to develop during growth of choroidal nevi and transformation to melanoma.^{82,89} The presence of subretinal fluid has been shown to be predictive of growth in choroidal nevi or small indeterminate melanocytic lesions.^{89,94,95,97,233} One study of a large number of uveal melanomas (N = 8033) reported that subretinal fluid was present in 75% of cases.¹⁶⁸ However, ocular metastases from other primary cancers (eg, breast, lung) can also give rise to subretinal fluid.¹⁸²

Orange Pigment

Orange pigment, also called lipofuscin, can be present in benign choroidal nevi;^{88,102} however, it has been shown to develop during nevi growth and transformation to uveal melanoma.^{82,89} In nevi or indeterminate small lesions, the presence of orange pigment is predictive of future growth and increases the likelihood of a future uveal melanoma diagnosis.^{86,89,93-99}

Biopsy

The use of biopsy as part of workup for uveal melanoma is an issue of some debate. Potential benefits of biopsy during workup are: 1) cytologic/histologic confirmation of diagnosis; 2) potential for molecular analysis that may impact eligibility for current or future clinical trials; and 3) potential for molecular analyses that may provide more accurate prognostic assessment for risk of metastasis, which may inform future follow-up surveillance. Potential harms of biopsy of the primary tumor include: 1) risk of complications from the procedure that damage the eye; 2) risk of tumor seeding leading to local or distant recurrence; and 3) risk

of inadequate sampling resulting in misdiagnoses or inaccurate or inconclusive molecular testing results. The likelihood of these potential benefits and harms is debated and may vary across practitioners.

There are a wide variety of biopsy techniques that have been tested and are sometimes used for choroidal or ciliary body tumors. Some involve a transscleral (direct) approach while others use a transvitreal (indirect) approach.^{234,235} Tumor location is a major determinant of which approach is likely to be successful and safe. [Table 2](#) provides a list of techniques for biopsying choroidal and ciliary body tumors that have been used to assist with diagnosis and/or prognostication in primary uveal melanomas. Any of these biopsy procedures can result in intraocular complications/morbidities (eg, hemorrhage, decrease in VA, retinal detachment, retinal perforation, hypotony, endophthalmitis) which if severe may require secondary procedures or other interventions for management.²³⁶⁻²⁴⁷ Longitudinal population-based studies have shown that biopsy does not impact all-cause mortality or disease-specific death (DSD) in patients with uveal melanoma.²⁴⁸⁻²⁵⁰

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNAB) is the simplest, most inexpensive, and most commonly used method for biopsy of choroid or ciliary body tumors presumed to be melanoma.^{234,251,252} Details of the technique are described in several review articles,^{234,251,252} as well as multiple primary reports from many different centers.^{91,236,237,239,253-255} FNAB can be done via a transvitreal or transscleral approach depending on the location of the tumor. The transvitreal approach is generally easier due to better intraoperative illumination and visualization options.^{234,252}

The disadvantage to FNAB is that multiple passes may be needed to obtain enough material for cytologic and molecular genetic analysis.^{236,240,255,256} The yield from FNAB varies across studies.^{91,236,237,239,240,249,250,253-262} Some studies suggest that transvitreal



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(vs. transscleral) approach is associated with improved FNAB yield, but some studies disagreed.^{236,237,239,260,262,263} It has also been postulated that FNAB yield is higher for larger and thicker tumors,^{237,250,254,260-262} but a recent study showed that high yields can be obtained even in thin tumors (<3.5-mm thick), with both the transscleral and transvitreal approach.²³⁶ FNAB can help distinguish between uveal melanoma and borderline or benign melanocytic nevus, even among small lesions,^{91,261} and between a primary uveal melanoma versus metastasis from another cancer, another type of primary ocular tumor, a melanocytoma, or RPE proliferation.²⁵⁵ Concerns about FNAB causing tumor seeding have been raised based on findings of melanoma cells left in the needle track,^{257,259,264-266} and some have suggested procedure adjustments for reducing the likelihood of tumor cell seeding by FNAB.^{252,257,265} A few case reports found local recurrences at FNAB entry sites.²⁶⁷⁻²⁶⁹ However, multiple follow-up studies with large patient populations have revealed no local recurrences after FNAB,^{91,236,239,249,250,254,255,258,259,263} and one case series found no increased risk of metastasis among untreated patients who had post-biopsy evidence of melanoma cell dissemination inside the eye.²⁶⁴ FNAB is therefore generally thought to be safe and to have low risk of seeding.

Other Biopsy Techniques

Other biopsy techniques that have been tested in large uveal melanoma populations use tools from vitrectomy systems to access tumor via a transvitreal/transretinal approach and to extract tumor tissue using the vitreous cutter and aspiration through the canula. These procedures do not necessarily include a vitrectomy. There are a variety of procedures that fall into this category, and are described in a series of publications based on clinical practices both in the United States and Europe.^{234,241,242,244,252,271,272} These techniques have been used successfully on anterior, posterior, equatorial, and peripapillary lesions.^{241-244,270} They generally result in larger sample sizes than FNAB, although like FNAB multiple passes may be necessary.^{241,242,271,272} For this reason it

has been suggested that these methods may be useful in patients with tumors that are too small or inaccessible for FNAB, or for tumors where FNAB has failed. One study reported that for choroidal melanomas with thickness of 2.0 mm or less, sufficient sample for prognostic evaluation was obtained in 100% of patients.²⁴¹ Reported yields from these procedures range from 89% to 99% for diagnosis of choroidal lesions, and 97% to 100% for prognostic testing on uveal melanomas.^{241-244,270,271} Studies have shown that these biopsy techniques can be used to diagnose tumors that are unclassifiable based on standard noninvasive diagnostic techniques, and can differentiate uveal melanoma from benign nevus, metastases from other cancers, vasoproliferative tumor, hemorrhage, gliosis, and scleritis.^{244,270}

Generally, these approaches are less broadly used than FNAB, are more expensive, and require additional expertise.^{234,252} Like FNAB, hemorrhage is the most common complication with these biopsy procedures, is normally localized, and usually resolves without intervention.^{241,243,244} Since these techniques are more invasive, however, retinal detachment and severe hemorrhage are more common, and more patients require intervention for management.^{238,242-244,252} Decrease in VA due to these procedures is not uncommon.^{242,243}

Like FNAB, studies have published evidence that these procedures may leave tumor cells along the access pathways. Nevertheless, most studies, including those with large patient samples, have not observed local recurrence during follow-up.^{243,244} There are a few case reports of local recurrences at biopsy entry sites.^{268,270,284,285}

Incisional biopsy techniques are more invasive than vitrectomy system-assisted biopsies, and likewise yield more material, but also are more likely to lead to complications.²⁴⁵⁻²⁴⁷ These methods have been used for cases that are particularly hard to diagnose. Excisional biopsy, using either transscleral resection or endoresection, was also explored as an



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option for both biopsy and primary treatment,²⁸⁶ but is not included in [Table 2](#) because it is no longer used due to technical challenges, risk of complications, and concerns about tumor seeding.^{178,273-283}

Observation for Uncertain Diagnosis in Patients with Low Risk

Findings from the clinical workup should be used to determine initial management. Observation may be appropriate for patients with uncertain diagnosis and/or fewer than three risk factors for lesion growth ([Table 1](#)). Studies have found that for patients with small choroidal lesions presumed to be nevi or indeterminate, deferring treatment until evidence of growth or features of malignancy develop (eg, orange pigment, subretinal fluid, symptoms) is associated with a very low risk of metastasis,^{94,98} and even lower risk of death from uveal melanoma.⁸⁷ For patients who meet the criteria for observation, regular follow-up is recommended to periodically re-evaluate for growth or features of malignancy. Follow-up tests should include the same tests recommended for initial workup and diagnosis that would help clarify if there is progression and determine the natural history of the indeterminate lesion. Initially, these patients should be re-evaluated every 2 to 6 months to determine rate of growth (if any) and to monitor for other changes indicative of malignancy. Close follow-up for 5 years is recommended to firmly establish whether or not there is any growth or progression; some lesions that initially seem stable may suddenly begin to grow and transform. The frequency of re-evaluation should depend on the index of suspicion, patient age, and medical frailty. For example, the presence of one to two risk factors for growth ([Table 1](#)), or evidence of changes would increase suspicion. If the size and features of a lesion appear static after 5 years of follow-up, the patient can be followed annually thereafter. Lesions that demonstrate growth or develop additional risk factors for growth (>3 total) should be managed as uveal melanoma, even if diagnosis is still uncertain.

Further Workup Prior to Treatment

Further workup prior to treatment may be needed in some cases to aid in treatment selection and planning. For example, for tumors that are large, close to the optic nerve, or have suspected extraocular extension, MRI should be performed, if not previously done, to confirm extraocular extension, determine whether RT or enucleation is needed, and for RT planning.^{47,83,178,189,222-224} MRI should be performed with and without contrast unless contraindicated. Ciliary body involvement or extraocular extension should be assessed and documented, as these features may impact the feasibility, safety, and efficacy of certain treatment options. Biopsy is typically performed before the tumor is irradiated and can often be performed at the time of primary treatment depending on the procedure modality. There is some evidence to suggest that RT may alter molecular genetic features of the tumors, reducing the accuracy of prognostication based on samples taken after RT treatment.²⁸⁷

Baseline imaging to screen for systemic disease is also recommended prior to treatment. Unless there is a specific contraindication to the administration of IV contrast, all cross-sectional imaging studies should be performed with and without IV contrast. Despite lack of treatment options for patients with distant metastatic disease, NCCN favors staging before primary treatment. For patients who have small, low-risk tumors, deferring extraocular baseline imaging until after primary treatment can be considered. The most frequent site of metastasis is the liver, and other sites include the lungs, skin/soft tissue, and bones.²³ At minimum, all patients should have contrast-enhanced MR or US of the liver, with modality preference determined by expertise at the treating institution. Additional imaging modalities may include chest/abdominal/pelvic CT with contrast. However, screening should limit radiation exposure whenever possible.



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Treatment for Localized Primary Uveal Melanoma

Most uveal melanomas are localized at first presentation, and only a small percentage of cases present with metastases (<3%).^{6,12-16} Local treatment for primary uveal melanoma is effective in preventing local recurrence in greater than 85% of cases,^{273,288} yet the rate of metastasis within 20 years after treatment is approximately 20% to 70% for patients who present with localized uveal melanoma, depending on tumor stage/size at diagnosis.^{10,15,28,289} Whereas surgical approaches historically are the mainstay of treatment for localized cutaneous melanoma, the field has moved away from using surgery in all patients.^{2,290} Different modalities, primarily various forms of RT, have been found to be just as safe and effective for those with limited disease, and can preserve the affected eye.²⁹¹⁻³⁰³ Some surgical approaches are still used in patients with extensive local disease, but most patients with localized primary uveal melanoma are treated with some form of RT.^{2,304} There are a number of other ablative techniques that are occasionally used for localized primary melanoma, including laser therapy, cryotherapy, and photodynamic therapy.

Selection among these techniques is guided by many case-specific factors, including the size and location of the tumor, presence of extraocular extension, visual potential, patient age, and preference. The recommended treatment options are largely based on data from choroidal melanomas. For small ciliary body and iris tumors (<3 clock hours), surgical excision may be considered.

For thin tumors (<2.5 mm) with largest diameter ranging from 5 to 19 mm, the recommended primary treatment options are plaque brachytherapy or particle beam RT. For highly select patients who are not good candidates for brachytherapy or particle beam RT, other options to consider include laser therapy or enucleation. Brachytherapy with scleral patch graft is recommended for cases with limited extraocular extension (See *Principles of Radiation Therapy* in the algorithm).

For tumors with largest diameter 19 mm or smaller and thickness 2.5 mm to 10 mm, brachytherapy and particle beam RT are also options. If there is concern that adequate response was not achieved from initial RT, additional treatment with resection, laser ablation, transpupillary thermotherapy (TTT), or cryotherapy can be considered. Although there is a trend toward avoiding enucleation, it is recommended for patients with neovascular glaucoma, tumor replacing greater than 50% of globe, or blind, painful eyes. Enucleation should also be considered in cases of extensive extraocular extension. Pathologic evaluation should follow the uveal melanoma synoptic report recommendations by the College of American Pathologists (available at:

<http://documents.cap.org/protocols/cp-uveal-melanoma-17protocol-4000.pdf>).³⁰⁵

Given the limitations in the size and RT penetrance of commercially available brachytherapy plaques (diameter ≤23 mm), this method is not recommended for tumors that are too large in diameter (>19 mm; any thickness), too thick (>10 mm; any diameter), or have optic nerve involvement and thickness (>8 mm; any diameter). RT options for such tumors include particle beam RT and SRS. The choice between these two RT modalities usually depends on which modality is available at the treating institution. In the rare scenario that the institution has both SRS and particle beam facilities, some practitioners would opt for particle beam because there are more data supporting its efficacy (See Guidelines section *UM-B Principles of Radiation Therapy* in the algorithm). Enucleation is recommended for cases with extensive extraocular extension, neovascular glaucoma, tumor replacing greater than 50% of globe, or blind, painful eyes.

Enucleation

Enucleation is historically the most widely used treatment for uveal melanoma. Results from the Collaborative Ocular Melanoma Study



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(COMS) prospective randomized trial suggest that enucleation is associated with a very low risk of local recurrence (~1%),³⁰⁶⁻³⁰⁸ notably lower than the rate of local recurrence reported for retrospective studies in patients treated with primary local resection.^{273-276,309-314} The few patients who developed local recurrences after enucleation all had distant metastases before the local recurrence developed.³⁰⁶ Retrospective studies reported similar findings, suggesting that development of distant metastasis is due to micrometastasis that developed prior to enucleation.³⁰⁸

Postoperative complications include pain, hemorrhage, nausea/vomiting, cardiovascular or pulmonary problems, urinary retention, fever, and local surgical problems.³⁰⁶ Enucleation procedures have been standardized; they involve complete removal of the eye and in most cases include insertion of an orbital implant.^{178,282,315,316} Both porous and nonporous implants have been shown to result in similar outcomes, although there may be a higher incidence of ptosis with acrylic implants, and a greater need for ophthalmologists' treatment (eg, topical antibiotics, polishing or refitting of prosthesis) with hydroxyapatite implants.³¹⁷

Pre-enucleation RT is generally not used. Results from the COMS randomized trial in large tumors (height ≥ 2 mm and diameter ≥ 16 mm; or height ≥ 10 mm and any diameter; or height ≥ 8 mm, any diameter, if proximal tumor border < 2 mm to optic disc) showed that pre-enucleation RT had no impact on survival compared with enucleation alone,^{306,318,319} confirming results of prior retrospective studies.³²⁰ The 5- and 10-year DSD reported in this trial were 28% and 40%, respectively, for patients treated with enucleation.³¹⁸

In the COMS randomized trial in small-to-medium choroidal melanomas (2.5–10.0 mm in apical height [2.5–8.0 mm if peripapillary] and ≤ 16 mm in maximum basal diameter, no extrascleral extension ≥ 2.0 mm thick), survival outcomes for enucleation were similar to those with iodine-125

brachytherapy.^{291,292} The 5- and 10-year DSD reported in this trial were 11% and 17%, respectively, for patients treated with enucleation, compared with 10% and 18%, respectively, for the brachytherapy arm.²⁹² Even after adjustment for age and maximum basal diameter, there were no treatment-dependent differences in all-cause mortality or mortality with confirmed melanoma metastasis at time of death.²⁹² One prospective and several retrospective studies also found that survival was similar after enucleation versus cobalt plaque brachytherapy,²⁹³⁻²⁹⁷ or a mix of brachytherapy plaque types,²⁹⁸ versus proton beam RT,²⁹⁹ or versus SRS.³⁰⁰⁻³⁰³ Relative to RT, enucleation is associated with worse effects on certain visual functions and physical and functional well-being. However, some studies have found that overall quality of life was similar between the two treatment modalities.³²¹⁻³²⁶

Radiation Therapy

Brachytherapy and charged particle RT are considered appropriate for primary therapy for most cases of uveal melanoma, whereas photon RT and SRT are less often used as primary treatment for uveal melanoma. SRS is sometimes used for large primary tumors, and photon RT is generally only used as an adjuvant to surgery.

Plaque Brachytherapy

Plaque brachytherapy is a commonly used form of definitive RT for the primary tumor.^{290,304,327-329} Prospective studies in patients with small choroidal tumors found that iodine-125 brachytherapy resulted in tumor regression in most cases (98%) and 98% rate of globe conservation.^{330,331} DSD at 5 years was 3.9%.³³¹ As discussed previously, results from the COMS trial showed that long-term outcomes were not significantly different with plaque brachytherapy versus enucleation for patients with small- to medium-sized choroidal melanomas.^{291,292} Local recurrence after brachytherapy, although rare, is more common than with enucleation. Prospective studies have reported local failure rates ranging from 0% to



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~20%, with most studies reporting rates of less than 10%.^{49,231,330-342} A systematic review (N >3000) found that the weighted mean rate of local failure after brachytherapy was 9.45%.²⁷³ Whereas some studies report median time to local recurrence between 2 and 4 years,^{335,338,341,343} most also show curves that never really plateau, with recurrences developing as late as 12 years or more after treatment.^{49,231,332,335,338,341,343}

More serious postoperative complications commonly reported for brachytherapy include radiation retinopathy, optic neuropathy, papillopathy, maculopathy, neovascular glaucoma, retinal detachment, and various types of hemorrhages and vascular abnormalities.^{331,335,341,344}

The 5-year cumulative rate of enucleation as a result of brachytherapy complications or growth of tumor was approximately 12% in prospective trials, most often due to treatment failure during the first 3 years after brachytherapy, and to eye pain beyond 3 years after treatment.

^{49,230,231,291,332,335,338,341,343,345} Loss of VA and cataracts are common long-term complications of brachytherapy, with approximately half of patients having lost six or more lines of VA after 3 years of follow-up.^{230,331,332,336,341,346-348}

More recent studies have reported local failure rates ranging from 0% to 20% for patients treated with iodine-125, ruthenium-106, palladium-103, and cesium-131 brachytherapy plaques.^{273,337,338,349-352} It is important to note that late treatment failures (up to 12 years) after brachytherapy have been observed.³³⁸ One prospective and several retrospective studies also found that survival was similar after enucleation versus cobalt plaque,²⁹³⁻²⁹⁷ or a mix of brachytherapy plaque types.²⁹⁸ A meta-analysis of studies testing Ru plaques reported a 5-year DSD of 6% for small and medium tumors (T1/T2), and 26% for large tumors (T3).³⁵³ Palladium-103 brachytherapy plaques appear to perform similarly to iodine-125 plaques.³⁴²

When evaluating patients for brachytherapy, it is important to consider the entry criteria and treatment parameters used in the COMS trial. The COMS trial included only patients with tumors that were choroidal;²⁹¹ those with tumors contiguous with the optic disc were excluded, as were those with metastases from melanoma or another cancer (except nonmelanoma skin cancers).²⁹² Only 16% of patients had tumors less than 2.0 mm from the optic disc.²⁹¹

Plaque Brachytherapy Dosing Considerations

Using iodine-125 COMS plaques, 85 Gy should be prescribed to the apex of the tumor at low dose-rate (≥ 0.6 Gy/h), as this was the dose used in the COMS study of medium-sized uveal melanomas, showing similar survival with brachytherapy versus enucleation.^{291,292} Other prospective and retrospective studies using iodine-125 brachytherapy dosing similar to COMS have reported similarly high rates of local control,^{338,350,354-357} and a retrospective study found that efficacy outcomes were similar to those in patients treated with SRT.³⁵⁸ Studies using iodine-125 brachytherapy doses higher than in COMS also reported recurrence rates that compared favorably with other treatment modalities (eg, TTT, proton beam RT).^{330,359} In contrast, studies using iodine-125 brachytherapy doses of less than or equal to 80 Gy reported recurrence rates higher than with particle beam RT.^{49,336,360-362} Whereas a few studies have associated a lower iodine-125 brachytherapy dose with local tumor recurrence and decreased systemic control,^{340,363-365} others have found no such correlation.^{349,356,366,367}

Another issue of debate is the relationship between brachytherapy dose and long-term complications. Several studies have found correlations between increasing iodine-125 dose and loss of VA, risk of RT-related complications (eg, cataract, optic neuropathy, glaucoma), and the need for secondary enucleation.^{347,356,364,366-371} Results are mixed, however, and retrospective analyses did not always find significant correlations between dose and these negative outcomes.^{369,372,373}



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Studies testing a wide range of doses for brachytherapy plaques made of other radioisotopes, such as ruthenium-106, palladium-103, strontium-90, and cobalt-60, have reported mean/median dose to the apex between 80 and 130 Gy.^{228,332,342,353,359,374-381} Although there is evidence to suggest that results differ between isotopes,^{359,375} the optimal dose has not been determined for any of these isotopes. Results are inconsistent across retrospective studies that evaluated the impact of dose on local/distant failure rate,^{374,379} or the impact of dose on RT-related complications and VA loss.^{228,378}

Particle Beam Radiation Therapy

Particle beam RT includes radiation with protons, carbon ions, or helium ions, and is a common form of definitive RT for the primary tumor.³²⁷ Prospective studies, a systematic review, and a retrospective study found that DSS in patients with uveal melanoma treated with particle beam RT was similar or better than for plaque brachytherapy.^{49,336,362,382} Compared with brachytherapy, particle beam RT was associated with higher rates of local control and similar or lower rates of enucleation during follow-up.^{49,336,362} Specifically, local control for particle versus plaque treatment was 100% versus 84% at 5 years, and 98% versus 79% at 12 years, respectively ($P = .0006$). Enucleation rate was 11% versus 22% at 5 years, and 17% versus 37% at 12 years, respectively ($P = .01$).⁴⁹ Across studies, local recurrence rates with charged particle therapy ranged from 3% to 10%.^{273,383} Tumor regression following particle beam RT can begin within 6 months of treatment, and tumor shrinkage may continue to occur throughout 5 years of follow-up.^{383,384} As with brachytherapy, local recurrence after particle beam RT as treatment for primary localized uveal melanoma occurs over a long time range, as early as 2 months after treatment and as late as 12 years.³⁸⁵⁻³⁸⁷ Prospective studies have found that most local recurrences occurred in the first 4 to 5 years, with median time to recurrence of less than 2 years.^{49,385-387} Multivariate analysis of a real-world database found that treatment with protons was associated with

poorer overall survival (OS) compared with brachytherapy treatment (5-year OS 51% vs. 77%; $P = .008$).³⁸⁸

Decrease in VA and loss of vision, similar to brachytherapy, can occur with particle beam RT.^{383,386,389} Commonly reported toxicities include vitreous hemorrhage, subretinal exudation in macula, posterior subcapsular opacity, radiation keratopathy, rubeosis/neovascular glaucoma, retinal detachment, radiation maculopathy, and papillopathy.^{383,385,389,390}

Stereotactic Radiation

Stereotactic RT (SRT) includes both single-fraction and hypofractionated stereotactic techniques, referred to collectively as SRS in these NCCN Guidelines. Compared with brachytherapy and particle beam RT, there are fewer prospective comparative study data on SRS for treatment of primary uveal melanoma.^{227,273,358,380,391-408} Studies using SRT as primary treatment for uveal melanoma have reported local failure rates ranging between 2% to 16%.^{227,273,358,380,392-405,409} Following SRT of the primary tumor, many uveal melanomas showed a transient increase in tumor height, volume, or both.³⁹⁸ Responses to SRT first began to appear 6 months after treatment, with progressive decreases in tumor height and volume continuing for at least 3 years.^{227,394,396,398,399,402-405,410}

Available data suggest that SRS may be as effective as other RT modalities, albeit with a higher risk of complications.^{358,392,394,395,397-407,410-418} One series that compared SRS with iodine-125 brachytherapy found that rates of tumor recurrence, distant metastasis, and secondary enucleation were similar across treatments.³⁵⁸ Risk of cataract appeared similar across treatments, but SRS appeared to be associated with higher rates of neovascular glaucoma, radiation retinopathy, and radiation papillopathy.^{358,413} Another study also reported similar rates of local control with brachytherapy versus SRS.³⁸⁰ A retrospective study comparing ruthenium-106 brachytherapy versus SRS found a nonsignificant trend toward increased secondary glaucoma after SRS.³⁷⁷ Retrospective studies



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comparing SRS versus proton beam RT reported similar rates of local control and eye retention across treatments, but higher rates of VA decline and vitreous hemorrhage with SRS.^{392,419}

RT Toxicity (Ocular)

In order to avoid secondary enucleation, a variety of methods for preventing or managing RT-associated complications have been tested in prospective studies. Toxicity management methods tested include panretinal photocoagulation for ocular ischemia,⁴²⁰ transscleral local resection for exudative retinal detachment,⁴²¹ and intravitreal anti-vascular endothelial growth factor (VEGF) (eg, bevacizumab, ranibizumab, aflibercept) or intravitreal corticosteroids (eg, triamcinolone, dexamethasone) for treating optic neuropathy, macular radiation vasculopathy, or papillopathy or macular edema.⁴²²⁻⁴²⁹ These intravitreal therapies have also been tested for prophylaxis.⁴³⁰⁻⁴³² The NCCN Guidelines for Melanoma: Uveal do not currently have recommendations for management of RT side effects.

Other Ablative Techniques

Laser photocoagulation has been used for treatment of primary or recurrent uveal melanomas, sometimes as monotherapy but more often as an adjunct to RT or surgery.^{47,48,179,278,282,387,433-447} The sparse data available suggest that laser photocoagulation is associated with high rates of recurrence if used as the sole primary therapy,^{433,438} but that when used as a supplement to brachytherapy can increase rate of tumor regression.⁴⁴³

TTT, also called diode laser hyperthermia, can be used to treat a large spot and has deep tissue penetration. TTT has been tested in prospective studies as the sole primary treatment for uveal melanoma tumors, but local recurrence rates varied widely across studies, with some studies reporting high rates of recurrence (>50%), even for small tumors.^{273,330,448-}

⁴⁵³ TTT has also been tested as an adjunct therapy to RT to reduce the risk of local recurrence.^{332,334,335,343,345,363,390,454,455} One prospective randomized trial found that TTT administered at 1, 6, and 12 months after proton RT reduced the likelihood of retinal detachment and lowered the secondary enucleation rate.³⁹⁰ A retrospective study found that addition of TTT to brachytherapy improved rate of tumor regression, 5-year tumor recurrence rate, eye-globe preservation, and recurrence-free survival.⁴⁵⁶ There was no impact on metastasis-free survival, OS, rate of complications, or visual outcomes.⁴⁵⁶ However, two other studies showed that adding TTT to brachytherapy did not improve the rate of globe conservation, and was associated with greater loss of VA.^{332,457} The larger of these studies (N = 449) also showed that rate of local failure, distant metastasis, and cause-specific death were not improved by TTT.³³²

Use of cryotherapy for treatment of primary or recurrent uveal melanomas, either alone or in conjunction with other therapies, has been described in case reports and case series in the literature.^{452,458-464} Retrospective reports and review articles suggest that this method is occasionally being used in clinical practice.^{28,298,465}

Treatment for Extraocular Extension

Extraocular extension has been reported to be present in approximately 3% of patients at diagnosis of uveal melanoma,^{167,168,195,466} is more common among tumors with higher T stage (12% of T4 tumors),²⁸⁹ and is associated with poor prognosis.^{20,28,288,467-469} Extraocular extension can be detected by preoperative imaging, or found or confirmed at the time of enucleation.^{306,470} In the COMS trial of patients with large uveal melanomas, unexpected extrascleral extension was found in 2% of patients who underwent enucleation, despite extensive clinical and imaging workup.^{306,319}



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Sometimes the evidence of extraocular extension is microscopically positive or close margins after enucleation, without clinical, intraoperative, or radiographic evidence of gross residual disease to the orbit. In this case, the patient can be observed, and map biopsy and/or RT using particle beam or proton beam to the orbit can be considered. In other cases, extraocular tumor is visible intraoperatively or intraoperative findings suggest that there may be gross disease to the orbit. In this case, biopsy of the extraocular tissue should be carried out, if possible, with consideration of one or more of the following options: intraoperative cryotherapy, orbital exenteration, or RT using particle beam or photon beam to the orbit.

For cases with extraocular extension and/or orbital invasion, orbital exenteration, the surgical removal of the globe and adjacent orbital contents, is recommended.^{43,191,229,439,442,471} Retrospective studies of large databases suggest that exenteration is used in less than 1% of patients,²⁸ and among patients undergoing enucleation, 2.5% need orbital extenteration.⁴⁷² The value of orbital exenteration is disputed in the literature, largely based on low-quality data such as case reports and retrospective studies. Some studies support orbital exenteration because it provided superior outcomes compared with other (nonsurgical) approaches,⁴⁷³ whereas others report poor outcomes after orbital exenteration, arguing that it may not be justified.^{474,475}

A retrospective study (N = 202) found that in patients treated with enucleation, postoperative RT improved survival, particularly in young patients (age <30 years) and those with choroidal tumor height greater than 3 mm.⁴⁷² Another small retrospective study reported a local recurrence rate of 6% in patients with extrascleral extension who were treated with enucleation followed by adjuvant external beam RT to the orbit.⁴⁷⁶

Follow-up

For patients whose primary uveal melanoma was treated with RT or surgery, the subsequent disease-free interval is highly variable, ranging from a few months to many years.^{335,336,338,341,343,386,403} Uveal melanoma is characterized by early micrometastasis (often before treatment) followed by variable latency period before emergence of overt metastasis.⁴⁷⁷ Local recurrence is rare, occurring in less than 10% of patients after treatment with the modalities recommended in these guidelines.^{49,231,273,306-308,330-342} Development of detectable distant metastatic disease is much more common than local recurrence, and happens in up to 70% of patients, depending on the stage and other risk factors at the time of diagnosis.^{10,15,28,289}

Follow-up for the Treated Eye

At NCCN Member Institutions, standard follow-up in the affected eye includes imaging with color fundus photography and ultrasonography every 3 to 6 months for 3 to 5 years, then every 6 to 12 months thereafter, if stable. Serial orbital MRI may be used as clinically indicated. The frequency of follow-up should depend on the size and location (eg, juxtapapillary location, ciliary body involvement) of the tumor at presentation, as these factors impact the risk for recurrence. Radiation-related retinopathy and other treatment-related complications may occur at any time following treatment.

For patients treated with enucleation in the COMS trial, there were follow-up clinical and ophthalmologic exams at 1 to 2 weeks after surgery to assess healing status, and at 6 months, 12 months, and annually thereafter, in which the eye socket and eyelids were examined for possible recurrence or complications, and the fit of prosthesis checked.^{291,319,478}

For patients treated with RT in prospective studies, follow-up exams typically included complete ophthalmologic exam of the treated eye, with



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indirect ophthalmoscopy, slit-lamp exam, tonometry, color fundus photography, A-scan and B-scan US, and measurement of VA and visual field. Many prospective studies also included fluorescein angiography in follow-up exams, either at regular intervals or as needed.^{49,227,230,231,330-332,334,336,338,341-343,345,346,379,383-385,395,398,399,402-404,410,478-480} A few prospective studies used gonioscopy,^{231,403} OCT,^{332,345,346} or MRI.^{398,410} For patients who were treated with brachytherapy in the COMS study, follow-up included an exam within 6 weeks of surgery, at 6 months after treatment, then every 6 months for 5 years, and every 12 months thereafter.²⁹¹ Patients with suspected tumor growth had more frequent follow-up exams. Whereas some prospective studies in patients treated with brachytherapy had follow-up protocols similar to COMS,^{331,338,379} others used more frequent follow-up, with more than 2 exams per year during the first year or first few years after treatment, and exams every 6 to 12 months during later years.^{49,330,334-336,341-343,347,480} Prospective studies following patients after particle beam RT or SRT sometimes had frequent follow-up during the first 6 months after treatment (eg, 3–5 exams in the first 6 months),^{227,394,395,398,399,481} and most had follow-up exams at least every 3 to 4 months during the first year or two.^{49,227,336,389,394,399,402-404} A few studies switched to the 6-month follow-up interval starting early (<1 year) from treatment.^{383,384,395,410,479,481} Long-term follow-up intervals ranged between 4 to 12 months.^{49,227,336,383,389,394,395,398,399,402,403,410,481}

Risk in Contralateral (Fellow) Eye

All patients should receive follow-up for the affected eye. In patients with uveal melanoma, the contralateral eye is not at increased risk of uveal melanoma,^{12,307,482,483} and should be followed with routine ophthalmologic care including routine eye protection for the remaining eye (eg, polycarbonate glasses).

In the COMS trials of patients with medium or large primary uveal melanoma tumors, prospective monitoring showed that less than 1% of

patients developed disease in the contralateral eye during follow-up after primary treatment.^{307,482,483} Moreover, for the majority of patients who did not develop disease in the contralateral eye, results from regular ophthalmologic exams showed that good VA was retained in their fellow eye throughout the 10 years of follow-up, regardless of the modality used to treat the primary lesion.⁴⁸⁴ Analysis of 8165 patients with ocular melanoma in the SEER database found bilateral involvement in 0.1% of patients.¹² One retrospective study of 52 cases of bilateral uveal melanoma suggests prognosis is similar to that of unilateral cases.⁴⁸⁵ Rare instances of uveal melanoma metastasizing to the contralateral eye are described in case studies.⁴⁸⁶⁻⁴⁹⁴

Patterns of Metastases

Most uveal melanomas are localized at first presentation, and only less than 3% of cases have detectable metastatic disease at the time of diagnosis.^{6,12-16,167,495} Development of distant metastatic disease is much more common, occurring in ~20% to 70% of patients within 20 years after treatment for primary uveal melanoma, depending on stage/size and genetic characteristics of the tumor at diagnosis.^{10,15,28,50,69,289} Large retrospective studies (N > 7000) found that after long-term follow-up, 20% of patients with stage I disease at diagnosis developed metastasis, in contrast to ~70% for those with stage III disease.^{15,289} Prospective studies have shown that the cumulative rate of development of distant metastatic disease steadily increases even after 6 to 20 years of follow-up.^{49,331,332,335,336,341,343,385,386,394,396,402,403,482,483} In the COMS studies, the Kaplan-Meier estimates of 2-, 5-, and 10-year metastasis rates were 10%, 25%, and 34%.⁴⁸³

Sites of Metastasis

Uveal melanoma most often metastasizes to the liver (90% of the time).^{21,23,24,167,307,482,483,496-503} Other common sites of metastasis, listed in order of decreasing prevalence, are lung, bone, skin/soft tissue, and lymph



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nodes.^{13,23,167,307,389,394,482,483} In large prospective studies following patients after treatment for primary uveal melanoma, metastasis to the lung was observed in 20% to 30% of patients who developed distant metastasis, to the bone in 16% to 18%, to skin/soft tissue in 11% to 12%, and to lymph nodes in 10% to 11%.^{307,482} Retrospective studies show similar trends.^{23,503} A few studies reported brain metastases in 4% to 5% of patients who developed distant metastases.^{23,307,482} Most patients who develop metastasis ultimately have multiple sites involved; however, the first site is typically the liver.^{21,23,24,307,482,499}

Risk Factors for Metastasis

Risk factors for metastasis include a variety of genetic markers as well as tumor size at presentation. The NCCN Guidelines list specific risk factors to be used for risk stratification to determine the frequency of surveillance imaging during follow-up. The NCCN Guidelines recommend using AJCC T stage for risk stratifying according to primary tumor size. T1 is considered low risk, T2 and T3 medium risk, and T4 high risk. For patients who had a biopsy of their primary tumor, certain molecular features have been shown to be prognostic for risk of distant spread, and should be used for risk stratification. Gene expression profiling (GEP) as described by Onken et al⁵⁰ is recommended to determine whether the tumor is Class 1A (low risk), Class 1B (medium risk), or Class 2 (high risk) to inform frequency of follow-up.⁵⁰⁴⁻⁵⁰⁶ It has been shown that Class 2 was associated with a 5-fold to 20-fold higher risk of metastasis than Class 1.^{50,256,507-517} The following chromosomal abnormalities are also considered risk factors that should inform frequency of follow-up: disomy 3 (low risk), gain of chromosome 6p (low risk), monosomy 3 (high risk), and gain of chromosome 8q (high risk). Mutations in several genes have also been shown to be prognostic for distant metastasis, and should be used for risk stratification: *EIF1AX* (low risk), *SF3B1* (medium risk), and *BAP1* (high risk). PRAME expression is also an indicator of high risk to be used to inform frequency of follow-up. If biopsy was not performed, medium- or

high-risk pathways should be followed, depending on whether any high-risk features are present.

Although the AJCC staging system is based on survival data from large epidemiologic studies,^{14,15,20} characteristics used for AJCC staging have also been shown to be prognostic for development of distant metastasis. T stage is based on the largest basal diameter and thickness of the primary tumor, as well as the presence or absence of ciliary body involvement and presence and size of extraocular extension.³³ Multiple prospective studies and several large retrospective studies (N > 1000) have shown that primary tumor diameter and/or thickness is associated with risk of metastasis after primary treatment.^{94,328,336,341,386,467,511} Additionally, several retrospective studies on large patient populations have found that risk of metastasis is correlated with AJCC T stage and with AJCC staging.^{10,15,288,503,516,518-521}

Multiple tumor molecular markers have been shown to be associated with increased risk and/or shorter time to development of distant metastases. Chromosomal changes were among the first molecular markers to be found to be associated with risk of distant metastasis in patients with uveal melanoma.⁵²² Multiple studies have found that monosomy 3 and gain of chromosome 8q, especially when numerous copies are found, in the primary uveal melanoma is associated with increased risk of metastasis.^{26,38,50,69,328,508,517,523-537} Risk of metastasis is even higher when both of these abnormalities are present.^{26,69,524,527,529,533} Some studies have identified additional chromosomal abnormalities associated with increased risk of metastasis, such as loss of 8p,^{26,524,526,527,529} loss of 1p,⁵²⁹ loss of 16q,⁵²⁴ and loss of 6q.²⁶ Gain of 6q may be protective against metastasis,⁵²⁹ at least in the context of monosomy 3 and gain of 8q.²⁶

Mutation and expression of certain genes have also been associated with risk of metastasis in patients with uveal melanoma. Multiple studies have found that *BAP1* mutation/deletion (observed in approximately half of



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uveal melanomas) and loss of *BAP* expression in the primary tumor is associated with increased risk of metastasis.^{38,74,512,517,518,520,534,538,539} One study showed that risk of metastasis is highest with *BAP1* somatic mutation, and somewhat elevated with *BAP1* germline mutation.⁵³¹ Other studies found that *BAP1* mutation was associated with early metastasis.^{540,541} Mutation in *EIF1AX*, found in up to 20% of uveal melanomas,^{38,512,536,542} has been associated with lower risk of distant metastasis.^{520,540,541} *SF3B1* mutation, which is present in approximately 20% of uveal melanomas, was associated with lower risk of metastasis,^{38,75} while some studies reported that patients with this mutation developed late metastases.^{520,540,541} PRAME expression, present in about a third of uveal melanomas, has also been associated with increased risk of metastasis.^{513,516,543}

Follow-up for Distant Metastasis

Given the lack of high-quality data to inform the frequency or modality of follow-up screening for distant metastatic disease, the NCCN recommendations are based on clinical practice at NCCN Member Institutions. Patients with no evidence of disease (NED) after treatment for uveal melanoma should be followed for signs of metastatic disease. The most frequent site of metastasis is the liver and other sites include lungs, skin/soft tissue, and bones. Recommended follow-up for distant metastatic disease includes imaging to evaluate signs or symptoms of distant metastasis, and may include regular surveillance imaging. Liver function tests (LFTs) may be considered as a component of follow-up visits, although some studies showed poor sensitivity for early detection of liver metastases.

For patients who elect to have surveillance imaging to screen for distant metastatic disease, options include contrast-enhanced MR or US of the liver, with modality preference determined by expertise at the treating institution. Additional imaging modalities may include

chest/abdominal/pelvic CT with contrast, or dual-energy subtraction chest x-ray. However, screening should limit radiation exposure whenever possible. Scans should be performed with IV contrast unless contraindicated. Recommendations for imaging modality are based on clinical practice at NCCN Member Institutions, as there are very few data to inform selection of modality. Providers may also want to discuss mental health resources with patients. See the NCCN Guidelines for Survivorship (www.NCCN.org). Participation in a clinical trial is strongly encouraged.

For those choosing to have regular surveillance, the recommended frequency is based on the risk of distant metastasis. The NCCN Guidelines recommend risk stratifying patients into low, medium, and high risk of distant metastasis based on the highest risk factor present. For patients with high risk of distant metastasis who opt to have surveillance imaging, the recommended frequency is every 3 to 6 months for 5 years, then every 6 to 12 months for years 6 through 10, then as clinically indicated. For patients with medium risk of distant metastasis who opt to have surveillance imaging, the recommended frequency is every 6 to 12 months for 10 years, then as clinically indicated. For patients with low risk of metastasis who opt to have surveillance imaging, consider imaging every 12 months. Adjusting follow-up frequency based on risk of metastasis is based on clinical practice at NCCN Member Institutions, and this approach has not been prospectively tested to determine whether it results in better yield from imaging or better outcomes.

There are few data to inform the frequency and modality of follow-up screening for development of metastatic disease. Prospective studies have typically monitored for development of distant metastasis using complete cancer-oriented physical exams, and one or more of the following: chest x-ray, liver US, and serum LFTs. Most of these studies followed patients every 6 months for at least the first 5 years.

^{21,23,24,49,167,307,319,330,332,336,338,379,395,399,403,479,482,483,499} For these studies, the



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total number of patients who developed distant metastases was usually too small to produce meaningful results regarding the sensitivity and specificity of different surveillance modalities. The value of surveillance imaging and tests is also controversial because it is unclear whether early detection of distant metastases improves outcomes, given that most treatments for distant metastatic disease are relatively ineffective. Some retrospective studies found that survival was better for patients whose distant metastases were asymptomatic at the time of detection,^{497,544} whereas other studies observed no such correlation.^{23,545,546}

The utility of LFTs for early detection of liver metastases is an issue of ongoing debate. In the COMS trials for patients with medium and large tumors, the sensitivity, specificity, positive predictive value, and negative predictive value associated with at least one abnormal LFT before first diagnosis of metastasis at any site was 14.7%, 92.3%, 45.7%, and 71.0%, respectively. Of the LFTs, APH had the highest diagnostic attributes. These results suggest that the use of LFT results followed by other diagnostic tests has high specificity and predictive values, but low sensitivity.⁴⁸² Whereas 739 patients had distant metastases detected during follow-up, 13 did not have their metastasis discovered until time of death.⁴⁸³ While some analyses supported LFTs as one of the most useful methods for screening,^{498,547-551} others argue that the specificity and sensitivity of these tests is too low to warrant routine use.^{501,502,552}

The optimal strategy for imaging surveillance is also an issue of debate. Each of the methods commonly used (ie, chest x-ray, CT, US, MRI, PET/CT) has produced varying results.^{498-502,549,553-564} Due to the low probability of metastasis at any specific time point, the yield of these tests is low, and there is concern regarding cumulative radiation exposure due to the long-term follow-up.⁵⁶⁵ Therefore, imaging is usually focused on the liver, and liver US and MRI are favored over CT or PET/CT. Some studies have found MRI to be moderately better than CT or PET/CT,^{553,557,559} and

in high-risk patients, showed promising results for early detection of liver metastases.^{502,560}

Risk of Developing Secondary Cancers During Follow-up

Due to the long-term surveillance needed for detection of distant metastatic disease in patients with uveal melanoma, it is not uncommon for screens to identify other primary cancers.^{13,162,163,165,563,566-569} The two COMS randomized trials in patients with medium to large primary uveal melanomas showed that the proportion of patients with secondary cancers increased steadily over the entire duration of follow-up (median 10 years, range 5–16 years).⁵⁶⁷ Various types of secondary malignancies were observed.^{162,567} Uveal melanoma may increase the risk of developing other cancers,¹⁶³ especially in patients with familial uveal melanoma or other familial cancers.^{116,117}



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Management of Ocular Recurrence

Workup for Ocular Recurrence

If a recurrence is detected, workup should include H&P to identify any signs or symptoms associated with recurrence or metastasis. Biopsy may also be appropriate. Whereas intraocular recurrence can often be diagnosed and managed without a biopsy, additional prognostic FNA biopsy may be valuable to determine whether the tumor has developed any high-risk features that warrant more frequent surveillance. Extraocular recurrence or metastasis should be confirmed histologically whenever possible or if clinically indicated. Appropriate biopsy techniques in this setting may include FNA or core biopsy. For patients with metastasis who are considering treatment with targeted therapy, tissue should be obtained for genetic analysis (screening for mutations that may be potential targets for treatment or to determine eligibility for a clinical trial) from either biopsy of the metastasis (preferred) or archival material. Broader genomic profiling may be considered if the results could inform future treatment decisions or eligibility for clinical trials.

Patients with local recurrence should have ocular orbital imaging (if not recently previously done or as clinically indicated) to evaluate the extent of local recurrence. Patients who develop distant metastatic disease after treatment of primary uveal melanoma should have ocular orbital imaging as part of workup to check for local recurrence, since asymptomatic local recurrences may be present at the time distant metastasis is discovered. Workup for patients with recurrence should include broader imaging to evaluate the extent of local recurrence/distant metastasis, and/or for baseline staging. Since the most frequent site of metastasis is the liver and other sites include lungs, skin/soft tissue, and bones, imaging options for baseline staging in patients with recurrence or metastasis include contrast-enhanced MR or US of the liver, with modality preference determined by expertise at the treating institution. Additional imaging may include chest/abdominal/pelvic CT with contrast and/or whole-body FDG

PET/CT; however, screening should limit radiation exposure whenever possible. Brain MRI with IV contrast may be performed if neurologic symptoms are present, but routine CNS imaging is not recommended. All scans should be performed with IV contrast unless contraindicated.

Treatment for Ocular Recurrence

The recommended treatment options for local recurrence depend on the extent of disease. For intraocular recurrence (limited to the eye, without orbital involvement), the recommended options include RT, either by plaque brachytherapy or particle beam, enucleation, or laser ablation. For small recurrences in patients who cannot undergo RT or surgery, TTT is recommended. TTT is usually reserved for small recurrences, particularly when recurrence is likely due to incomplete plaque coverage during primary brachytherapy; it is generally not appropriate for recurrences occurring within the RT field or recurrences that may be too thick (>3 mm) for laser treatment to reach the base. If there is extraocular involvement, surgical resection is needed, but can be coupled with RT to the orbit (particle beam or photon beam) and/or cryotherapy to the orbital tumor. Surgical resection may potentially include partial orbital tumor resection, enucleation, or exenteration. Besides surgical resection, RT with plaque brachytherapy or particle beam alone might be offered. If there is orbital involvement and the patient has had prior enucleation, options include surgical resection or cryotherapy to the orbital tumor, and/or RT to the orbit (particle beam or photon beam) (See *Principles of Radiation Therapy* in the algorithm).

Given the rarity of local recurrence after treatment of primary uveal melanoma, data on treatment of local recurrences are scant, and it is unclear which approaches result in the best outcomes. Most studies had fewer than 10 patients with local recurrence, and many studies either managed all local recurrences with enucleation or did not report on retreatment approaches. In the few studies that reported outcomes after



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treatment of local recurrence (N ≥ 10),^{361,387,403,440,455,570-574} reasonably high rates of local control were achieved with the following globe-conserving modalities: laser photocoagulation,^{361,387} TTT,^{455,573} proton-beam RT,^{387,440,571-573} and plaque brachytherapy RT.^{403,455,573,574} Similar to the primary treatment setting, some patients treated with globe-conserving therapy for local recurrence subsequently underwent enucleation due to (suspected or confirmed) tumor regrowth or complications such as pain and neovascular glaucoma.^{361,387,440,570,571,573,574} Results from one retrospective study of 73 patients with local recurrence suggest that treating recurrence with proton-beam RT (N = 31) versus enucleation (N = 42) may result in similar metastasis-free survival and OS.⁵⁷² Another retrospective analysis of 51 patients with local recurrence found that local control after treatment of recurrence was more likely in those with longer intervals between primary treatment and development of recurrence.³⁶¹

Management of Metastatic Disease

Survival after detection of distant metastatic disease varies widely across studies, including those with large patient samples (N > 100), with median OS ranging from 3 to 30 months.^{23-25,483,497,575-578} Several studies have found that a small percentage of patients with uveal melanoma metastasis experience long-term survival (≥5 years) after development of distant metastatic disease.^{21,23,483} Others have shown a bimodal distribution of separate populations with short-term survival (median OS <1 year) and long-term survival (median OS >2 years).^{21,23,579} Conflicting data exist for a wide range of factors that have been associated with OS after detection of metastasis including older age, male sex, and poor performance status.^{21-24,483,499,503,545,575,578,580-582} Other factors include the presence of symptoms versus asymptomatic metastasis detected by surveillance, shorter disease-free interval before metastasis, higher number of anatomic sites involved, involvement of the liver, and greater disease volume.^{21-24,499,503,544-546,558,575,578,580-587} In addition, elevated liver enzymes at the time of diagnosis of metastasis, particularly lactate dehydrogenase (LDH) and alkaline phosphatase (APH), have been associated with shorter OS.^{21,22,24,499,575,578,580-582,585}

Whereas in recent years the options for treating metastatic cutaneous melanoma have dramatically improved, treatment of distant metastases from uveal melanoma still presents a major clinical challenge. Several retrospective studies suggest that treatment for distant metastases from uveal melanoma improves survival, although it is unclear whether these results are influenced by selection bias.^{23,25,503,582,586} Other studies did not find that treatment improved survival.^{483,581} Patients treated with supportive care reported a median OS ranging from 1.7 to 4.9 months, although those opting for supportive care are more likely to have risk factors for poor survival.^{25,503,586} For treatment of distant metastasis from uveal melanoma, a wide variety of approaches have been tested, including surgery, RT, ablative approaches, vaccines, systemic therapies



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(chemotherapies, immunotherapies, targeted therapies, and combined regimens), and localized chemotherapy/immunotherapy.^{24,575-577,587-589}

Systematic reviews, meta-analyses, and retrospective studies suggest that the best outcomes are seen in patients who received liver-directed treatments, particularly those treated with surgery when complete resection was achieved.^{21,24,502,544,545,575,576,580,582,583,587,590,591} It is unclear whether these effects are due to other factors, such as lower volume of metastatic disease, which would make a patient eligible for surgery and/or liver-directed treatments, and more likely to have complete resection. One phase III randomized trial (EORTC 10821) found no difference in OS in 171 patients with liver metastasis from uveal melanoma treated with IV fotemustine versus hepatic arterial infusion (HAI) with fotemustine, despite the HAI approach showing higher response rates and longer progression-free survival (PFS).⁵⁹² A few studies suggest that better survival was seen in those who had a response to therapy for metastatic disease,^{23,575} but some did not find an association.²¹

Workup for Distant Metastatic Disease

Workup for distant metastatic disease includes biopsy if clinically appropriate. Similar to workup for ocular recurrence, metastasis should be confirmed histologically whenever possible or if clinically indicated. Biopsy techniques may include FNA or core. Tissue should be obtained for genetic analysis (screening for mutations that may be potential targets for treatment or determine eligibility for a clinical trial) from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling should be considered if the test results might guide future decisions or eligibility for participation in a clinical trial. Imaging can be considered for baseline staging and to evaluate specific signs and symptoms. Since the most frequent site of metastasis is the liver and other sites include lungs, skin/soft tissue, and bones, imaging options include contrast-enhanced MR or US of the liver, with modality preference determined by expertise at

the treating institution. Additional imaging may include chest/abdominal/pelvic CT with contrast and/or whole-body FDG PET/CT; however, screening should limit radiation exposure whenever possible. Brain MRI with IV contrast may be performed if neurologic symptoms are present, but routine CNS imaging is not recommended. All scans should be performed with IV contrast unless contraindicated. Testing of LFTs, including LDH, and alkaline phosphatase should be considered for their potential prognostic value.

Treatment for Distant Metastatic Disease

Given that there are no treatments for metastatic uveal melanoma, except for the recently FDA-approved tebentafusp, that have clearly and consistently been shown to improve outcomes, it is important to consider all clinical trial options carefully, and when available and clinically appropriate, enrollment in a clinical trial is recommended. For those who are not appropriate for treatment in the context of a clinical trial, the recommended options are largely based on clinical practice at NCCN Member Institutions. It is important to be aware that even among therapies often used at NCCN Member Institutions, efficacy is limited, and it is not clear which approaches are most effective. Therefore, the guidelines indicate that a combination of approaches may be needed, and it is important to consider each patient's prognosis and treatment goals to determine whether palliative care is the most appropriate option.

Selection of treatment should depend on the location and extent of disease. For patients with metastasis to the liver, liver-directed therapies should be considered. Options include: hepatic isolation perfusion, embolization (ie, chemotherapy, radiation, immunotherapy), and ablative procedures (ie, thermal ablation, cryotherapy). For patients with extrahepatic disease or hepatic disease that is not amenable to liver-directed therapy, systemic therapy can be considered. A recently reported phase III randomized trial was conducted in previously untreated HLA-



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A*02:01-positive patients with metastatic uveal melanoma. Patients were randomized to tebentafusp (a bispecific protein) or investigator's choice of either pembrolizumab, ipilimumab, or dacarbazine. Results showed that treatment with tebentafusp resulted in longer OS compared with control therapy.⁵⁹³ The literature is not directive regarding other systemic therapies. However, individual patients may derive benefit on occasion from agents used to treat metastatic melanoma of cutaneous origin. Clinical trials are preferred given the lack of data.

For both hepatic and extrahepatic metastases, patients with limited or symptomatic disease should consider resection and/or RT by photon beam or SRS. Recommendations for treating uveal melanoma metastases with RT can be found within *Principles of Radiation Therapy* in the algorithm and within *Principles of Radiation for Metastatic Disease* in the NCCN Guidelines for Melanoma: Cutaneous (available at www.NCCN.org).

Following treatment for metastatic disease, patients should receive imaging to assess response or progression. The recommended cross-sectional imaging modalities are the same as those recommended for workup. Those with NED after treatment for metastases may be eligible for clinical trials testing adjuvant therapies. If they opt to forgo adjuvant treatment, then the recommended follow-up surveillance is similar to the follow-up for patients with NED after treatment of localized disease (Refer to Guidelines section *UM-4 Follow-up* in the algorithm). If post-treatment imaging shows residual or progressive disease, the NCCN Panel recommends trying other options for treatment of distant metastatic disease.

Resection of Metastases

As mentioned above, multiple prospective and retrospective studies and meta-analyses have found that among patients with metastatic uveal

melanoma, those who can be treated with surgery have the best outcomes, especially if complete resection is achieved.^{23,544,545,575-577,583,587,591,594-598} Multiple studies have reported median OS greater than 20 months after resection of uveal melanoma metastases.^{23,544,545,577,587,591,594,595,597-602} For liver metastases, rates of complete resection ranged from 27% to 88%.^{23,545,583,587,594,595,598,600} Multiple studies reported on combination therapy with resection and hepatic arterial infusion, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), or adjuvant systemic therapy.^{544,545,577,587,594,599,603-605}

Liver-Directed Therapy

Regional Isolation Perfusion

Several techniques have been developed for localized delivery of pharmaceutical therapy to the liver since theoretically, higher doses can be administered locally than would be feasible systemically due to toxicity. Methods include isolated hepatic infusion (IHP), percutaneous hepatic perfusion (PHP), HAI, and embolization techniques. Liver metastases derive most of their blood supply from the hepatic artery, whereas the blood source for benign hepatocytes is primarily the portal vein.⁶⁰⁶ IHP and HAI both deliver therapy via the hepatic artery to maximize drug delivery to liver metastases while limiting exposure to healthy parenchyma.⁶⁰⁷ Whereas IHP is done during surgery, has risk of morbidity, and usually can only be done once, HAI and PHP are less invasive techniques, with lower risk of morbidity, and have the potential to be performed multiple times to increase depth of response.^{577,591,607-609}

IHP is an open surgical procedure involving vascular isolation of the liver, allowing high doses of heated chemotherapy to be directly delivered to the organ through an arterial catheter.⁵⁹¹ Several small prospective studies (n < 40)⁶¹⁰⁻⁶¹⁴ and a few retrospective studies (N = 19-68)⁶¹⁵⁻⁶¹⁸ have tested hyperthermic IHP in patients with liver metastasis from uveal melanoma.



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The agent most commonly used in these studies was melphalan, with or without tumor necrosis factor alpha (TNF-alpha) or cisplatin.⁶¹⁰⁻⁶¹⁴ Good response rates to IHP have been reported in some of these prospective studies (overall response rate [ORR], 50%–68%),⁶¹⁰⁻⁶¹³ as well as retrospective studies (ORR, 67%–83%).⁶¹⁵⁻⁶¹⁷ However, the IHP procedure is often lengthy (>8 hours),^{577,591,609-611} involves significant blood loss (median 2–3.5 L),^{577,610,611} involves long hospital stays (7–10 days),^{591,609-611,617,618} can result in significant complications/morbidities (eg, portal vein thrombosis, transient grade 3/4 hepatic toxicity),^{591,609-612,615-618} and mortalities from the procedure were also observed.^{609,610,615,618} For these reasons IHP is not widely used.

PHP is a simpler, less invasive alternative to IHP that can be repeated.^{591,608} It uses a double-balloon catheter inserted into the inferior vena cava to isolate hepatic venous blood that is then filtered extracorporeally.^{591,608} Several prospective studies tested PHP in patients with liver metastases from uveal melanoma, but efficacy results are lacking.⁶¹⁹⁻⁶²¹ Retrospective studies suggest good response rates (>40%), especially if multiple rounds are used.⁶²²⁻⁶²⁵ In all these studies melphalan was the agent used.⁶¹⁹⁻⁶²⁵ PHP appears to be somewhat better tolerated than IHP, with no treatment-related fatalities, but many patients still experienced hematologic grade 3–4 events, some had non-hematologic grade 3–4 adverse events (AEs) (eg, bleeds, thromboembolism), and some had extended hospital stays (4–5 days) or had to be readmitted.^{621-623,626}

HAI is a technique using catheters in the hepatic artery to deliver chemotherapy directly to the liver.⁵⁹¹ The number of times HAI can be repeated depends on the type of catheter used.⁵⁹¹ Efficacy of HAI for liver metastases from uveal melanoma has been reported in several small prospective studies (N = 8–31)⁶²⁷⁻⁶³¹ and several retrospective studies (N = 10–100).⁶³²⁻⁶³⁶ Most of these studies used fotemustine,^{628,629,632,633,635} but

other agents tested include carboplatin,^{627,635} nab-paclitaxel,⁶³⁰ decitabine,⁶³¹ a combination of cisplatin, vinblastine and dacarbazine,⁶³⁴ and melphalan.⁶³⁶ Response rates to HAI were lower and more variable than for IHP in both prospective (ORR, 0%–44%)⁶²⁷⁻⁶³¹ and retrospective studies (16%–36%).^{632,635} In the phase III randomized trial EORTC 10821 in patients with liver metastasis from uveal melanoma, no difference in OS was observed for IV fotemustine versus HAI fotemustine (median OS, 13.8 vs. 14.6 months), despite the HAI approach showing higher response rates (2.4 vs. 10.5%) and longer PFS (median 3.5 vs. 4.5 months; HR, 0.62; 95% CI, 0.45–0.84, *P* = .002).⁵⁹² Complication rates varied widely across studies, but in general appear to be lower than those reported for IHP, and are manageable.^{592,627-629,632,633,635,636} Grade 3/4 AEs were mostly hematologic (eg, anemia, leukopenia, thrombocytopenia, neutropenia).^{592,627,631-633} Grade 3–4 catheter-related complications occurred in a minority of patients (≤12%), as did liver toxicity (<10%).^{592,632} Deaths from toxicity were reported in one study,⁵⁹² but not in others.

Hepatic Embolization

Hepatic arterial embolization is a method for delivering to the liver chemotherapy, immunotherapy, or radioactive agents, while increasing dwell time and providing selective ischemia.^{591,609}

Hepatic Chemoembolization

There are no standard protocols for hepatic chemoembolization, also called hepatic TACE or hepatic arterial chemoembolization (HACE). In general, two approaches have been used for treatment of uveal melanoma metastases to the liver. One involves HAI with the active agent, followed by addition of either a transient or permanent embolic agent.^{591,609} The active agent is usually mixed with ethiodized oil (to increase dwell time), and embolization agents include absorbable gelatin sponge or polyvinyl alcohol particles.^{591,609} The other approach uses drug-eluting beads produced from a polyvinyl alcohol hydrogel that has been modified with



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sulfonate groups for the controlled loading and delivery of chemotherapy agents.⁶⁰⁹ These beads provide localized drug delivery and serve as an embolic agent to render tumors ischemic.⁶⁰⁹

Multiple retrospective⁶³⁷⁻⁶⁴⁴ as well as a few prospective studies⁶⁴⁵⁻⁶⁴⁸ have evaluated chemoembolization for the treatment of hepatic metastasis in patients with uveal melanoma. Using traditional methods (active agent infusion + addition of embolic agent), response rates varied widely, but could be as high as 57%.^{637,638,640,641,643-649} Chemotherapies used included BCNU, mitomycin C, fotemustine, cisplatin, carboplatin, doxorubicin, and 1,3-bis (2-chloroethyl)-1-nitrosourea; embolic agents used included gelatin sponge, polyvinyl sponge, resorbable microspheres, and polyvinyl alcohol particles.^{637,639,640,642-649} Only a few studies reported outcomes for patients with liver metastases from uveal melanoma that were treated with trans-arterial chemotherapy-eluting beads.⁶⁵⁰⁻⁶⁵² One phase II study reported 100% ORR in the 10 patients treated with irinotecan-loaded polyvinyl alcohol microspheres.⁶⁵⁰ In contrast, a retrospective study of irinotecan-loaded beads in 28 patients reported much lower response rates.⁶⁵² A retrospective study including 58 patients treated with TACE using irinotecan-charged microbeads reported an ORR of 27.5% (all partial responses).⁶⁵³ Another prospective noncontrolled study testing beads loaded with doxorubicin only reported toxicity and quality of life.⁶⁵¹

Comparisons of hepatic chemoembolization with other treatments for uveal melanoma liver metastasis are limited. One retrospective study compared cisplatin-based chemoembolization (TACE) versus HAI or systemic therapy, and found that chemoembolization was associated with the best response rate, although OS did not differ between the groups.⁶³⁸ However, those who responded to TACE had better OS than those who did not respond and better than those treated with HAI or systemic therapy.⁶³⁸ Other studies also reported that OS was better in responders to

chemoembolization versus non-responders,^{638,641,642,644,645,647} whereas others did not find a significant association.^{646,653}

Chemoembolization seems to be generally well tolerated, with few or no treatment-related deaths.^{640,646,648,649,651-654} AEs reported in more than one study include abdominal pain, fever, nausea, vomiting, liver dysfunction, and thrombocytopenia.^{637,640,643,644,648,650,652,653} Some studies recommend supportive treatment with antibiotic and antiemetic prophylaxis, IV hydration, and major analgesic before and after the procedure.^{648,650}

Hepatic Radioembolization

Hepatic radioembolization, also called hepatic transarterial radioembolization (TARE) or selective internal RT (SIRT), is a procedure in which glass or resin yttrium-90 microspheres are introduced to the hepatic artery, both as a mechanism for radiation delivery and for embolization.⁶⁰⁹ Response rates from retrospective studies varied widely (6%–100%), but disease control rate was consistently greater than 50%.⁶⁵⁵⁻⁶⁶⁰ A phase II study reported ORR of 39% in the 23 patients who received radioembolization as first-line treatment for liver metastasis, and ORR of 33% in the 24 patients who received radioembolization after progression on immunoembolization, with disease control rates of 87% and 58%, respectively.⁶⁶¹ Across studies, radioembolization was well tolerated, with most toxicities being grade 1–2 and self-limiting, and no treatment-related deaths.⁶⁵⁵⁻⁶⁵⁹ AEs included abdominal pain/discomfort, nausea and vomiting, LFT elevation (sometimes due to progression), transient lymphopenia, and gastric ulcer.^{656-659,661}

Hepatic Immunoembolization

Hepatic immunoembolization involves infusion of an immunologic stimulant into the hepatic artery, followed by addition of an embolizing agent.⁶⁰⁹ Several studies have tested immunoembolization using granulocyte-macrophage colony-stimulating factor (GM-CSF) ethiodized



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oil plus a gelatin sponge.^{662,663} A phase I trial with 34 uveal melanoma patients and unresectable liver metastases occupying less than 50% of total liver volume reported an ORR in the liver of 32%, and response correlated with better OS.⁶⁶² A phase II randomized trial with 52 patients with uveal melanoma and hepatic metastases only (also <50% liver volume) reported an ORR of 21.2% for the 25 patients treated with immunoembolization versus 16.7% for the 27 who received bland embolization (GM-CSF replaced with saline).⁶⁶³ In this study hepatic response was not correlated with OS, but was associated with better PFS. AEs associated with immunoembolization in these studies included abdominal pain, fever, nausea, and transient increases in hepatic enzymes and there were no treatment-related deaths.^{662,663}

Ablative Procedures for Liver Metastases

Although ablative procedures such as thermal ablation and cryotherapy have been used with some success for liver metastases from other kinds of cancer, there are very few reported clinical data on the efficacy of these techniques for liver metastases from uveal melanoma.^{599,604,664-667} The supposed advantage of ablative techniques is that these techniques can be useful for tumors that are difficult to resect, and compared to surgery, are tissue-sparing, less invasive, cost-saving, and have lower rates of complications, while still being potentially curative.⁶⁶⁸ The most commonly used methods of thermal ablation for liver tumors include RFA and microwave ablation (MWA).⁶⁶⁸⁻⁶⁷⁰ Both methods use heat induction and destroy tissue through thermally induced coagulative necrosis. Based on data from other (non-uveal) types of liver tumors, safety of MFA and RFA appears similar with rare major complications (<3%).⁶⁷⁰⁻⁶⁷⁴ On the other hand, cryoablation dehydrates and causes irreversible cell damage and cell death by using rapid gas expansion at a probe tip to quickly cool surrounding tissues to as low as -140°C.^{668,669,675-677} Complications may include pain, infection (eg, wound infection, pneumonia), hemorrhage, biliary injury, thrombocytopenia, pleural effusion, and renal

impairment.^{669,675,677,678} Whereas some studies found that cryoablation was more likely to cause complications compared with RFA, other analyses suggest that complication rates are similar to RFA, especially in more recent studies.^{668,669,675,676,678-680}

Outcomes have been reported for patients with liver metastases from uveal melanoma treated with RFA^{599,604,665,667} and laser-induced interstitial thermotherapy (LITT).⁶⁶⁴ The efficacy and safety of ablative techniques is difficult to ascertain, because most of these studies contained fewer than 20 patients with uveal melanoma,^{604,664-667} combined results for patients with uveal melanoma and other types of melanoma,^{665,666} or combined results for the ablative therapy with other therapies.^{599,604,664,667}

Nonetheless, several retrospective studies reported relatively long median OS of greater than 20 months in cohorts of uveal melanoma patients with liver metastases treated with LITT (±TACE),⁶⁶⁴ RFA,⁶⁶⁵ or percutaneous thermal ablation (± systemic therapy).⁶⁶⁶ In a retrospective study of uveal melanoma patients with liver metastases treated with surgery alone (N = 57) or a combined approach in which some metastases were resected and others treated with RFA (N = 13), those treated with the combination approach had similar disease-free survival as those treated with surgery alone (median 7 vs. 10 months) and OS (median 28 vs. 27 months).⁵⁹⁹ Moreover, there were no recurrences at the 22 sites treated with RFA after a median follow-up of 63 months.⁵⁹⁹ These results suggest that RFA may be as effective as surgery, and could be used in lieu of surgery for metastases that are difficult to resect.

External Beam Radiation for Uveal Melanoma Metastases

Published data on external beam RT for uveal melanoma metastases are extremely scant with no study reporting outcomes or palliative effects.



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Systemic Therapy for Distant Metastatic Disease

Many systemic therapies have been tested in prospective trials as treatment for metastatic uveal melanoma, including immunotherapies,⁶⁸¹⁻⁶⁹⁴ chemotherapies,^{592,695-705} targeted therapies,^{702-704,706-716} and systemic therapy combinations.^{698,701,717-735} For treatment of metastatic uveal melanoma, systemic therapies have largely been tested in small phase II studies and most have shown little activity (response rate <10%),^{589,591,593,736-738} especially compared with the efficacy of checkpoint immunotherapies and BRAF/MEK inhibitor combinations in metastatic cutaneous melanoma.⁷³⁹⁻⁷⁴⁷ The few larger randomized phase II/III trials comparing systemic therapies for metastatic uveal melanoma have failed to identify any systemic therapies that are consistently more effective than chemotherapy,^{698,701-704,710,712,731} except recent data for tebentafusp.⁵⁹³ As noted above, meta-analyses suggest that for metastatic uveal melanoma, systemic therapy appears to result in worse outcomes than localized treatment (surgery or liver-directed therapies), although differing patient selection criteria across studies may be a confounding factor in these analyses.^{24,576,577,591} For patients who are not appropriate for localized therapy, selection of systemic therapy is very challenging, necessitating further study into better options.

Immunotherapy

Immunotherapies for which there are efficacy data from prospective studies in metastatic uveal melanoma include tebentafusp (formerly IMCgp100),^{681,758} dendritic cell vaccination,⁶⁸³ adoptive transfer of TILs,⁶⁸² or bleomycin/vincristine/lomustine/dacarbazine (BOLD) in combination with IFNα-2b^{727,728,730} or in combination with IFNα-2b and IL-2.⁷²⁹ Most recently and notably, tebentafusp was tested in a large phase III randomized trial (N = 378) in previously untreated HLA-A*02:01-positive patients with metastatic uveal melanoma. Patients were randomized 2:1 to receive tebentafusp or investigator's choice of single-agent pembrolizumab, ipilimumab, or dacarbazine (control group). OS at 1 year

was significantly higher in the tebentafusp group versus the control group (73% vs. 59%; HR for death, 0.51; 95% CI, 0.37–0.71; $P < .001$). The same was true for PFS (31% vs. 19%; HR for disease progression or death, 0.73; 95% CI, 0.58–0.94; $P = .01$). The OS advantage but relatively low response rate (9% in the tebentafusp group vs. 5% in the control group) suggests that recipients of tebentafusp live longer but there might not be tumor shrinkage. Therefore, patients who present with symptomatic liver metastases may prefer to start with liver-directed therapies or nivolumab/ipilimumab. Treatment-related events infrequently led to discontinuation of the trial treatment (2%) and no treatment-related death was reported.⁵⁹³ Tebentafusp was associated with cytokine-release syndrome, at least for the first few cycles; therefore, hospitalization to monitor for and treat this condition should be indicated.

Checkpoint immunotherapies tested in prospective studies for metastatic uveal melanoma include anti-CTLA-4 agents ipilimumab and tremelimumab,^{685,686,693} anti-PD-1 agents nivolumab and pembrolizumab,⁶⁸⁸⁻⁶⁹¹ and nivolumab/ipilimumab combination therapy.^{692,694,748,749} In prospective trials,^{685,686,693} expanded access programs (EAPs),⁷⁵⁰⁻⁷⁵⁵ and a named patient program,⁷⁵⁶ anti-CTLA-4 agents resulted in response rates ranging between 0% to 6.5%, median PFS between 2 to 4 months, and median OS of less than 13 months. Meta-analyses have concluded that anti-CTLA-4 systemic therapy results in outcomes that are similar or worse than conventional systemic chemotherapy.^{576,589,737} Results for other immune checkpoint inhibitor regimens in patients with metastatic uveal melanoma look somewhat more promising. Although one prospective study reported no responses in 17 patients treated with anti-PD-1 systemic therapy,⁶⁸⁹ three other prospective trials and one EAP reported ORRs between 6% to 38%, with eight responses among a total of 81 patients treated (8%).^{688,690,691,757} Median PFS ranged from 2.3 to 11 months.^{688-690,757} Two phase II trials testing nivolumab/ipilimumab in patients with metastatic uveal melanoma



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have reported ORRs of 11.5% and 18%, respectively.^{692,694,748,749} The median OS and PFS were 12.7 and 3.0 months, respectively, in one study⁷⁴⁹ and 19.1 and 5.5 months, respectively, in the other.⁷⁴⁸

Comparative studies are needed to determine whether combination anti-CTLA-4/anti-PD-1 consistently improves outcomes in patients with metastatic uveal melanoma.

Cytotoxic Regimens

A wide variety of chemotherapies have been tested in prospective trials in patients with metastatic uveal melanoma, and outcomes have been reported for the following single-agent chemotherapies: dacarbazine,⁷⁰¹⁻⁷⁰⁴ paclitaxel,⁶⁹⁷ temozolomide,^{695,702,704} DHA-paclitaxel,⁶⁹⁶ fotemustine,⁵⁹² bendamustine,^{699,700} treosulfan,⁶⁹⁸ liposomal vincristine,⁷⁰⁰ arsenic trioxide,⁷⁰⁵ and lenalidomide.⁷⁵⁹ Most studies evaluated patients for response to treatment, but responses to these therapies were rarely observed.^{592,695-705,759} The few responses observed were in patients treated with fotemustine (2/83),⁵⁹² liposomal vincristine (1/4),⁷⁰⁰ dacarbazine (3/36),⁷⁰³ and DHA-paclitaxel (1/22).⁶⁹⁶ For the studies that measured PFS and OS with these single-agent chemotherapy regimens, median PFS was always less than 4 months,^{592,695,696,698,701-704} and median OS was nearly always greater than 10 months.^{592,695,696,702-704} EORTC 10821, a phase III randomized trial, reported a median OS of 13.8 months for patients treated with IV fotemustine, but this longer OS is likely due to the trial including only patients with liver metastases (no extrahepatic metastases).⁵⁹² It remains unclear whether any single-agent chemotherapy improves survival relative to best supportive care.

Combination chemotherapies that have been tested in prospective trials for metastatic uveal melanoma include gemcitabine/treosulfan,^{698,717-721} dacarbazine/treosulfan,⁷²³ cisplatin/gemcitabine/treosulfan,^{722,760} cisplatin/dacarbazine/vinblastine,⁷²⁴ docetaxel/carboplatin,⁷²⁵ and tirapazamine/cisplatin.⁷²⁶ All of these were tested in pilot, phase I, or

phase II studies, most of which reported response rates of less than 5%. Due to an early pilot study that reported a response rate of nearly 29% for patients with metastatic uveal melanoma (n = 14),⁷²¹ gemcitabine/treosulfan was tested in multiple studies, but in the five subsequent studies the response rate was much lower, ranging from 0% to 4.2%.^{698,717-720} Four of these studies (including the pilot) reported PFS and OS data, with median PFS ranging from 2.5 to 6.7 months, and median OS ranging from 7.5 to 14.2 months.^{698,717,718,720,721} Results from one phase II study suggested that higher treosulfan doses (≥ 3500 mg/m²) provided better outcomes with this combination. Nonetheless the response rate at these higher doses was only 5.2%.⁷¹⁷ A randomized phase II study found that gemcitabine/treosulfan combination, using the higher treosulfan dose, did provide better PFS and a trend for better response compared with treosulfan alone, but the overall response was still relatively low (4.2% in the combination arm), and the PFS relatively short (mean 3 months in the combination arm).⁶⁹⁸ Addition of cisplatin to gemcitabine/treosulfan did not improve results—there were no responses in both of the studies that tested this triplet.^{722,760} There were also no responses seen in the phase II trials that tested dacarbazine/treosulfan,⁷²³ docetaxel/carboplatin,⁷²⁵ and tirapazamine/cisplatin.⁷²⁶ The one phase II study testing cisplatin/dacarbazine/vinblastine reported a surprisingly high ORR of 20%, with median PFS of 5.5 months and median OS of 13.0 months.⁷²⁴ This result needs to be repeated, and may be a product of patient selection.

Meta-analyses combining results across studies that tested chemotherapy in patients with metastatic uveal melanoma report ORRs ~4%,⁵⁸⁹ median PFS of 2.6 months,²⁴ and median OS ranging from 9 to 11 months.^{24,576}

Targeted Therapy

Targeted therapies that have been tested in prospective studies as single-agent therapy for patients with metastatic uveal melanoma include the



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tyrosine kinase inhibitors (TKIs) imatinib^{706,707,761} and sunitinib,^{703,709} the mitogen-activated protein kinase (MEK) inhibitors trametinib^{710,711} and selumetinib,⁷⁰² the multi-kinase inhibitor sorafenib,⁷⁰⁸ the receptor TKI cabozantinib,^{704,712} the VEGF inhibitor aflibercept,⁷¹⁵ the HSP90 inhibitor ganetespib,⁷¹³ and the topoisomerase inhibitor 9-nitro-camptothecin.⁷¹⁶ Targeted therapy combinations that have been tested in prospective trials include trametinib plus uprosertib, an inhibitor of protein kinase B (AKT);⁷¹⁰ binimetinib (MEK inhibitor) plus sotrastaurin (PKC inhibitor);⁷³⁸ and everolimus (mTOR inhibitor) plus pasireotide (IG1FR inhibitor).⁷¹⁴ Prospective studies in patients with metastatic uveal melanoma have also tested combinations of chemotherapy plus targeted therapy, including carboplatin/paclitaxel/sorafenib,⁷³⁴ fotemustine/sorafenib,⁷⁶² dacarbazine/selumetinib,⁷⁰¹ temozolomide/bevacizumab,⁷³⁵ and carboplatin/paclitaxel/bevacizumab ± everolimus.⁷³¹ These prospective studies were pilot studies, phase I trials, and phase II trials, and in most of them the overall response was less than 10%.^{702,706-708,710-716,761} Taken together, most meta-analyses concluded that targeted therapy did not improve outcomes relative to conventional chemotherapy.^{24,576,589,738}

Although uveal melanomas often express KIT, they rarely harbor the c-KIT mutations associated with response to imatinib in other cancers.^{61,706,761,763} It is thus perhaps not surprising that response rates to imatinib were low in patients with metastatic uveal melanoma.^{706,707,761} Two studies reported no responses,^{706,707} and 8% response was observed in a third study that selected patients with high KIT expression.⁷⁶¹ Given the unimpressive median PFS (2.8 months) and OS (6.9 months) for the 25 patients in this study, imatinib is not considered a good option for patients with metastatic uveal melanoma.⁷⁶¹ Results were similar for the other TKI, sunitinib. A pilot study in 20 patients with metastatic uveal melanoma expressing KIT reported an ORR of 5% for patients treated with sunitinib,⁷⁰⁹ but a subsequent larger phase II randomized study reported no response in the 38 patients treated with sunitinib (vs. ORR of 8% with dacarbazine), and

PFS and OS with sunitinib were no better than the comparator dacarbazine.⁷⁰³

Although *BRAF* mutations are rare in uveal melanoma,^{36,53,55,56,62,64,65} most uveal melanomas carry mutations in *GNAQ* or *GNA11* that result in constitutive activation of the RAS/RAF/MEK/ERK pathway.^{36,37,53,66,68,71,72,764} Prospective studies of MEK inhibitors have yielded mixed results in patients with metastatic uveal melanoma.^{702,710,711} A large phase II randomized trial in 101 patients with metastatic uveal melanoma reported responses in 14% of the 50 patients treated with selumetinib, and no responses in the 51 patients in the comparator arm (chemotherapy with temozolomide or dacarbazine).⁷⁰² Selumetinib modestly improved PFS compared with chemotherapy (median 3.7 vs. 1.6 months; $P < .001$), although the effect on OS was not significant (median 11.8 vs. 9.1 months; $P = .09$).⁷⁰² However, in a phase III randomized trial in 129 patients with metastatic uveal melanoma that compared selumetinib plus dacarbazine versus placebo plus dacarbazine, selumetinib did not improve response (3% vs. 0%) or PFS (median 2.8 vs. 1.8 months).⁷⁰¹ Results from other MEK inhibitors were not impressive. No responses to trametinib were observed in the 16 patients with metastatic uveal melanoma in a phase I trial, and the median PFS was unremarkable (1.8 months).⁷¹¹ In a subsequent phase II study, 1 of 18 (5.6%) patients with metastatic uveal melanoma responded to single-agent trametinib, and PFS was slightly better (median 3.6 months).⁷¹⁰ Addition of uprosertib, an AKT inhibitor, yielded very similar results (ORR 4.8%, PFS median 3.6 months).⁷¹⁰ A phase Ib/II trial of combination binimetinib and sotrastaurin yielded no responses in patients with metastatic uveal melanoma.⁷³⁸ Across studies it appeared that *GNAQ* and *GNA11* mutation status did not impact response rate or outcomes in patients treated with MEK inhibitors.^{701,702,711} Taken together, these data show that some patients with uveal melanoma may respond to the MEK inhibitor selumetinib, and there are limited data suggesting that trametinib may also be marginally



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effective. Although the data are strongest for selumetinib, it was not FDA approved for use in humans at the time of the most recent Guidelines update, so it could not be included as a recommended option. Trametinib is included as a recommended option based on the positive data for

selumetinib and the general lack of systemic therapy options for patients with uveal melanoma. Further study of trametinib for uveal melanoma is needed.

A large, light gray circular graphic with a double-line border. Inside the circle, the text "Discussion update in progress" is written in a bold, sans-serif font, centered vertically and horizontally.

Discussion
update in
progress



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Table 1. Risk Factors for Growth in Small Intraocular Melanocytic Lesions

Risk Factor	Studies Demonstrating Correlation with Tumor Growth	Detection Method(s)
Symptoms	Augsburger, 1989 ⁹³ ; Butler, 1994 ⁹⁸ ; Shields, 1995 ⁹⁴ ; Shields, 2000 ⁹⁵ ; Singh, 2006 ⁹⁶ ; Shields, 2009 ⁹⁷ ; Lane, 2010 ⁸⁷	History and physical
Lesion thickness (>2 mm)	Augsburger, 1989 ⁹³ ; Butler, 1994 ⁹⁸ ; Shields, 1995 ⁹⁴ ; COMS 1997 ⁸⁶ ; Shields, 2000 ⁹⁵ ; Singh, 2006 ⁹⁶ ; Lane, 2010 ⁸⁷ ; Shields, 2009 ⁹⁷ ; Dalvin, 2019 ⁹⁹	Ultrasound
Lesion diameter (>5 mm)	COMS 1997 ⁸⁶ ; Dalvin, 2019 ⁹⁹	Comprehensive eye exam, color fundus photography, ultrasound
Subretinal fluid	Shields, 1995 ⁹⁴ ; Shields, 2000 ⁹⁵ ; Shields, 2009 ⁹⁷	Color fundus photography, comprehensive eye exam Ancillary option: OCT
Orange pigment (lipofuscin)	Augsburger, 1989 ⁹³ ; Butler, 1994 ⁹⁸ ; Shields, 1995 ⁹⁴ ; COMS 1997 ⁸⁶ ; Shields, 2000 ⁹⁵ ; Singh, 2006 ⁹⁶ ; Shields, 2009 ⁹⁷ ; Dalvin, 2019 ⁹⁹	Color fundus photography, comprehensive eye exam Ancillary options: ocular fundus autofluorescence, OCT
Proximity to optic disc (tumor margin <3 mm)	Augsburger, 1989 ⁹³ ; Shields, 1995 ⁹⁴ ; Shields, 2000 ⁹⁵ ; Shields, 2009 ⁹⁷	Comprehensive eye exam, color fundus photography
Ultrasound hollowness	Shields, 2009 ⁹⁷ ; Dalvin, 2019 ⁹⁹	Ultrasound (A- and B-scan)
Absence of halo	Shields, 2009 ⁹⁷	Comprehensive eye exam, color fundus photography

OCT, optical coherence tomography

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Table 2. Biopsy Options for Choroidal or Ciliary Body Tumors^{a,234,252}

Biopsy Type	Surgical Approach ^b	Tumor Location ^c	Sample Analysis ^d	Studies Describing Technique, Reporting Yield or Safety ^e (number of patients biopsied)	
Fine-needle aspiration biopsy (FNAB)	Transscleral	Anterior	Cytopathology	Glasgow, 1988 ²⁶⁵ (n=6) Eide, 1999 ²⁵⁵ (n=50) Shields, 2007 ²⁶³ (n=73) Shields, 2007 ²⁶² (n=24; ≤3 mm thick) McCannel, 2012 ²⁵⁰ (n=170) Chang, 2014 ²⁶⁰ (n=38)	Grixti, 2014 ²³⁸ (n=291) Sellam, 2016 ²³⁹ (n=185) Singh, 2016 ²³⁷ (n=71) Kim, 2018 ²³⁶ (n=11) Matet, 2019 ²⁵³ (n=24)
	Transvitreal	Posterior	Cytopathology	Glasgow, 1988 ²⁶⁵ (n=15) Eide, 1999 ²⁵⁵ (n=14) Cohen, 2001 ²⁵⁴ (n=83) Augsburger, 2002 ⁹¹ (n=34; diameter ≤10 mm; thickness, ≥1.5 mm but ≤3 mm) Shields, 2007 ²⁶³ (n=67) Shields, 2007 ²⁶² (n=32; ≤3 mm thick) Correa, 2014 ²⁵⁶ (n=159)	Chang, 2014 ²⁶⁰ (n=38) Augsburger, 2015 ²⁴⁰ (n=80) Singh, 2016 ²³⁷ (n=64) Sellam, 2016 ²³⁹ (n=32) Kim, 2017 ²⁵⁹ (n=10) Kim, 2018 ²³⁶ (n=33) Reddy, 2017 ²⁵⁸ (n=57) Singh, 2017 ²⁵⁷ (n=20)
Vitrectomy system (vitreous-cutter)-assisted biopsy ^f	Transvitreal/transretinal	Posterior or equatorial	Cytopathology or Histopathology (depends on exact technique used)	Jensen, 1997 ²⁴⁴ (n=92) Bechrakis, 2002 ²⁷⁰ (n=23) Sen, 2006 ²⁷¹ (n=14) Bagger, 2013 ²⁴³ (n=123) Grixti, 2014 ²³⁸ (n=448)	Bagger, 2015 ²⁷² (n=39) Nagiel, 2017 ²⁴¹ (n=17; ≤2.0 mm thick) Grewal, 2017 ²⁴² (n=18)
Incisional biopsy ^g with Essen forceps	Transvitreal	Anterior	Histopathology	Akgul, 2011 ²⁴⁶ (n=20)	
Incisional biopsy ^g (standard forceps)	Transvitreal	Posterior	Histopathology	Kvanta, 2005 ²⁴⁷ (n=10) Seregard, 2013 ²⁴⁵ (n=46)	

^a Although review articles include excisional biopsy,^{234,252} and historical literature includes reports of transscleral resection or endoresection being used for uveal melanoma biopsy, these methods are not included in this table because they are no longer commonly used due to technical challenges, risk of complications, and concerns about tumor seeding.^{178,273-283}

^b The transscleral (direct) approach involves approaching the tumor from the outside, with the needle first puncturing the sclera over the tumor, then the tumor itself, leaving the retina intact.²³⁴ The transvitreal (indirect) approach involves anterior entry through the pars plana opposite the tumor, going through the vitreous body and retina to reach the tumor.²³⁴

^c Although each biopsy method may be used successfully in a range of locations, the feasibility and success rate vary based on tumor location. The table lists the tumor location(s) for which the biopsy method was developed and/or is most often used.

^d Sample Analysis: Some methods provide cellular aspirate that can be used for cytopathology; others provide tissue samples that can be sectioned for histopathology. The table reflects the type of sample usually obtained by each of the biopsy methods listed. Both types of samples can be used for molecular analyses for prognostication.

^e For each biopsy method, the table lists representative studies including at least 10 cases that reported at least one of the following: detailed description of biopsy technique used, analysis of yield and safety, risk assessment of tumor seeding. Note that inclusion criteria varied across studies listed in the table. Whereas some studies included only patients with suspected or confirmed uveal melanoma, others included patients with other intraocular conditions.

^f Vitrectomy system (vitreous-cutter)-assisted biopsy: Includes a variety of methods that use vitrectomy tools both to access tumor via a transvitreal/transretinal approach and to extract tumor tissue using the vitreous cutter and aspiration through the canula. These procedures do not necessarily include a vitrectomy.

^g Incisional biopsy techniques described in the literature sometimes included use of a vitreous cutter, vitrectomy, and other procedures to access the biopsy site, wherein the tumor tissue was incised with a diamond knife and removed with forceps.



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Discussion
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