



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uveal Melanoma

Version 1.2018 — March 15, 2018

NCCN.org



Download Clinical Guidelines

Continue



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2018 Panel Members

Uveal Melanoma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

Daniel G. Coit, MD/Chair ¶
Memorial Sloan Kettering Cancer Center

John A. Thompson, MD ‡ †/Vice-Chair
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Mark R. Albertini, MD †
University of Wisconsin
Carbone Cancer Center

Alain Algazi, MD † ¶
UCSF Helen Diller Family
Comprehensive Cancer Center

Robert Andtbacka, MD ¶
Huntsman Cancer Institute
at the University of Utah

Christopher Barker, MD §
Memorial Sloan Kettering Cancer Center

Christopher K. Bichakjian, MD ☞
University of Michigan
Comprehensive Cancer Center

William E. Carson, III, MD ¶
The Ohio State University
Comprehensive Cancer Center -
James Cancer Hospital and
Solove Research Institute

Gregory A. Daniels, MD, PhD ¶ ‡ †
UC San Diego Moores Cancer Center

Dominick DiMaio, MD ≠
Fred & Pamela Buffett Cancer Center

Ryan C. Fields, MD ¶
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Martin D. Fleming, MD ¶
The University of Tennessee
Health Science Center

Anjela Galan, MD ≠
Yale Cancer Center/Smilow Cancer Hospital

Brian Gastman, MD ¶
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer
Center and Cleveland Clinic Taussig Cancer
Institute

Rene Gonzalez, MD †
University of Colorado Cancer Center

Valerie Guild ¥
AIM at Melanoma

Douglas Johnson, MD †
Vanderbilt-Ingram Cancer Center

Richard W. Joseph, MD ‡ †
Mayo Clinic Cancer Center

Julie R. Lange, MD, ScM ¶
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Kim Margolin, MD †
City of Hope Comprehensive
Cancer Center

Miguel Materin, MD ☼
Duke Cancer Institute

Sameer Nath, MD §
University of Colorado Cancer Center

Anthony J. Olszanski, MD †
Fox Chase Cancer Center

Patrick Ott, MD, PhD † ‡ ¶
Dana-Farber/Brigham and Women's
Cancer Center

Aparna Priyanath Gupta, MD ¶
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

P. Kumar Rao, MD ☼
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University
School of Medicine

Ramesh Rengan, MD §
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Merrick I. Ross, MD ¶
The University of Texas
MD Anderson Cancer Center

April K. Salama, MD †
Duke Cancer Institute
Joseph Skitzki, MD ¶
Roswell Park Cancer Institute

Jeffrey Sosman, MD ‡
Robert H. Lurie Comprehensive
Cancer Center of Northwestern
University

Susan M. Swetter, MD ☞
Stanford Cancer Institute

Kenneth K. Tanabe, MD ¶
Massachusetts General Hospital
Cancer Center

Marshall M. Urist, MD ¶
University of Alabama at
Birmingham Comprehensive
Cancer Center

Evan Wuthrick, MD §
Moffitt Cancer Center

☼ Ophthalmology
† Medical oncology
¶ Internal medicine
☞ Dermatology
¶ Surgery/Surgical oncology
≠ Pathology
¥ Patient advocacy
‡ Hematology/Hematology oncology
§ Radiotherapy/Radiation oncology

Continue

[NCCN Guidelines Panel Disclosures](#)

NCCN
Anita Eng, PhD
Nicole McMillan, MS



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2018 Sub-Committee

Uveal Melanoma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

Uveal Melanoma Sub-committee

P. Kumar Rao, MD/Lead ☼
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Alain Algazi, MD † ▮
UCSF Helen Diller Family
Comprehensive Cancer Center

Christopher Barker, MD §
Memorial Sloan Kettering Cancer Center

Daniel G. Coit, MD ¶
Memorial Sloan Kettering Cancer Center

Richard Joseph, MD ‡ †
Mayo Clinic Cancer Center

Miguel Materin, MD ☼
Duke Cancer Institute

Ramesh Rengan, MD §
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Jeffrey Sosman, MD ‡
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

John A. Thompson, MD ‡ †
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

☼ Ophthalmology
† Medical oncology
▮ Internal medicine
¶ Surgery/Surgical oncology
‡ Hematology/Hematology oncology
§ Radiotherapy/Radiation oncology

Continue

[NCCN Guidelines Panel Disclosures](#)



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2018 Table of Contents

Uveal Melanoma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

[NCCN Uveal Melanoma Panel Members](#)

[NCCN Uveal Melanoma Subcommittee Members](#)

[Clinical Presentation, Workup and Diagnosis \(UM-1\)](#)

[Workup and Staging, Tumor Size, Primary Treatment \(UM-2\)](#)

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

[Systemic Imaging Based on Risk Stratification \(UM-4\)](#)

[Treatment for Recurrence/Metastasis \(UM-5\)](#)

[Treatment of Metastatic Disease \(UM-6\)](#)

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

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

[Systemic Therapy for Metastatic or Unresectable Disease \(UM-C\)](#)

[Staging \(ST-1\)](#)

Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/physician.html](#).

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

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

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2018.



NCCN Guidelines Version 1.2018

Uveal Melanoma

CLINICAL PRESENTATION

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

WORKUP AND DIAGNOSIS

- Clinical evaluation, including:
 - ▶ H&P, including history of prior or current cancers (outside the eye)
 - ▶ Color fundus photography
 - ▶ Ultrasound of eye and orbit
 - ▶ Comprehensive eye exam: Examine the front and back of eye (biomicroscopy)
 - ◊ Dilated fundus exam (indirect ophthalmoscopy)
 - ◊ Measure vision acuity
 - ◊ Measure and document location and the size of the tumor (diameter, thickness)
 - ◊ Assess and document if present:
 - Subretinal fluid
 - Orange pigment
- Additional testing options include:
 - ▶ Autofluorescence of the ocular fundus
 - ▶ Optical coherence tomography
 - ▶ Retinal fluorescein angiography of the ocular fundus
 - ▶ Transillumination
 - ▶ MRI occasionally needed to confirm diagnosis
- Consider biopsy if needed to confirm diagnosis^c or for prognostic analysis for risk stratification^d

CLINICAL STAGING

Diagnosis uncertain and/or <3 risk factors for growth^e

Observe and re-evaluate for growth or features of malignancy^f

- Every 1–4 months^g until clinically stable
- Then close follow-up for 5 years^g
- Then annually thereafter

Uveal melanoma

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

^aThis guideline does not include the management of iris melanoma.

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

^cBiopsy 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.

^dBiopsy of the primary tumor does not impact outcome, but may provide prognostic information that can help inform frequency of follow-up and may be needed for eligibility for clinical trials. Specimen should be sent for histology, chromosome analysis, and/or gene expression profiling. The risks/benefits of biopsy for prognostic analysis should be carefully considered and discussed.

^eRisk factors or 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 disk, ultrasound hollowness, absence of halo.

^fThe 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.

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

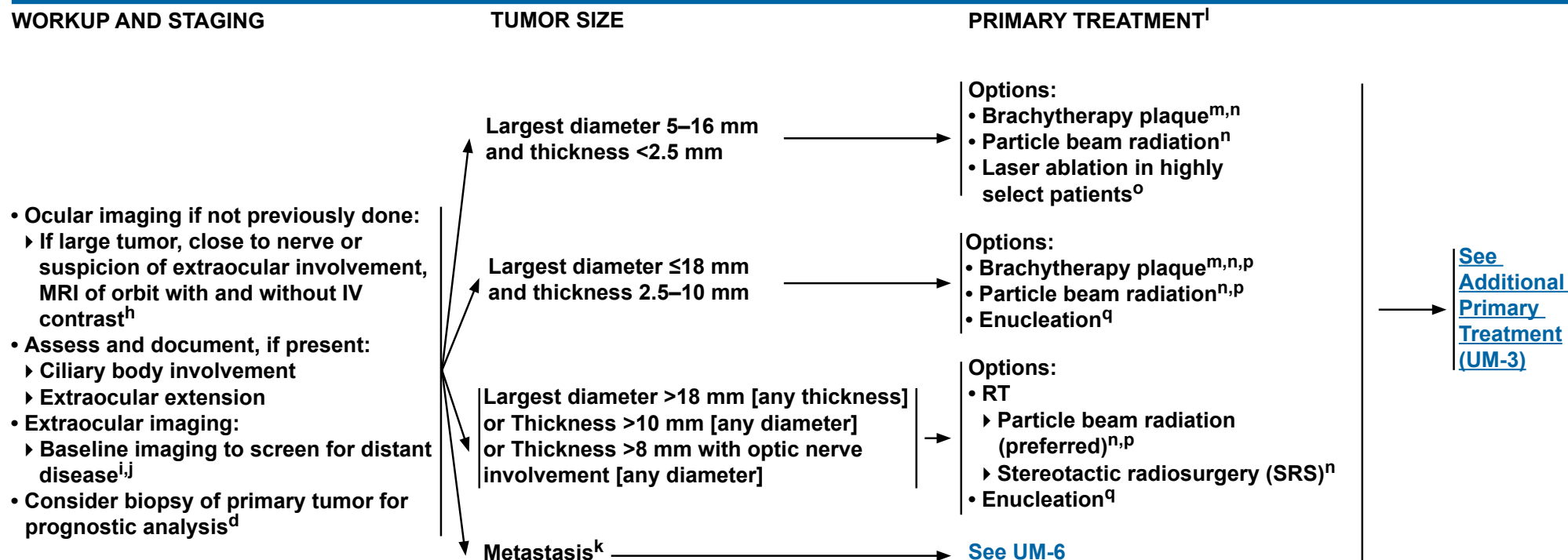
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018

Uveal Melanoma



^dBiopsy of the primary tumor does not impact outcome, but may provide prognostic information that can help inform frequency of follow-up and may be needed for eligibility for clinical trials. Specimen should be sent for histology, chromosome analysis, and/or gene expression profiling. The risks/benefits of biopsy for prognostic analysis should be carefully considered and discussed.

^hIf contrast not medically contraindicated.

ⁱDespite lack of treatment options for patients with distant metastatic disease, NCCN favors staging before primary treatment. For small, low-risk tumors, imaging after primary treatment can be considered.

^jThe most frequent sites of metastasis are liver, 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/abdominal/pelvic CT with contrast. However, screening should limit radiation exposure whenever possible. Scans should be performed with IV contrast unless contraindicated.

^kPatients 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.

¹An essential feature of high-quality care is that clinical decisions are informed by a variety of case-specific factors (eg, patient characteristics and preferences like age, status of the other eye among others, disease characteristics, medical history), such that for some patients the best clinical approach may not be an option listed in the guidelines.

^mThe plaque should cover the tumor with a ≥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 22 mm in diameter; thus, plaque brachytherapy is recommended only for tumors with largest basal diameter <18 mm.

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

^oConsider laser ablation for patients who are not good candidates for radiation or surgery.

^pConsider additional treatment with resection, laser ablation, transpupillary thermotherapy, or cryotherapy if concerned that adequate response was not achieved from initial radiation.

^qWhile 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.

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

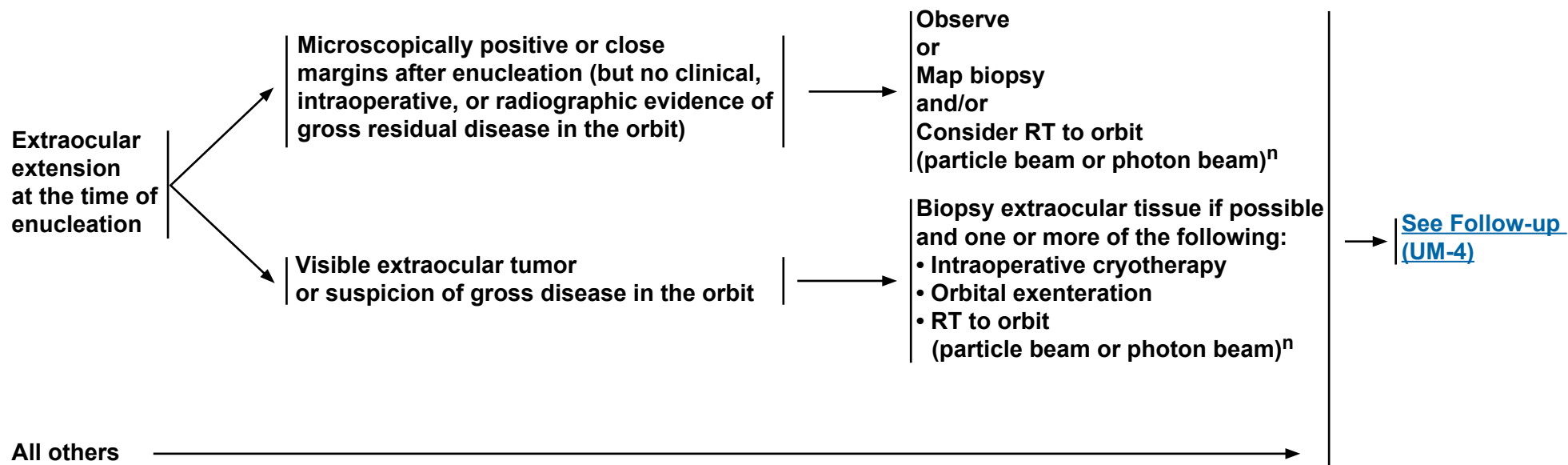
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018

Uveal Melanoma

ADDITIONAL PRIMARY TREATMENT



ⁿSee Principles of Radiation Therapy (UM-B).

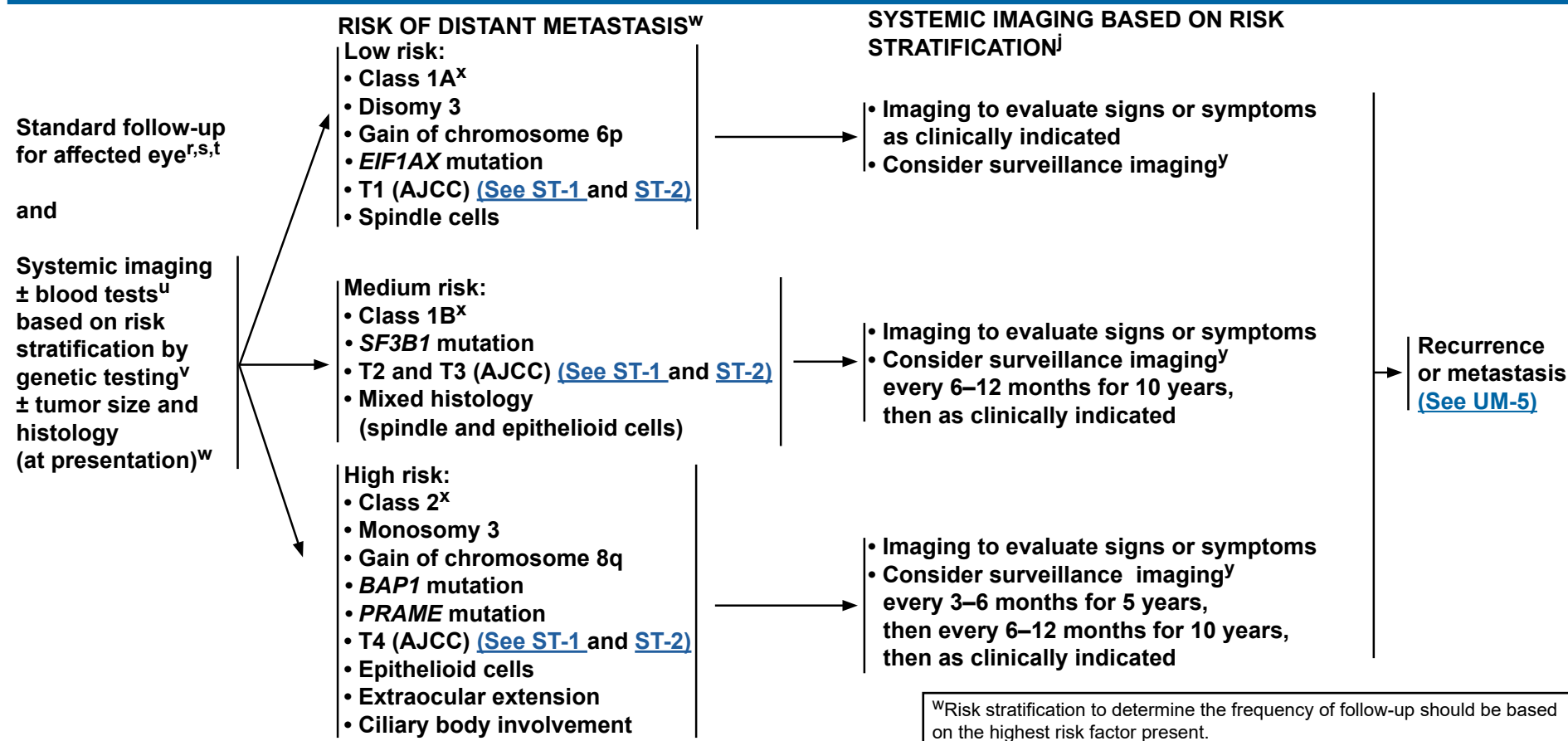
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018

Uveal Melanoma



^jThe most frequent sites of metastasis are liver, 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/abdominal/pelvic CT with contrast. However, screening should limit radiation exposure whenever possible. Scans should be performed with IV contrast unless contraindicated.

^rThe 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. 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 often occur between 18 months to 3 years after treatment.

^sThe contralateral eye is not at increased risk of uveal melanoma, and can be followed with routine ophthalmologic care.

^tAdditional risk factors for recurrence: Juxtapapillary location and ciliary body involvement.

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

^vIf biopsy not performed, then follow medium- or high-risk pathways, depending on whether any high-risk features are present.

^xOnken, MD, Worley LA, Char DH, et al. Collaborative ocular oncology group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology* 2012;119:1596-1603.

^yRecognizing that there are limited options for systemic recurrence and that regular imaging may cause patient anxiety, some patients may elect to forgo surveillance imaging.

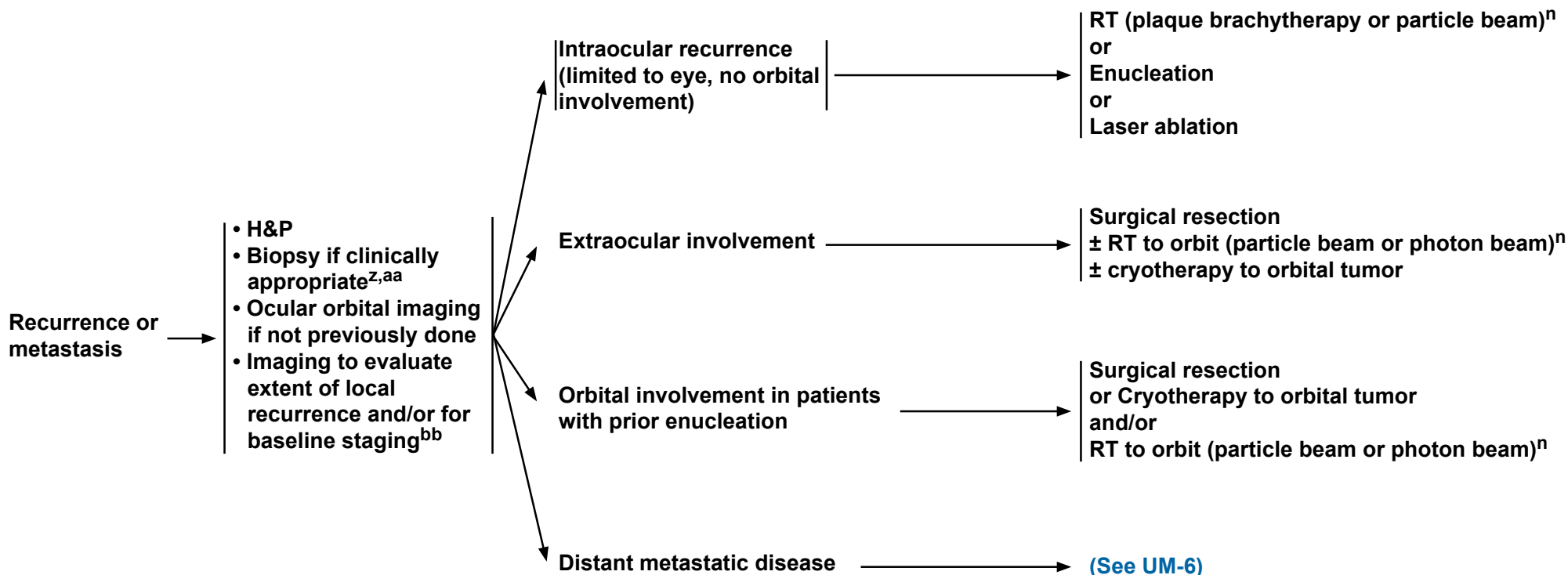
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



WORKUP

TREATMENT FOR RECURRENCE/METASTASIS



ⁿSee Principles of Radiation Therapy (UM-B).

^zExtraocular recurrence or metastasis should be confirmed histologically whenever possible or if clinically indicated. Biopsy techniques may include FNA or core.

Obtain tissue 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. Consider broader genomic profiling if the test results might guide future decisions or eligibility for participation in a clinical trial.

^{aa}Intraocular recurrence can often be diagnosed and managed without a biopsy.

^{bb}The most frequent sites of metastasis are liver, 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 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. Scans should be performed with IV contrast unless contraindicated.

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

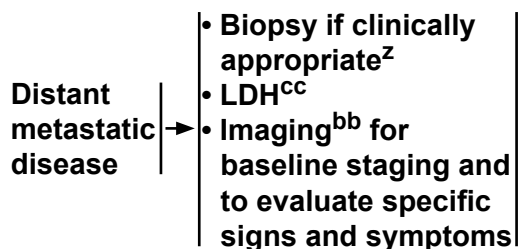
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018

Uveal Melanoma

WORKUP



TREATMENT OF METASTATIC DISEASE

One or more of the following options:

- Clinical trial (preferred)
- Liver-directed therapies:
 - Regional isolation perfusion of the liver
 - Chemoembolization
 - Radioembolizationⁿ
- Therapies for systemic disease:
 - Systemic therapy^{dd}
 - Consider resection and/or RT (photon beam or SRS)ⁿ for limited or symptomatic disease^{ee}
- Best supportive/palliative care ([See NCCN Guidelines for Palliative Care](#))

Imaging^{bb} to assess response or progression

No evidence of disease

Clinical trial (preferred) or Observation ([See Follow-up UM-4](#))

Residual or progressive disease

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

^zExtraocular recurrence or metastasis should be confirmed histologically whenever possible or if clinically indicated. Biopsy techniques may include FNA or core. Obtain tissue 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. Consider broader genomic profiling if the test results might guide future decisions or eligibility for participation in a clinical trial.

^{bb}The most frequent sites of metastasis are liver, 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 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. Scans should be performed with IV contrast unless contraindicated.

^{cc}LDH is a validated prognostic indicator in cutaneous melanoma. However, its role in risk stratification of metastatic uveal melanoma is unknown.

^{dd}In general, uveal melanomas may have lower response rates to drug-based therapies than cutaneous melanoma, but efficacy has in general been more limited; however, individual patients on occasion may derive substantial benefit. Regionally directed therapies such as hepatic chemoembolization or radioembolization should be considered. [See Systemic Therapy for Metastatic or Unresectable Disease \(UM-C\).](#)

^{ee}[See Principles of Radiation for Metastatic Disease \(ME-G\) in the NCCN Guidelines for Melanoma \(cutaneous\).](#)

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



RISK FACTORS FOR DEVELOPMENT OF UVEAL MELANOMA

- **Patients with the following risk factors are at increased risk of developing uveal melanoma:**
 - **Choroidal nevi**
 - **Ocular/oculodermal melanocytosis (hyperpigmentation of episclera, uvea, and skin)**
 - **Familial uveal melanoma (eg, germline *BAP1* mutation, neurofibromatosis [NF-1], dysplastic nevus syndrome [BK-mole])**
- **The presence of cutaneous melanoma does not increase the risk of uveal melanoma.**

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF RADIATION THERAPY

Plaque Brachytherapy

- 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 and ≤16 mm in maximum basal diameter randomized to plaque brachytherapy or enucleation.²
- Plaque brachytherapy is appropriate for patients with tumors ≤18 mm in largest base diameter, ≤10 mm in thickness.
- 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 may be used for preoperative planning.
- Using ¹²⁵Iodine Collaborative Ocular Melanoma Study (COMS) plaques with 85 Gy should be prescribed to the apex of the tumor at low dose rate (≥0.6 Gy/h). The plaque margin on the tumor border should be ≥2 mm when feasible (diameter of plaque ≥4 mm larger than largest base 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 22 mm in diameter; thus, plaque brachytherapy is recommended only for tumors with largest basal diameter ≤18 mm.
- Using other radioisotopes (eg, ¹⁰⁶ruthenium, ¹⁰³palladium, ⁹⁰strontium, ⁶⁰cobalt, ¹³¹cesium), or non-COMS ¹²⁵Iodine plaques, 60–100 Gy may be prescribed at low dose rate to the tumor apex; alternatively, a minimum dose may be prescribed to the base of the tumor. The plaque margin on the tumor border may vary for other radioisotopes.
- Round plaques are most commonly used, although non-round plaques (eg, notched) can be considered for tumors in specific locations (eg, peripapillary).

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF RADIATION THERAPY

Particle Beam Therapy

- 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.⁵
- 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.⁶
- 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.^{6,7,8}
 - ▶ Using carbon ions, 60–85 CGyE in 5 fractions should be prescribed to encompass the planning target volume surrounding the tumor.⁹
 - ▶ 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.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF RADIATION THERAPY

Stereotactic Radiosurgery (SRS)

- SRS is the least often used and non-preferred form of definitive radiotherapy for the treatment of primary or recurrent intraocular tumors. Few prospective studies have assessed the efficacy and safety of radiosurgery.^{10,11}
- Tumor localization, fiducial marker use, and planning for SRS are generally consistent with particle beam therapy approaches.
- 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

- 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).
- A dose of 20–30 Gy in 5 fractions should be prescribed to the clinical target volume at risk for recurrence^{12,13} using intensity-modulated techniques with image guidance.
- Photon beam radiotherapy can be used for treatment of distant metastases at risk for causing symptoms or for palliation of symptomatic distant metastases.
 - ▶ Doses of 8–30 Gy in 1–10 fractions should be prescribed to the appropriate target volume¹⁴ using appropriate 3-D or intensity-modulated radiation therapy (IMRT) techniques with or without image guidance.

Radioembolization

- Selective internal radiation therapy for patients with liver metastases using ⁹⁰Yttrium has been reported in retrospective studies.¹⁵
- Further study is required to determine the appropriate patients for and risks and benefits of this approach.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018

Uveal Melanoma

PRINCIPLES OF RADIATION THERAPY (References)

- ¹Abrams MJ, Gagne NL, Melhus CS, Mignano JE. Brachytherapy vs. external beam radiotherapy for choroidal melanoma: Survival and patterns-of-care analyses. Brachytherapy 2016;15:216-223.
- ²Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. Arch Ophthalmol 2006;124:1684-1693.
- ³American Brachytherapy Society - Ophthalmic Oncology Task Force. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy 2014;13:1-14.
- ⁴Almony A, Breit S, Zhao H, et al. Tilting of radioactive plaques after initial accurate placement for treatment of uveal melanoma. Arch Ophthalmol 2008;126:65-70.
- ⁵Mishra KK, Quivey JM, Daftari IK, et al. Long-term results of the UCSF-LBNL randomized trial: Charged particle with helium ion versus iodine-125 plaque therapy for choroidal and ciliary body melanoma. Int J Radiat Oncol Biol Phys 2015;92:376-383.
- ⁶Hrbacek J, Mishra KK, Kacpersek A, et al. Practice patterns analysis of ocular proton therapy centers: The International OPTIC Survey. Int J Radiat Oncol Biol Phys 2016;95:336-343.
- ⁷Hartsell WF, Kapur R, Hartsell SO, et al. Feasibility of proton beam therapy for ocular melanoma using a novel 3D treatment planning technique. Int J Radiat Oncol Biol Phys 2016;95:353-359.
- ⁸Gragoudas 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.
- ⁹Tsuji H, Ishikawa H, Yanagi T, et al. Carbon-ion radiotherapy for locally advanced or unfavorably located choroidal melanoma: a phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 2007;67:857-862.
- ¹⁰Muller K, Nowak PJ, de Pan C, et al. Effectiveness of fractionated stereotactic radiotherapy for uveal melanoma. Int J Radiat Oncol Biol Phys 2005;63:116-122.
- ¹¹Zehetmayer M, Kitz K, Menapace R, et al. Local tumor control and morbidity after one to three fractions of stereotactic external beam irradiation for uveal melanoma. Radiother Oncol 2000;55:135-144.
- ¹²The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma III: local complications and observations following enucleation COMS report no. 11. Am J Ophthalmol 1998;126:362-372.
- ¹³Ang KK, Peters LJ, Weber RS, et al. Postoperative radiotherapy for cutaneous melanoma of the head and neck region. Int J Radiat Oncol Biol Phys 1994;30:795-798.
- ¹⁴Huguenin PU, Kieser S, Glanzmann C, et al. Radiotherapy for metastatic carcinomas of the kidney or melanomas: an analysis using palliative end points. Int J Radiat Oncol Biol Phys 1998;41:401-405.
- ¹⁵Jia Z, Jiang G, Zhu C, et al. A systematic review of yttrium-90 radioembolization for unresectable liver metastases of melanoma. Eur J Radiol 2017;92:111-115.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE¹ (Clinical Trial Preferred)

Consider one or more of the following options:

Immunotherapy

- Anti PD-1 monotherapy
 - Pembrolizumab^{2,3}
 - Nivolumab^{2,3}
- Nivolumab/ipilimumab^{2,3}
- Ipilimumab^{2,3}

Cytotoxic Regimens

- Dacarbazine
- Temozolomide
- Paclitaxel
- Albumin-bound paclitaxel
- Carboplatin/paclitaxel

Targeted Therapy^{2,4}

- Trametinib

¹When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific systemic agent(s) offering superior outcomes, but does provide evidence that uveal melanoma is sensitive to some of the same systemic therapies used to treat cutaneous melanoma. Although uveal melanomas have lower response rates to systemic therapies than cutaneous melanoma, individual patients on occasion may derive substantial benefit. The agents listed above have been used with some success in patients with uveal melanoma.

²See [Management of Toxicities Associated with Immunotherapy and Targeted Therapy from the NCCN Guidelines for Melanoma \(cutaneous\) \(ME-I\)](#).

³See [NCCN Guidelines for Management of Immunotherapy-Related Toxicities](#).

⁴The 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.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Immunotherapy

Pembrolizumab and Nivolumab

- Kottschade LA, McWilliams RR, Markovic SN, et al. The use of pembrolizumab for the treatment of metastatic uveal melanoma. *Melanoma Res* 2016;26:300-303.
- Algazi AP, Tsai KK, Shoushtari AN, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer* 2016;122:3344-3353.

Nivolumab/ipilimumab

- Piulats JM, Cruz-Merino LDL, Garcia MTC, et al. Phase II multicenter, single arm, open label study of nivolumab (NIVO) in combination with ipilimumab (IPI) as first line in adult patients (pts) with metastatic uveal melanoma (MUM): GEM1402 NCT02626962 (abstract). *J Clin Oncol* 2017;35:Abstr 9533.

Ipilimumab

- Zimmer L, Vaubel J, Mohr P, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. *PLoS One* 2015;10:e0118564.
- Danielli R, Ridolfi R, Chiarion-Sileni V, et al. Ipilimumab in pretreated patients with metastatic uveal melanoma: safety and clinical efficacy. *Cancer Immunol Immunother* 2012;61:41-48.
- Luke JJ, Callahan MK, Postow MA, et al. Clinical activity of ipilimumab for metastatic uveal melanoma: a retrospective review of the Dana-Farber Cancer Institute, Massachusetts General Hospital, Memorial Sloan-Kettering Cancer Center, and University Hospital of Lausanne experience. *Cancer* 2013;119:3687-3695.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018

Uveal Melanoma

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Cytotoxic Regimens

Dacarbazine

- Serrone L, Zeuli M, Sega FM, et al. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res 2000;19:21-34.

Temozolomide

- Bedikian AY, Papadopoulos N, Plager C, et al. Phase II evaluation of temozolomide in metastatic choroidal melanoma. Melanoma Res 2003;13:303-306.

Paclitaxel

- Wiernik PH and Einzig AI. Taxol in malignant melanoma. J Natl Cancer Inst Monogr 1993;15:185-187.

Albumin-bound paclitaxel

- Hersh EM, O'Day SJ, Ribas A, et al. A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naïve patients with metastatic melanoma. Cancer 2010;116:155-163.
- Kottschade LA, Suman VJ, Amatruda T, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage iv melanoma: a north central cancer treatment group study, N057E(1). Cancer 2011;117:1704-1710.

Paclitaxel/carboplatin

- Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 2006;106:375-382.
- Homsí J, Bedikian AY, Papadopoulos NE, et al. Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in patients with metastatic uveal melanoma. Melanoma Res 2010;20:507-510.

Targeted Therapy

Trametinib

- Falchook GS, Lewis KD, Infante JR, et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol 2012;13:782-789.
- Shoushtari AN, Kudchadkar RR, Panageas K, et al. A randomized phase 2 study of trametinib with or without GSK2141795 in patients with advanced uveal melanoma. J Clin Oncol 2016;34:9511-9511.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018 Staging Uveal Melanoma

Table 1

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

Definition of Primary Tumor (T)

Choroidal and Ciliary Body Melanomas	
T Category	T Criteria
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
1. Primary ciliary body and choroidal melanomas are classified according to the four tumor size categories defined in Figure 1. (See SI-4) 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.	

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer International Publishing, on behalf of the AJCC.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018 Staging Uveal Melanoma

Table 1 (continued)**Definition of Primary Tumor (T)****Choroidal and Ciliary Body Melanomas**

T Category	T Criteria
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

T Category	T Criteria
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

Note:

1. Primary ciliary body and choroidal melanomas are classified according to the four tumor size categories defined in Figure 1. ([See ST-4](#))
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.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer International Publishing, on behalf of the AJCC.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018 Staging Uveal Melanoma

Table 1 (continued)**Choroidal/Ciliary Body Melanomas****Definition of Regional Lymph Node (N)**

N Category	N Criteria
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).

Definition of Distant Metastasis (M)

M Category	M Criteria
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

Histologic Grade (G)

G	G Definition
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, i.e. epithelioid cells detected) and contrast them with grade 1 (spindle, ie, no epithelioid cells detected).

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

AJCC PROGNOSTIC STAGE GROUPS

Choroidal and Ciliary Body Melanomas			
	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

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer International Publishing, on behalf of the AJCC.



NCCN Guidelines Version 1.2018 Staging Uveal Melanoma

FIGURE 1: CLASSIFICATION OF CILIARY BODY AND CHOROID UVEAL MELANOMA BASED ON THICKNESS AND DIAMETER

Thickness (mm)								
		Largest basal diameter (mm)						
		≤3.0	3.1–6.0	6.1–9.0	9.1–12.0	12.1–15.0	15.1–18.0	>18.0
>15.0						4	4	4
12.1–15.0						3	4	4
9.1–12.0					3	3	3	4
6.1–9.0		2	2	2	2	3	3	4
3.1–6.0		1	1	1	2	2	3	4
≤3.0		1	1	1	1	2	2	4

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer International Publishing, on behalf of the AJCC.

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2018

Uveal Melanoma

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus 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 noted.