National Comprehensive Cancer Network®

## NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Uveal Melanoma

Version 1.2018 — March 15, 2018

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# NCCN Guidelines Version 1.2018 Panel Members
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# NCCN Guidelines Version 1.2018 Sub-Committee
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**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.

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## 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 ophthalmolscopy)
    - ◊ 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)

[a]This guideline does not include the managment of iris melanoma.

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

[c]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.

[d]Biopsy 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.

[e]Risk 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.

[f]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.

[g]Frequency of evaluation should depend on index of suspicion, patient age, and medical frailty.

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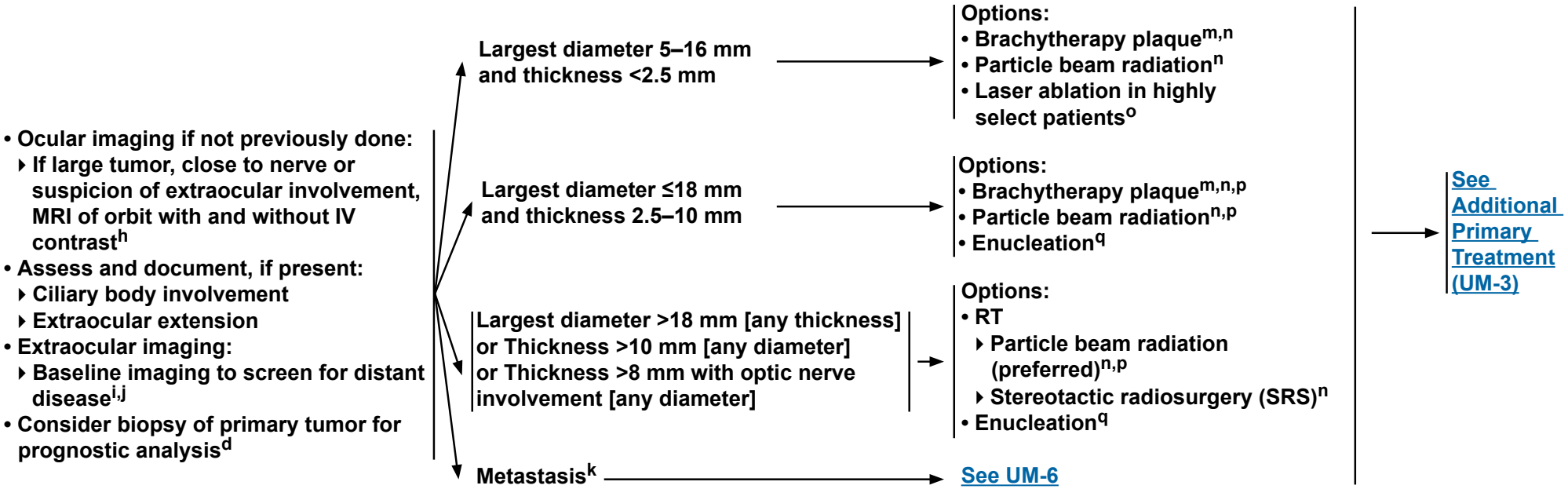


[d]Biopsy of the primary tumor does not impact outcome, but may provide prognostic information that can help inform frequency of follow-up and may be needed for eligibility for clinical trials. Specimen should be sent for histology, chromosome analysis, and/or gene expression profiling.The risks/benefits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

[h]If contrast not medically contraindicated.

[i]Despite 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.

[j]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 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.

[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.

[l]An 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.

[m]The 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.

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

[o]Consider laser ablation for patients who are not good candidates for radiation or surgery.

[p]Consider additional treatment with resection, laser ablation, transpupillary thermotherapy, or cryotherapy if concerned that adequate response was not achieved from initial radiation.

[q]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.

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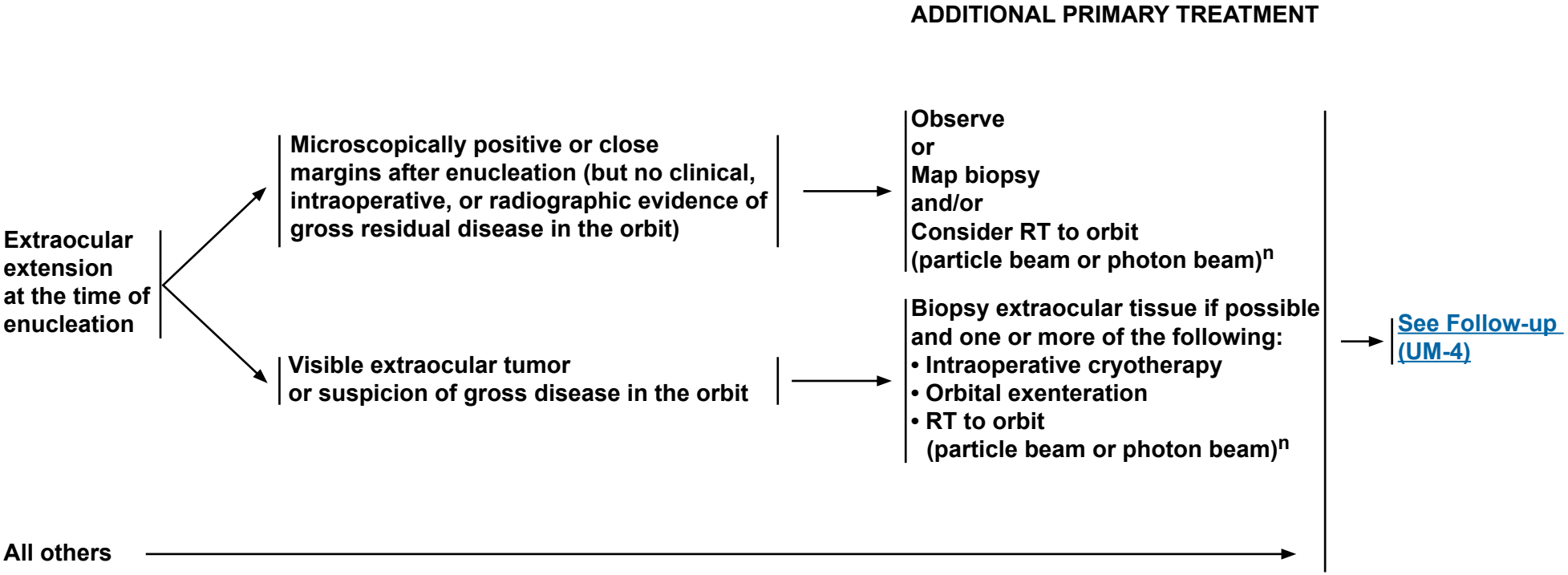


[n] See Principles of Radiation Therapy (UM-B).

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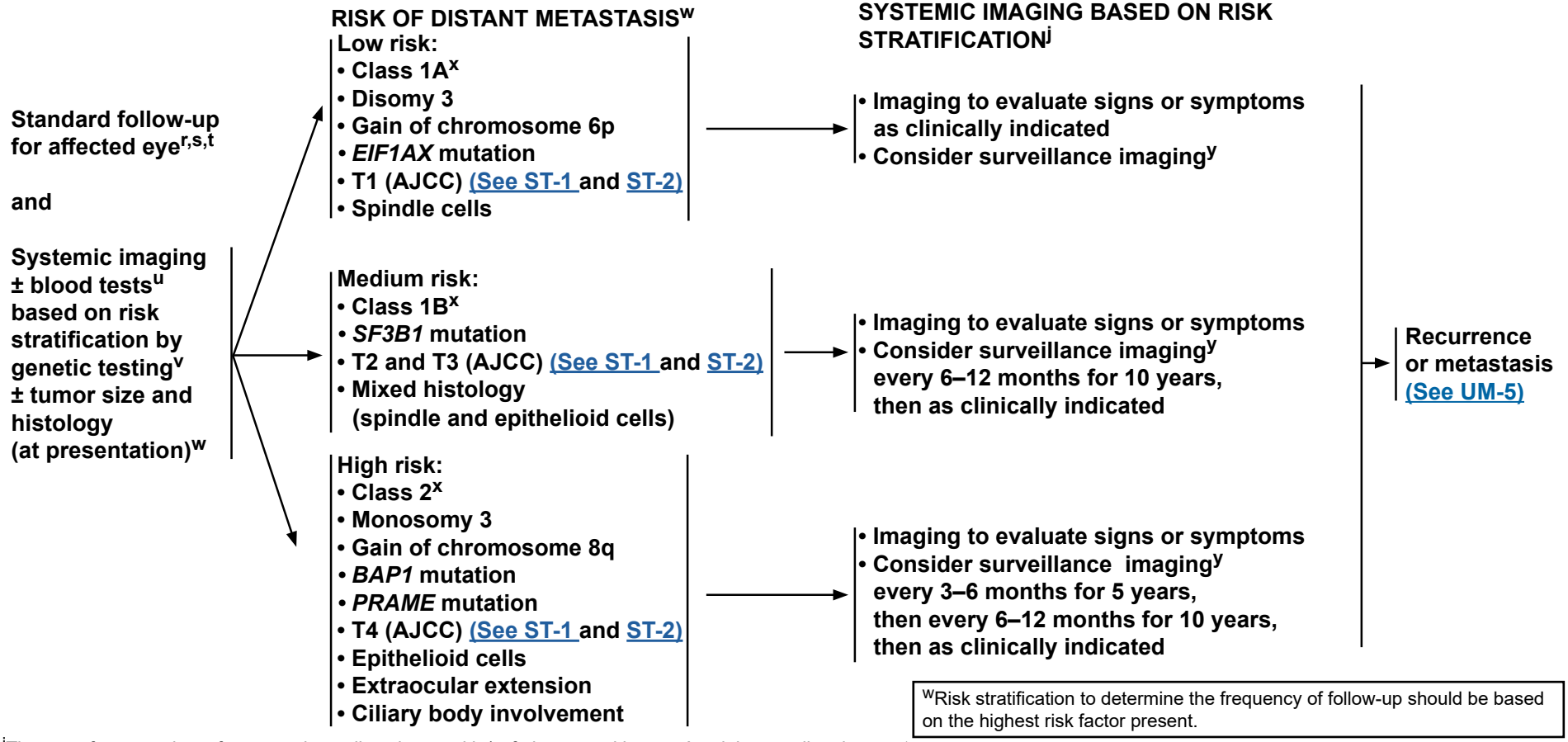


[w]Risk stratification to determine the frequency of follow-up should be based on the highest risk factor present.

[j]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 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.

[r]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. 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.

[s]The contralateral eye is not at increased risk of uveal melanoma, and can be followed with routine opthalmologic care.

[t]Additional risk factors for recurrence: Juxtapapillary location and ciliary body involvement.

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

[v]If biopsy not performed, then follow medium- or high-risk pathways, depending on whether any high-risk features are present.

[x]Onken, 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.

[y]Recognizing that there are limited options for systemic recurrence and that regular imaging may cause patient anxiety, some patients may elect to forgo surveillance imaging.

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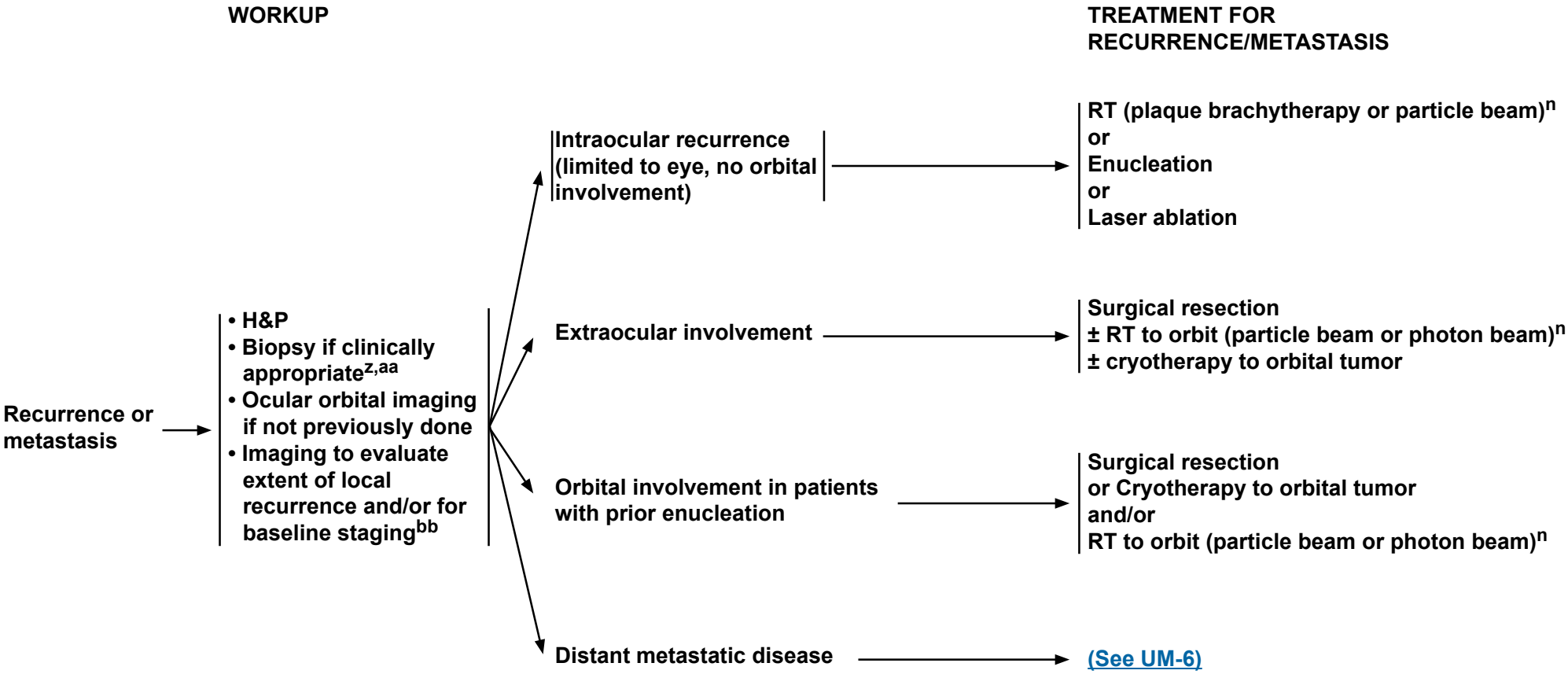


[n]See Principles of Radiation Therapy (UM-B).

[z]Extraocular 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 eligiblity 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.

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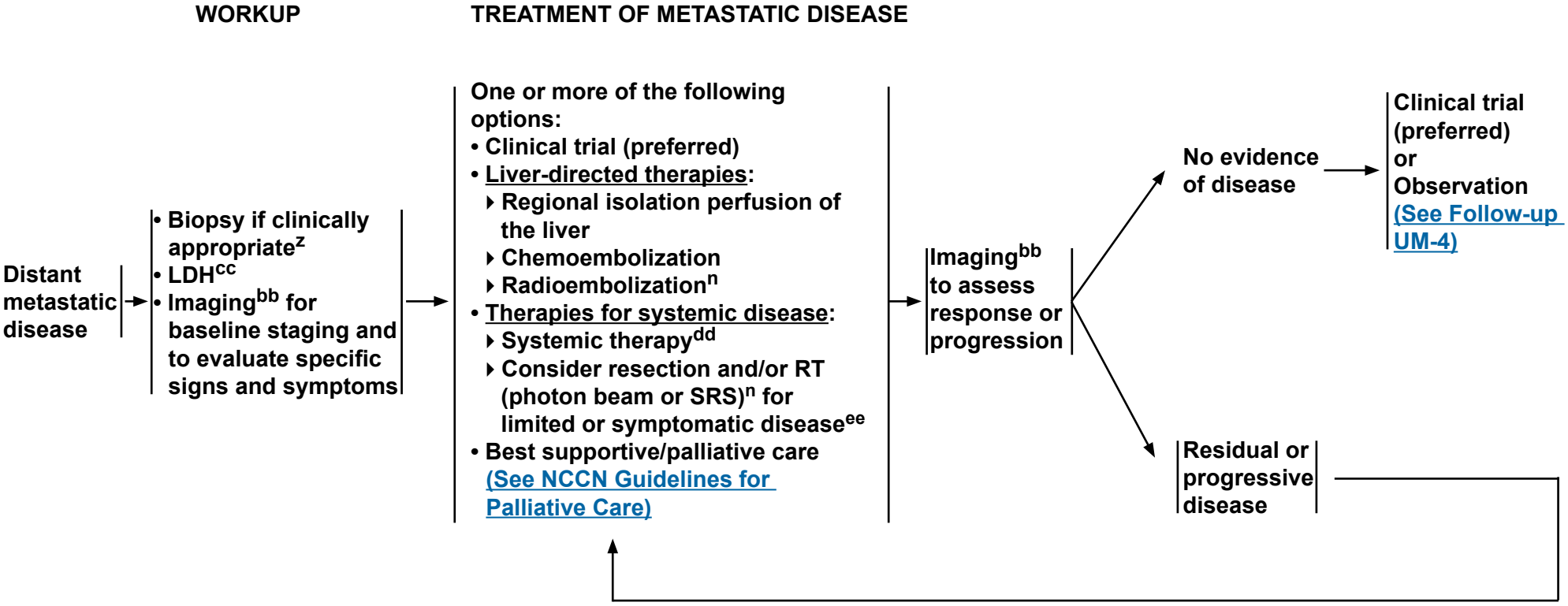


[n]See Principles of Radiation Therapy (UM-B).

[z]Extraocular 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 eligiblity 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).

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## 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.**

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## 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 $^{125}$iodine 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, $^{106}$ruthenium, $^{103}$palladium, $^{90}$strontium, $^{60}$cobalt, $^{131}$cesium), or non-COMS $^{125}$iodine 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).

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## 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.

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## 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 volume[14] 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 $^{90}$Yttrium has been reported in retrospective studies.[15]
- Further study is required to determine the appropriate patients for and risks and benefits of this approach.

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## PRINCIPLES OF RADIATION THERAPY
**(References)**

[1]Abrams 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.
[2]Collaborative 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.
[3]American 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.
[4]Almony 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.
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[10]Muller 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.
[11]Zehetmayer 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.
[12]The 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.
[13]Ang 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.
[14]Huguenin 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.
[15]Jia 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.

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## SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[1]
## (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**

[1]When 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.

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

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

[4]The listed systemic therapy options do not cover *BRAF* or *KIT* mutated tumors. In general, uveal melanomas rarely have *BRAF or KIT* mutations.

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## 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-naive 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.

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## 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.
- Homsi 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.


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***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 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.



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***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.



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***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). | |

### 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 |



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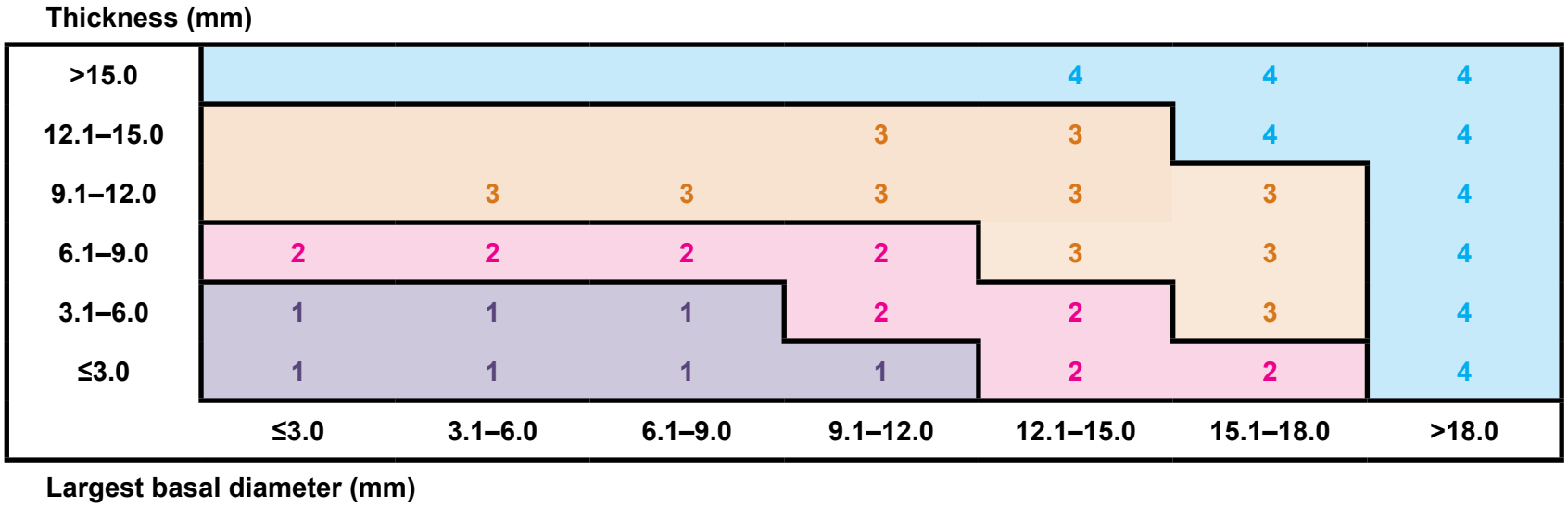
## FIGURE 1: CLASSIFICATION OF CILIARY BODY AND CHOROID UVEAL MELANOMA BASED ON THICKNESS AND DIAMETER



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## 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: B**ased upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**