Protocol for the Examination of Specimens from Patients with Uveal Melanoma

Protocol applies to malignant melanoma of the uvea. This protocol does not apply to cutaneous melanoma.

Based on:

AJCC/UICC TNM, 8th edition
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None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol UvealMelanoma 4.0.0.0.

Procedures Covered in this Protocol:

- Local Resection
- Enucleation
- Limited Exenteration
- Complete Exenteration

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The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

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Molecular Considerations:

Monosomy 3 and defined abnormalities of chromosomes 6 and 8 have been associated with metastatic death in choroidal and ciliary body melanoma. The strongest single predictor of prognosis is loss of heterozygosity detected in chromosome 3; because of the possibility of isochromosome, some patients falsely appear to be disomic, e.g., in fluorescent in situ hybridization (FISH) analysis. Studies have shown that genetic profiling is a more accurate way than karyotyping to differentiate uveal melanoma patients with favorable and adverse prognosis.

- Techniques for assessing chromosome status include:
  - Karyotype
    - Submit fresh, sterile tissue in a suitable transport media for karyotypic analysis
  - Fluorescent in situ hybridization (FISH)
  - Comparative genomic hybridization (CGH)
  - DNA polymorphism analysis

- Techniques for assessing class 1 or class 2 gene expression profiles include:
  - Microarray
  - PCR

With the exception of karyotype, the above molecular tests may be performed with formalin fixed paraffin embedded tissue sections (FFPE).

Immunohistochemistry Considerations:

Uveal melanoma is positive for S100, HMB-45, melan-A, and SOX10. Immunohistochemical (IHC) staining for the presence or absence of BAP1 protein immunoreactivity should be reported.

Further IHC studies, in additional to genetic tests, can help indicate the risk for metastasis. EIF1AX mutation (with disomy 3 and gain of chromosome 6p) suggests low risk, SF3B1 mutation suggests medium risk, and BAP1 and PRAME mutations (with Monosomy 3 and gain of chromosome 8q) suggests a higher risk.

These tests can be performed on formalin fixed paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

  - Local Resection
  - Enucleation
  - Limited Exenteration
  - Complete Exenteration
  - Other (specify)

- **Specimen Size and Extent of Resection:**

  - Enucleation:
    - Anteroposterior diameter in mm
    - Horizontal diameter in mm
    - Vertical diameter in mm
    - Optic nerve segment – Length and diameter in mm

  - Exenteration:
    - Provide three dimensions of specimen and attached structures in cm.

- **Specimen Laterality:**

  - Specify right or left.

- **Globe Orientation:** *(Figure 1)*

  The orientation of a globe may be determined by identifying extraocular muscle insertions, optic nerve, and other landmarks. The terms *temporal* and *nasal* are generally used in place of *lateral* and *medial* with reference to ocular anatomy.

  - The inferior oblique muscle insertion is located temporal (lateral) to the optic nerve on the sclera.
  - The inferior oblique fibers travel inferonasally from its insertion.
  - The long posterior ciliary artery is seen as a blue-gray line in the sclera on either side of the optic nerve and marks the horizontal meridian of the globe.

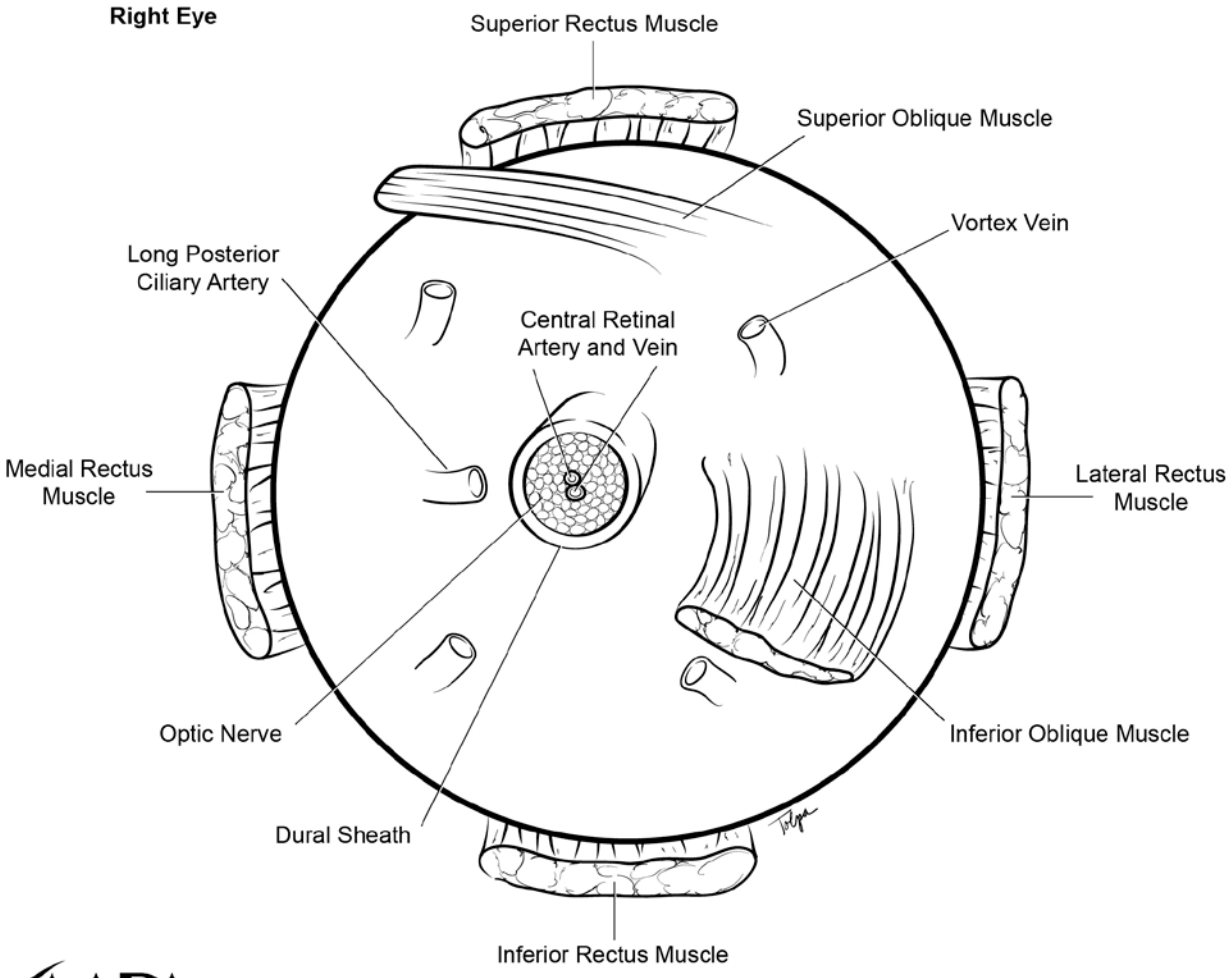

Figure 1: Anatomic Landmarks of the Posterior Aspect of the Globe

- **Specimen Integrity and Adequacy:**

  Any defects or irregularity of the specimen should be described with relation to anatomic landmarks. This is particularly important if these defects affect the surgical margins, most importantly the optic nerve margin. The surgeon may need to be consulted in this case for clarification.

- **Specimen Handling:**

  - **Fixation:**
    The minimum fixation time for whole globes with intraocular tumors is 48 hours with a 10:1 ratio of 10% neutral buffered formalin volume to specimen volume. Incisions or windows in the globe are not recommended and are not necessary for adequate fixation. Injection of fixative into the globe is also not recommended.

- **Orientation:**
  As previously stated, the orientation of a globe can be determined by identification of the extraocular muscle insertions, the optic nerve, and the long posterior ciliary body. The position of the inferior oblique muscle relative to the optic nerve is most helpful in orienting the globe.

- **Sectioning:** *(Figure 2)*
  The globe is generally sectioned in the horizontal or vertical plane, taking care to include the pupil and optic nerve in the section to be submitted for microscopic examination. If the mass cannot be included with horizontal or vertical sectioning, the globe is sectioned obliquely to include the tumor, pupil, and optic nerve.

  After transillumination, the tumor base is applied with ink, if possible, included in the pupil-optic (P-O) nerve section, and submitted for processing. If tumor is found in either of the calottes, these may also be submitted for sectioning. The meridian in which the globe was sectioned should be included in the macroscopic description. It is not uncommon to induce an artifactitious retinal detachment while sectioning the globe. This can be minimized by gentle handling and by avoiding a sawing motion with the blade.

  Note: The macroscopic features of ocular specimens provide valuable information. Macroscopic photography of these valuable specimens is highly recommended and establishes a permanent documentation of the macroscopic features.

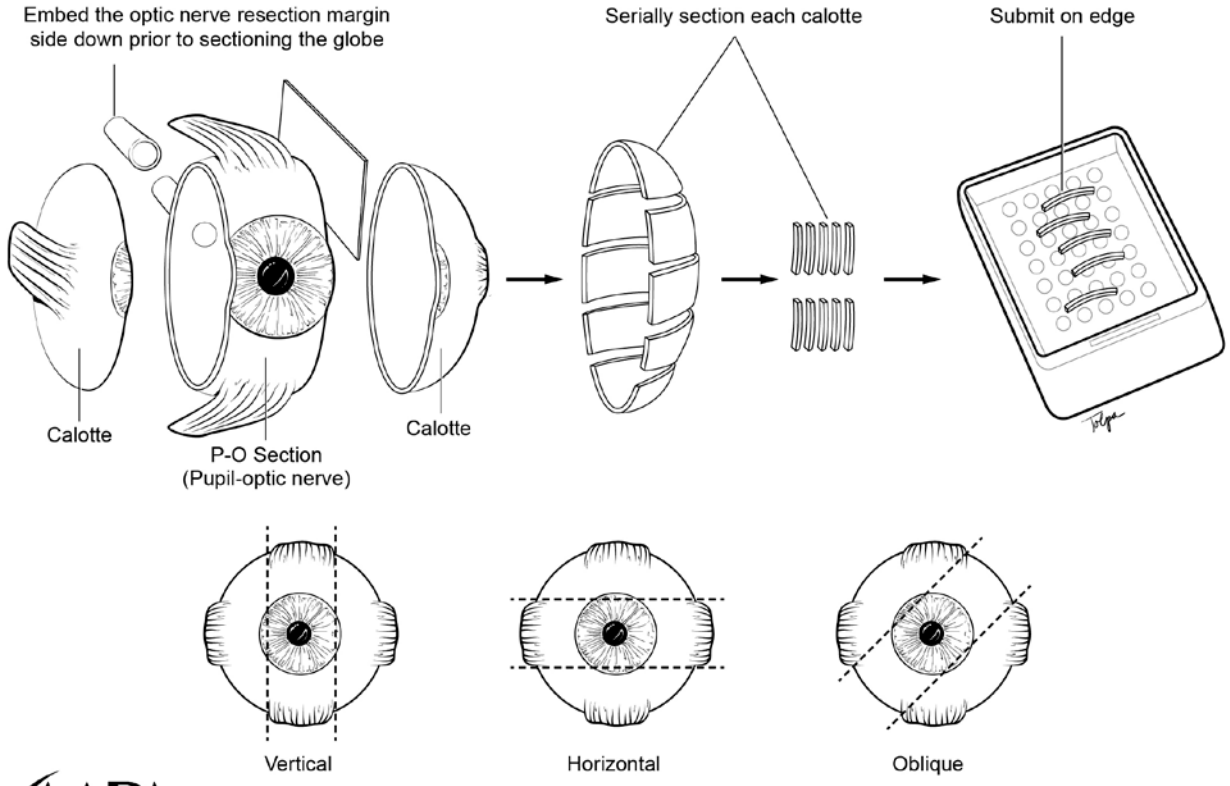

Figure 2: Common Methods of Sectioning the Globe

TUMOR ("T" of TNM)

- **Tumor Size:**

  - Tumor Basal Size on Transillumination: *
    - Anterior posterior length in mm
    - Transverse length in mm

  **Transillumination provides an estimation of tumor size and is used to determine the best method of sectioning the globe.*

  - Tumor Size after Sectioning:

    - Cannot be determined.
    - Provide the greatest basal diameter in mm.**
      - Provide the measurement of the base at cut edge in mm.
    - Provide the greatest thickness in mm.
      - Provide the thickness at the cut edge in mm.

  *** It is generally accepted that the largest basal tumor diameter is the predominant predictor of prognosis, however, tumor thickness is an independent clinical prognostic indicator, even when ciliary body involvement and extraocular extension are taken into account.*

  The size of uveal melanoma and the presence of extrascleral extension are strongly associated with risk for metastasis. Small tumors have a more favorable prognosis.

  - Small tumors:
    Smaller than medium or large tumors as defined below

  - Medium tumors:
    Greater than or equal to 2.5 mm, less than or equal to 10 mm in height, and less than or equal to 16 mm in basal diameter

  - Large tumors:
    Greater than 10 mm in height *or*
    Greater than 2 mm in height and greater than 16 mm in basal diameter *or*
    Greater than 8 mm in height with optic nerve involvement

  Note: The size and location of uveal melanoma are interrelated: melanomas of the iris are usually small, and those arising from or extending to the ciliary body are typically large.

- **Tumor Site(s):**

  Tumor location affects prognosis. Tumors confined to the iris carry the most favorable prognosis, followed by those confined in the choroid; ciliary body involvement carries the least favorable prognosis.

  - Specify location of tumor by macroscopic examination / transillumination:
    - Cannot be determined
    - Superotemporal quadrant of globe
    - Superonasal quadrant of globe
    - Inferotemporal quadrant of globe

  - Inferonasal quadrant of globe
  - Anterior chamber
  - Between ___ and ___ o'clock
  - Other (specify):

- Specify tumor location after sectioning:
  - Cannot be determined
  - Superonasal
  - Inferonasal
  - Superotemporal
  - Inferotemporal
  - Provide the distance from the anterior edge of tumor to the limbus at the cut edge in mm.
  - Provide the distance of the posterior margin of tumor base from the edge of optic disc in mm.

- **Tumor Depth of Invasion, Tumor Growth Patterns and Relationship to Attached Organs / Structures:**

  Assessment of the extent of tumor, measured in clock hours of involvement, basal dimensions, tumor thickness, and margins of resection, are necessary for pathologic staging.

  Extraocular extension is diagnosed if the tumor grows outside the bulb with invasion of the orbit, optic nerve, outer eye muscles, lacrimal apparatus or conjunctiva.

  Maximum tumor thickness, scleral basal diameter, and the presence and extent of ciliary body and extraocular extension are the strongest prognostic indicators.

  - Indicate Tumor Involvement of Other Ocular Structures including:

    - Sclera
    - Vortex vein(s)
    - Optic nerve head
    - Vitreous
    - Choroid
    - Ciliary body
    - Iris
    - Lens
    - Anterior chamber
    - Extrascleral extension (anterior)
    - Extrascleral extension (posterior)
    - Angle / Schlemm's canal
    - Optic nerve
    - Retina
    - Cornea
    - Other (specify)
    - Cannot be assessed

  - Growth Pattern*

    - Solid mass
    - Dome shape
    - Mushroom shape

- o Diffuse (ciliary body ring)
- o Diffuse (flat)

*Primary uveal melanoma usually arises from the ciliary body or choroid as an ellipse or almond-shaped mass which eventually breaks through Bruch's membrane and becomes mushroom shaped.

Size Category Classification Table for Ciliary Body and Choroid Melanoma Thickness and Diameter (mm) *

Four tumor sizes have been defined by the AJCC TNM system:
T1 – Small
T2 – Medium
T3 – Large
T4 – Very large

Thicker than 15 mm					4	4	4
12.1 to 15.0 mm				3	3	4	4
9.1 to 12.0 mm		3	3	3	3	3	4
6.1 to 9.0 mm	2	2	2	2	3	3	4
3.1 to 6.0 mm	1	1	1	2	2	3	4
Less than 3.0 mm	1	1	1	1	2	2	4
Largest basal diameter (mm)	Less than 3 mm	3.1 to 6.0 mm	6.1 to 9.0 mm	9.1 to 12.0 mm	12.1 to 15.0 mm	15.1 to 18.0 mm	Larger than 18.0 mm

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*The size of uveal melanoma is strongly associated with risk for metastasis.

Definition of Primary Tumor (pT)

Iris Melanomas

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor limited to the iris
pT1a	Tumor limited to the iris, not more than 3 clock hours in size
pT1b	Tumor limited to the iris, more than 3 clock hours in size
pT1c	Tumor limited to the iris with secondary glaucoma
pT2	Tumor confluent with or extending into the ciliary body, choroid, or both
pT2a	Tumor confluent with or extending into the ciliary body, without secondary glaucoma
pT2b	Tumor confluent with or extending into the ciliary body and choroid, without secondary glaucoma
pT2c	Tumor confluent with or extending into the ciliary body, choroid, or both, with secondary glaucoma

pT3	Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension
pT4	Tumor with extrascleral extension
pT4a	Tumor with extrascleral extension ≤5 mm in largest diameter
pT4b	Tumor with extrascleral extension >5 mm in largest diameter

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Choroidal and Ciliary Body Melanomas

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor size category 1
pT1a	Tumor size category 1 without ciliary body involvement and extraocular extension
pT1b	Tumor size category 1 with ciliary body involvement
pT1c	Tumor size category 1 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
pT1d	Tumor size category 1 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
pT2	Tumor size category 2
pT2a	Tumor size category 2 without ciliary body involvement and extraocular extension
pT2b	Tumor size category 2 with ciliary body involvement
pT2c	Tumor size category 2 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
pT2d	Tumor size category 2 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
pT3	Tumor size category 3
pT3a	Tumor size category 3 without ciliary body involvement and extraocular extension
pT3b	Tumor size category 3 with ciliary body involvement
pT3c	Tumor size category 3 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
pT3d	Tumor size category 3 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
pT4	Tumor size category 4
pT4a	Tumor size category 4 without ciliary body involvement and extraocular extension
pT4b	Tumor size category 4 with ciliary body involvement
pT4c	Tumor size category 4 without ciliary body involvement but with extraocular extension ≤5 mm in largest diameter
pT4d	Tumor size category 4 with ciliary body involvement and extraocular extension ≤5 mm in diameter
pT4e	Any tumor size category with extraocular extension >5 mm in largest diameter

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Provide clear distinctions when the "T" score upstages due to involvement of adjacent structures.

TNM Descriptors:

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

pT(m)NM: The "m" suffix indicates the presence of multiple primary tumors in a single site.

ycTNM or ypTNM: The "y" prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). It categorizes the extent of tumor actually present at the time of examination; it is not an estimate of tumor prior to multimodality therapy.

rTNM: The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval.

aTNM: The "a" prefix designates the stage determined at autopsy.

Residual Tumor (R) Category

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites

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- **Margins:**

  - Note if tumor is present or not present at the margins (optic nerve and soft tissue margins) and submit for microscopic examination if appropriate.
  - Specify if there is extrascleral extension of tumor (for enucleation specimens).
  - Specify any other margin(s) involved.

    - If melanoma is completely excised (margins are macroscopically uninvolved by tumor): *(refer to figure 2, page 8)*

      - Optic Nerve Margin: provide the clearance measurement, declare the specific location(s), and demonstrate for microscopic evaluation the closest margin approach(s) of tumor with a transverse section.

      - Extrascleral Extension (for enucleation specimens): provide the clearance measurement, declare the specific location(s), and demonstrate for microscopic evaluation the closest margin approach(s) of tumor.

      - Soft Tissue Margins (for exenteration specimens): provide the clearance measurement, declare the specific location(s) and demonstrate for microscopic evaluation the closest margin approach(es) of tumor.

    - If melanoma is macroscopically present at surgical margins*: (refer to Figure 2, page 8)*

      - Optic Nerve Margin: demonstrate for microscopic examination with a transverse section.

      - Extrascleral Extension (for enucleation specimens): declare the specific location(s) and demonstrate for microscopic examination.

      - Soft Tissue Margins (for exenteration specimens): declare the specific location(s) and demonstrate for microscopic examination.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:** (if applicable)

Definition of Regional Lymph Node (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Regional lymph node metastases or discrete tumor deposits in the orbit
pN1a	Metastasis in one or more regional lymph nodes
pN1b	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)

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Regional lymph node involvement is rare in uveal melanoma. This category applies only to uveal melanomas with anterior extrascleral extension and conjunctival or adnexal lymphatic invasion.

- Regional lymph nodes:
  - Preauricular (parotid)
  - Submandibular
  - Cervical

Although rare, if lymph nodes are encountered or submitted, follow the recommendations below:

- Count lymph nodes identified or submitted.
- Specify site of lymph nodes identified or as submitted.

- **For macroscopically positive lymph nodes**:
  - Give a precise size of the lymph node and tumor implant.
  - Representative sampling of these lymph nodes is adequate.
  - Sample areas where extranodal extension is seen or cannot be excluded.
    - If macroscopically inconclusive, submit the entire capsule of the lymph node for possible extranodal extension.
  - If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
  - Take steps to ensure that an accurate lymph node count can be rendered.

- **For small lymph nodes or macroscopically negative larger lymph nodes**:
  - Submit small lymph nodes in toto.
  - Section larger lymph nodes at 2 mm intervals and entirely submit.
  - If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
  - If the lymph node is large but macroscopically negative, submit sequentially so that a size calculation can be established.
  - Take steps to ensure that an accurate lymph node count can be rendered.

METASTASIS ("M" of TNM)

- **Metastasis:**

Definition of Distant Metastasis (pM)

pM Category	pM Criteria
pM1	Distant metastasis
pM1a	Largest diameter of the largest metastasis ≤3 cm
pM1b	Largest diameter of the largest metastasis 3.1-8.0 cm
pM1c	Largest diameter of the largest metastasis ≥8.1 cm

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Specify site(s), if known.

- M1 classification is determined by presence of tumor beyond the globe. This does not include direct extension from the globe into adjacent soft tissues in an exenteration specimen.
- Uveal melanoma can metastasize to various visceral organs. The liver is the most common initial site for metastasis in over 90% of patients.
- Less common sites of metastasis include the lung, subcutaneous tissues, bone, and brain. These sites are usually involved later in the course of dissemination.

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