

# Uveal Melanoma

## Protocol applies to malignant melanoma of the uvea.

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*Protocol revision date: January 2004  
Based on AJCC/UICC TNM, 6<sup>th</sup> edition*

### Procedures

- **Cytology** (No Accompanying Checklist)
- **Biopsy** (No Accompanying Checklist)
- **Resection Specimen (Enucleation, Limited/Complete Exenteration)**

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**Surgical Pathology Cancer Case Summary (Checklist)**

*Protocol revision date: January 2004  
Applies to melanomas of the uvea only  
Based on AJCC/UICC TNM, 6<sup>th</sup> edition*

**Uveal Melanoma: Resection**

Patient name:

Surgical pathology number:

<b>Note: Check 1 response unless otherwise indicated.</b>
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**MACROSCOPIC****Specimen Type** Enucleation Limited exenteration Complete exenteration Other (specify): \_\_\_\_\_ Not specified**Laterality** Right Left Unspecified**Specimen Size**For Enucleation

Anteroposterior diameter \_\_\_\_ mm

Horizontal diameter \_\_\_\_ mm

Vertical diameter \_\_\_\_ mm

Length of optic nerve \_\_\_\_ mm

Diameter of optic nerve \_\_\_\_ mm

 Cannot be determined (see Comment)For Exenteration

Greatest dimension: \_\_\_\_ mm

\*Additional dimensions: \_\_\_\_ x \_\_\_\_ mm

 Cannot be determined (see Comment)

2

\* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

**Tumor Site and Extent (macroscopic examination/transillumination)****(check all that apply)**

- Cannot be determined
- Superotemporal quadrant of globe
- Superonasal quadrant of globe
- Inferotemporal quadrant of globe
- Inferonasal quadrant of globe
- Anterior chamber
- Extrascleral extension
- Optic nerve

**\*Tumor Basal Dimensions on Transillumination**\*  Cannot be determined

\*Specify: \_\_\_ x \_\_\_ mm

**Tumor Dimensions After Sectioning**

- Cannot be determined
- Base at cut edge: \_\_\_ mm
- \*  Height at cut edge: \_\_\_ mm
- Maximal tumor height: \_\_\_ mm

**\*Tumor Location After Sectioning**\*  Cannot be determined\*  Distance from anterior edge of tumor to limbus at cut edge: \_\_\_ mm\*  Distance of posterior margin of tumor base from edge of optic disc: \_\_\_ mm**Tumor Involvement or Gross Pathology of Other Ocular Structures****(check all that apply)**

- Cannot be determined
- Sclera
- Vortex vein(s)
- Optic disc
- Vitreous
- Choroid
- Ciliary body
- Iris
- Lens
- Anterior chamber
- Extrascleral extension
- Angle/Schlemm's canal
- \*  Cornea
- \*  Retinal detachment

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**Growth Pattern**

- Cannot be determined
- Solid mass
- Ciliary body ring
- Diffuse

**MICROSCOPIC**

**Histologic Type**

- Cannot be determined
- Spindle cell type
- \*  Spindle cell type, spindle A
- \*  Spindle cell type, spindle B
- Epithelioid cell type
- Mixed cell type
- Necrotic
- \*  Balloon cell

**\*Tumor Location**

- \*  Cannot be determined
- \*  Anterior margin located anterior to equator of globe
- \*  Within 1 mm of optic disc
- \*  None of above

**Scleral Involvement**

- Cannot be determined
- None
- Extrascleral
- Intrasceral

**Involvement of Other Structures (check all that apply)**

- Cannot be determined
- Vortex vein
- Optic Nerve
- Vitreous
- Retina
- Angle/Schlemm's canal
- Other(s) (specify): \_\_\_\_\_

**Pathologic Staging (pTNM)**Primary Tumor (pT): Iris

- 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 melanomalytic glaucoma
- pT2: Tumor confluent with or extending into the ciliary body and/or choroid
  - pT2a: Tumor confluent with or extending into the ciliary body and/or choroid with melanomalytic glaucoma
- pT3: Tumor confluent with or extending into the ciliary body and/or choroid with extrascleral extension
  - pT3a: Tumor confluent with or extending into the ciliary body with extrascleral extension and melanomalytic glaucoma
- pT4: Tumor with extraocular extension

Primary Tumor (pT): Ciliary Body and Choroid

- pTX: Primary tumor cannot be assessed
- pT0: No evidence of primary tumor
- pT1: Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness)
  - pT1a: Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) without microscopic extraocular extension
  - pT1b: Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with microscopic extension
  - pT1c: Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with macroscopic extraocular extension
- pT2: Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness)
  - pT2a: Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) without microscopic extraocular extension
  - pT2b: Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with microscopic extraocular extension
  - pT2c: Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with macroscopic extraocular extension
- pT3: Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) without extraocular extension
- pT4: Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) with extraocular extension

*Note: When dimension and elevation show a difference in classification, the highest category should be used for classification.*

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Regional Lymph Nodes (pN)

- pNX: Regional lymph nodes cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Regional lymph node metastasis

Distant Metastasis (pM)

- pMX: Cannot be assessed
- pM1: Distant metastasis  
\*Specify site(s), if known: \_\_\_\_\_

**Margins**

- Cannot be assessed
- No melanoma at margins
- Extrascleral extension (for enucleation specimens)
- Other margin involved (specify): \_\_\_\_\_

**\*Additional Pathologic Findings (check all that apply)**

- \*  None identified
- \*  Mitotic rate (number of mitoses per 40X objective with a field area of 0.152 mm<sup>2</sup>): \_\_\_\_\_
- \*  Necrosis
- \*  Microvascular patterns
- \*  Vascular invasion (tumor vessels or other vessels)
- \*  Degree of pigmentation
- \*  Inflammatory cells/tumor infiltrating lymphocytes
- \*  Drusen
- \*  Retinal detachment
- \*  Invasion of Bruch's membrane
- \*  Nevus
- \*  Hemorrhage
- \*  Neovascularization
- \*  Other (specify): \_\_\_\_\_

**\*Comment(s)**

## Background Documentation

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*Protocol revision date: January 2004*

### **I. Cytologic Material**

#### **A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
  - a. Relevant history
    - (1) clinical findings
    - (2) past ocular history
    - (3) previous ocular surgery
    - (4) previous treatment
  - b. Relevant findings (eg, liver function tests, ultrasound)
  - c. Clinical diagnosis
  - d. Procedure (eg, fine-needle aspiration [FNA], anterior chamber paracentesis)
  - e. Operative findings
  - f. Anatomic site (right or left eye; part of eye sampled)

#### **B. Macroscopic Examination**

1. Specimen
  - a. Unfixed/fixed (specify fixative)
  - b. Number of slides received
  - c. Quantity and appearance of fluid specimen
  - d. Other (eg, core of tissue in needle shaft)
  - e. Intraoperative/intraprocedure consultation
2. Material submitted for microscopic evaluation (eg, cytocentrifuge, smear, filter preparation)
3. Material submitted for special studies (specify) (eg, immunocytochemistry)

#### **C. Microscopic Examination**

1. Adequacy of specimen for evaluation (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present
  - a. Histologic type, if possible (Note **A**)
  - b. Other characteristics (Note **B**)
    - (1) presence of pigment
    - (2) cytoplasmic indentation of nucleus
    - (3) cytoplasmic vacuolization
3. Additional pathologic findings, if present (eg, presence of retinal tissue, inflammatory cells)
4. Retinal tissue
5. Results/status of special studies (specify)
6. Comments
  - a. Correlation with intraprocedural consultation

- b. Correlation with other specimens, as appropriate
- c. Correlation with clinical information, as appropriate

## II. Biopsy

### A. Clinical Information

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
  - a. Relevant history
    - (1) clinical findings
    - (2) past ocular history
    - (3) previous ocular surgery
    - (4) previous treatment
  - b. Relevant findings (eg, liver function tests, ultrasound)
  - c. Procedure (eg, peripheral iridectomy, iridocyclectomy, sclerouveectomy)
  - d. Operative findings
  - e. Anatomic site of specimen (right or left eye)

### B. Macroscopic Examination

1. Specimen
  - a. Unfixed/fixed (specify fixative)
  - b. Orientation (if indicated by surgeon by written instruction, diagram, or suture); ink margins of excisional biopsy specimens
  - c. Previously opened
  - d. Number of pieces
  - e. Size(s) (3 dimensions, if possible)
  - f. Tumor
    - (1) size (3 dimensions, if possible)
    - (2) Presence of necrotic tissue
    - (3) descriptive features
  - g. Other tissues, as appropriate
  - h. Results or intraoperative consultation
2. Tissue submitted for microscopic evaluation (specify)
3. Special studies (specify) (eg, special histochemical stains, immunohistochemical stains)

### C. Microscopic Evaluation

1. Tumor
  - a. Histologic type (Note **A**)
  - b. Histologic grade
  - c. Extent
    - (1) involvement of adjacent structures such as ciliary body
    - (2) extraocular extension
    - (3) invasion of normal vessels or tumor vessels
  - d. Other prognostic features (Note **B**)
2. Additional pathologic findings, if present

- a. Drusen
  - b. Neovascularization
  - c. Nevus
  - d. Ectropion uveae
  - e. Other(s)
3. Results/status of special studies(specify)
  4. Comments
    - a. Correlation with intraoperative consultation
    - b. Correlation with other specimens, as appropriate
    - c. Correlation with clinical information, as appropriate

### **III. Resection Specimen (Enucleation, Limited/Complete Exenteration)**

#### **A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age(birth date)
  - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Other clinical information
  - a. Relevant history
    - (1) clinical findings
    - (2) past ocular history
    - (3) previous ocular surgery
    - (4) previous treatment
  - b. Relevant findings (eg, liver function tests, ultrasound)
  - c. Clinical diagnosis
  - d. Procedure (usually enucleation)
  - e. Operative findings
  - f. Anatomic site of specimen (right or left eye)
5. Documentation of areas marked by surgeon for orientation (eg, suture, diagram)

#### **B. Macroscopic Examination**

1. Specimen
  - a. Organ(s)/tissue(s) included
  - b. Unfixed/fixed (specify fixative) (Note **C**)
  - c. Orientation (Note **D**)
  - d. Description of other tissues, as appropriate
  - e. Results of intraoperative consultation
2. Globe
  - a. Evidence of previous excision or treatment
  - b. Note if previously opened/sectioned and in what fashion (Note **E**)
  - c. Size
    - (1) anteroposterior, horizontal, vertical dimensions of globe
    - (2) length and diameter of attached optic nerve
    - (3) corneal horizontal and vertical diameter
    - (4) diameter of pupil (if visible)

- d. Transillumination (helpful to identify location of tumor and measure basal dimension prior to sectioning globe)
    - (1) quality of transillumination (eg, poor light transillumination, transilluminates light well)
    - (2) transillumination defect
      - i. location
      - ii. quadrant/relationship to equator of globe
      - iii. relationship to limbus
      - iv. clock-hour(s) of iris/globe
      - v. size (2 dimensions)
  - e. Mark outline with marking implement
  - f. Extrascleral extension, if present
  - g. Sectioning of specimen (globe) (Note **E**)
  - h. Mass/tumor, if present
    - (1) location
    - (2) size (Notes **F** and **G**)
      - i. base at cut edge (ie, portion of tumor closest to sclera)
      - ii. height at cut edge
    - (3) distance of anterior margin of tumor base from limbus at cut edge
    - (4) distance of posterior margin of tumor base from edge of optic disc
    - (5) other descriptive features (color, consistency, shape)
    - (6) structures involved and extent (Note **G**)
      - i. retinal involvement
      - ii. optic nerve involvement
      - iii. macroscopic involvement of vitreous
      - iv. involvement of ciliary body
      - v. macroscopic involvement of anterior chamber angle
  - i. Features of other (uninvolved) ocular tissues
    - (1) cornea (eg, clear, cloudy, opaque)
    - (2) anterior chamber (eg, deep, shallow, flat)
    - (3) angle (eg, open, narrow, closed)
    - (4) iris (eg, color, any abnormalities)
    - (5) ciliary body
    - (6) lens (eg, clear, cataractous, presence of lens implant, absence)
    - (7) vitreous (eg, color, consistency, hemorrhage)
    - (8) retina (eg, detachment, total or partial; hemorrhages)
    - (9) choroid
    - (10) sclera (eg, thinning, defects)
    - (11) optic disc (eg, pallor, increased cup/disc ratio)
3. Tissues submitted for microscopic examination (specify) (Note **F**)
4. Special studies (specify) (eg, immunohistochemistry)

### C. Microscopic Evaluation

- 1. Tumor
  - a. Site (choroid/ciliary body/iris) (Note **G**)
  - b. Histologic type (Note **A**)
  - c. Histologic grade
  - d. Extent of invasion (Note **G**)
  - e. Size (Note **F**)
  - f. Anatomic extent (Notes **B** and **G**)

- (1) anterior margin of tumor
- (2) retinal or scleral involvement
- (3) angle involvement
- (4) vitreal involvement
- (5) optic nerve involvement
2. Margins
  - a. Extrascleral extension (Notes **B** and **G**)
  - b. Surgical margin of optic nerve (Note **B**)
3. Other prognostic features (Note **B**)
4. Additional pathologic findings, if present
  - a. Cancer-related
    - (1) cataract
    - (2) vitreous hemorrhage
    - (3) glaucomatous optic atrophy
    - (4) secondary angle closure
    - (5) secondary open-angle glaucoma
    - (6) iris neovascularization
    - (7) retinal atrophy
  - b. Other
    - (1) corneal disease
    - (2) diabetic retinopathy
5. Results/status of special studies (specify)
6. Comments
  - a. Correlation with intraoperative consultation
  - b. Correlation with other specimens, as appropriate
  - c. Correlation with clinical information, as appropriate

## Explanatory Notes

### A. Histologic Type

The modified Callender classification shown below is used for determining cell type, but has prognostic significance only for tumors of the choroid and ciliary body, not those of the iris, which generally have a benign course.<sup>1-4</sup>

Spindle cell nevus: slender cells with fusiform nuclei, delicate nuclear chromatin and inapparent nucleoli, no mitoses are found

Spindle cell melanoma<sup>#</sup>

Spindle A: slender cells with a thin, oval nucleus, indistinct nucleoli and often a longitudinal fold in the nuclear membrane

Spindle B: larger, plumper nuclei with sharply defined, round nucleoli

Mixed cell melanoma: both spindle and epithelioid cells present

Epithelioid cell melanoma<sup>#</sup>: larger, more pleomorphic, polygonal cells with large, sometimes multiple nucleoli

<sup>#</sup> Spindle cell melanomas have the most favorable prognosis, and epithelioid cell melanomas the least favorable in terms of survival.

### B. Other Pathologic Features of Prognostic Significance

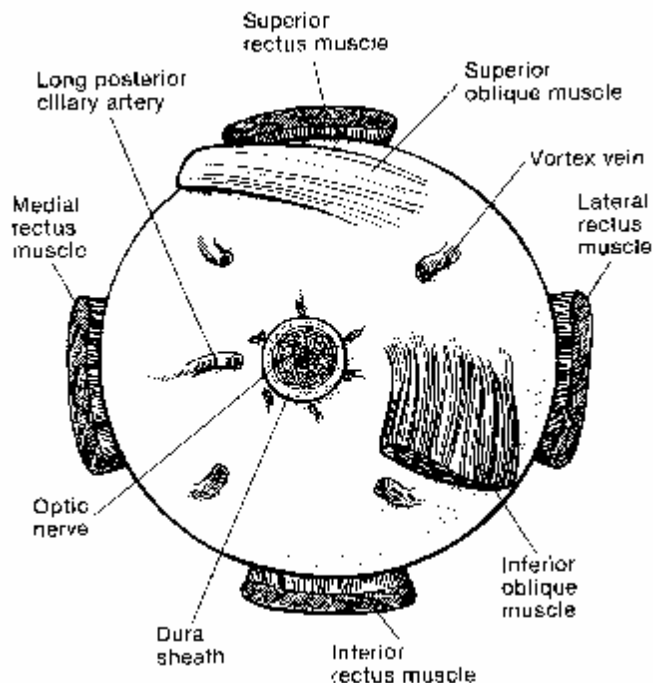
Other histologic features with prognostic significance in choroidal and ciliary body melanoma include the number of mitoses in 40 high-powered fields, pigmentation, degree of inflammation, growth pattern (diffuse choroidal melanomas and ring melanomas of the ciliary body have a much less favorable prognosis), location of anterior margin of tumor, degree and patterns of vascularity, blood vessel invasion (both tumor vessels and normal vessels), tumor necrosis, extraocular extension and optic nerve involvement.<sup>4-15</sup>

### C. Fixative

The minimum recommended fixation time for whole globes with intraocular tumors is 48 hours. The globe should be fixed in an adequate volume of fixative with a 10:1 ratio of fixative volume to specimen volume recommended. Incisions or windows in the globe are not necessary for adequate penetration of fixative and are not recommended. Injection of fixative into the globe is also not recommended.

### D. Orientation

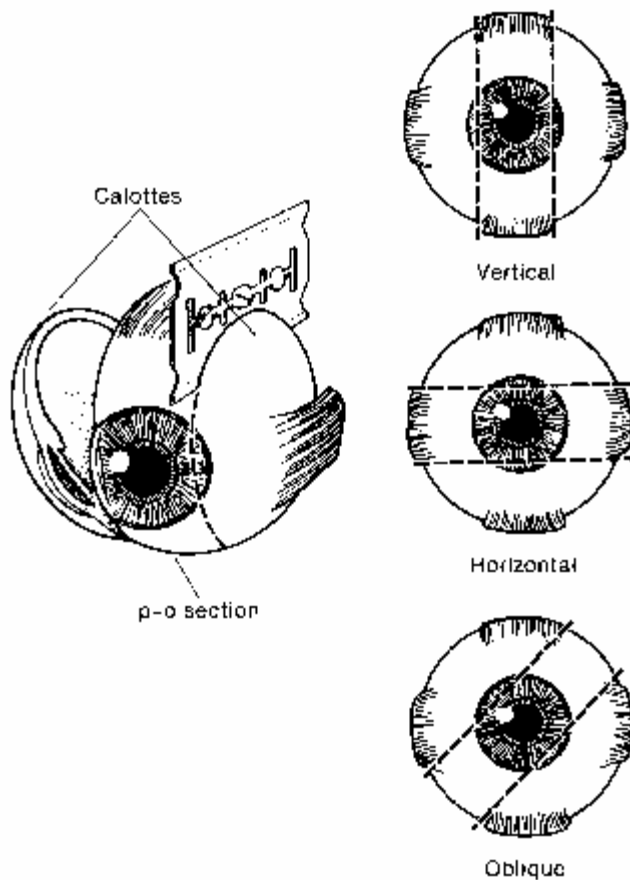
The orientation of a globe may be determined by identification of extraocular muscle insertions, the optic nerve, and other landmarks, as illustrated in Figure 1. The terms *temporal* and *nasal* are generally used in place of *lateral* and *medial* with reference to ocular anatomy.



**Figure 1.** Anatomic landmarks of the posterior aspect of the globe (right eye). The position of the inferior oblique muscle relative to the optic nerve is most helpful in orienting the globe. The inferior oblique muscle insertion is located temporal (lateral) to the optic nerve on the sclera, and its fibers travel inferonasally from its insertion. The long posterior ciliary artery is often seen as a blue-gray line in the sclera on either side of the optic nerve and marks the horizontal meridian of the globe. *Reprinted with permission from WB Saunders Company.*

### E. Sectioning the Globe

The globe is generally sectioned in the horizontal or vertical plane with 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, as illustrated in Figure 2. Alternative methods of sectioning have been described.<sup>16</sup>



**Figure 2.** The most common methods of sectioning a globe. After transillumination, the tumor base is marked, if possible, and 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 gross description of the pathology report. It is not uncommon to induce an artifactual retinal detachment while sectioning the globe. This can be minimized by gentle handling and by avoiding a sawing motion with the blade. *Reprinted with permission from WB Saunders Company.*

**F. Tumor Size**

Tumor size has prognostic significance. Many studies of choroidal and ciliary body melanoma have defined small tumors as being less than 10 mm in greatest diameter.<sup>4</sup> More recently, an ongoing study started in 1986, the Collaborative Ocular Melanoma Study<sup>17,18</sup> defined the following size classification based on clinical measurements.

Small tumors <sup>#</sup> :	Smaller than medium or large tumors 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 <i>or</i> Greater than 2 mm in height and greater than 16 mm in basal diameter <i>or</i> Greater than 8 mm in height with optic nerve involvement

<sup>#</sup> Small tumors have a more favorable prognosis.<sup>6,7</sup>

**G. TNM Stage Groupings**

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM staging systems for uveal melanoma of the iris, ciliary body, and choroid are shown below.<sup>19,20</sup>

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**Primary Tumor (T): All Uveal Melanomas**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor

**Primary Tumor (T): Iris**

- T1 Tumor limited to the iris
- T1a Tumor limited to the iris not more than 3 clock hours in size
- T1b Tumor limited to the iris more than 3 clock hours in size
- T1c Tumor limited to the iris with melanomalytic glaucoma
- T2 Tumor confluent with or extending into the ciliary body and/or choroid
- T2a Tumor confluent with or extending into the ciliary body and/or choroid with melanomalytic glaucoma
- T3 Tumor confluent with or extending into the ciliary body and/or choroid with extrascleral extension
- T3a Tumor confluent with or extending into the ciliary body with extrascleral extension and melanomalytic glaucoma
- T4 Tumor with extraocular extension

**Primary Tumor (T): Ciliary Body and Choroid**

- T1<sup>#</sup> Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness)
- T1a Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) without microscopic extraocular extension
- T1b Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with microscopic extension
- T1c Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with macroscopic extraocular extension
- T2<sup>#</sup> Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness)
- T2a Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) without microscopic extraocular extension
- T2b Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with microscopic extraocular extension
- T2c Tumor 10 mm to 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with macroscopic extraocular extension
- T3<sup>#</sup> Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) without extraocular extension
- T4 Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) with extraocular extension

<sup>#</sup> When basal dimension and apical height do not fit this classification, the largest tumor diameter should be used for classification. In clinical practice, the tumor base may be estimated in optic disc diameters (dd) (average: 1 dd = 1.5 mm). The height may be estimated in diopters (average: 3 diopters = 1 mm). Techniques such as ultrasonography, visualization, and photography are frequently used to provide more accurate measurements.

**Regional Lymph Nodes (N)**

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

**Distant Metastasis (M)**

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

**TNM Stage Groupings**

Stage I	T1	N0	M0
	T1a	N0	M0
	T1b	N0	M0
	T1c	N0	M0
Stage II	T2	N0	M0
	T2a	N0	M0
	T2b	N0	M0
	T2c	N0	M0
Stage III	T3	N0	M0
	T4	N0	M0
Stage IV	Any T	N1	M0
	Any T	Any N	M1

It should be noted that regional lymph node involvement is rare in uveal melanoma, but metastasis to the liver and direct extension into the orbit are more common.<sup>19</sup>

**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.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

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

**Additional Descriptors**Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
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R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

### Vessel Invasion

By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

#### Lymphatic Vessel Invasion (L)

LX	Lymphatic vessel invasion cannot be assessed
L0	No lymphatic vessel invasion
L1	Lymphatic vessel invasion

#### Venous Invasion (V)

VX	Venous invasion cannot be assessed
V0	No venous invasion
V1	Microscopic venous invasion
V2	Macroscopic venous invasion

### References

1. Callender GR. Malignant melanotic tumors of the eye: a study of histologic types in 111 cases. *Trans Am Acad Ophthalmol Otolaryngol.* 1931;36:131-142.
2. McLean IW, Zimmerman LE, Evans RM. Reappraisal of Callender's spindle A type of malignant melanoma of choroid and ciliary body. *Am J Ophthalmol.* 1978; 86:557-564.
3. McLean IW, Foster WD, Zimmerman LE. Modifications of Callender's classification of uveal melanoma at the Armed Forces Institute of Pathology. *Am J Ophthalmol.* 1983;96:502-509.
4. Zimmerman LE. Malignant melanoma of the uveal tract. In: Spencer WH, ed. *Ophthalmic Pathology. An Atlas and Textbook.* 3<sup>rd</sup> ed. Philadelphia, Pa: WB Saunders Co; 1986:2072-2139.
5. Font RL, Spaulding AG, Zimmerman LE. Diffuse malignant melanoma of the uveal tract: a clinicopathologic report of 54 cases. *Trans Am Acad Ophthalmol Otolaryngol.* 1968;72:877-894.
6. McLean IW, Foster WD, Zimmerman LE. Prognostic factors in small malignant melanomas of choroid and ciliary body. *Arch Ophthalmol.* 1977;95:48-58.
7. Affeldt JC, Minckler DS, Azen SP, Yeh L. Prognosis in uveal melanoma with extraocular extension. *Arch Ophthalmol.* 1980;98:1975-1979.
8. McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis. *Hum Pathol.* 1982;13:123-132.

9. Weinhaus RS, Seddon JM, Albert DM, Gragoudas ES, Robinson N. Prognostic factor study of survival after enucleation for juxtapapillary melanomas. *Arch Ophthalmol*. 1985;103:1673-1677.
10. Gamel JW, McCurdy JB, McLean IW. A comparison of prognostic covariates for uveal melanoma. *Invest Ophthalmol Vis Sci*. 1992;33:1919-1922.
11. Folberg R, Peier J, Gruman LM, et al. The morphologic characteristics of tumor blood vessels as a marker of tumor progression in primary human uveal melanoma: a matched case-control study. *Hum Pathol*. 1992;23:1298-1305.
12. Coleman K, Baak JP, Van Diest P, Mullaney J, Farrell M, Fenton M. Prognostic factors following enucleation of 111 uveal melanomas. *Br J Ophthalmol*. 1993;77:688-692.
13. Folberg R, Rummelt V, Parys-Van Ginderdeuren R, et al. The prognostic value of tumor blood vessel morphology in primary uveal melanoma. *Ophthalmology*. 1993;100:1389-1398.
14. Folberg R, Rummelt V, Gruman LM, et al. Microcirculation architecture of melanocytic nevi and malignant melanomas of the ciliary body and choroid: a comparative histopathologic and ultrastructural study. *Ophthalmology*. 1994;101:718-727.
15. Rummelt V, Folberg R, Woolson RF, Hwang T, Peier J. Relation between the microcirculation architecture and the aggressive behavior of ciliary body melanomas. *Ophthalmology*. 1995;102:844-851.
16. Folberg R, Verdick R, Weingeist TA, Montague PR. The gross examination of eyes removed for choroidal and ciliary body melanomas. *Ophthalmology*. 1986;93:1643-1647.
17. The Collaborative Ocular Melanoma Study Group. Design and methods of a clinical trial for a rare condition: COMS report no. 3. The Collaborative Ocular Melanoma Study Group. *Control Clin Trials*. 1993;14:362-391.
18. Collaborative Ocular Melanoma Study Group. *COMS Manual of Procedures*. Springfield, Va: National Technical Information Service; 1989. NTIS Accession No. PB90-115536.
19. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*. 6th ed. New York: Springer; 2002.
20. Sobin LH, Wittekind C. *UICC TNM Classification of Malignant Tumours*. 6<sup>th</sup> ed. New York: Wiley-Liss; 2002.

### Bibliography

- Albert DM. Principles of pathology. In: Albert DM, Jakobiec FA, eds. *Principles and Practice of Ophthalmology*. Vol. 4. Philadelphia, Pa: WB Saunders Co; 1994:2101-2126.
- Albert DM, Dryja TP. The eye. In: Cotran RS, Kumar V, Robbins SL, eds. *Pathologic Basis of Disease*. 4th ed. Philadelphia, Pa: WB Saunders Co; 1998.
- Yanoff MF, Fine BS. *Ocular Pathology. A Text and Atlas*. 3<sup>rd</sup> ed. Philadelphia, Pa: JB Lippincott Co; 1989:652-678.

# Retinoblastoma

## **Protocol applies to retinoblastoma only.**

*Protocol revision date: January 2004  
Based on AJCC/UICC TNM, 6<sup>th</sup> edition*

### **Procedures**

- **Cytology** (No Accompanying Checklist)
- **Biopsy** (No Accompanying Checklist)
- **Resection (Globe)**

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**Surgical Pathology Cancer Case Summary (Checklist)**

*Protocol revision date: January 2004  
Applies to retinoblastoma only  
Based on AJCC/UICC TNM, 6<sup>th</sup> edition*

**RETINOBLASTOMA: Enucleation, Partial or Complete Exenteration**

Patient name:

Surgical pathology number:

**Note: Check 1 response unless otherwise indicated.**

**MACROSCOPIC****Specimen Type** Enucleation Limited exenteration Complete exenteration Other (specify): \_\_\_\_\_ Not specified**Laterality** Right Left Not specified**Specimen Size**For Enucleation

Anteroposterior diameter: \_\_\_ mm

Horizontal diameter: \_\_\_ mm

Vertical diameter: \_\_\_ mm

Length of optic nerve: \_\_\_ mm

Diameter of optic nerve: \_\_\_ mm

 Cannot be determined (see Comment)For Exenteration

Greatest dimension: \_\_\_ cm

\*Additional dimensions: \_\_\_ x \_\_\_ cm

 Cannot be determined (see Comment)

2

\* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

**Tumor Site and Extent****(macroscopic examination/transillumination) (check all that apply)**

- Cannot be determined
- Superotemporal quadrant of globe
- Superonasal quadrant of globe
- Inferotemporal quadrant of globe
- Inferonasal quadrant of globe
- Anterior chamber
- Extrascleral extension
- Optic nerve

**Tumor Basal Dimensions on Transillumination**

- Cannot be determined
- Size: \_\_\_ x \_\_\_ mm

**Tumor Dimensions After Sectioning**

- Cannot be determined
- Base at cut edge: \_\_\_ mm
- Height at cut edge: \_\_\_ mm
- Maximal tumor height: \_\_\_ mm

**Tumor Location After Sectioning:**

- Cannot be determined
- Distance from anterior edge of tumor to limbus at cut edge: \_\_\_ mm
- Distance of posterior margin of tumor base from edge of optic disc: \_\_\_ mm

**Tumor Involvement or Gross Pathology of Other Ocular Structures****(check all that apply)**

- Cannot be determined
- Optic disc
- Choroid minimal (Bruch's membrane destroyed by 3 or less microscopic cell clusters without deeper penetration)
- Choroid, massive (anything beyond minimal)
- Vitreous
- Retinal detachment
- Ciliary body
- Iris
- Lens
- Anterior chamber
- Angle
- Sclera
- Cornea

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**MICROSCOPIC****Histologic Features (check all that apply)**

- Cannot be determined  
 Undifferentiated  
 Differentiated  
   \*  Homer Wright rosettes  
   \*  Flexner-Wintersteiner rosettes  
   \*  Fleurettes  
 Necrotic

**Growth Pattern**

- Cannot be determined  
 Endophytic  
 Exophytic  
 Combined exophytic/endophytic  
 Diffuse

**Extent of Optic Nerve Invasion**

- Cannot be determined  
 None  
 Anterior to lamina cribrosa  
 At lamina cribrosa  
 Posterior to lamina but not to end of nerve  
 To cut end of optic nerve

**Involvement of Other Structures (check all that apply)**

- Cannot be determined  
 Choroid  
 Vitreous  
 Sclera  
 Vortex vein  
 Iris  
 Other(s) (specify): \_\_\_\_\_

**Pathologic Staging (pTNM)**Primary Tumor (pT)

- pTX: Primary tumor cannot be assessed
- pT0: No evidence of primary tumor
- pT1: Tumor confined to the retina, the vitreous, or subretinal space. No optic nerve or choroidal invasion
- pT2: Minimal invasion of the optic nerve and/or optic coats
- pT2a: Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa
- pT2b: Tumor invades choroid focally
- pT2c: Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa and invades the choroid focally
- pT3: Significant invasion of the optic nerve and/or optic coats
- pT3a: Tumor invades optic nerve through the level of the level cribrosa but not to the line of resection.
- pT3b: Tumor massively invades the choroid
- pT3c: Tumor invades the optic nerve through the level of the lamina cribrosa but not to the line of resection and massively invades the choroid
- pT4: Extraocular tumor extension that includes any of the following: invasion of optic nerve to the line of resection; invasion of orbit through the sclera; extension both anteriorly or posteriorly into the orbit; extension into the brain; extension to, but not through, the chiasm; extension into the brain beyond the chiasm

Regional Lymph Nodes (pN)

- pNX: Regional lymph nodes cannot be assessed
- pN0: No regional lymph node metastasis
- pN1: Regional lymph node metastasis

Distant Metastasis (pM)

- pMX: Cannot be assessed
- pM1: Distant metastasis
- pM1a: Bone marrow
- pM1b: Other sites
- \*Specify site(s), if known: \_\_\_\_\_

**Margins**

- Cannot be assessed
- No tumor at margins
- Tumor present at surgical margin of optic nerve
- Extrascleral extension (for enucleation specimens)
- Other margin involved
- Specify: \_\_\_\_\_

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**\*Additional Pathologic Findings (check all that apply)**

- \*  None identified
- \*  Calcifications
- \*  Mitotic rate: Number of mitoses per 40x objective with a field area of 0.152 mm<sup>2</sup>: \_\_\_\_
- \*  Necrosis
- \*  Apoptosis
- \*  Basophilic vascular deposits
- \*  Inflammatory cells
- \*  Hemorrhage
- \*  Neovascularization (specify site): \_\_\_\_\_
- \*  Other (specify): \_\_\_\_\_

**\*Comment(s)**

6                   \* Data elements **with asterisks** are **not required** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

## Background Documentation

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*Protocol revision date: January 2004*

### **I. Cytologic Material (Note A)**

#### **A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Clinical information
  - a. Relevant history
    - (1) clinical findings
    - (2) status of other eye
    - (3) previous treatment
    - (4) family history
  - b. Relevant findings (eg, laboratory and radiologic studies)
  - c. Clinical diagnosis
  - d. Procedure (eg, anterior chamber paracentesis)
  - e. Operative findings
  - f. Anatomic site of specimen (right or left eye; part of eye sampled)

#### **B. Macroscopic Examination**

1. Specimen
  - a. Fixed/unfixed (specify fixative) (Note B)
  - b. Number of slides received
  - c. Quantity and appearance of fluid specimen
  - d. Other (eg, tissue received for cytologic preparation)
  - e. Results of intraprocedural consultation
2. Material submitted for microscopic evaluation (eg, smear, cytocentrifuge, filter preparation)
3. Special studies (specify) (eg, cytochemistry, immunocytochemistry, DNA analysis [specify type], morphometry, cytogenetics) (Note C)

#### **C. Microscopic Examination**

1. Adequacy of specimen for evaluation (indicate if unsatisfactory or limited for evaluation; specify reason)
2. Tumor
  - a. Histologic type (if possible) (Note D)
  - b. Histologic grade (if possible) (Note D)
  - c. Other features
    - (1) necrosis
    - (2) calcification
    - (3) apoptosis
    - (4) other
3. Additional pathologic findings, if present
  - a. Inflammatory cells
  - b. Other(s)
4. Results/status of special studies (specify)

5. Comments
  - a. Correlation with intraoperative consultation
  - b. Correlation with other specimens, as appropriate
  - c. Correlation with clinical information, as appropriate

## **II. Biopsy (Note A)**

### **A. Clinical Information**

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Clinical information
  - a. Relevant history
    - (1) clinical findings
    - (2) status of other eye
    - (3) previous treatment
    - (4) family history
  - b. Relevant findings (eg, laboratory and radiologic studies)
  - c. Clinical diagnosis
  - d. Procedure (eg, anterior chamber biopsy)
  - e. Operative findings
  - f. Anatomic site of specimen (right or left eye; part of eye sampled)

### **B. Macroscopic Examination**

1. Specimen
  - a. Fixed/unfixed (specify fixative) (Note **B**)
  - b. Number of pieces
  - c. Largest dimension of each piece
  - d. Results of intraoperative consultation
2. Tumor, if discernible
  - a. Descriptive features
3. Tissue submitted for microscopic evaluation
  - a. Submit all (after selection of fragments for special studies, if performed)
  - b. Frozen section fragment(s), if applicable
4. Special studies (specify) (eg, histochemistry, immunohistochemistry, DNA analysis [specify type], electron microscopy, morphometry, cytogenetics) (Note **C**)

### **C. Microscopic Examination**

1. Tumor
  - a. Histologic type, if possible (Note **D**)
  - b. Histologic grade, if possible (Note **D**)
  - c. Other features
    - (1) necrosis
    - (2) calcification
    - (3) apoptosis
    - (4) involvement of intraocular structures, if able to determine
    - (5) other

2. Additional pathologic findings, if present
  - a. Inflammatory cells
  - b. Other(s)
3. Results/status of special studies (specify)
4. Comments
  - a. Correlation with intraoperative consultation
  - b. Correlation with other specimens, as appropriate
  - c. Correlation with clinical information, as appropriate

### III. Resection (Globe)

#### A. Clinical Information

1. Patient identification
  - a. Name
  - b. Identification number
  - c. Age (birth date)
  - d. Sex
2. Responsible physician(s)
3. Date of procedure
4. Clinical information
  - a. Relevant history
    - (1) clinical findings
    - (2) status of other eye
    - (3) previous treatment
    - (4) family history
  - b. Relevant findings (eg, laboratory and radiologic studies)
  - c. Clinical diagnosis
  - d. Procedure (eg, enucleation)
  - e. Operative findings
  - f. Anatomic site(s) (left/right eye)
  - g. Results of intraoperative consultation

#### B. Macroscopic Examination

1. Specimen
  - a. Fixed/unfixed (specify fixative) (Notes **B** and **C**)
  - b. External aspect
  - c. Orientation of globe (based on identification of extraocular muscle insertions and other landmarks) (Note **F**)
  - d. Dimensions
    - (1) anteroposterior, horizontal, vertical dimensions of globe
    - (2) length and diameter of optic nerve
    - (3) corneal horizontal and vertical diameter
    - (4) diameter of pupil, if visible
  - e. Transillumination (helpful to identify location of tumor and measure basal dimension prior to sectioning globe)
    - (1) quality of transillumination (eg, transilluminates light well/poorly)
    - (2) transillumination defects
      - i. location (eg, inferotemporal quadrant of globe posterior to equator)
      - ii. size (2 dimensions)
      - iii. trace outline with marking implement

- f. Sectioning of specimen (globe) (surgical end of optic nerve cross-sectioned, inked/marked to maintain orientation, and submitted separately) (Notes **C** and **G**)
2. Tumor(s), if discernible
  - a. Location
  - b. Color
  - c. Consistency
  - d. Shape
  - e. Size
    - (1) base at cut edge (ie, portion of tumor closest to sclera)
    - (2) height at cut edge
    - (3) maximal tumor height
  - f. Distance of anterior margin of tumor base from limbus at cut edge
  - g. Distance of posterior margin of tumor base from optic disc
  - h. Extrascleral extension, if present
    - (1) location
    - (2) extent (2 dimensions)
      - i. structures involved and extent (eg, extent of retinal involvement, optic nerve involvement, macroscopic involvement of vitreous)
3. Other (uninvolved) ocular tissues
  - a. Cornea (clear/cloudy/opaque)
  - b. Anterior chamber (deep/shallow/flat)
  - c. Angle (open/narrow/closed)
  - d. Iris (abnormal blood vessels/color)
  - e. Ciliary body
  - f. Lens (cataractous/clear)
  - g. Vitreous (color/consistency/hemorrhage)
  - h. Retina (detachment, total or partial; hemorrhage)
  - i. Choroid
  - j. Sclera (thinning/defects)
  - k. Optic disc/nerve (pallor; increased cup-disc ratio)
4. Section(s) submitted for microscopic evaluation (Note **H**)
  - a. Tumor (multiple)
  - b. Optic nerve
  - c. Frozen section fragment(s), if applicable
5. Special studies (specify) (eg, histochemistry, immunohistochemistry, DNA analysis [specify type], electron microscopy, morphometry, cytogenetic) (Note **C**)

### **C. Microscopic Evaluation**

1. Tumor
  - a. Histologic features (Note **D**)
  - b. Degree of differentiation (Note **E**)
  - c. Growth pattern (Notes **E** and **I**)
    - (1) endophytic
    - (2) exophytic
    - (3) mixed endophytic-exophytic
    - (4) diffuse infiltrating
  - d. Location (eg, within retina, subretinal space, surface of retina, retinal periphery, macula, relation to equator of globe)
  - e. Size (Note **E**)

- f. Involvement of other structures (Notes **E** and **J**)
  - (1) choroid
  - (2) ciliary body
  - (3) iris
  - (4) vitreous
  - (5) iris
  - (6) angle
  - (7) sclera
- g. Extent of growth (Notes **E** and **J**)
  - (1) anterior extent of tumor (eg, peripheral retina, anterior chamber)
  - (2) posterior extent of tumor (eg, posterior to equator, to edge of optic disc, optic nerve anterior to lamina cribrosa, optic nerve posterior to lamina cribrosa, to cut edge of optic nerve)
- h. Additional features of prognostic significance (eg, basophilic staining of tumor vessels) (Note **E**)
- 2. Additional pathologic findings, if present
  - a. Evidence of previous excision or treatment
  - b. Cancer-related lesions
    - (1) neovascularization of iris
    - (2) iris bombé with angle occlusion
    - (3) peripheral anterior synechiae
    - (4) intraocular hemorrhage
    - (5) other(s)
  - c. Non-cancer-related lesions
    - (1) congenital angle anomaly
    - (2) corneal anomalies
    - (3) cataract
    - (4) other(s)
- 3. Margins
  - a. Optic nerve (Notes **E** and **J**)
    - (1) no tumor present
    - (2) tumor present
- 4. Results/status of special studies (specify)
- 5. Comments
  - a. Correlation with intraoperative consultation
  - b. Correlation with other specimens, as appropriate
  - c. Correlation with clinical information, as appropriate (Note **J**)

## Explanatory Notes

### A. Cytology/Biopsy

Cytologic and biopsy specimens are rarely obtained from eyes with suspected retinoblastoma owing to the potential risk of tumor seeding. An anterior chamber paracentesis may be performed if indicated by clinical findings and is not associated with risk of tumor seeding.<sup>1,2</sup>

### B. Fixation

The minimum recommended fixation time for whole globes with intraocular tumors is 48 hours. The globe should be fixed in an adequate volume of fixative with a 10:1 ratio

of fixative volume to specimen volume recommended. Incisions or windows in the globe are not necessary for adequate penetration of fixative and are not recommended. Injection of fixative into the globe is also not recommended.

### C. Additional Studies

Genetic studies may be requested on neoplastic tissue and should be harvested prior to fixation.<sup>3</sup> The surgical margin of the optic nerve should be obtained prior to opening the globe (Note **G**). Once tissue is harvested for genetic studies, the globe can be fixed prior to completing macroscopic examination. The appropriate materials/medium required by the laboratory performing genetic testing should be obtained prior to the procedure.

### D. Histologic Features

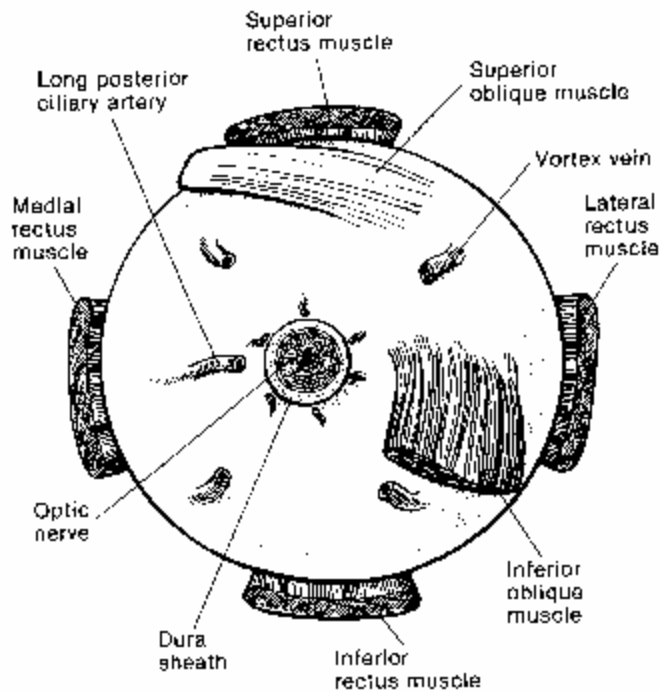
Typical histologic features include cells with large, basophilic nuclei and scant cytoplasm. Mitoses are generally frequent. Calcification and necrosis are common with sleeves of viable cells typically surrounding blood vessels (pseudorosettes). Apoptotic cells may be seen. The extent of differentiation may be judged based on the presence and type of rosettes. Homer-Wright rosettes similar to those seen in neuroblastoma or medulloblastoma may be seen and are not a sign of significant differentiation. Flexner-Wintersteiner rosettes are evidence of higher differentiation. Fleurettes are considered the most differentiated form of rosette found in the tumor. A benign variant of retinoblastoma termed *retinocytoma* or *retinoma* has been described. This tumor consists entirely of benign, well-differentiated cells often with associated calcification. The cells have smaller, less hyperchromatic nuclei and abundant cytoplasm. Necrosis is typically absent and mitotic figures are rare.<sup>4-9</sup> Retinoblastomas may arise in multicentric foci.

### E. Histologic Features of Additional Prognostic Significance

Histologic features with prognostic significance for survival include the following: invasion of optic nerve, particularly if tumor is present at the surgical margin (most important feature); invasion of sclera; invasion of choroid; tumor size; basophilic staining of tumor vessels; seeding of vitreous; degree of differentiation; involvement of anterior segment; and growth pattern.<sup>10-16</sup> This list should not be confused with the Reese-Ellsworth classification, which is intended as a predictor for visual outcome, not survival.<sup>17</sup>

### F. Orientation of Globe

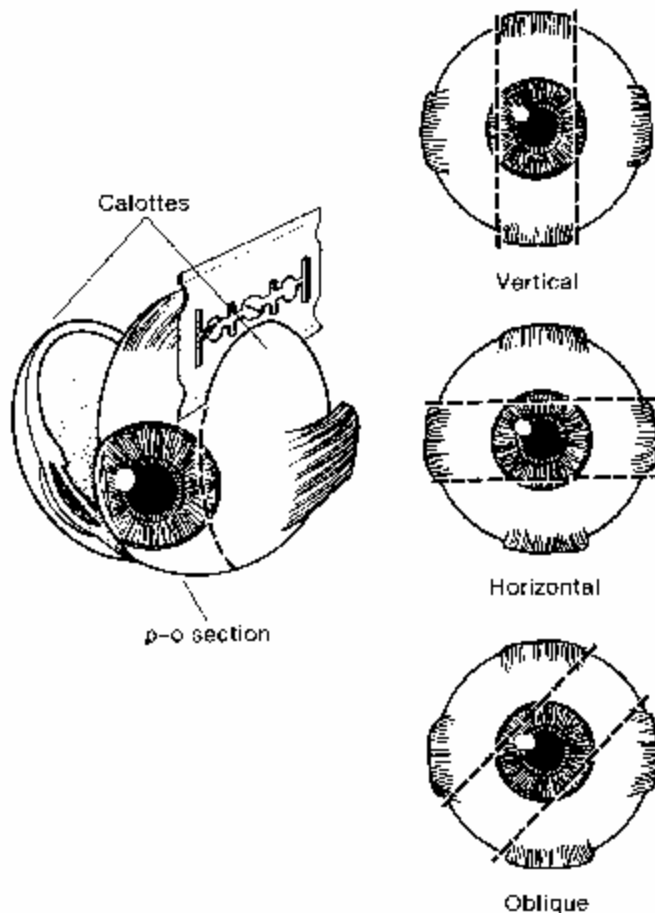
The orientation of a globe may be determined by identifying extraocular muscle insertions, optic nerve and other landmarks as illustrated in Figure 1. The terms *temporal* and *nasal* are generally used in place of *lateral* and *medial* with reference to ocular anatomy.



**Figure 1.** Anatomic landmarks of the posterior aspect of the globe (right eye). The position of the inferior oblique muscle relative to the optic nerve is most helpful in orienting the globe. The inferior oblique muscle insertion is located temporal (lateral) to the optic nerve on the sclera, and its fibers travel inferonasally from its insertion. The long posterior ciliary artery is often seen as a blue-gray line in the sclera on either side of the optic nerve and marks the horizontal meridian of the globe. *Reprinted with permission from WB Saunders Company.*

### G. Sectioning the Globe

The globe is generally sectioned in the horizontal or vertical plane, with care to include the pupil and optic nerve in the cassette to be submitted for microscopic examination. If the mass cannot be included with horizontal or vertical sectioning, the globe is sectioned obliquely to include tumor, pupil, and optic nerve (Figure 2). The surgical margin of the optic nerve should be sectioned and submitted prior to sectioning the globe to ensure that intraocular malignant cells do not contaminate this important surgical margin.<sup>3</sup> Retinoblastoma is an extremely friable tumor.



**Figure 2.** The most common methods of sectioning a globe. After transillumination, the tumor base is marked, if possible, and 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 gross description of the pathology report. It is not uncommon to induce an artifactual retinal detachment while sectioning the globe. This can be minimized by gentle handling and by avoiding a sawing motion with the blade. *Reprinted with permission from WB Saunders Company.*

#### H. Sections Submitted for Microscopic Examination

Multiple sections should be examined, with special attention to sections containing optic nerve and tumor. The nerve should be sectioned along the various levels to determine tumor extension.

#### I. Growth Pattern

Endophytic growth pattern indicates growth from the inner retinal surface into the vitreous cavity. Exophytic tumors grow primarily from the outer surface of the retina into the subretinal space toward the choroid. Mixed growth pattern exhibits features of both endophytic and exophytic growth. Diffuse infiltrating tumors grow laterally within the retina without significant thickening.

**J. TNM and Stage Groupings**

The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM staging system for retinoblastoma is shown below.<sup>18,19</sup>

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

**Clinical TNM Classifications:****Primary Tumor (T)**

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Tumor confined to the retina (no vitreous seeding or significant retinal detachment). No retinal detachment or subretinal fluid more than 5 mm from the base of the tumor
  - T1a Any eye in which the largest tumor is less than or equal to 3 mm in height and no tumor is located closer than 1 DD (1.5 mm) to the optic nerve or fovea
  - T1b All other eyes in which the tumor(s) are confined to the retina regardless of location or size (up to half the volume of the eye). No vitreous seeding. No retinal detachment or subretinal fluid more than 5 mm from the base of the tumor
- T2 Tumor with contiguous spread to adjacent tissues or spaces (vitreous or subretinal space)
  - T2a Minimal tumor spread to vitreous and/or subretinal space. Fine local or diffuse vitreous seeding and/or serous retinal detachment up to total detachment may be present, but no clumps, lumps, snowballs, or avascular masses are allowed in the vitreous or subretinal space. Calcium flecks in the vitreous or subretinal space are allowed. The tumor may fill up to 2/3 the volume of the eye.
  - T2b Massive tumor spread to the vitreous and/or subretinal space. Vitreous seeding and/or subretinal implantation may consist of lumps, clumps, snowballs or avascular tumor masses. Retinal detachment may be total. Tumor may fill up to 2/3 the volume of the eye.
  - T2c Unsalvageable intraocular disease. Tumor fills more than 2/3 of the eye or there is no possibility of visual rehabilitation or 1 or more of the following are present:
    - Tumor-associated glaucoma, either neovascular or angle closure
    - Anterior segment extension of tumor

- Ciliary body extension of tumor
  - Hyphema ( significant)
  - Massive vitreous hemorrhage
  - Tumor in contact with lens
  - Orbital cellulitis-like clinical presentation (massive tumor necrosis)
- T3 Invasion of the optic nerve and/or optic coats
- T3a Tumor(s) involve(s) more than 50% of the retina and/or tumor cells in the vitreous
- T3b Tumor(s) involve(s) the optic disc
- T3b Tumor(s) involve(s) anterior chamber and/or uvea
- T4 Extraocular tumor
- T4a Tumor invades retrobulbar optic nerve
- T4b Extraocular extension other than invasion of the optic nerve

Note: The following suffixes may be added to the appropriate T categories: "m" indicates multiple tumors (eg, T2 [m2]); "f" indicates cases with a known family history; and "d" indicates diffuse retinal involvement without the formation of discrete masses.

#### Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis involvement (preauricular, submandibular, or cervical)
- N2 Distant lymph node involvement

It should be noted that regional lymph node involvement is rare and direct extension into the CNS is more common.<sup>18</sup>

#### Distant Metastasis (M)

- MX Presence of distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Metastasis to central nervous system and/or bone, bone marrow, or other sites

#### Pathologic TNM Classifications:

##### Primary Tumor (pT)

- pTX Primary tumor cannot be assessed
- pT0 No evidence of primary tumor
- pT1 Tumor confined to the retina, the vitreous, or subretinal space. No optic nerve or choroidal invasion
- pT2 Minimal invasion of the optic nerve and/or optic coats
- pT2a Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa
- pT2b Tumor invades choroid focally
- pT2c Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa and invades the choroid focally
- pT3 Significant invasion of the optic nerve and/or optic coats
- pT3a Tumor invades optic nerve through the level of the lamina cribrosa but not to the line of resection.
- pT3b Tumor massively invades the choroid

- PT3c Tumor invades the optic nerve through the level of the lamina cribrosa but not to the line of resection and massively invades the choroid
- pT4 Extraocular tumor extension that includes:  
 Invasion of optic nerve to the line of resection  
 Invasion of orbit through the sclera  
 Extension both anteriorly or posteriorly into the orbit  
 Extension into the brain  
 Extension to, but not through, the chiasm  
 Extension into the brain beyond the chiasm

**Regional Lymph Nodes (pN)**

- pNX Regional lymph nodes cannot be assessed  
 pN0 No regional lymph node metastasis  
 pN1 Regional lymph node metastasis

**Distant Metastasis (pM)**

- pMX Presence of distant metastasis cannot be assessed  
 pM0 No distant metastasis  
 pM1 Distant metastasis  
 pM1a Bone marrow  
 pM1b Other sites

**TNM Stage Groupings**

No stage grouping applies.

**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.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

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

**Additional Descriptors**Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

**Vessel Invasion**

By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

Lymphatic Vessel Invasion (L)

LX	Lymphatic vessel invasion cannot be assessed
L0	No lymphatic vessel invasion
L1	Lymphatic vessel invasion

Venous Invasion (V)

VX	Venous invasion cannot be assessed
V0	No venous invasion
V1	Microscopic venous invasion
V2	Macroscopic venous invasion

**References**

1. Karcioğlu ZA, Gordon RA, Karcioğlu GL. Tumor seeding in ocular fine needle aspiration biopsy. *Ophthalmology*. 1985;92:1763-67.
2. Stevenson KE, Hungerford J, Garner A. Local extraocular extension of retinoblastoma following intraocular surgery. *Br J Ophthalmol*. 1989;73:739-742.
3. Shields JA, Shields CL, De Potter P. Enucleation technique for children with retinoblastoma. *J Ped Ophthalmol Strabismus*. 1992;29:213-215.
4. Zimmerman LE. Retinoblastoma and retinocytoma. In: Spencer WH, ed. *Ophthalmic Pathology. An Atlas and Textbook*. 3<sup>rd</sup> ed. Philadelphia, Pa: WB Saunders Co; 1986:1292-1351.
5. Tso MOM, Fine BS, Zimmerman LE. The Flexner-Wintersteiner rosettes in retinoblastoma. *Arch Pathol*. 1969;88:665-671.
6. Tso MOM, Fine BS, Zimmerman LE. The nature of retinoblastoma, I: photoreceptor differentiation: a clinical and histologic study. *Am J Ophthalmol*. 1970;69:339-350.

7. Tso MOM, Fine BS, Zimmerman LE. The nature of retinoblastoma, II: photoreceptor differentiation: an electron microscopic study. *Am J Ophthalmol.* 1970;69:350-359.
8. Margo C, Hidayat A, Kopelman J, Zimmerman LE. Retinocytoma: a benign variant of retinoblastoma. *Arch Ophthalmol.* 1983;101:1519-1531.
9. Gallie BL, Ellsworth RM, Abramson DH, Phillips RA. Retinoma: spontaneous regression of retinoblastoma or benign manifestation of the mutation? *Br J Cancer.* 1982;45:513-521.
10. Redler LD, Ellsworth RM. Prognostic importance of choroidal invasion in retinoblastoma. *Arch Ophthalmol.* 1973;90:294-296.
11. Kopelman JE, McLean IW. Multivariate analysis of clinical and histological risk factors for metastasis in retinoblastoma [abstract]. *Invest Ophthalmol Vis Sci.* 1983;24(ARVO suppl):50.
12. Kopelman JE, McLean IW. Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. *Ophthalmology.* 1987;94:371-377.
13. Haik BG, Dunleavy SA, Cooke C, et al. Retinoblastoma with anterior chamber extension. *Ophthalmology.* 1987;94:367-370.
14. Magrann I, Abramson DH, Ellsworth RM. Optic nerve involvement in retinoblastoma. *Ophthalmology.* 1989;96:217-222.
15. Shields CL, Shields JA, Baez KA, Cater J, De Potter PV. Choroidal invasion of retinoblastoma: metastatic potential and clinical risk factors. *Br J Ophthalmol.* 1993;77:544-548.
16. Shields CL, Shields JA, Baez K, Cater JR, De Potter P. Optic nerve invasion of retinoblastoma: metastatic potential and clinical risk factors. *Cancer.* 1994;73:692-698.
17. Reese AB, Ellsworth RM. The evaluation and current concept of retinoblastoma therapy. *Trans Am Acad Ophthalmol Otolaryngol.* 1963;67:164-172.
18. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002.
19. Sobin LH, Wittekind C. *UICC TNM Classification of Malignant Tumours.* 6<sup>th</sup> ed. New York: Wiley-Liss; 2002.

### Bibliography

- Albert DM, Dryja TP. The eye. In: Cotran RS, Kumar V, Robbins SL, eds. *Pathologic Basis of Disease.* 4th ed. Philadelphia, Pa: WB Saunders Co; 1998.
- Albert DM. Principles of pathology. In: Albert DM, Jakobiec FA, eds. *Principles and Practice of Ophthalmology.* Vol. 4. Philadelphia, Pa: WB Saunders Co; 1994:2101-2126.
- Sahel JA, Brini A, Albert DM. Pathology of the retina and vitreous. In: Albert DM, Jakobiec FA. *Principles and Practice of Ophthalmology.* Vol. 4. Philadelphia, Pa: WB Saunders Co; 1994:2239-2280.
- Yanoff MF, Fine BS. *Ocular Pathology. A Text and Atlas.* 3<sup>rd</sup> ed. Philadelphia, Pa: JB Lippincott Co; 1989:684-694.
- Zimmerman LE. Retinoblastoma and retinocytoma. In: Spencer WH, ed. *Ophthalmic Pathology. An Atlas and Textbook.* 3<sup>rd</sup> ed. Philadelphia, Pa: WB Saunders Co; 1986:1292-1351.