Protocol for the Examination of Specimens from Patients with Uveal Melanoma

Protocol applies to malignant melanoma of the uvea.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2009

Procedures
• Resection (Local Resection, Enucleation, Limited or Complete Exenteration)

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

UVEAL MELANOMA: Resection (Local Resection, Enucleation, Limited or Complete Exenteration) (Note A)

Select a single response unless otherwise indicated.

Procedure
___ Local resection
___ Enucleation
___ Limited exenteration
___ Complete exenteration
___ Other (specify): _____
___ 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: ___ mm
*Additional dimensions: ___ x ___ mm
___ Cannot be determined (see Comment)

Specimen Laterality
___ Right
___ Left
___ Unspecified

Tumor Site (macroscopic examination/transillumination) (select all that apply) (Note B)
___ Cannot be determined
___ Superotemporal quadrant of globe
___ Superonasal quadrant of globe
___ Inferotemporal quadrant of globe
___ Inferonasal quadrant of globe
___ Other (specify): _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

***Tumor Basal Size on Transillumination**
*___ Cannot be determined
*Specify: ___ x ___ mm

Tumor Size After Sectioning (Note C)
___ Cannot be determined
Base at cut edge: ___ mm
*Height at cut edge: ___ mm
Greatest height: ___ mm

***Tumor Location After Sectioning (Note D)**
*___ 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 of Other Ocular Structures (select all that apply)
___ Cannot be determined
___ Sclera
___ Vortex vein(s)
___ Optic disc
___ Vitreous
___ Choroid
___ Ciliary body
___ Iris
___ Lens
___ Anterior chamber
___ Extrascleral extension (anterior)
___ Extrascleral extension (posterior)
___ Angle/Schlemm's canal
___ Optic nerve
___ Retina
*___ Cornea

Growth Pattern
___ Cannot be determined
___ Solid mass
___ Diffuse (ciliary body ring)
___ Diffuse (flat)

Histologic Type (Note E)
___ 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

Histopathologic Type (Note E)
___ Spindle cell melanoma (greater than 90% spindle cells)
___ Mixed cell melanoma (>10% epithelioid cells and <90% spindle cells)
___ Epithelioid cell melanoma (greater than 90% epithelioid cells)

Histologic Grade (pG)[#]
___pGX: Grade cannot be assessed
___pG1: Spindle cell melanoma
___pG2: Mixed cell melanoma
___pG3: Epithelioid cell melanoma

[#] Because of general lack of agreement regarding which proportion of epithelioid cells classifies a tumor as mixed and epithelioid in type, some ophthalmic pathologists currently combine grades 2 and 3 (nonspindle, epithelioid cells detected) and contrast them with grade 1 (spindle, no epithelioid cells detected).

Microscopic Tumor Extension

*Tumor Location
*___ Anterior margin between equator and iris
*___ Anterior margin between disc and equator
*___ Posterior margin between equator and iris
*___ Posterior margin between disc and equator
*___ Cannot be determined
*___ None of above

Scleral Involvement
___ Cannot be determined
___ None
___ Extrascleral
___ Intrascleral

Margins
___ Cannot be assessed
___ No melanoma at margins
___ Extrascleral extension (for enucleation specimens)
___ Other margin(s) involved (specify): _____

Pathologic Staging (pTNM) (Note F)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (post-treatment)

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 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, choroid, or both, with secondary glaucoma
pT3: Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension
___ pT3a: Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension and secondary glaucoma
pT4: Tumor with extrascleral extension
___ pT4a: Tumor with extrascleral extension less than or equal to 5 mm in diameter
___ pT4b: Tumor with extrascleral extension more than 5 mm in diameter

Ciliary Body and Choroid

___ 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 less than or equal to 5 mm in diameter
___ pT1d: Tumor size category 1 with ciliary body involvement and extraocular extension less than or equal to 5 mm in 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 less than or equal to 5 mm in diameter
___ pT2d: Tumor size category 2 with ciliary body involvement and extraocular extension less than or equal to 5 mm in 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 less than or equal to 5 mm in diameter
___ pT3d: Tumor size category 3 with ciliary body involvement and extraocular extension less than or equal to 5 mm in 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 less than or equal to 5 mm in diameter
___ pT4d: Tumor size category 4 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
___ pT4e: Any tumor size category with extraocular extension more than 5 mm in diameter

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)
___ Not applicable
___ pM1:Distant metastasis
___ pM1a: Largest diameter of the largest metastasis 3 cm or less
___ pM1b: Largest diameter of the largest metastasis 3.1-8.0 cm
___ pM1c: Largest diameter of the largest metastasis 8 cm or more

***Additional Pathologic Findings (select all that apply) (Note G)**
*___ None identified
*___ Mitotic rate (number of mitoses per 40X objective with a field area of 0.152 mm^2) (specify): ____
*___ 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)**

Explanatory Notes

A. 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.

B. 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.

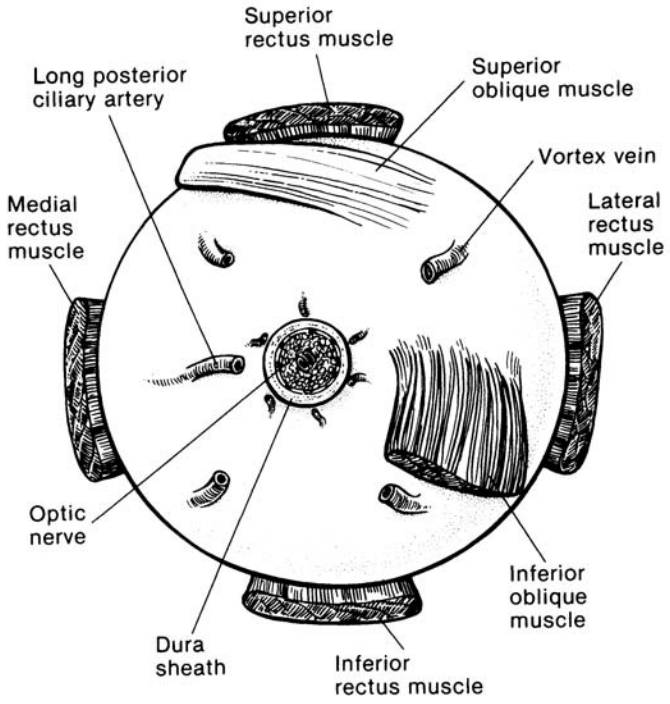


Figure 1. Anatomic landmarks of the posterior aspect of the globe (right eye). The position of the inferior oblique muscle relative to the optic nerve is most helpful in orienting the globe. The inferior oblique muscle insertion is located temporal (lateral) to the optic nerve on the sclera, and its 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.*

C. 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.[1] More recently, an ongoing study started in 1986, the Collaborative Ocular Melanoma Study[2,3] defined the following size classification based on clinical measurements.

Small tumors[#]:	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 *or* Greater than 2 mm in height and greater than16 mm in basal diameter *or* Greater than 8 mm in height with optic nerve involvement

[#] Small tumors have a more favorable prognosis.[4,5]

D. 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.[6]

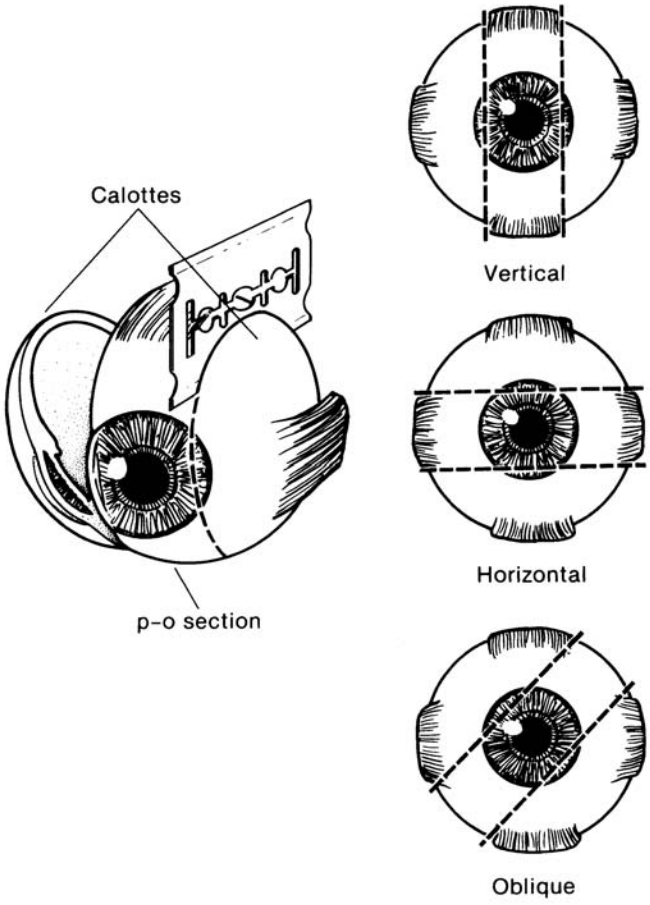


Figure 2. The most common methods of sectioning a globe. After transillumination, the tumor base is marked, if possible, and included in the pupil-optic (p-o) nerve section and submitted for processing. If tumor is found in either of the calottes, these may also be submitted for sectioning. The meridian in which the globe was sectioned should be included in the gross description of the pathology report. It is not uncommon to induce an artifactitious 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.*

E. 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.[1,7-9] The American Joint Committee on Cancer (AJCC) defined the histopathologic types as follows[10]:[#]

Spindle cell melanoma (greater than 90% spindle cells)
Mixed cell melanoma (>10% epithelioid cells and <90% spindle cells)
Epithelioid cell melanoma (greater than 90% epithelioid cells)

[#] Spindle cell melanomas have the most favorable prognosis, and epithelioid cell melanomas the least favorable in terms of survival.

F. 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.[10]

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

<u>All Uveal Melanomas</u>

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

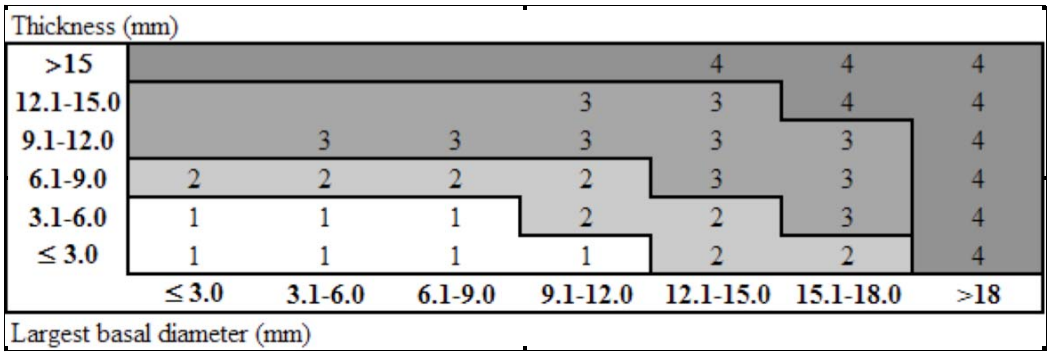
<u>Iris[#]</u>

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 secondary glaucoma
T2	Tumor confluent with or extending into the ciliary body, choroid, or both

T2a Tumor confluent with or extending into the ciliary body, choroid, or both, with secondary glaucoma
T3 Tumor confluent with or extending into the ciliary body, choroid or both, with scleral extension
T3a Tumor confluent with or extending into the ciliary body, choroid or both, with scleral extension and secondary glaucoma
T4 Tumor with extrascleral extension
T4a Tumor with extrascleral extension less than or equal to 5 mm in diameter
T4b Tumor with extrascleral extension more than 5 mm in diameter

[#] Iris melanomas originate from, and are predominantly located in, this region of the uvea. If less than half of the tumor volume is located within the iris, the tumor may have originated in the ciliary body, and consideration should be given to classifying it accordingly.

Ciliary Body and Choroid
Primary ciliary body and choroidal melanomas are classified according to the 4 tumor size categories below[10]:



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 less than or equal to 5 mm in diameter
T1d Tumor size category 1 with ciliary body involvement and extraocular extension less than or equal to 5 mm in 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 less than or equal to 5 mm in diameter
T2d Tumor size category 2 with ciliary body involvement and extraocular extension less than or equal to 5 mm in 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 less than or equal to 5 mm in diameter
T3d Tumor size category 3 with ciliary body involvement and extraocular extension less than or equal to 5 mm in 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 less than or equal to 5 mm in diameter
T4d Tumor size category 4 with ciliary body involvement and extraocular extension less than or equal to 5 mm in diameter
T4e Any tumor size category with extraocular extension more than 5 mm in diameter

Note: In clinical practice, the largest tumor basal diameter may be estimated in optic disc diameters (dd, average: 1 dd = 1.5 mm). Tumor thickness may be estimated in diopters (average: 2.5 diopters = 1 mm). However, techniques such as ultrasonography and fundus photography are used to provide more accurate measurements. Ciliary body involvement can be evaluated by the slit-lamp, ophthalmoscopy, gonioscopy, and transillumination. However, high-frequency ultrasonography (ultrasound biomicroscopy) is used for more accurate assessment. Extension through the sclera is evaluated visually before and during surgery, and with ultrasonography, computed tomography, or magnetic resonance imaging.

When histopathologic measurements are recorded after fixation, tumor diameter and thickness may be underestimated because of tissue shrinkage.

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)
M0 No distant metastasis
M1 Distant metastasis
M1a Largest diameter of the largest metastasis 3 cm or less
M1b Largest diameter of the largest metastasis 3.1-8.0 cm
M1c Largest diameter of the largest metastasis 8 cm or more

Stage Grouping

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

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.[10]

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).

Lymph-Vascular Invasion (LVI)
LVI indicates whether microscopic lymph-vascular invasion is identified in the pathology report. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion.

By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

G. 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.[1,11-19]

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