Retinoblastoma

At-A-Glance

SUMMARY OF CHANGES

Clinical Classification
- The definitions of T1–T4 were modified
- The definitions for M1 were modified

Pathologic Classification
- Minor modifications were made to the definitions for pT2–pT4
- Definition of choroidal invasion, focal versus massive
- The definitions for pM1 were modified

Other
- A description of proper processing of the enucleated retinoblastoma globe for pathological examination was added

ANATOMIC STAGE/PROGNOSTIC GROUPS

No stage grouping applies

ICD-O-3 TOPOGRAPHY CODES
C69.2 Retina

ICD-O-3 HISTOLOGY CODE RANGES
9510–9514

ANATOMY

Primary Site. The retina is composed of neurons and glial cells. The precursors of the neuronal elements give rise to retinoblastoma, whereas the glial cells give rise to astrocytomas, which are benign and extremely rare in the retina. The retina is limited internally by a membrane that separates it from the vitreous cavity. Externally, it is limited by the retinal pigment epithelium (RPE) and Bruch’s membrane, which separate it from the choroid and act as natural barriers to extension of retinal tumors into the choroid. The continuation of the retina with the optic nerve allows direct extension of retinoblastomas into the optic nerve and then to the subarachnoid space. Because the retina has no lymphatics, spread of retinal tumors is either by direct extension into adjacent structures or by distant metastasis through hematogenous routes.

Regional Lymph Nodes. Because there are no intraocular lymphatics, this category of staging applies only to anterior extrascleral extension. The regional lymph nodes are preauricular (parotid), submandibular, and cervical.

Local Extension. Local extension anteriorly can result in soft tissue involvement of the face or a mass protruding from between the lids. Posterior extension results in retinoblastoma extending into the orbit, paranasal sinuses, and/or brain.

Metastatic Sites. Retinoblastoma can metastasize through hematogenous routes to various sites, most notably the bone marrow, skull, long bones, and brain.

RULES FOR CLASSIFICATION

Choroidal Invasion. The presence and the extent (focal vs. massive) of choroidal invasion by tumor should be stated. Differentiation should be made between true choroidal invasion and artifactual invasion due to seeding of fresh tumor
cells during postenucleation retrieval of tumor tissue and/or gross sectioning.

Artifactual invasion is identified when there are groups of tumor cells present in the open spaces between intraocular structures, extracocular tissues, and/or subarachnoid space.

True invasion is defined as one or more solid nests of tumor cells that fills or replaces the choroid and has pushing borders. Note: Invasion of the sub-RPE space, where tumor cells are present under the RPE (but not beyond Bruch’s membrane into the choroid) is not choroidal invasion.

Focal choroidal invasion is defined as a solid nest of tumor that measures less than 3 mm in maximum diameter (width or thickness).

Massive choroidal invasion is defined as a solid tumor nest 3 mm or more in maximum diameter (width or thickness).

Clinical Staging. All suspected cases of retinoblastoma should have a neural imaging scan. If it is possible to obtain only one imaging study, computerized tomography (CT) is recommended because detection of calcium in the eye on CT confirms the clinical suspicion of retinoblastoma. The request should include cuts through the pineal region of the brain. Magnetic resonance imaging is particularly useful if extension into either the extracocular space or the optic nerve is suspected or if there is a concern about the possible presence of a primitive neuroectodermal tumor (PNET) in the pineal region (trilateral retinoblastoma).

A staging examination under anesthesia should include ocular ultrasound and retinal drawings of each eye, with each identifiable tumor measured and numbered. Digital images of the retina may be very helpful. In bilateral cases, each eye must be classified separately. Tumor size or the distance from the tumor to the disc or fovea is recorded in millimeters. These millimeter distances are measured by ultrasound, estimated by comparison with a normalized optic disc (1.5 mm), or deduced from the fact that the field of a 28-diopter condensing lens has a retinal diameter of 13 mm.

Pathologic Staging. If one eye is enucleated, pathologic staging of that eye provides information supplemental to the clinical staging. First, the pathology should provide histologic verification of the disease. All clinical and pathologic data from the resected specimen are to be used.

Processing the Enucleated Retinoblastoma Globe. In certain situations fresh tumor material may be needed from the enucleated globe for research purposes or genetic testing. In these cases the globe should be moved to a sterile area in the Operating Room away from the operative field. After collecting the specimen, the surgeon should change his/her gloves before reentering the operative field.

Processing With Tumor Sampling. To collect the tumor specimen, the optic nerve should be removed before opening the globe to prevent the optic nerve from accidentally becoming contaminated with artifactual clumps of tumor cells (so-called floaters). The surgeon should first ink the surgical margin of the optic nerve, then cut the optic nerve stump off from the sclera with a sharp razor about 2 mm behind the globe. The optic nerve stump should be placed into a jar of 10% buffered formaldehyde that will be kept separate from the globe. Then, a sample of tumor should be obtained by opening a small sclero-choroidal window adjacent to the tumor near the equator with a 6–8 mm corneal trephine. Once the opening into the vitreous chamber is established, tumor tissue should be gently removed with forceps and scissors. It is best to leave a hinge on one side of the scleral flap so that it can be closed with one or two suture(s) following the removal of tumor sample. This is done in an attempt to maintain the overall spherical architecture of the specimen during fixation. The globe should be placed in a second jar of formalin (separate from the optic nerve stump) and be allowed to fix for at least 24–48 h.

Processing Without Tumor Sampling. If there is no need for fresh tissue sampling, the enucleated globe should simply be fixed in 10% buffered formaldehyde for at least 24 and preferably 48 h. When the fixed globe is examined by the pathologist, if the optic nerve was not previously amputated in the operative room, that should be performed first as described previously. The surgical margin of the nerve stump should be embedded face down in paraffin for sectioning (i.e., thereby obtaining cross-sections of the nerve, starting at the surgical margin). Then, the eye itself is sectioned. First, a section should be made that extends from pupil through the optic nerve (the “P-O” section), which contains the center of the optic nerve with all the optic nerve structures (optic nerve head, lamina cribrosa, and postlaminar optic nerve). Preferably this plane should bisect the largest dimension of the tumor, previously identified by transillumination and during clinical examination. When possible, the plane should avoid the scleral opening if one was made for fresh tumor sampling. This section is critical for evaluation of the optic nerve for tumor invasion. The P-O section and minor calottes are then embedded in paraffin. The embedded P-O calotte is then sectioned every 100–150 µm (each section being about 5 µm thick), for a total of about 10–20 sections. Additional sections should also be made anterior-posteriorly in a bread loaf fashion through the minor calottes if they contain visible tumor. These segments should be submitted in one cassette per calotte on edge to evaluate the choroid for invasion. Three levels of this block are usually sufficient for examination. In total, four cassettes are submitted: the optic nerve stump, the P-O section, and the two minor calottes (unless one or both of these has no visible tumor).

PROGNOSTIC FEATURES

There are a number of key prognostic factors that are important to collect in retinoblastoma even though they are not required for staging algorithms. These include the presence or absence of an RB gene mutation, a family history of retinoblastoma, and whether the primary globe-sparing treatment
failed, and the greatest extent of choroid involved by choroidal tumor invasion.

## DEFINITIONS OF TNM

### Clinical Classification (cTNM)

#### Primary Tumor (T)

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **T1**: Tumors no more than 2/3 the volume of the eye with no vitreous or subretinal seeding
- **T1a**: No tumor in either eye is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea
- **T1b**: At least one tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea. No retinal detachment or subretinal fluid beyond 5 mm from the base of the tumor
- **T1c**: At least one tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea, with retinal detachment or subretinal fluid beyond 5 mm from the base of the tumor
- **T2**: Tumors no more than 2/3 the volume of the eye with vitreous or subretinal seeding. Can have retinal detachment
- **T2a**: Focal vitreous and/or subretinal seeding of fine aggregates of tumor cells is present, but no large clumps or “snowballs” of tumor cells
- **T2b**: Massive vitreous and/or subretinal seeding is present, defined as diffuse clumps or “snowballs” of tumor cells
- **T3**: Severe intraocular disease
- **T3a**: Tumor fills more than 2/3 of the eye
- **T3b**: One or more complications present, which may include tumor-associated neovascular or angle closure glaucoma, tumor extension into the anterior segment, hyphema, vitreous hemorrhage, or orbital cellulitis
- **T4**: Extraocular disease detected by imaging studies
- **T4a**: Invasion of optic nerve
- **T4b**: Invasion into the orbit
- **T4c**: Intracranial extension not past chiasm
- **T4d**: Intracranial extension past chiasm

#### Regional Lymph Nodes (N)

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

### Pathologic Classification (pTNM)

#### Primary Tumor (pT)

- **pTX**: Primary tumor cannot be assessed
- **pT0**: No evidence of primary tumor
- **pT1**: Tumor confined to eye with no optic nerve or choroidal invasion
- **pT2**: Tumor with minimal optic nerve and/or choroidal invasion:
  - **pT2a**: Tumor superficially invades optic nerve head but does not extend past lamina cribrosa or tumor exhibits focal choroidal invasion
  - **pT2b**: Tumor superficially invades optic nerve head but does not extend past lamina cribrosa and exhibits focal choroidal invasion
- **pT3**: Tumor with significant optic nerve and/or choroidal invasion:
  - **pT3a**: Tumor invades optic nerve past lamina cribrosa but not to surgical resection line or tumor exhibits massive choroidal invasion
  - **pT3b**: Tumor invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion
- **pT4**: Tumor invades optic nerve to resection line or exhibits extra-ocular extension elsewhere
  - **pT4a**: Tumor invades optic nerve to resection line but no extra-ocular extension identified
  - **pT4b**: Tumor invades optic nerve to resection line and extra-ocular extension identified

#### Regional Lymph Nodes (pN)

- **pNX**: Regional lymph nodes cannot be assessed
- **pN0**: No regional lymph node involvement
- **pN1**: Regional lymph node involvement (preauricular, cervical)
- **N2**: Distant lymph node involvement

### Metastasis (M)

- **M0**: No metastasis
- **M1**: Systemic metastasis
- **M1a**: Single lesion to sites other than CNS
- **M1b**: Multiple lesions to sites other than CNS
- **M1c**: Prechiasmatic CNS lesion(s)
- **M1d**: Postchiasmatic CNS lesion(s)
- **M1e**: Leptomeningeal and/or CSF involvement

- **cM0**: No metastasis
- **pM1**: Metastasis to sites other than CNS
- **pM1a**: Single lesion
- **pM1b**: Multiple lesions
- **pM1c**: CNS metastasis
- **pM1d**: Discrete mass(es) without leptomeningeal and/or CSF involvement
- **pM1e**: Leptomeningeal and/or CSF involvement
## ANATOMIC STAGE/PROGNOSTIC GROUPS
No stage grouping applies

## PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)
(Recommended for Collection)

<table>
<thead>
<tr>
<th>Required for staging</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant</td>
<td>Extension evaluated at enucleation</td>
</tr>
<tr>
<td></td>
<td>RB gene mutation</td>
</tr>
<tr>
<td></td>
<td>Positive family history of retinoblastoma</td>
</tr>
<tr>
<td></td>
<td>Primary globe-sparing treatment failure</td>
</tr>
<tr>
<td></td>
<td>Greatest linear extent of choroid involved by choroidal tumor invasion</td>
</tr>
</tbody>
</table>

## HISTOLOGIC GRADE (G)
Grade is reported in registry systems by the grade value.
A two-grade, three-grade, or four-grade system may be used.
If a grading system is not specified, generally the following system is used:

| GX | Grade cannot be assessed |
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |
| G4 | Undifferentiated |

## HISTOPATHOLOGIC TYPE
This classification applies only to retinoblastoma.

## BIBLIOGRAPHY
### Retinoblastoma Staging Form

<table>
<thead>
<tr>
<th>CLINICAL</th>
<th>STAGE CATEGORY DEFINITIONS</th>
<th>PATHOLOGIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of disease before any treatment</td>
<td></td>
<td>Extent of disease through completion of definitive surgery</td>
</tr>
<tr>
<td>☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery</td>
<td></td>
<td>☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery</td>
</tr>
<tr>
<td>☐ T0</td>
<td>No evidence of primary tumor</td>
<td>☐ pT0</td>
</tr>
<tr>
<td>☐ T1</td>
<td>Tumors no more than 2/3 the volume of the eye with no vitreous or subretinal seeding.</td>
<td>☐ pT1</td>
</tr>
<tr>
<td>☐ pT1</td>
<td>Tumor confined to eye with no optic nerve or choroidal invasion.</td>
<td>☐ pT2</td>
</tr>
<tr>
<td>☐ T1a</td>
<td>No tumor in either eye is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea.</td>
<td>☐ pT2a</td>
</tr>
<tr>
<td>☐ T1b</td>
<td>At least one tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea. No retinal detachment or subretinal fluid beyond 5 mm from the base of the tumor.</td>
<td>☐ pT2b</td>
</tr>
<tr>
<td>☐ T1c</td>
<td>At least one tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea. With retinal detachment or subretinal fluid beyond 5 mm from the base of the tumor.</td>
<td>☐ pT3</td>
</tr>
<tr>
<td>☐ T2</td>
<td>Tumors no more than 2/3 the volume of the eye with vitreous or subretinal seeding. Can have retinal detachment.</td>
<td>☐ pT3a</td>
</tr>
<tr>
<td>☐ pT2</td>
<td>Tumor with minimal optic nerve and/or choroidal invasion</td>
<td>☐ pT3b</td>
</tr>
<tr>
<td>☐ T2a</td>
<td>Focal vitreous and/or subretinal seeding of fine aggregates of tumor cells is present, but no large clumps or “snowballs” of tumor cells.</td>
<td>☐ pT4</td>
</tr>
<tr>
<td>☐ pT2a</td>
<td>Tumor superficially invades optic nerve head but does not extend past lamina cribrosa or tumor exhibits focal choroidal invasion.</td>
<td>☐ pT4a</td>
</tr>
<tr>
<td>☐ T2b</td>
<td>Massive vitreous and/or subretinal seeding is present, defined as diffuse clumps or “snowballs” of tumor cells.</td>
<td>☐ pT4b</td>
</tr>
<tr>
<td>☐ pT2b</td>
<td>Tumor superficially invades optic nerve head but does not extend past lamina cribrosa and exhibits focal choroidal invasion.</td>
<td>☐ T4</td>
</tr>
<tr>
<td>☐ T3</td>
<td>Severe intraocular disease</td>
<td>☐ T4a</td>
</tr>
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<td>☐ pT3</td>
<td>Tumor with significant optic nerve and/or choroidal invasion</td>
<td>☐ T4b</td>
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<tr>
<td>☐ T3a</td>
<td>Tumor fills more than 2/3 of the eye.</td>
<td>☐ T4c</td>
</tr>
<tr>
<td>☐ pT3a</td>
<td>Tumor invades optic nerve past lamina cribrosa but not to surgical resection line or tumor exhibits massive choroidal invasion.</td>
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<tr>
<td>☐ T3b</td>
<td>One or more complications present, which may include tumor-associated neovascular or angle closure glaucoma, tumor extension into the anterior segment, hyphema, vitreous hemorrhage, or orbital cellulitis.</td>
<td>☐ pT3b</td>
</tr>
<tr>
<td>☐ pT3b</td>
<td>Tumor invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion.</td>
<td>☐ pT4</td>
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<tr>
<td>☐ T4</td>
<td>Extraocular disease detected by imaging studies.</td>
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<td>Tumor invades optic nerve to resection line or exhibits extraocular extension elsewhere.</td>
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</tr>
<tr>
<td>☐ T4b</td>
<td>Invasion into the orbit.</td>
<td></td>
</tr>
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</table>
### REGIONAL LYMPH NODES (N)

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

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

### DISTANT METASTASIS (M)

- **Clinical**
  - M0: No distant metastasis (no pathologic M0; use clinical M to complete stage group)
  - M1: Systemic metastasis
    - M1a: Single lesion to sites other than CNS
    - M1b: Multiple lesions to sites other than CNS
    - M1c: Prechiasomatic CNS lesion(s)
    - M1d: Postchiasomatic CNS lesion(s)
    - M1e: Leptomeningeal and/or CSF involvement

- **Histologic Grade (G)**
  - 2 grade system
  - 3 grade system
  - 4 grade system
  - No 2, 3, or 4 grade system is available

- **Grade**
  - Grade I or 1
  - Grade II or 2
  - Grade III or 3
  - Grade IV or 4

### PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

**Required for Staging:** None

**Clinically Significant:**
- Extension evaluated at enucleation
- RB gene mutation
- Positive family history of retinoblastoma
- Primary globe-sparing treatment failure
- Greatest linear extent of choroid involved by choroidal tumor invasion

**Histologic Grade (G)** (also known as overall grade)

**Grade**
- Grade I or 1
- Grade II or 2
- Grade III or 3
- Grade IV or 4

**General Notes:**
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.

- **m** suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.
- **y** prefix indicates those cases in which classification is performed during or following initial multimodality 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"
ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists’ (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- Lymph-Vascular Invasion Not Present (absent)/Not Identified
- Lymph-Vascular Invasion Present/Identified
- Not Applicable
- Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

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

categorization is not an estimate of tumor prior to multimodality therapy. r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

A prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

Clinical stage was used in treatment planning (describe): ________________________________

National guidelines were used in treatment planning □ NCCN □ Other (describe): ________________________________

__________________________  ________________________
Physician signature Date/Time
Indicate on diagram primary tumor and regional nodes involved.
AJCC Cancer Staging Manual
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