Diagnosis and Staging of Uveal Melanoma

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Learning Objectives
By the end of this session, the participant will be able to:
1. Describe the gross and microscopic features of uveal melanoma
2. Identify clinical, histologic, and molecular features that portend a worse prognosis for a patient with uveal melanoma
3. Properly stage a patient with uveal melanoma using the 7th Ed. AJCC guidelines

Outline
I. Introduction
II. Clinical aspects of uveal melanoma
III. Pathology of uveal melanoma
IV. Staging of uveal melanoma

I. Introduction
The uveal tract is the middle, vascular coat of the eye between the sclera and retina, and is composed of the iris, ciliary body, and choroid. Melanocytes are a normal component of the uveal stroma, and may give rise to neoplasms, including nevi and melanomas. Melanomas can arise in any part of the uveal tract, but choroidal involvement is most common (~80%), ciliary body less common, and iris least common.

Iris melanomas usually arise from pre-existing iris nevi, and behave much less aggressively, metastasizing rarely. In contrast, ciliary body and choroidal tumors (posterior uveal melanoma) have a more malignant histologic appearance, are detected later, and more frequently metastasize. Diagnosis of ciliary body and choroidal melanomas is usually made on clinical grounds, and with high rates of accuracy. However, mortality due to posterior uveal melanoma remains unchanged, with an approximately 50% chance of dying from metastatic melanoma. Although this is true for the population of patients with ciliary body and choroidal melanoma, an individual patient’s prognosis may vary based on different factors. As
II. Clinical aspects of uveal melanoma

Epidemiology and risk factors. Although rare, uveal melanoma is the most common primary intraocular malignancy in white adults, with an estimated incidence of 5 to 7 per million per year. Unlike cutaneous melanoma, the incidence of uveal melanoma has remained stable since the early 1970s. The average age at detection of ciliary body or choroidal melanomas is 55-60 years, and the risk increases with age. It is more common in white patients compared to African-American, Asian, and Hispanic patients. Risk factors for the development of uveal melanoma include white race, light iris color (blue or gray), history of intense sun exposure, ocular melanocytosis, and dysplastic nevus syndrome.

Clinical presentation. Most choroidal or ciliary body melanomas are asymptomatic, and are detected on routine ophthalmic examination. Some patients may experience visual symptoms such as blurred vision, visual field defect, flashes or floaters. Patients with ciliary body melanoma may complain of eye redness due to episcleral vascular injection overlying the tumor (“sentinel vessels”). Occasionally, patients with advanced melanoma may present with pain secondary to glaucoma or tumor necrosis.

Diagnostic evaluation. The evaluation of a patient with suspected uveal melanoma should include a complete history, ophthalmic examination, and ancillary studies. On examination, ciliary body and choroidal melanomas have variable degrees of pigmentation. Some ciliary body melanomas may be seen through a dilated pupil as a dome-shaped mass. If the tumor is large enough it may sublux the lens or cause a sectoral cataract. Less commonly, a ciliary body melanoma may involve the ciliary body circumferentially and take on a ring configuration. Smaller choroidal tumors appear dome-shaped or nodular. As the tumor becomes larger, it may rupture Bruch’s membrane and take on a mushroom or lobular shape. A less common variant of choroidal melanoma is the diffuse melanoma, which may be difficult to detect because of extensive lateral spread and minimal elevation. Secondary non-rhegmatogenous retinal detachment is often associated with the tumor.

Sometimes the ophthalmologist may not be able to directly visualize the tumor because of media opacity (e.g. corneal edema, cataract, intraocular hemorrhage) and must use other methods to make a diagnosis, such as ultrasonography, CT scan, or MRI.

Using A-scan ultrasonography, the tumor shows an initial prominent spike followed by low-to-medium internal reflectivity. B-scan examination can help measure the size of the
tumor, and illustrate the general shape (usually dome- or mushroom-shaped). Ultrasound biomicroscopy (UBM) may be helpful to determine the extent of ciliary body tumors.

**Differential diagnosis.** The differential diagnosis is extensive, but the most common lesions that should be considered include nevus, age-related macular degeneration, congenital hypertrophy of the RPE (CHRPE), choroidal hemangioma, hemorrhagic detachment of the choroid or RPE, melanocytoma, metastatic carcinoma, and choroidal osteoma.

**Metastatic workup.** Uveal melanoma disseminates via hematogenous spread because there are no lymphatics inside the eye. The tumor usually metastasizes first to the liver, then other organs such as lung, bone, skin and subcutaneous tissue. Lymphatic spread may occur if the tumor has extraocular extension that involves the conjunctiva. Tumors can metastasize many years after primary diagnosis and treatment. The COMS reported an incidence of metastatic disease of 25% at 5 years after initial treatment and 34% at 10 years. Kujala and colleagues reported the incidence of metastatic uveal melanoma to be as high as 50% at 25 years after treatment for choroidal melanoma. Survival with metastatic uveal melanoma is poor, with a median survival of less than six months.

All patients should have metastatic workup prior to definitive treatment for uveal melanoma. The initial workup should include a complete history and physical examination, baseline lab tests including liver function tests, and imaging studies, such as abdominal ultrasound, CT scan, or total body PET/CT. Chest x-ray is also usually performed initially to help rule out the possibility of the uveal tumor being a metastasis, but is low yield as a screening test for lung metastases of uveal melanoma. Thereafter, patients should be screened yearly for metastases. If an abnormality is detected, biopsy can confirm the presence of metastatic disease. With early detection of metastases, patients may be treated with surgical resection, chemotherapy, intra-arterial chemotherapy or chemoembolization, which may provide additional months of survival.

### III. Pathology of uveal melanoma

**Gross features.** When examining eyes enucleated for uveal melanoma, a careful gross examination is important for detecting scleral melanocytosis, nodules of extraocular extension, and tumor growth pattern. Tumors are variably pigmented, ranging from amelanotic to partly pigmented to deeply pigmented. Ciliary body tumors may be associated with an indented or subluxed lens, or invasion of the iris and angle. Choroidal tumors may be dome- or mushroom-shaped, and less commonly, diffuse. In mushroom-shaped tumors, the “cap” of the mushroom often has dilated, congested vessels. There is usually an overlying retinal detachment. Sometimes scleral invasion or invasion along scleral canals may be seen.
Microscopic features. Ciliary body and choroidal melanomas have three basic cell types: spindle A, spindle B, and epithelioid. Spindle A cells have low nuclear-to-cytoplasmic ratio, and a central stripe along the longitudinal axis of the nucleus. Spindle B cells have a higher nuclear-to-cytoplasmic ratio and elongated nucleus with a distinct nucleolus. Epithelioid cells have abundant eosinophilic cytoplasm, and a large vesicular nucleus with prominent nucleolus.

Tumors are classified cytologically using the modified Callender classification into spindle cell nevus (composed of spindle A cells only), spindle cell melanoma (composed of a mixture of spindle A and spindle B cells), mixed-cell melanoma (composed of a mixture of spindle and epithelioid cells), and epithelioid melanoma (composed of epithelioid cells). Prognosis is progressively worse with increasing proportion of epithelioid cells.

Limitations of the modified Callender classification are: 1) minimum number of epithelioid cells required to be classified as a mixed-cell melanoma; and 2) difficulty of reproducibility between experienced ophthalmic pathologists.

IV. Staging of uveal melanoma

Cancer staging has several purposes. First, it allows the physician to assess the extent of the cancer in order to treat it appropriately. It helps the physician determine the most appropriate treatment to either cure the disease, decrease the tumor burden, or relieve symptoms. It allows comparison of local treatment results with national data by providing a common language to communicate, thereby expediting data exchange and research. And, for the individual patient, it provides prognostic information.

Prognostic factors. Various clinical, histopathologic, and genetic factors have been shown to predict survival in uveal melanoma. The presence of the following factors portends a worse prognosis. Clinical factors include older age, male gender, size (largest basal diameter is probably more predictive than tumor thickness), and the presence of ciliary body involvement or extraocular spread. Histologic factors include cell type (presence of epithelioid cells), nucleolar size reported as mean of the ten largest nucleoli (MLN), presence of looping vasculogenic mimicry patterns, microvascular density, presence of tumor-infiltrating lymphocytes, and cell proliferation. Genetic factors include loss of chromosome 3, gain of chromosome 8, gain of chromosome 6p, loss of chromosome 1p, and a “class 2” gene expression profile.

Staging. As pathologists, what information should we provide to help the ophthalmologist stage the patient? Tumor size and cell type are two of the most important factors associated with survival in ciliary body and choroidal melanoma. To define size, the Collaborative Ocular...
Melanoma Study (COMS) provided criteria by which tumors could be classified (see table 1). Likewise, the modified Callender classification provided criteria to describe cell type.

<table>
<thead>
<tr>
<th>Table 1: COMS definitions of choroidal melanoma size</th>
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<tr>
<td>Size</td>
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<tr>
<td>Small</td>
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<tr>
<td>Medium</td>
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<td>Large</td>
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Given the list of features that portend a worse prognosis, size and cell type are probably insufficient for prognosticating and comparing outcomes. In 2004, the Association of Directors of Anatomic and Surgical Pathology disseminated their “Recommendations for the reporting of tissues removed as part of the surgical treatment of common malignancies of the eye and its adnexa” to provide guidelines for reporting “information necessary for patient management, prognostic and predictive factor assessment, grading, staging, analysis of outcomes and tumor registries”. Their recommendations included guidelines for reporting general information about the specimen (e.g. how the specimen was received, how the specimen was identified, the laterality of the lesion, the location of the tumor, and type of surgical procedure), gross features (e.g. dimensions of the eye, length of optic nerve attached, gross evidence of extraocular extension, etc.), and microscopic features (e.g. location, extraocular extension, growth pattern, cell type, mitotic rate, presence of tumor-infiltrating lymphocytes, presence of looping vasulogenic mimicry patterns, other).

Pathologists are very familiar with the TNM classification system for other organ systems. Eye cancer is relatively new to the TNM classification system, appearing for the first time in the 4th ed. of the AJCC Manual published in 1992. However, this classification was untested and rarely used outside cancer registries. Since its first appearance in the AJCC Manual, the ophthalmic section has undergone two major revisions, most recently for the 7th edition. Unlike prior iterations of the classification, the current TNM classification of ciliary body and choroidal melanoma is based on baseline and survival data of 7369 patients. (See appendix for full TNM staging.)

The T category is based on four tumor size categories (T1-T4), read from a table with tumor thickness and largest basal diameter (see below). Each size category is grouped according to survival probability. The T subcategory is determined by the presence or absence of ciliary body and extraocular extension.
The N category reflects the absence (N0) or presence (N1) of regional lymph node metastasis. This is rare in uveal melanoma unless extraocular extension with involvement of the conjunctiva is present.

The M category reflects the absence (M0) or presence (M1) of distant metastasis. M1 is further subclassified based on the largest diameter of the largest metastasis because this was the single strongest indicator of prognosis in metastatic disease.

Using the TNM system, uveal melanomas can now be staged into one of seven stages, I, IIA-B, IIIA-C, IV. The five-year survival ranges from 96% for stage I to 3% for stage IV disease. The 15-year mortality from metastatic melanoma is 19, 31, 42, 66, and 82% for stages I-IIIIB, respectively. Although the current TNM system does not factor in many of the prognostic factors discussed in the section above, it encourages the recording of such data, which may be used in future editions of the classification scheme. This data includes histopathologic features such as mitotic count, mean of the ten largest nucleoli, presence of vasculogenic mimicry, and microvascular density, as well as genetic features such as chromosomal abnormalities and gene expression profiling. The current 7th edition AJCC Staging System is a useful tool for clinical care and research in uveal melanoma.
Appendix: 7th Edition AJCC Staging System for Ciliary body and Choroidal Melanomas

**Primary tumor (T)**
- **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

**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 8.1 cm or more

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a</th>
<th>N0</th>
<th>M0</th>
</tr>
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<tbody>
<tr>
<td>Stage I</td>
<td>T1b-d</td>
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<td>M0</td>
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<td>Stage IIA</td>
<td>T2a</td>
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<td>M0</td>
</tr>
<tr>
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<td>M0</td>
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<tr>
<td>Stage IIIIB</td>
<td>T2c-d</td>
<td>N0</td>
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<tr>
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<td>T3b-c</td>
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<td>T4b-c</td>
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<td>M0</td>
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<tr>
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<td>T4d-e</td>
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<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1a-c</td>
</tr>
</tbody>
</table>

Any T   Any N   M1a-c
References


http://www.adasp.org/Checklists/checklists.htm (accessed 1/21/13)

http://www.cancerstaging.org/products/pasteditions.html (accessed 1/21/13)


