UPDATED AJCC CLASSIFICATION FOR POSTERIOR UVEAL MELANOMA



A case example of a patient with choroidal melanoma is discussed in light of the latest edition of this cancer staging manual.

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The American Joint Committee on Cancer (AJCC) updates the *AJCC Cancer Staging Manual* every 6 to 8 years to serve as a universal standard for classification of cancer extent using clinical, pathologic, and genetic measures.[1] Since the release of the first edition of the manual in 1977, this staging system has been developed and updated for many anatomic sites.[1] With regard to ocular neoplasms, the AJCC provides classifications for uveal melanoma, retinoblastoma, conjunctival melanoma, conjunctival and eyelid carcinoma, ocular adnexal lymphoma, and orbital sarcoma.[1]

Uveal melanoma is the most common primary intraocular malignancy in adults, with a mean age-adjusted incidence of 5.1 per million new cases annually in the United States and with 98% of cases occurring in whites.[2-4] The choroid is the most common site to develop uveal melanoma, representing 90% of new cases. By comparison, iris melanoma represents only 4% of new cases.[3,4] Systemic prognosis is more serious with posterior uveal melanoma than iris melanoma, as the 10-year rate of metastasis was 25% for choroidal, 34% for ciliary body, and 7% for iris melanoma.[4]

In January 2017, the AJCC released the updated 8th edition of the *AJCC Cancer Staging Manual*, providing revised guidelines for tumor classification and staging. In an earlier installment of this column, we discussed the updated classification for uveal melanoma in the 8th edition with particular attention to iris melanoma.[5] In this installment, we further discuss the updated classification for uveal melanoma in the 8th edition in the context of a patient with choroidal melanoma.

CASE REPORT

A 54-year-old white woman with a 1-month history of floaters was referred for evaluation of a pigmented choroidal mass in her right eye (OD). On ocular examination, visual acuity was 20/60 OD and 20/20 in the left eye (OS). Intraocular pressures were normal in each eye (OU). Anterior segment examination OU and fundus examination OS were unremarkable.

Fundus evaluation OD revealed a juxtapapillary pigmented choroidal mass measuring 10 mm in base and 3.5 mm in thickness, with overlying subretinal fluid and orange pigment (lipofuscin) (Figure, A). Lipofuscin hyperautofluorescence was documented, and optical coherence tomography (OCT) revealed shallow subretinal fluid (Figure, B, D, and E). On ultrasonography, the tumor was acoustically hollow and measured 3.5 mm in thickness (Figure, C). Clinical and imaging features were consistent with the diagnosis of juxtapapillary choroidal melanoma. The tumor was

AT A GLANCE

- Uveal melanoma is the most common primary intraocular malignancy in adults and is more likely to develop in white individuals than in people of other races.
- Systemic prognosis is more serious with posterior uveal melanoma than with iris melanoma.
- The posterior uveal melanoma section in the latest edition of the *AJCC Cancer Staging Manual* includes a new subcategory to the N category that differentiates between patients with extrascleral extension and those with regional spread into the orbit not contiguous with the eye.

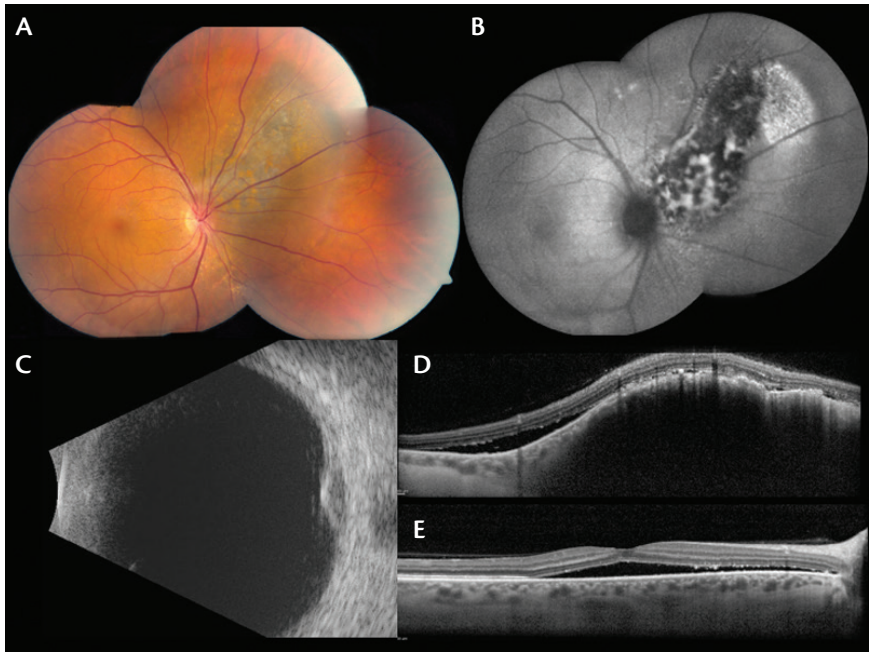

Figure. AJCC category T2a N0 M0 melanoma. Subtle juxtapapillary pigmented choroidal melanoma with overlying subretinal fluid and orange pigment (A), fundus autofluorescence imaging revealing hyperautofluorescence of lipofuscin (B), ultrasound depicting hollow tumor with thickness of 3.5 mm (C), and OCT showing melanoma with overlying subretinal fluid (D) extending into the fovea (E).

clinically classified using the AJCC 8th edition as T2a N0 M0.

Treatment of choice was iodine-125 (I-125) plaque radiotherapy combined with two sessions of transpupillary thermotherapy. At 1-year follow-up, the tumor demonstrated complete regression.

At 18 months after treatment, circumpapillary recurrence and optic nerve edema were detected, and enucleation was advised and performed. Histopathology of the tumor revealed choroidal melanoma, mixed cell type, with AJCC 8th edition histologic grade G2. The patient has been followed for 4 years with no evidence of systemic metastasis.

DISCUSSION

The *AJCC Cancer Staging Manual* provides uniform guidance for cancer staging and assessing anatomic dimensions, anatomic structure involvement, and histopathologic factors utilizing the available evidence.[1] The 7th edition of the AJCC staging of posterior uveal melanoma, released in 2009, was redesigned based on a recent study[6] using clinical evidence from a collaborative database of 7,369 patients to create the year-plus old 8th edition AJCC staging system.

Multiple studies have validated the 7th edition AJCC classification for uveal melanoma.[7-10] Shields et al independently analyzed 7,731 patients and found that the case distribution included stage 1 in 2,767 patients (36%), stage 2 in 3,735 (48%), stage 3 in 1,220 (16%), and stage 4 in nine (<1%).[7] Compared with uveal melanoma classified as AJCC stage 1, the rate of metastasis and/or death was three times greater for stage 2, nine to 10 times greater for stage 3, and not assessable for stage 4.[7]

Furthermore, the AJCC Ophthalmic Task Force released a validation study of 3,217 patients from 10 other ocular

TABLE 1. AJCC CLASSIFICATION OF POSTERIOR UVEAL MELANOMA (CHOROIDAL AND CILIARY BODY), T CATEGORY

Thickness (mm)							
>15.0	4	4	4	4	4	4	4
12.1 to 15.0	3	3	3	3	3	4	4
9.1 to 12.0	3	3	3	3	3	3	4
6.1 to 9.0	2	2	2	2	3	3	4
3.1 to 6.0	1	1	1	2	2	3	4
≤ 3.0	1	1	1	1	2	2	4
	≤ 3.0	3.1-6.0	6.1-9.0	9.1-12.0	12.1-15.0	15.1-18.0	>18.0
	Largest basal diameter (mm)						

Source: Adapted from the *AJCC Cancer Staging Manual*, 8th ed.[1]

TABLE 2. AJCC CLASSIFICATION OF POSTERIOR UVEAL MELANOMA (CHOROIDAL AND CILIARY BODY), T CATEGORY SUBCLASSIFICATION

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor base ≤9 mm with thickness ≤6 mm Tumor base 9.1-12 mm with thickness ≤3 mm
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 ≤5 mm in largest diameter
T1d	Tumor size category 1 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T2	Tumor base ≤9 mm with thickness 6.1-9 mm Tumor base 9.1-12 mm with thickness 3.1-9 mm Tumor base 12.1-15 mm with thickness ≤6 mm Tumor base 15.1-18 mm with thickness ≤3 mm
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 ≤5 mm in largest diameter
T2d	Tumor size category 2 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T3	Tumor base 3.1-9 mm with thickness 9.1-12 mm Tumor base 9.1-12 mm with thickness 9.1-15 mm Tumor base 12.1-15 mm with thickness 6.1-15 mm Tumor base 15.1-18 mm with thickness 3.1-12 mm
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 ≤5 mm in largest diameter
T3d	Tumor size category 3 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T4	Tumor base 12.1-15 mm with thickness >15 mm Tumor base 15.1-18 mm with thickness >12 mm Tumor base >18 mm with any thickness
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 ≤5 mm in largest diameter
T4d	Tumor size category 4 with ciliary body involvement and extraocular extension ≤5 mm in largest diameter
T4e	Any tumor size category with extraocular extension >5 mm in largest diameter

Source: Adapted from the *AJCC Cancer Staging Manual*, 8th ed.[1]

oncology centers internationally, revealing case distribution of stage 1 in 1,030 (32%), stage 2 in 1,805 (56%), stage 3 in 382 (12%), and stage 4 in 67 patients (2%).[8] These authors independently found the risk of metastasis at 10 years to increase by approximately twofold for each AJCC stage.[8]

Bagger et al evaluated the prognostic effect of AJCC 7th edition staging combined with genetic status in patients with posterior uveal melanoma and concluded that a normal genetic status of chromosomes 3 and 8 minimized the prognostic effect of AJCC staging, while a combination of genetic status and AJCC staging provided accurate prediction of survival in those with abnormal chromosome 3 and 8 status.[9]

Additionally, the European Ophthalmic Oncology Group conducted a study of pediatric choroidal and ciliary body melanoma, collecting data on 299 patients from 24 centers (114 children age <18 and 185 young adults age 18-25 at the time of diagnosis).[10] In individuals aged 25 years and younger, they found that increasing AJCC stage was associated with poorer survival at 10 years from diagnosis, with stage 1 at 100% survival, stage 2 at 86% survival, and stage 3 at 76% survival.[10] They concluded that children younger than 18 years have a more favorable survival rate than young adults aged 18 to 25 years, adjusting for TNM stage and sex.[10]

The 8th edition of the *AJCC Cancer Staging Manual* guides users in assessing the extent of the primary tumor (T), the presence or absence of lymph node involvement (N), and the presence or absence of distant metastasis (M).[1] More specifically, T is organized based on the tumor's largest basal diameter and thickness into increasing size categories and then subclassified according to ciliary body involvement and extraocular extension (Tables 1 and 2). N is classified by regional lymph node involvement (Table 3). Similarly, M is classified by distant metastasis and

TABLE 3. AJCC CLASSIFICATION OF POSTERIOR UVEAL MELANOMA (CHOROIDAL AND CILIARY BODY), REGIONAL LYMPH NODES AND DISTANT METASTASIS

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node metastasis or discrete tumor deposits in the orbit
N1a	Metastasis in one or more regional lymph node(s)
N1b	No regional lymph nodes are positive, but there are discrete tumor deposits in the orbit that are not contiguous to the eye
M Category	**M Criteria**
M0	No distant metastasis by clinical classification
M1	Distant metastasis
M1a	Largest diameter of the largest metastasis ≤3.0 cm
M1b	Largest diameter of the largest metastasis 3.1-8.0 cm
M1c	Largest diameter of the largest metastasis ≥8.1 cm

Source: Adapted from the *AJCC Cancer Staging Manual*, 8th ed.[1]

TABLE 4. AJCC CLASSIFICATION OF POSTERIOR UVEAL MELANOMA (CHOROIDAL AND CILIARY BODY), STAGING

When T is ...	And N is ...	And M is ...	Then the stage group is ...
T1a	N0	M0	I
T1b-d	N0	M0	IIA
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T3a	N0	M0	IIB
T2c-d	N0	M0	IIIA
T3b-c	N0	M0	IIIA
T4a	N0	M0	IIIA
T3d	N0	M0	IIIB
T4b-c	N0	M0	IIIB
T4d-e	N0	M0	IIIC
Any T	N1	M0	IV
Any T	N1	M1a-c	IV

Source: Adapted from the *AJCC Cancer Staging Manual*, 8th ed.[1]

TABLE 5. AJCC CLASSIFICATION OF POSTERIOR UVEAL MELANOMA (CHOROIDAL AND CILIARY BODY), HISTOLOGIC GRADE

G Category	G Criteria
GX	Grade cannot be assessed
G1	Spindle cell melanoma (>90% spindle cells)
G2	Mixed cell melanoma (>10% epithelioid cells and <90% spindle cells)
G3	Epithelioid cell melanoma (>90% epithelioid cells)

Source: Adapted from the *AJCC Cancer Staging Manual*, 8th ed.[1]

metastatic tumor dimension (Table 3).

The AJCC classification system for uveal melanoma additionally organizes each specific combination of the individual T, N, and M into prognostic stages (stages 1-4) (Table 4). Each increasing stage indicates increasingly higher risk for metastasis and mortality.

When available following enucleation, histologic grading (G) should be assessed (Table 5). Grading includes spindle cell (G1), mixed cell (G2), and epithelioid cell types (G3). Although G is not currently used in prognostic staging, it may be incorporated in the future.

For posterior uveal melanoma, the 8th edition of the AJCC manual added a subcategory to the N category, but it is otherwise largely unchanged from the 7th edition. The N1 category now has N1a and N1b subcategories to separate regional lymph node involvement from discrete tumor deposits in the orbit that are not contiguous to the eye without regional lymph node involvement. This is important because, as stated in the AJCC manual 8th edition, the previous edition did not differentiate patients with extrascleral extension, which is typically adherent to the eye, from those with regional spread into the orbit not contiguous with the eye.

THE AJCC CANCER STAGING SYSTEM FOR POSTERIOR UVEAL MELANOMA HAS BEEN LARGELY VALIDATED IN RECENT YEARS, AND IT HELPS TO IMPROVE UNDERSTANDING OF THE PROGNOSIS OF THIS MALIGNANCY.

STAY IN THE KNOW

The AJCC cancer staging system for posterior uveal melanoma has been largely validated in recent years, and it helps to improve understanding of the prognosis of this malignancy. We encourage all ocular oncologists to utilize this classification system to maintain a uniform method of predicting outcomes. ■

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