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American Joint Committee on Cancer Classification of Uveal Melanoma (Anatomic Stage) Predicts Prognosis in 7731 Patients

The 2013 Zimmerman Lecture

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Purpose: To analyze the clinical features and prognosis of posterior uveal melanoma based on the American Joint Committee on Cancer (AJCC) (7th edition) tumor staging.

Design: Retrospective interventional case series.

Participants: A total of 7731 patients.

Methods: Uveal melanoma management.

Main Outcome Measures: Melanoma-related metastasis and death.

Results: Of 7731 patients with posterior uveal (ciliary body and choroidal) melanoma, the AJCC tumor staging was stage I in 2767 (36%), stage II in 3735 (48%), stage III in 1220 (16%), and stage IV in 9 (<1%). Based on tumor staging (I, II, III, and IV), features that showed significant increase with tumor staging included age at presentation (57, 58, 60, 60 years) ($P < 0.001$), tumor base (8, 12, 17, 17 mm) ($P < 0.001$), tumor thickness (2.9, 6.0, 10.1, 10.2 mm) ($P < 0.001$), distance to optic disc (3, 5, 5, 5 mm) ($P < 0.001$), distance to foveola (3, 5, 5, 5 mm) ($P < 0.001$), mushroom configuration (6%, 24%, 34%, 33%) ($P < 0.001$), plateau configuration (3%, 4%, 7%, 11%) ($P < 0.001$), tumor pigmentation (48%, 53%, 69%, 78%) ($P < 0.001$), and extraocular extension (0%, 1%, 11%, 22%) ($P < 0.001$). After therapy, Kaplan–Meier estimates of metastasis at 1, 5, 10, and 20 years were <1%, 5%, 12%, and 20% for stage I, 2%; 17%, 29%, and 44% for stage II; 6%, 44%, 61%, and 73% for stage III, and 100% by 1 year for stage IV. Kaplan–Meier estimates of death at 1, 5, 10, and 20 years were <1%, 3%, 6%, and 8% for stage I; <1%, 9%, 15%, and 24% for stage II; 3%, 27%, 39%, and 53% for stage III, and 100% by 1 year for stage IV. Compared with stage I, the hazard ratio for metastasis/death was 3.1/3.1 for stage II and 9.3/10.1 for stage III.

Conclusions: Compared with uveal melanoma classified as AJCC stage I, the rate of metastasis/death was 3 times greater for stage II, 9 to 10 times greater for stage III, and further greater for stage IV. Early detection of posterior uveal melanoma, at a point when the tumor is small, can be lifesaving. *Ophthalmology 2015;■:1–7 © 2015 by the American Academy of Ophthalmology.*

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The American Joint Committee on Cancer (AJCC) classification is now in its 7th edition, officially released in January 2010. This classification uses the universal tumor (T), node (N), and metastasis (M) (TNM) staging and has become increasingly pertinent to the field of ocular oncology. This TNM staging is designed for both iris melanoma and posterior uveal melanoma involving the ciliary body and choroid.[1] The AJCC posterior uveal melanoma classification involves categorization and then staging of the melanoma. The categorization portion involves measurement of tumor thickness and basal diameter and fitting into one of 4 size-designation groups listed as T1, T2, T3, and T4. The staging portion involves merging results from categorization and information on lymph node (N) and metastatic (M) disease to fit into 1 of 4 anatomic stages designated as stage I, II, III, and IV. The intent of the AJCC is to stratify uveal melanoma by anatomic stage for prognostication of metastatic disease and death.

We have previously explored and validated the AJCC classification for conjunctival squamous cell carcinoma,[2] conjunctival melanoma,[3] and posterior uveal melanoma.[4,5] In our analysis for posterior uveal melanoma classified by

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Table 1. Posterior Uveal Melanoma Category Based on American Joint Cancer Committee (7th Edition) Classification*

Primary tumor (T)	
T1	Tumor base <3–9 mm with thickness ≤6 mm Tumor base 9.1–12 mm with thickness ≤3 mm
T1a	T1 tumor without ciliary body involvement and extraocular extension
T1b	T1 tumor with ciliary body involvement
T1c	T1 tumor without ciliary body involvement but with extraocular extension ≤5 mm in diameter
T1d	T1 tumor with ciliary body involvement and extraocular extension ≤5 mm in diameter
T2	Tumor base <9 mm with thickness 6–9 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	T2 tumor without ciliary body involvement and extraocular extension
T2b	T2 tumor with ciliary body involvement
T2c	T2 tumor without ciliary body involvement but with extraocular extension ≤5 mm in diameter
T2d	T2 tumor with ciliary body involvement and extraocular extension ≤5 mm in 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	T3 tumor without ciliary body involvement and extraocular extension
T3b	T3 tumor with ciliary body involvement
T3c	T3 tumor without ciliary body involvement but with extraocular extension ≤5 mm in diameter
T3d	T3 tumor with ciliary body involvement and extraocular extension ≤5 mm in 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	T4 tumor without ciliary body involvement and extraocular extension
T4b	T4 tumor with ciliary body involvement
T4c	T4 tumor without ciliary body involvement but with extraocular extension ≤5 mm in diameter
T4d	T4 tumor with ciliary body involvement and extraocular extension ≤5 mm in diameter
T4e	Any tumor size with extraocular extension >5 mm in diameter

*Source: Edge SB, Byrd DR, Compton CC, et al, eds. Malignant melanoma of the uvea. In: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010:547–59.

AJCC, we assessed only tumor category based on size, which alone was found to be significantly predictive of metastatic outcome. In that report, 10-year risk for metastasis was 15% for T1, 25% for T2, 49% for T3, and 63% for T4.[4] Stated by relative risk, compared with posterior uveal melanoma classified as T1, the rate of metastasis and death was 2 times greater for T2, 4 times greater for T3, and 8 times greater for T4.[4] In this current investigation, we explore further the predictive value of the AJCC anatomic stage classification for posterior uveal melanoma metastasis and death.

Methods

Institutional review board approval was obtained for this retrospective analysis. The computerized database on the Ocular Oncology Service at Wills Eye Hospital was searched for the clinical diagnosis of choroidal melanoma or ciliary body melanoma. Included were patients evaluated and managed between August 25, 1970, and August 27, 2008. There were 7731 patients with adequate tumor information enabling retrospective classification of uveal melanoma using the AJCC (7th edition).

The patient data were reviewed for demographic information including age at diagnosis (years), gender, and race (white, African-American, Hispanic, Asian, Native American, Middle Eastern, Asian Indian). Anterior and posterior segment findings were recorded. The tumor data included laterality (unilateral, bilateral), location of tumor epicenter (ciliary body, choroid), quadrant location of tumor epicenter (superior, nasal, inferior, temporal, macula), clock-hour location of the tumor epicenter, anteroposterior location of tumor epicenter (macula, macula-equator, equator-ora serrata), distance of posterior tumor margin to optic disc margin and foveola (millimeters), largest tumor basal dimension and thickness (millimeters), tumor configuration (mushroom, dome, plateau), color (pigmented, nonpigmented, mixed), and associated features of Bruch's membrane rupture, subretinal fluid, intraocular hemorrhage, and extraocular extension. Tumor basal diameter was estimated by indirect ophthalmoscopy and ultrasonography, and tumor thickness was measured by ultrasonography. All findings were documented with a large fundus drawing, fundus photography, fluorescein angiography, and ultrasonography. On the basis of tumor features (melanoma basal diameter, thickness, location, and extraocular extension) (Fig 1, available at www.aaojournal.org), status of regional lymph nodes, and systemic metastasis, each tumor was staged according to the AJCC (7th edition) (Tables 1 and 2).

Treatment options included laser photocoagulation, transpupillary thermotherapy, plaque radiotherapy, local resection, enucleation, and exenteration. The risks and benefits of each treatment modality were discussed with the patient, and appropriate treatment was performed. The tumor management was recorded. Systemic monitoring and screening for metastasis were performed by a medical oncologist with twice-yearly physical examination, liver function tests, once-yearly liver imaging (magnetic resonance,