American Joint Committee on Cancer Classification of Posterior Uveal Melanoma (Tumor Size Category) Predicts Prognosis in 7731 Patients

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Purpose: To evaluate the clinical features and prognosis of posterior uveal (ciliary body and choroid) melanoma based on the American Joint Committee on Cancer (AJCC) classification (7th edition) of primary tumor (T).

Design: Retrospective, interventional case series.

Participants: Seven thousand seven hundred thirty-one patients.

Intervention: Ocular management including plaque radiotherapy, enucleation, local resection, or laser therapy.

Main Outcome Measures: Melanoma-related metastasis and death.

Results: Of 7731 patients with posterior uveal melanoma, the AJCC classification based on T was category T1 in 3557 (46%), T2 in 2082 (27%), T3 in 1599 (21%), and T4 in 493 (6%). Based on tumor categories T1, T2, T3, and T4, respectively, features that showed significant increase with tumor category included patient age at presentation (57, 58, 58, and 61 years; $P<0.001$), tumor base (8, 12, 15, and 20 mm; $P<0.001$), tumor thickness (3.5, 5.2, 8.9, and 11.4 mm; $P<0.001$), mushroom configuration (8%, 20%, 38%, and 39%; $P<0.001$), associated subretinal fluid (64%, 80%, 82%, and 83%; $P<0.001$), intraocular hemorrhage (5%, 12%, 17%, and 18%; $P<0.001$), rupture of Bruch's membrane (9%, 24%, 40%, and 40%; $P<0.001$), and extraocular extension (1%, <1%, 4%, and 12%; $P<0.001$). After therapy, Kaplan-Meier estimates of metastasis at 5, 10, and 20 years were 8%, 15%, and 25% for category T1, 14%, 25%, and 40% for category T2, 31%, 49%, and 62% for category T3, and 51%, 63%, and 69% for category T4, respectively ($P<0.001$). Kaplan-Meier estimates of death at 5, 10, and 20 years were 4%, 8%, and 11% for category T1, 8%, 13%, and 24% for category T2, 19%, 27%, and 36% for category T3, and 30%, 43%, and 51% for category T4, respectively ($P<0.001$). Compared with category T1, the hazard ratio for metastasis and death for T2 was 1.8 and 1.9, respectively, that for T3 was 4.5 and 4.7, respectively, and that for T4 was 8.2 and 8.8, respectively.

Conclusions: Based on the AJCC classification, increasing tumor category was associated with older age, larger tumor, and greater incidence of subretinal fluid, hemorrhage, and extraocular extension. Compared with 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. The risk for metastasis and death increased 2-fold with each increasing melanoma category.

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Posterior uveal melanoma (ciliary body [CB] and choroidal melanoma) represents 96% of all uveal melanoma.[1,2] Management of melanoma is focused on early detection,[3,4] with therapeutic interventions of enucleation, radiotherapy, resection, and forms of laser photocoagulation, transpupillary thermotherapy, and photodynamic therapy.[2] Despite local therapeutic efforts, systemic prognosis remains guarded because melanoma can metastasize early in the course of disease[5] and primarily is dependent on tumor genetics and size.[6–11]

Posterior uveal melanoma generally is classified into size categories based on thickness, including small (≤3 mm), medium (>3–8 mm), and large (>8 mm), with prognosis directly related to tumor size.[11,12] Estimates of 10-year mortality revealed 12% for small melanoma, 26% for medium melanoma, and 49% for large melanoma.[11] More precise risk estimates based on ultrasonographically measured tumor thickness in millimeters disclosed that each 1-mm gain imparted approximately a 5% increased risk for metastasis.[11]

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The American Joint Committee on Cancer (AJCC) staging manual, 7th edition, provides a detailed classification for uveal melanoma with the intent of improving understanding and prognostication of this malignancy.[13] In this classification, the tumor is graded according to size category based on a combination of basal diameter and thickness and labeled as T1, T2, T3, and T4 with increasing category. Subclassification of each category is judged by (1) the absence of CB involvement and extraocular extension, (2) the presence of CB involvement, (3) the presence of extraocular extension of 5 mm or less, and (4) the presence of both CB involvement and extraocular extension. In this analysis, we explored the correlation of melanoma clinical features and melanoma-related metastasis and death with the AJCC classification.

Methods

This investigation was a retrospective, nonrandomized, noncomparative, interventional case series. Institutional review board approval was obtained. The medical records of all patients with the clinical diagnosis of posterior uveal melanoma involving the CB or choroid and managed by the Ocular Oncology Service at Wills Eye Institute between August 25, 1970, and August 27, 2008, were reviewed. Of 7784 patients with posterior uveal melanoma during the study period, adequate tumor information enabling retrospective classification using the AJCC manual, 7th edition, was available for 7731 patients, and these patients were included in this study. The remaining 53 patients with inadequate tumor information for classification based on the AJCC manual were excluded.

The patient data were reviewed for demographic information, clinical findings, and management. Each patient was evaluated for age at diagnosis (years), sex (male or female), and race (Caucasian, black, Hispanic, Asian, Native American, Middle Eastern, Asian Indian). A comprehensive ocular examination was performed in each case with assessment of intraocular pressure (in millimeters of mercury), status of the anterior segment by slit-lamp biomicroscopy, and status of the posterior segment by indirect ophthalmoscopy. The tumor data included laterality (unilateral, bilateral), location of tumor epicenter (iris, CB, 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 the posterior tumor margin to the optic disc margin and foveola (in millimeters), largest tumor basal dimension, and thickness (in millimeters). Tumor basal diameter was estimated by indirect ophthalmoscopy and ultrasonography, whereas tumor thickness was measured by ultrasonography. Other clinical features included tumor configuration (dome, mushroom, tapioca, plateau), color (pigmented, nonpigmented, mixed), associated features of Bruch's membrane rupture, subretinal fluid, intraocular hemorrhage, and extraocular extension. Based on melanoma basal diameter, thickness, location, and extraocular extension, each tumor (T) was classified according to the AJCC manual, 7th edition (Table 1, available at http://aaojournal.org). The categories for node (N) and metastasis (M) at date first seen were 0 (indicating no evidence of disease) in all cases. All findings were documented with a large fundus drawing, fundus photography, fluorescein angiography, and ultrasonography.

Potential risks and benefits of each treatment method were discussed with the patient and a signed informed consent was obtained. Treatment options included plaque radiotherapy, local resection, laser photocoagulation, transpupillary thermotherapy, enucleation, and exenteration. The method of tumor management was recorded. Systemic monitoring and screening for metastasis was performed by a medical oncologist with twice-yearly physical examination and liver function tests (lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase), once-yearly liver imaging (magnetic resonance imaging, computed tomography, or ultrasonography), and chest imaging (chest radiography, magnetic resonance imaging, or computed tomography). The date and interval to systemic melanoma-related metastasis were recorded. If the patient was deceased, the date and interval to melanoma-related death as indicated by the family or local physician were recorded.

The tumor features and patient outcomes of melanoma-related metastasis and death then were analyzed based on primary tumor size category (category T1, T2, T3, and T4). Statistical analysis was performed on the entire group to identify significant relationships.

Statistical Analysis

Based on the AJCC classification (Table 1, available at http://aaojournal.org), data were summarized as numbers and percentages for each major category of T1, T2, T3, and T4 (Fig 1; Table 2, available at http://aaojournal.org). The demographic (Table 3) and tumor (Table 4, available at http://aaojournal.org) features were compared for each group using the chi-square test, and paired comparisons were performed using the Fisher exact test. The demographic and tumor features that were measured on a continuous scale were compared using an analysis of variance followed by post hoc comparisons using Bonferroni correction.

Kaplan-Meier analysis was performed to estimate the cumulative probability of metastasis (Table 5, available at http://aaojournal.org) and death (Table 6, available at http://aaojournal.org) resulting from metastasis at 1, 3, 5, 10, and 20 years of follow-up within each AJCC clinical category. The hazard ratios of metastasis and death were estimated for each AJCC clinical category and then were compared with category T1 results (Table 7).

The factors predictive of melanoma-related metastasis and death were analyzed using a Cox proportional hazard model (Table 8, available at http://aaojournal.org). The factors found significant on univariate analysis at a 5% level of significance were considered for multivariate analysis using the forward stepwise method. The factors significant at a 0.05 level on multivariate analysis were reported. The hazard ratios accompanied by 95% confidence intervals (CIs) were listed.

Results

Of 7731 patients with posterior uveal melanoma, 3557 (46%) were classified as category T1, 2082 (27%) were classified as category T2, 1599 (21%) were classified as category T3, and 493 (6%) were classified as category T4 (Table 2, available at http://aaojournal.org). Patient demographic data are listed in Table 3. Overall, the median age at presentation was 59 years, 98% were Caucasian, and 49% were female. Factors that statistically differed per category (T1, T2, T3, T4) included median age (58, 59, 59.5, and 63.8 years, respectively; $P<0.0001$), Caucasian race (98%, 98%, 97%, and 96%, respectively; $P<0.001$), and female sex (52%, 50%, 44%, and 45%, respectively; $P<0.001$).

The tumor features of posterior uveal melanoma are presented in Table 4 (available at http://aaojournal.org). Factors that statistically differed per category (T1, T2, T3, T4) included anteroposterior location ($P<0.001$), quadrantic location ($P<0.001$), clock hour location ($P<0.001$), distance to foveola ($P<0.001$) and optic disc ($P<0.001$), tumor base ($P<0.001$) and thickness