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Association between Tumor Regression Rate and Gene Expression Profile after Iodine 125 Plaque Radiotherapy for Uveal Melanoma

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Purpose: Gene expression profile (GEP) testing segregates uveal melanoma (UM) into 2 main prognostic classes. It is unknown if a greater tumor regression response after iodine 125 (I^{125}) brachytherapy correlates with class 2 GEP status. The purpose of this study was to determine whether there is a significant relationship between the rate of UM height regression and GEP classification testing after I^{125} plaque brachytherapy.

Design: Multicenter, retrospective cohort study.

Participants: Adult UM patients treated with I^{125} plaque brachytherapy who had concurrent tumor biopsy at the time of surgery with a GEP test result from January 1, 2010 through June 30, 2014.

Methods: Baseline clinical data and GEP class assignments were obtained. The ultrasonographic tumor height was recorded at baseline and at 3, 6, 9, and 12 months and at the most recent final follow-up visits. Subanalysis of paired cases based on pretreatment ultrasound height was performed. Statistical analysis was performed using Wilcoxon rank-sum tests, the Fisher exact test, and Kaplan-Meier analysis.

Main Outcome Measures: Percentage change in tumor height from baseline.

Results: A total of 353 patients were included in the study. Median follow-up was 2.1 years (range, 0.5–5.3 years). Gene expression profile status was class 1 in 247 tumors (70%) and class 2 in 106 tumors (30%). Increased patient age, larger tumor dimensions, and greater tumor thickness were associated with class 2 GEP status ($P = 0.006$, $P < 0.001$, and $P < 0.001$, respectively). The percentage reduction in tumor height from baseline was significantly greater in class 1 than class 2 tumors at 3 months (17.5% vs. 11.8%; $P = 0.007$) and 6 months (26.8% vs. 17.1%; $P = 0.007$), respectively, but there was no significant difference in reduction between class 1 and 2 tumors at 9 months ($P = 0.26$) and 12 months ($P = 0.57$) after treatment. Class 1A and 1B tumors showed similar reduction compared with class 2 tumors ($P < 0.05$).

Conclusions: Class 1 UM tumors tend to regress more rapidly than class 2 tumors in the first 6 months after plaque radiotherapy. Class 1A and 1B tumors regress at similar rates after plaque radiotherapy. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

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Plaque brachytherapy is the most widely used globe-sparing treatment for uveal melanoma (UM) because it delivers a highly concentrated radiation dose to the tumor with relatively less radiation to surrounding unaffected tissues. Three groups have published previously that a faster rate of regression, especially in the first 6 to 12 months after radiation therapy, may be a negative prognostic factor for survival associated with metastatic disease and death.[1–3] This finding has been reproduced across several radiation isotopes used in ocular brachytherapy including iodine 125 (I^{125}), cobalt 60, and ruthenium 106.[1,3–5] However, these were all studies performed in single-center settings with variable approaches to assessing mortality prediction.

Gene expression profile (GEP) testing has been demonstrated prospectively to be superior to both high-risk clinical features and cytogenetic abnormalities, such as monosomy 3 status, in predicting UM metastasis. Class 2 tumors are known to be larger at baseline, to be located more commonly near the ciliary body, and to have more aggressive histopathologic features.[6,7] Because the response to radiation therapy targets dividing tumors cells that are in active cell cycle, one may predict that aggressive class 2 tumors would show a more robust response to radiation therapy, leading to faster and more sustained tumor regression. Nonetheless, previously published studies have demonstrated mixed results in predicting regression of UM after plaque brachytherapy. Rao et al,[8] in a single-institution review of 138 nonmatched cases, noted earlier regression at 3 months in class 1 tumors. Other reports have found no correlation between GEP status and tumor regression response with either I^{125} brachytherapy or proton-beam irradiation.[6,7]

No large multi-institutional studies have been performed to explore whether GEP class designation impacts the rate of

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tumor height response to I^{125} brachytherapy. Such knowledge may help to counsel patients as to the expected rate of tumor response after GEP class is known and may help to counsel patients who have declined or are poor candidates for tumor biopsy. The current study sought to answer whether GEP class 2 designation predicts faster tumor radiation response to I^{125} plaque brachytherapy in patients with posterior UM.

Methods

Institutional review board approval was obtained in each of the participating institutions in this study. The study adhered to the tenets of the Declaration of Helsinki, and all work using patient information was performed in compliance with the Health Insurance Portability and Accountability Act. A multi-institutional retrospective study was performed of eligible patients with posterior UM, defined as involving either the choroid or ciliary body, treated with I^{125} plaque brachytherapy and whose concurrent choroidal tumor biopsy sample was submitted for GEP testing with a reported result dating between January 1, 2010 and June 30, 2014. A concurrent biopsy for separate cytopathologic verification was performed at the discretion of the operating surgeon in 151 eyes (44%), but was not stipulated as part of entry criteria. Biopsy methods and cytopathologic diagnostic yield will be reported separately. Plaque brachytherapy technique was not standardized by protocol, but each of the fellowship-trained ocular oncologists in the study had similar techniques, including identifying the tumor, performing tumor biopsy, placing the active I^{125} plaque, confirming appropriate plaque placement (technique varied), and then removing the plaque 3 to 7 days later.

Inclusion criteria included: adult patients (>18 years), a preoperative diagnosis of UM with clinical examination results documenting size and location, concurrent choroidal tumor biopsy performed just before placement of I^{125} brachytherapy plaque with GEP test results, and at least 3 months (±40 days) of follow-up. Patients who received adjuvant transpupillary thermotherapy treatment or had follow-up outside of the designated periods (3, 6, 9, and 12 months) were excluded.

Data were entered into a security-encrypted Research Electronic Data Capture database, accessible by password, at each of the approved 9 participating ocular oncology centers: Duke Eye Center, Durham, North Carolina (coordinating center); University of Miami/Bascom Palmer Eye Institute, Miami, Florida; University of Southern California/USC Roski Eye Institute, Los Angeles, California; Oregon Health Sciences/Casey Eye Institute, Portland, Oregon; Smilow Cancer Hospital at Yale New Haven, New Haven, Connecticut; University of Michigan, Ann Arbor, Michigan; Colorado Retina Associates/Rocky Vista University, Denver, Colorado; Retina Specialists of Michigan, Grand Rapids, Michigan; and Retina Consultants of Houston/Blanton Eye Institute at Houston Methodist Hospital, Houston, Texas.

Relevant baseline information was collected consisting of patient demographics (age, gender, eye involved); melanoma tumor status before therapy (location, size [clinical and B-scan ultrasound] by Collaborative Ocular Melanoma Study and American Joint Committee on Cancer eighth edition criteria, presence of subretinal fluid, surface changes, color, and presence of Bruch's membrane breakthrough); radiation treatment details, plaque brachytherapy surgical, and radiation dosing details (including dose to tumor and scleral base); and GEP class test result (class 1 [1A/1B] or class 2, and discriminant score value).[9,10] Follow-up clinical examination data were collected, when available, at 3, 6, 9, and 12 months (±40 days in each period) and final follow-up after 1 year, including: visual acuity, clinical signs of tumor regression, subretinal fluid status, presence radiation maculopathy, and tumor size (both by clinical and ultrasound evaluation).

Statistical Methods

Secure data were downloaded from the Research Electronic Data Capture database as an SAS file and were analyzed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC). Descriptive statistics were computed. Tumor height was examined for normality at each time point. The primary analysis was to compare the change in tumor height at 3 months in the class 1 and 2 tumor groups. A regression model was created using variables with significant differences between class 1 and 2 tumors including GEP class status, baseline tumor height, baseline tumor base measurements, and patient age. Because the change in height may depend on the baseline tumor height, analysis of covariance was used to assess the difference in the slopes between groups while adjusting for baseline tumor height. To test whether the association between GEP class and response is affected by initial tumor height, an interaction term for group and baseline tumor height was included and was eliminated if nonsignificant. In a secondary analysis, a case-matched cohort was identified. Separately by GEP groups, patients were sorted by exact baseline tumor height, then by basal ultrasound tumor dimension, within 5 mm. This process resulted in 75 pairs with matched baseline data (n = 150). The data from subsequent visits then were obtained for these patients. The significance of the difference between class 1 and 2 GEP results was assessed using the Wilcoxon rank-sum test for continuous variables for the primary analysis and the paired *t* test of the mean difference for the secondary analysis. The Fisher exact test was used to test class differences for categorical variables; *P* values less than 0.05 were considered significant.

Results

Baseline Features: Overall Cohort

A total of 376 eyes of 376 patients were identified for entry and 353 eyes of 353 UM patients (94%) met the study inclusion criteria; 23 patients were excluded for inadequate follow-up time or visit dates outside of data windows (18 patients) or for technical failure to obtain GEP results (5 patients). The median age of the overall cohort was 62 years (range, 19−93 years), 51% were men, and the right eye was affected in 176 participants (50%). Baseline median visual acuity was 20/44 Snellen equivalent and intraocular pressure was 14.8 mmHg (Table 1). Median follow-up was 2.1 years (range, 0.5−5.3 years).

The tumors were located predominantly in the mid-equatorial fundus (51%). Most had tumor-associated subretinal fluid (73%), and 28% had an exudative retinal detachment. The tumor was dome shaped in 308 eyes (82%) and collar-stud shaped with breakthrough of Bruch's membrane in 29 eyes (8%). The median tumor height was 3.9 mm, and most had ultrasound tumor dimensions consistent with a Collaborative Ocular Melanoma Study criteria for a medium tumor. Individual tumors were categorized by American Joint Committee on Cancer eighth edition guidelines into stage I (n = 95), stage IIA (n = 130), stage IIB (n = 89), stage IIIA (n = 34), and stage IIIB (n = 1). Tumor location, when noted, was macular in 53 eyes (15%), between macula and equator in 179 eyes (51%), between the equator and ora serrata in 72 eyes (20%), and involving the ciliary body in 58 eyes (16%).