AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Local Recurrence Significantly Increases the Risk of Metastatic Uveal Melanoma

The Ophthalmic Oncology Task Force

Purpose: To assess of the effect of local recurrence of uveal melanoma on metastasis using a multicenter international tumor registry.

Design: Retrospective study using an online tumor registry.

Participants: Patients with uveal melanoma diagnosed between 2001 and 2011.

Methods: A committee was formed to create uveal melanoma patient-specific data fields. Ten subspecialty ophthalmic oncology centers from 4 continents shared data. Patient selection criteria included diagnosis of uveal melanoma and adequate records to allow tumor staging by American Joint Committee on Cancer (AJCC) criteria and follow-up for metastatic melanoma.

Main Outcome Measures: Local tumor recurrence and metastatic uveal melanoma.

Results: Of 3809 total entries, 3217 patients with ciliary body and choroidal (CBC) melanoma and 160 with iris melanoma were evaluated. There was a median follow-up of 3.7 years (95% confidence interval [CI], 3.5−3.8). One hundred fifty-two patients (4.7%) with CBC melanoma experienced local recurrence, with a cumulative incidence of 11%. Kaplan-Meier point estimates for remaining free of local recurrence were 99% (95% CI, 99−99) at 1 year, 93% (95% CI, 92−94) at 5 years, and 89% (95% CI, 86−91) at 10 years. Five- and 10-year metastasis-free Kaplan-Meier estimates for the recurrence-free group were 87% (95% CI, 86−89) and 82% (95% CI, 79−84), and those for the local recurrence group were 71% (95% CI, 62−78) and 62% (95% CI, 49−72). The difference between these 2 groups was statistically significant ($P < 0.001$). Furthermore, local tumor recurrence increased the risk of metastasis by a hazard ratio (HR) of 6.28 (95% CI, 4.4−8.9; $P < 0.001$). Local recurrence was detected up to 9.8 years after treatment. Extrascleral extension also was associated with local recurrence (HR, 3.2; 95% CI, 1.5−6.7; $P = 0.003$), but higher AJCC T-size category was not ($P = 0.63$). Five patients (n = 5/161 [3.1%]) with iris melanoma demonstrated local recurrence and 1 metastasized.

Conclusions: International multicenter data sharing was used to evaluate the effect of local tumor recurrence on metastatic rate. In that local tumor recurrence was associated with a significantly higher risk of systemic metastasis, effective initial treatment and long-term surveillance of treated uveal melanoma patients is necessary. *Ophthalmology 2016;123:86-91 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Local tumor control is a primary goal in the treatment of cancer.[1] In 2002, the Collaborative Ocular Melanoma Study reported that local treatment failure occurred in 10.3% of Collaborative Ocular Melanoma Study patients who underwent iodine 125 plaque brachytherapy.[2] More recent studies, including a literature review of 49 articles, revealed local recurrence rates ranging from 0% to 55.6%.[3] Local orbital recurrence rates after enucleation are poorly documented, but are believed to be less than 1%.[4] These data are important, in that local tumor recurrence is a complication thought to be associated with an increased risk of uveal metastasis and thus decreased survival.[5−8] However, this current assumption that recurrence equals increased risk is supported by a relatively few, small single-center studies and 1 multicenter study; all are limited to 70 or fewer patients with local recurrence.[6−8]

The Ophthalmic Oncology Task Force comprises members of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control and includes eye cancer specialists from around the world.[9] For this study, 10 centers pooled their uveal melanoma patient data in an effort to study this disease.[10] We first used this database successfully to test the seventh edition AJCC uveal melanoma staging system.[11] In this study, we analyzed the data to define the relationships among local recurrence, extrascleral extension (EXE), and AJCC tumor size (T size). However, our primary goal was to investigate the largest collection of uveal melanomas with local recurrence and the impact of local recurrence on metastasis-free survival.

Methods

The Ophthalmic Oncology Task Force collaborated to develop an Internet-based retrospective registry to evaluate uveal melanoma outcomes. The methods of data collection and security have been

http://dx.doi.org/10.1016/j.ophtha.2015.09.014
ISSN 0161-6420/15

described previously.[11] Each participating center obtained local ethics and institutional review board approval for participation and entry of patient data into the online database. This study conforms to the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996.

Patient Eligibility

Patient eligibility criteria included patients with primary melanoma of the iris, ciliary body, and choroid consecutively diagnosed and treated in a 10-year span from April 1, 2001 through April 30, 2011. Primary tumor treatment methods varied by center, with each type chosen at the discretion of the eye cancer specialists at each center. These were reported to include, but were not limited to, brachytherapy, enucleation or local resection (endoresection and lamellar eye wall resection), transpupillary thermotherapy with and without adjuvant radiation therapy, and stereotactic radiotherapy. However, no numerical treatment-related data were required for this database.

Detection of local tumor recurrence was determined by ultrasonography, comparative fundus photography, or inspection and palpation of the anophthalmic orbit (after enucleation). Local recurrence was determined by clinical and imaging studies used at each individual center. There were no exclusions to type of recurrence. Therefore, this study represents site-determined global clinical practice at 10 centers during this decade. Patients were excluded from analysis if they had metastasis (stage 4 disease) at initial staging.

Recorded outcome measures included local recurrence and metastasis. There were no limitations on the methods of screening for metastasis. However, these included abdominal ultrasound imaging, computed tomography, magnetic resonance imaging, or combined whole body positron emission tomography and computed tomography, as was the custom and practice at each center. Based on the current assumption that there is no current curative treatment for almost all patients with metastatic uveal melanoma and the recognized difficulties confirming the actual cause of death, this study defined metastasis to be synonymous with metastatic death.

Statistical Analysis

Categorical variables were described using frequencies and proportions. Time to local recurrence was measured from the date of initial staging. Patients who were alive and free of local recurrence at last follow-up were censored. One hundred thirty patients (4%) died without local recurrence. Because the number of competing risk events (death without local recurrence) was small relative to the size of the data set, these patients were censored at their date of death. Standard methods were used for analysis, rather than implementing competing risks methodology. Kaplan-Meier plots, a standard Cox proportional hazards model, and the log-rank test for trend were implemented to test for a trend relationship between time to local recurrence and T size (based on the AJCC 7th edition criteria).[12] The standard log-rank test was implemented to test for a relationship between time to local recurrence and EXE.

Time to metastasis was measured from the date of staging until the date of metastasis; patients who were alive and free of metastasis at last follow-up were censored. Twenty-five patients died without metastasis. Because the number of patients in this latter category was small relative to the size of the data set, these patients were censored at their date of death rather than treating their death as a competing risk event. A Kaplan-Meier plot and the log-rank test were implemented to test for a relationship between time to metastasis and local recurrence at last follow-up.

The effect of a local recurrence on the risk of metastasis after staging also was investigated using Cox models, with local recurrence treated as a time-varying covariate. In the univariate model, other factors were not taken into account. An unadjusted (univariate) model and a model adjusted for stage, T-size category, and ciliary body involvement or EXE grouping were implemented. Kaplan-Meier plots, a standard Cox proportional hazards model, and the log-rank test were implemented to test for a relationship between time to local recurrence and EXE.

In the analysis of time to metastasis after a local recurrence, only patients who experienced a local recurrence were included. Patients who experienced metastasis before a local recurrence or on the same date as local recurrence were included with their time to metastasis set to 0.00001 years. Those who had no metastasis and no follow-up after their local recurrence were excluded. The related estimates are generalizable to all patients who had a local recurrence. The Kaplan-Meier curves estimate the probability of being free of metastasis after a local recurrence. The 95% confidence limits for this sub-analysis were calculated using the method of Greenwood[13] and the complementary log-log transformation.

The survival package in R software (R Core Team, Vienna, Austria) version 2.15.1 was used to generate Kaplan-Meier plots; SAS TS level 1M1 version 9.3 software (SAS Inc, Cary, NC) was used to perform all other statistical analyses. Statistical significance was set to 0.05.

Table 1. Summary of Studies Focused on Local Treatment Failure Rates of Choroidal Melanoma and Effect on Metastasis or Death

Authors	Treatment Method	Single or Multicenter	Median Follow-up (Range), Years	No. of Patients	No. of Patients with Local Recurrence	Local Failure Incidence (%)	Risk of Metastasis or Death
Jampol et al (COMS)[2]	Iodine 125 plaque	Multicenter	5.6 (0–12.8)	650	57	10.3*	Adjusted risk ratio, 1.5 for LR ($P = 0.08$)
Vrabec et al[8]	Cobalt 60 plaque	Single	4.9 (1.8–10.7; LR group)	445	70	15.7	Estimated 5-yr survival: 87% for LR-free, 58% for LR ($P < 0.0001$)
Cajoulle et al[6]	Proton beam	Single	No LR: 3.93 (0–17.84) LR: 5.11 (0.22–17.86)	1102	61	6.1	Overall survival at 10 years: 83.6% for LR-free, 43.1% for LR
Gragoudas et al[7]	Proton beam	Single	5.2 (n/a)	1922	62	3.2	Relative risk, 4.1 for LR
Present study	**Varied**	**Multicenter**	**3.7 (0.1–12.6)**	**3217**	**152**	**4.7, 11***	**Hazard ratio, 6.3 for LR ($P < 0.001$)**

COMS = Collaborative Ocular Melanoma Study; LR = local recurrence; n/a = not available.
*cumulative estimate.