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Early Treatment in Patients With Small and Medium-Small Class 2 Gene Expression Profiling Uveal Melanoma to Reduce Mortality

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Abstract

Purpose: To evaluate the class 2 gene expression profiling of patients with small and medium-small uveal melanoma, focusing on tumor control, metastases, and mortality. **Methods:** This retrospective case series evaluated patients treated for small or medium-small uveal melanoma by the same surgeon. Patients with small uveal melanoma were treated with microincision vitrectomy surgery or brachytherapy, and patients with medium-small uveal melanoma were treated with brachytherapy. All patients were gene expression profiling class 2. **Results:** Forty-two patients (21 with a diagnosis of small melanoma; 21 with a diagnosis of medium-small melanoma) with a mean age of 58 years and a confirmed diagnosis of class 2 gene expression profiling melanoma were identified. The melanoma-specific mortality at the 5-year follow-up was 4.8% (1/21) for patients with small melanoma and 14.3% (3/21) for patients with medium-small melanoma. The rate of melanoma-specific active metastasis at 5 years was 4.8% (1/21) for patients with small melanoma and 14.3% (3/21) for patients with medium-small melanoma. In both groups, the enucleation rate at 5 years was 0%. **Conclusions:** Small tumor management achieves excellent anatomic and visual outcomes but mandates diagnostic accuracy and defined long-term outcomes as well as follow-up (5-year minimum in this series). Gene expression profiling classification is important in prognostication; however, early treatment of small tumors significantly decreases the predicted mortality and has the greatest potential effect on patient survival, even for class 2 melanomas.

Keywords

GEP class 2 melanoma, small uveal melanoma, medium-small uveal melanoma, brachytherapy, microincision vitrectomy surgery (MIVS)

Introduction

Uveal melanoma is the most common intraocular tumor, with an estimated incidence of 5 to 10 cases per million. These tumors primarily occur in the choroid but may also develop in the ciliary body and iris.[1] The incidence of uveal melanoma most often increases with age, peaking at 70 years and then plateauing.[2] Symptoms vary depending on multiple factors, such as location, and may include metamorphopsia, photopsia, pain, and visual loss. The most important differential diagnosis are benign nevi. Some findings that suggest the malignant potential include subretinal fluid (SRF), orange pigment, hemorrhaging, and growth.[3]

Molecular science has played a pivotal role in the treatment of uveal melanoma over the years. Chromosomal analysis and gene expression profiling have been instrumental for disease management and prognostication.[4,5] Class 1 tumors have a low metastatic risk, while class 2 tumors have a high metastatic risk.[6] In a report by the Collaborative Ocular Melanoma Study, older age and larger tumor diameter were the primary predictors of time to death from all causes and death with melanoma metastasis.[7]

At present, there is no consensus on the standardized care for small choroidal melanoma, and treatment plans are rapidly evolving. The purpose of our study was to evaluate the class 2 gene expression profiling of patients with small and medium-small uveal melanoma, focusing on tumor control, metastases, and mortality in a single-surgeon ocular oncology practice.

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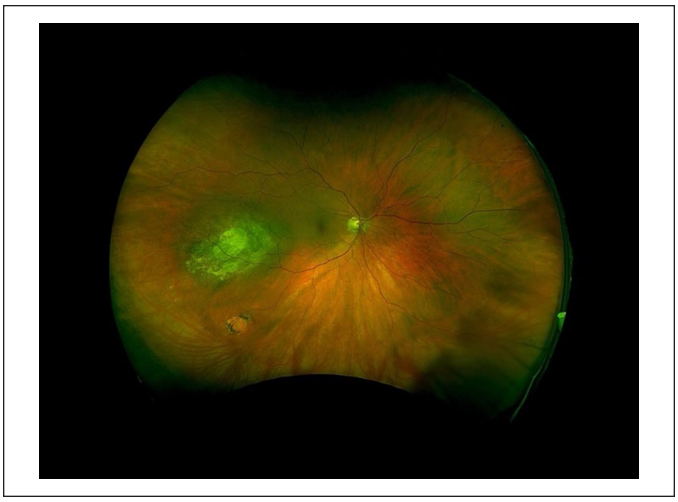

Figure 1. Fundus photograph shows an enlarging pigmented lesion and increasing subretinal fluid in a 72-year-old woman. The visual acuity is 20/25, and the apical height is 2.3 mm.

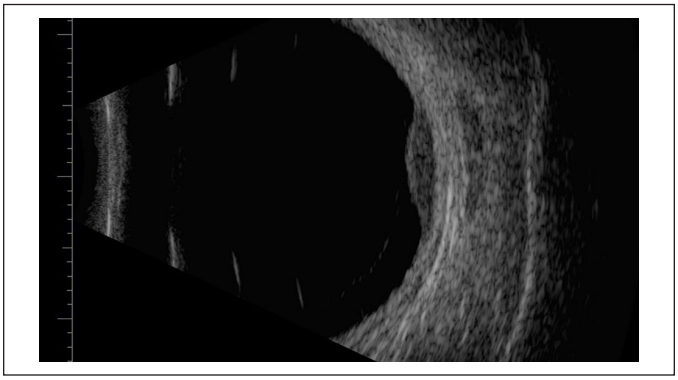

Figure 2. Choroidal melanoma seen on B-scan ultrasonography.

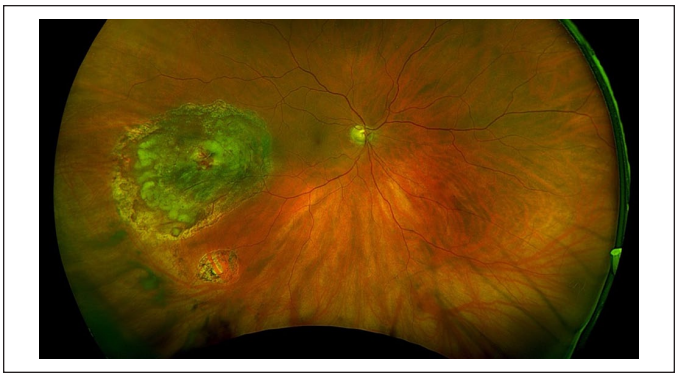

Figure 3. Fundus photograph 1 month after endolaser ablation for choroidal melanoma. The visual acuity is 20/25.

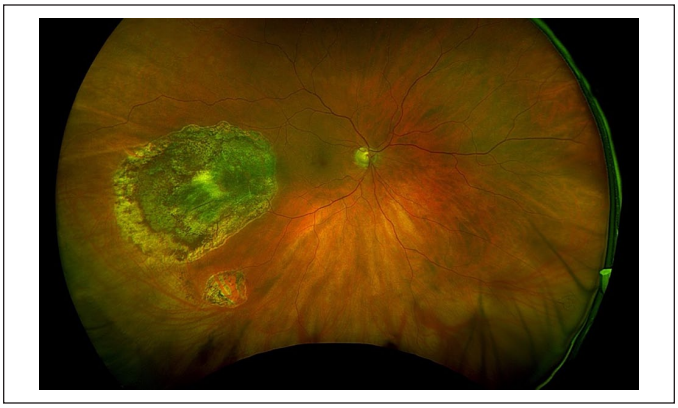

Figure 4. Fundus photograph 63 months after endolaser ablation for choroidal melanoma. The visual acuity is 20/25.

Methods

The institutional review board approved this consecutive retrospective case series of 42 patients who were treated for small or medium-small uveal melanoma. The study conformed to the tenets of the Declaration of Helsinki.

Patients were selected based on tumor apical height and gene expression profiling classification. Follow-up was conducted for a minimum of 5 years to assess tumor control, metastases, and mortality. Patients with small uveal melanoma (apical height < 2.5 mm) were treated with either microincision vitrectomy surgery (MIVS) endolaser tumor ablation or brachytherapy, and patients with medium-small uveal melanoma (apical height 2.5-5.0 mm) were treated with brachytherapy (Figures 1–4).

Inclusion criteria for this study were limited to patients with a tumor apical height less than 5.0 mm and who were classified as gene expression profiling class 2. Tumors with an apical height of 5.0 mm or greater were excluded from the study, as were patients with gene expression profiling class 1 melanoma.

All patients in the study had definitive treatment by the same surgeon (T.G.M.) based on a clinical diagnosis of uveal melanoma. Gene expression profiling, which identified the tumors as type 2, was performed after the clinical treatment decision was made. Thus, treatment was not influenced by gene expression profiling classification, and the type 2 status was determined retrospectively. The tumors were also classified according to American Joint Committee on Cancer staging criteria based on apical height, basal dimension, and ciliary body involvement. No nodal or metastatic involvement were present at the time of diagnosis for all patients (N0, M0).

Results

Forty-two patients with a mean age of 58 years and a confirmed class 2 gene expression profiling uveal melanoma were identified. Twenty-one patients had small uveal melanoma and 21 patients had medium-small uveal melanoma. Among the 21 patients with small tumors, 14 were classified as T1a, 3 as T1b, 1 as T2a, and 3 as T2b. In the 21 patients with medium-small tumors, 2 were classified as T1b, 9 as T2a, and 10 as T2b. The mean

tumor apical height was 1.9 mm (range, 1.0-2.4 mm) in patients with small uveal melanoma and 4.1 mm (range, 2.5-5.0 mm) in patients with medium-small melanoma.

Melanoma-specific mortality at the 5-year follow-up was 4.8% (1/21) for patients with small melanoma and 14.3% (3/21) for patients with medium-small melanoma. In this series, melanoma-specific mortality was a result of metastatic disease. The rate of melanoma-specific active metastasis at 5 years was 4.8% (1/21) for patients with small melanoma (1 deceased) and 14.3% (3/21) for patients with medium-small melanoma (3 deceased). The secondary enucleation rate at 5 years was 0% for patients with a small melanoma as well as those with medium-small melanoma.

Conclusions

At present, there is no consensus on the standardized care for uveal melanoma and treatment plans are rapidly evolving. Current treatment options include radiotherapy, phototherapy, local resection, and enucleation in advanced cases. The choice of treatment depends on various factors, including patient demographics, tumor size, tumor location, and previous therapy.[8] Historically, enucleation was the primary treatment of choice. However, after the Collaborative Ocular Melanoma Study trial, primary treatment shifted to brachytherapy.[7] This pivotal trial demonstrated comparable outcomes regarding tumor control and metastatic risk in patients who underwent primary enucleation and brachytherapy.

Several studies have suggested that increasing age and a larger basal tumor diameter increase the risk of metastasis and death.[7,9] However, treatment of small uveal melanomas is still a topic of controversy, mainly because small uveal melanomas may be difficult to distinguish from atypical benign nevi. Previous studies have shown excellent tumor control rates (98.3%) at the 5-year follow-up when endolaser is applied at the time of gene expression profiling of small uveal melanoma.[5] Previously, these lesions were observed, partly because of the adverse effects associated with brachytherapy, including optic neuropathy, retinal detachment, neovascular glaucoma, and radiation retinopathy.[10–12] Nonetheless, a study by Sobrin et al[11] that examined survival outcomes of patients having plaque radiotherapy of suspected small choroidal melanomas after growth showed that delayed therapy resulted in a melanoma-specific mortality of 3.9%. An increased risk for mortality has also been reported in patients who defer treatment.[13]

The tumor selection process in uveal melanoma is complex and may vary depending on multiple factors, including tumor size, high-risk characteristics (such as SRF and orange pigment), symptoms, and patient expectations. Historically, smaller tumors have been approached more conservatively, often observed for signs of progression before the treatment is initiated. However, even small tumors lacking classic high-risk clinical characteristics may harbor significant metastatic potential and gene expression profiling. Therefore, the diagnosis and management of small subfoveal uveal melanoma is particularly controversial. In light of these considerations, we advocate for a personalized clinical approach to managing small subfoveal tumors.[14]

With advancements in gene expression profiling, small uveal melanomas can be sampled to evaluate genetic alterations and elucidate prognostic information that is more valuable than clinical and pathologic features.[15,16] Tumors can be stratified into the following 3 classes: 1A, 1B, and 2. The Castle Biosciences, Inc. assay reveals varying metastasis rates at 5 years: 2% for class 1A, 11% for class 1B, and 72% for class 2.[5]

The information provided by gene expression profiling has changed the way ocular oncologists evaluate the metastatic risk potential. It has been proposed that molecular tumor profiling with gene expression profiling analysis may be possible, even in cases in which fine-needle aspiration biopsy yields an insufficient sample with minimal cell counts.[17] Gene expression profiling provides invaluable information, helping with risk stratification and management decision-making as well as aiding in guiding personalized surveillance and adjunctive treatment strategies.[5] In the past, there has been hesitation to perform fine-needle aspiration biopsy in these tumors because of the fear of tumor seeding or spread after the procedure. Recent studies have shown that the metastatic risk after biopsy is a rare, but possible, complication.[15,18,19] Treatment at the time of biopsy of small uveal melanoma provides immediate local tumor control and eliminates the need for additional procedures or further delays in therapy.

It is also important to highlight that untreated class 1 tumors may convert to class 2 or metastasize. Therefore, definitive treatment is critical at the time of biopsy. Furthermore, a study by Schefler et al[20] showed that Preferentially Expressed Antigen in Melanoma (PRAME) expression is significantly associated with higher metastatic risk in uveal melanoma, regardless of the gene expression profiling class. Specifically, 28% of class 1A and 29% of class 1B tumors expressed PRAME, while 56% of class 2 tumors were PRAME positive. Overall, PRAME expression status is linked to a worse prognosis, suggesting other tumor factors may also play a role in the development of metastasis.

In our study, patients with class 2 small uveal melanoma were treated with MIVS endolaser tumor ablation or brachytherapy, while patients with medium-small uveal melanoma were treated with brachytherapy. The 5-year follow-up showed lower melanoma-specific mortality in tumors that received earlier treatment despite high-risk molecular features.

Moreover, our study highlights the influence of early treatment on metastatic and mortality rates, underscoring its significance in uveal melanoma management. Our findings demonstrate a disparity in metastatic and mortality outcomes compared with previous studies that report a metastasis incidence of 72% for class 2 tumors at 5 years. One potential limitation of our study is the possibility of lead-time bias, where early detection and treatment might overestimate survival rates without extending overall survival. We attempted to mitigate this by ensuring a minimum follow-up period of 5 years for all patients, thus allowing for a more accurate assessment of long-term outcomes.

Our analysis found a substantial reduction in metastatic rates in our cohort, 28.6% (6/21) for medium-small melanomas and 4.8% (1/21) for small melanomas. This significant difference emphasizes the importance of early intervention strategies in

mitigating metastatic risk, particularly in cases of small uveal melanomas. Despite our small sample, the statistical significance of treatment impact further supports the clinical relevance of our findings. We observed that larger tumors had a higher metastatic risk, similar to findings in previous reports. The most recent study from the Collaborative Ocular Oncology Group Study No. 2, which enrolled 1687 patients with uveal melanoma, showed a 5-year metastasis-free survival of 58.3% for class 2/PRAME negative and 44.8% for class 2/PRAME positive.[14] In our study, metastasis-free survival at 5 years was 95.2% (20/21) for patients with small melanoma and 85.7% (18/21) for patients with medium-small melanoma. This significant discrepancy compared with previous validated studies could be attributed to differences in patient populations, early treatment, or other factors unique to the study cohort.

Limitations of our study include a sole surgeon performing the procedures, a single institution, retrospective analysis, and a small case series. Conversely, potential benefits comprise a unified surgical method, a standardized molecular tumor examination, specified patient inclusion criteria, and extensive long-term monitoring.

Patient-centered management is crucial in cases of small and medium-small uveal melanoma. A thorough discussion of risks and benefits of all treatment options and providing the patient with complete information is necessary to tailor treatment appropriately. Treatment should prioritize preservation of life; however, earlier treatment may also improve morbidity associated with radiation therapy.

Personalized early treatment of uveal melanoma improves patient survival. Small tumor management achieves excellent anatomic and visual outcomes but mandates diagnostic accuracy and well-defined long-term outcomes as well as follow-up (5-year minimum in the current series). Gene expression profiling is important in prognostication; however, early treatment of small tumors significantly decreases the predicted mortality and has the single greatest potential effect on patient survival, even for class 2 melanomas. In cases in which treatment is chosen for small choroidal melanomas, ensuring excellent local tumor control from the start is imperative.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information were performed in a US Health Insurance Portability and Accountability Act–compliant manner.

Statement of Informed Consent

Informed consent, including permission for publication of all photographs and images included herein, was obtained before the procedure was performed.

Declaration of Conflicting Interests

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