# ADVANCED MANAGEMENT OF SMALL UVEAL MELANOMA

Targeted surgical ablation and use of personalized molecular genomics may lead to better outcomes.

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Uveal melanoma continues to represent a therapeutic challenge, despite its being the most common primary intraocular malignant tumor in adults.[1,2] Furthermore, the mechanisms and risk factors leading to primary uveal melanoma remain poorly elucidated.[3,4] The incidence of malignant uveal melanoma has been reported to be as high as one case per 200,000 per year.[2] Although brachytherapy has been widely used to treat medium uveal melanoma over the past 20 years, significant morbidity and mortality are still associated with this disease.[3,5]

Small malignant melanoma (< 2.5 mm in height) is a challenging diagnosis because of its clinical overlap with benign uveal nevi with atypical features. Because radiation retinopathy and radiation optic neuropathy can be seen in virtually all patients with macular and juxtapapillary tumors after brachytherapy, ocular oncologists have historically observed small atypical lesions until clear growth is evident.[6-8]

Molecular tests have been developed to assess prognostic information for these tumors. These tests now include karyotype analysis, comparative genomic hybridization, fluorescence in situ hybridization, multiplex ligation-dependent probe amplification, mutational profiling, and gene expression profiling (GEP), either by incisional biopsy or fine needle aspiration biopsy. Although therapeutic options for metastatic uveal melanoma are limited, molecular classification of uveal melanoma may allow ocular oncologists to develop better management strategies. This article discusses molecular genomics, particularly GEP, and its role in the management of patients with small uveal melanoma.

## THE GEP STORY

GEP is a relatively new technique developed by Harbour et al to detect the up-regulation or down-regulation of particular genes that have been associated with increased metastatic potential.[9] The technique involves the isolation of RNA from a tissue sample, followed by conversion to cDNA, amplification, hybridization, and microarray analysis.[10] The amplification of the cDNA allows the GEP assay to have a high technical success rate with small fine needle aspiration biopsy aspirate. The assay has been validated in a multicenter prospective clinical trial by the Collaborative Ocular Oncology Group, in which it correctly classified tumors in 97.2% of cases.[11]

Castle Biosciences has developed a commercially available assay

## AT A GLANCE

- Despite being the most common primary intraocular malignant tumor in adults, uveal melanoma continues to represent a therapeutic challenge.
- Most ocular oncologists observe small uveal melanoma before deciding on a definitive treatment plan because treatment with brachytherapy carries significant visual morbidity.
- Therapeutic options for metastatic uveal melanoma are limited, but advances in gene expression profiling of uveal melanoma may allow earlier treatment of tumors with less morbid strategies.

(DecisionDx-UM) that allows clinicians to routinely provide prognostic information to their patients with uveal melanoma.[12] The assay stratifies tumors into three classes: 1A, 1B, and 2. Patients with class 1A, 1B, and 2 tumors have a 2%, 11%, and 72% incidence of metastasis at 5 years, respectively.

However, the data from this assay may be limited by tumor genetic heterogeneity. A recent study by Augsburger et al found that in 11% of cases in which two fine needle biopsy aspirates were performed, the two aspirates had discordant GEPs.[13] This difference was accentuated in smaller tumors. Therefore, sampling multiple areas may lessen the probability of underestimating the prognostic risk and may yield higher positive predictive values in patients with class 1 tumors.

GEP has also been analyzed in conjunction with tumor size. In a study that evaluated 299 patients with posterior uveal melanoma with a mean follow-up of 33 months, patients with class 2 tumors and tumor basal diameter of less than 12 mm had a lower risk of metastasis compared with patients with class 2 tumors with larger basal diameters.[14] A similar study performed by Walter et al that included 339 patients (mean follow-up 33 months) also suggested that class 2 tumors with basal diameter of less than 12 mm had a low risk of metastasis.[15] These findings may be explained by lead-time bias, especially because the mean follow-up time in both studies was approximately 30 months. However, these studies suggest that earlier treatment of class 2 tumors may be associated with improved survival.

## PERSONALIZED THERAPY

Historically, patients with suspected uveal malignant melanoma routinely underwent enucleation to eradicate the primary tumor.

**THE FACTS THAT METASTASIS IS LIKELY TO OCCUR EARLY IN THE DISEASE PROCESS OF UVEAL MELANOMA AND THAT CLINICIANS OFTEN DELAY DEFINITIVE TREATMENT ARE KEY TO UNDERSTANDING WHY METASTASIS RATES HAVE NOT CHANGED DURING THE PAST 3 DECADES.**

In 1985, the Collaborative Ocular Melanoma Study (COMS), the largest randomized controlled trial to date addressing uveal melanoma, determined that brachytherapy was as effective as enucleation in the treatment of uveal melanoma. Furthermore, the COMS found that increased basal diameter and increasing age were associated with increased risk of metastasis-associated death.[6,7] It is because of this trend in metastasis-associated death that ocular oncologists in the past 2 decades have gravitated toward treating smaller tumors when high-risk characteristics are present.[16] However, small uveal melanomas are a challenging diagnosis due to their clinical overlap with benign nevi. In addition, treatment with brachytherapy has significant visual morbidity. Therefore, most ocular oncologists, in line with the COMS investigators, observe small lesions before deciding on a definitive treatment plan. Advances in GEP of uveal melanoma may allow us to treat earlier using less morbid therapeutic strategies.

The facts that metastasis is likely to occur early in the disease process of uveal melanoma and that clinicians often delay definitive treatment are key to understanding why metastasis rates have not changed during the past 3 decades. It also highlights the need for the development of individualized risk-dependent treatments that can decrease metastasis rates.

Since the discovery during the COMS that high doses of radiation are adequate treatment for uveal melanoma, investigation of radiation-sparing treatments has been ongoing. A recent study by Mashayekhi et al reported a 10-year recurrence rate as low as 18% in patients with choroidal melanoma who underwent primary transpupillary thermotherapy (TTT) with infrared diode laser.[17] Tumors that regressed to a flat scar were the least likely to recur. A similar study that evaluated 256 patients treated with TTT found tumor control in more than 90% of cases, with 1% tumor-related mortality.[18]

These studies suggest that TTT performed by trained ocular oncologists may lead to reasonable control rates in selected patients.

## EARLY TREATMENT KEY FOR SMALL CHOROIDAL MELANOMA

Treatment of small uveal malignant melanoma (Figure 1) is controversial. GEP allows prognostication for small uveal melanomas with minimal surgical risk (Figures 2 and 3). This technology affords clinicians the opportunity to treat earlier in the disease process, thereby minimizing the

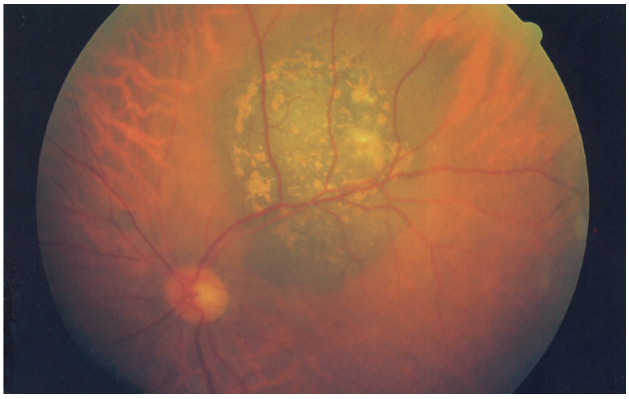

Figure 1. Small malignant melanoma with significant orange pigment and exudative retinal detachment.

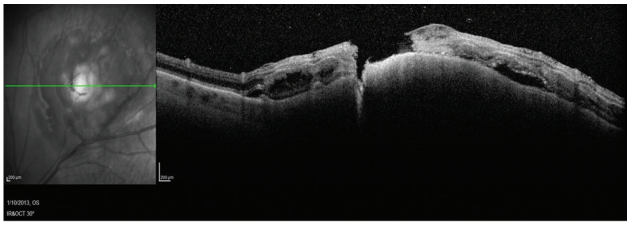

Figure 2. Spectral-domain OCT scan 1 day after transvitreal biopsy.

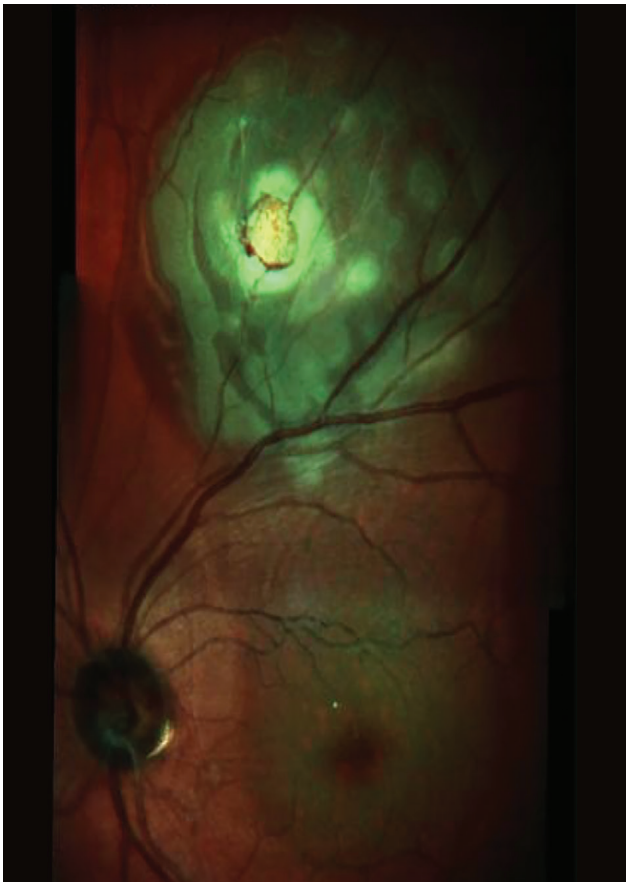

Figure 3. Multicolor montage of fine needle aspiration biopsy site 1 day postoperative.

likelihood of metastatic spread.

At our center, tumors identified by GEP as class 2 tumors subsequently undergo iodine-125 (I-125) brachytherapy with a cumulative dose of 85 Gy to the tumor apex. GEP class 1 tumors do not undergo plaque brachytherapy but are observed closely. We have performed more than 50 treatments using this protocol. Retinal detachment risk is similar to that of eyes after cataract surgery,[19,20] but this may vary significantly depending on surgeon expertise.

GEP evaluation via transvitreal biopsy combined with vitrectomy and laser ablation provides a two-pronged technique, allowing definitive tumor ablation of small lesions while also stratifying risk. This management protocol significantly reduces radiation-associated visual loss secondary to neovascular glaucoma, radiation maculopathy, and radiation optic neuropathy. It also reduces the patient's lifelong need for intravitreal injections with antiangiogenic and corticosteroid agents for the treatment of radiation complications.[21]

A study that compared immediate treatment of medium uveal melanomas against delayed treatment found increased mortality in patients with delayed therapy compared with the findings of the COMS.[22] A previous report found a similar result.[23] Therefore, observation of small uveal melanomas and atypical nevi may be associated with some risk of metastasis. A randomized prospective clinical trial comparing visual and survival outcomes in patients managed by observation versus prompt treatment is needed.

## IT PAYS NOT TO WAIT

At this time, clinical examination cannot reliably predict when a tumor will exhibit micrometastasis with remission. We know from other fields of medicine that patient survival and outcomes are heavily dependent on early identification and treatment of small neoplastic lesions. Larger tumors are more invasive and present a much higher risk of metastasis. Once tumor cells have left the primary focus, prognosis declines significantly. Patients should be aware of the risks associated with observation of small lesions. The morbidity associated with biopsy might be lower than the risk of mortality associated with observation. Further studies will elucidate long-term outcomes. ■

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