Uveal Melanoma: Diagnosis, Prognosis and Current Treatments For Primary and Metastatic Disease

Jasmine H. Francis, MD, FACS*
Alexander N. Shoushtari, MD**
Christopher A. Barker, MD***
David H. Abramson, MD, FACS*
*Ophthalmic Oncology Service
**Melanoma and Immunotherapeutics Service
***Radiation Oncology
Memorial Sloan Kettering Cancer Center
New York, NY

Uveal melanoma, the most common primary intraocular malignancy in adults, represents approximately 5 percent of all melanomas recorded in the United States. The incidence of uveal melanoma has remained relatively constant, between five and six cases per million people in the United States and Europe.\(^1\) These melanomas vary in frequency depending on their location in the uveal tract: Approximately 5 percent occur in the iris, 5 percent in the ciliary body and at least 90 percent in the choroid. Choroidal, also called ciliochoroidal, melanoma, is the predominant form of the disease in the uveal tract, and the themes to be discussed here primarily concern that form of the disease.

Uveal melanoma is most common among middle-aged Caucasians of European descent. Unlike cutaneous melanomas, uveal melanomas have no known association with ultraviolet (UV) light; nor is smoking believed to be a risk factor. However, we do know several obscure and controversial risk factors for the disease, including exposure to welding and use of L-dopa. Furthermore, the literature documents

From the Editors

To date, melanomas of the eye have resisted the revolutionary strides made in treating cutaneous melanomas over the past five years. Although uveal melanoma, the most common primary intraocular malignancy, has many similarities to its cutaneous counterpart, it differs in key ways that present barriers to progress.

First, it can be less conspicuous to detect. While most cutaneous melanomas are readily discovered on the skin surface, only about 5 percent of uveal melanomas arise in the iris, where they can be easily found by routine ophthalmic examination of the outer eye. More than 90 percent arise behind the pupil, where they can only be visualized with special tools. This has especially been a problem for males, who are less likely to go in for routine eye examination; they are typically diagnosed at a later stage, after they come in reporting visual symptoms.

Uveal melanomas also exhibit a higher proclivity than cutaneous melanomas for eventual metastasis. Though over 90 percent of patients have no evidence of metastatic disease when diagnosed, half of all patients ultimately develop metastatic disease. Five-year mortality rates, far greater than for cutaneous

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possible associations with melanosis oculi, neurofibromatosis, dysplastic nevus syndrome, myotonic dystrophy and BRCA-associated protein-1 (BAP-1) hereditary cancer syndrome. Females are typically diagnosed on routine ophthalmic exam, while males commonly present with visual symptoms and are subsequently found to have uveal melanoma. We can diagnose the disease clinically with a high degree of accuracy, so it does not warrant biopsy for diagnosis. Nonetheless, many centers perform biopsies to help determine prognosis based on molecular analysis of the tumor.

Prognosis and Genetics

Although 97 to 98 percent of patients with uveal melanoma have no evidence of metastatic disease at the time of diagnosis, and though the success rate for local treatment surpasses 90 percent, half of all patients ultimately develop metastatic disease. For this reason, there is great interest in narrowing in on prognosis for primary intraocular melanoma in patients with different risk profiles. This can be achieved with a limited degree of certainty. For instance, older and male patients are considered at higher risk for metastases. Uveal melanomas can also be divided by size, e.g., into small, medium and large, as was done by the Collaborative Ocular Melanoma Study; increasing size portends a higher risk for developing metastases. Finally, tumors occurring in the ciliary body or with extraocular extension have a poorer prognosis.

For tumors with adequate specimen (typically those that are enucleated), metastatic risk can be established with histopathological findings. For instance, epithelioid versus spindle cells are considered poorer prognosis. High mitotic index, increased lymphatic invasion and a diffuse infiltrating pattern are also considered higher-risk. Furthermore, microvascular networks or vasculo-genic mimicry patterns have been identified in tumors with higher metastatic potential. Cytogenetics can further refine risk assessment for uveal melanoma. Many chromosomal and copy number alterations have been determined, including those on chromosomes 1, 6 and 8. Perhaps the most profound chromosomal alteration associated with poor prognosis in uveal melanoma is either a partial or complete loss of chromosome 3. This was confirmed with the discovery of somatic BAP1 mutations on the short arm of chromosome 3, which are present in the majority of higher-risk uveal melanomas.

It has been theorized that BAP1 is essential for the preservation of melanocyte identity in uveal melanoma, and that deletion of BAP1 results in uveal melanomas assuming a stem-like cell phenotype. Unlike with cutaneous melanoma, the genetic aberrations in uveal melanoma are comparatively bland. Other mutations besides BAP1 mutations do exist and confer either a neutral or a relatively better prognosis. For instance, guanine nucleotide-binding protein, Q polypeptide (GNAQ) or alpha 11 (GNA11) encodes a G-protein alpha subunit that mediates signals from G-protein-coupled receptors (GPCRs) to the mitogen-activated protein kinase (MAPK) pathway. Somatic mutations, most often mutually exclusive in either codon 183 or 209 of GNAQ or GNA11, have been revealed in a number of melanocytic neoplasms, including over 85 percent of uveal melanomas.

Finally, about 15 percent of uveal melanomas are believed to have somatic mutations in SF3B1 and EIF1AX. An overwhelming majority of these mutations occur in disomy 3 tumors compared to monosomy 3 tumors and with a male patient predominance; these are associated with favorable prognostic features and better diagnosis. At the level of ribonucleic acids, a gene expression profile generated from only a few tumor cells can differentiate uveal melanoma into three classes: class Ia with a low risk of metastasis, class Ib with a risk of late metastasis and class II with a higher risk of metastasis. mRNA expression of
PRAME (preferentially expressed antigen in melanoma) may be a prognostic biomarker for seemingly lower-risk tumors (class 1 or disomy 3).

Regardless of the prognostication method, the dichotomous theory of risk we have outlined here has its limitations and does not fully consider clonal heterogeneity nor clonal evolution of an individual tumor.

Treatment of Primary Uveal Melanoma

The Collaborative Ocular Melanoma Study (COMS) was a multicenter randomized clinical trial with patient accrual spanning over a decade (1987 to 1998), and it has guided our present management of primary uveal melanoma.\textsuperscript{10} It revealed that small melanomas (<2.5/3.0 mm height, <16 mm diameter) had equivalent melanoma-specific mortality if treated with either plaque brachytherapy or enucleation (complete removal of the eye), thus making either treatment option reasonable.\textsuperscript{11} Large melanomas (>10 mm height, >16 mm diameter) had equivalent melanoma-specific mortality if treated with enucleation either with or without preoperative external beam radiation (EBR); thus, preoperative EBR has since fallen out of favor.\textsuperscript{12}

Our group at Memorial Sloan Kettering Cancer Center was the largest center in the COMS, and we led the trial of selumetinib (a targeted oral MEK inhibitor), the first study ever to demonstrate a benefit (in progression-free survival) for the treatment of metastatic uveal melanoma.\textsuperscript{17} Our center and others offer integrated programs utilizing the following treatments:

Radiation Therapy

Radiation therapy (RT) has been used to treat uveal melanoma since 1930.\textsuperscript{13} Today, approximately 75 to 85 percent of uveal melanomas are treated with radiotherapy, primarily in two forms: plaque brachytherapy and proton beam radiotherapy (teletherapy). Brachytherapy is more common, and refers to the application of a radioactive source near the tumor: The advantage is that the radiation is physically brought directly to the melanoma, and does not traverse healthy tissues and organs, thus enabling delivery of high-dose radiation to the tumor while limiting side effects. We attach the radioactive source to a shielding device (“plaque”) and secure it to the sclera during a surgical procedure; this stays in place for several days (3 to 7) while we deliver the desired dose of radiation (70-100 Gy). Teletherapy refers to the projection of radiation through space as a beam. Multiple photon beams produced by a linear accelerator or fixed radioactive sources can be directed to converge at the tumor in a procedure called “stereotactic radiosurgery.” Alternatively, a charged particle beam (particle teletherapy) can be directed at the tumor. The advantage of teletherapy is that tumors of any size or location are accessible. The total dose of radiation delivered during teletherapy may be divided into several “fractions” (usually 4 to 10) to maximize the therapeutic index of treatment.

Several important randomized controlled trials have demonstrated the effect of RT for uveal melanoma. A study of 1,317 patients comparing enucleation of the eye to plaque brachytherapy in patients with medium-sized uveal melanoma found no difference in metastasis-free or overall survival.\textsuperscript{11} Local tumor recurrence occurred in 10 percent of the RT patients. Another study compared particle teletherapy to plaque brachytherapy, and reported higher rates of local control with the former, but found no difference in cause-specific or overall survival.\textsuperscript{14} In another study, based on the hypothesis that surgical manipulation of “large” uveal melanomas at the time of enucleation fostered metastatic spread, researchers undertook a controlled trial of 1,003 patients randomized to either neoadjuvant pre-enucleation teletherapy or no preoperative treatment. This study found no difference in metastasis-free or overall survival in patients receiving RT before surgery.\textsuperscript{12}

In many instances, and using a variety of techniques, RT allows for effective destruction of the primary tumor, while preserving the eye and vision. Nevertheless, eye damage after RT is common, and important efforts are under way or planned to mitigate these effects through technique refinement and biologic modulation. A randomized study of two different radiation doses of teletherapy suggested that lower doses may produce fewer side effects and comparable cancer control rates.\textsuperscript{15} We need similar prospective studies of brachytherapy. As most long-term side effects of radiation are related to vascular and immunologic effects, we need to study the use of agents that modulate these processes. Early and ongoing studies suggest that agents such as bevacizumab and corticosteroids may be beneficial, but further study is necessary.

Enucleation

Enucleation had been the standard of care for uveal melanoma since the latter part of the 19th century. Following the results of COMS, this treatment method is now predominantly performed on large melanomas, while patients with medium
tumors have a choice of two treatments that are identical for patient survival. An enucleation involves removing the globe (or eye) and optic nerve and retaining the surrounding orbital adnexal tissue (extraocular muscles, orbital fat, perios- teum, cranial nerves, etc.). During the surgery, the six extraocular muscles are detached from the globe and the optic nerve is severed near its exit at the optic foramen. Once the eye is removed, a spherical orbital implant replaces it (various materials are available), and the conjunctiva and Tenon’s capsule are closed over this. Based on the surgical technique used, we may attach the extraocular muscles to the implant. A conformer, similar to a thick contact lens, is placed in the intrpalpebral fissure (the space between the eyelids) during the immediate postoperative period. Approximately four weeks after the surgery, we replace the conformer with a custom-made prosthetic, which is designed to cosmetically emulate the fellow normal eye. The prosthetic has optimal cosmesis in primary gaze, but may not move to the same degree as the fellow eye, particularly in extreme gazes.

Other Treatments

Less commonly used treatments for primary intraocular melanoma include local resection of the tumor, often combined with neoadjuvant or adjuvant radiation therapy. Lasers can also be used, possibly with dye or agent-enhancement, but this treatment is restricted by tumor size and location.

Current Treatment of Metastatic Uveal Melanoma

Historically, median overall survival (OS) for metastatic uveal melanoma has been estimated to be 6 to 12 months. More recent analyses have reported longer median OS of 17 to 20 months. In contrast to the recent OS benefits achieved with therapies for metastatic cutaneous melanoma, no prospective randomized trial of therapy for metastatic uveal melanoma has ever demonstrated an improvement in OS. The increases in reported median OS may be due to lead-time bias from active surveillance programs utilizing modern radiographic techniques.

The recommended frontline approach for treatment of metastatic uveal melanoma remains clinical trial participation. The only systemic therapy to date that has shown efficacy in a randomized trial was the MEK inhibitor selumetinib, which improved PFS compared to investigator’s choice chemotherapy (HR: 0.46; 95% CI, 0.30–0.71; p < .001). The phase 3 registration trial randomized patients to dacarbazine with or without selumetinib. Unfortunately, the trial failed to meet its primary endpoint of improved PFS by blinded central radiology review. Given that there was no pure selumetinib arm, this trial could not confirm that MEK inhibition alone improves outcomes in metastatic UM, and it did not appear to improve PFS in conjunction with chemotherapy. Nonetheless, the trial serves as a model for future collaboration and proves that the timely completion of randomized, multinational trials is possible with this rare disease.

References


Solving the Riddle of Advanced Uveal Melanoma

Bercin Tarlan, MD
Matthew G. Field, MS
J. William Harbour, MD
Bascom Palmer Eye Institute
Sylvester Comprehensive Cancer Center
and Interdisciplinary Stem Cell Institute
University of Miami Miller School of Medicine

Conflict of Interest: Dr. Harbour is the inventor of intellectual property related to subjects mentioned in this article. He is a paid consultant for Castle Biosciences, which licensed this intellectual property, and he receives royalties from its commercialization.

Uveal melanoma is the most common primary intraocular malignancy and the second most common form of melanoma. It has many similarities to cutaneous melanoma, such as their common ancestry from neural-crest-derived melanocytes and their strong tendency for metastasis. There are also striking differences. Whereas cutaneous melanoma demonstrates regional lymphatic dissemination as well as distant metastasis to the liver, lungs, bone, brain and other sites, uveal melanoma exhibits a strong proclivity for hematogenous metastasis to the liver.

The mutation landscape of cutaneous melanoma is also extraordinarily different than that of uveal melanoma. And whereas metastatic cutaneous melanoma frequently responds to immune checkpoint inhibitors, metastatic uveal melanoma rarely does.

However, recent advances in understanding the molecular pathogenesis of uveal melanoma are beginning to impact on management of advanced disease.

Difficulties in Detection

Uveal melanoma can arise in the iris, where it is readily discovered by inspection of the external eye (Figure 1A). However, about 95 percent of these lesions arise posterior to the pupil, in the ciliary body and/or choroid, where they cannot be visualized without special equipment such as slit lamp biomicroscopy and indirect ophthalmoscopy (Figure 1B). Only about half of uveal melanomas are discovered during a routine eye exam, when they are still asymptomatic. The other half present with symptoms such as light flashes, floaters, blind spots and blurriness, none of which are specific to uveal melanoma.

For borderline or indeterminate lesions that overlap in size between small uveal melanomas and large uveal nevi, certain clinical features, such as subretinal fluid, orange autofluorescent lipofuscin pigment deposition and tumor thickness greater than 2 mm are used to help estimate malignant potential. However, these features are far from perfect predictors, and more accurate biomarkers are needed.

The Need for Enhanced Prognosis

The 5-year mortality rates for patients with uveal melanoma are about 15 percent for small tumors, 30 percent for medium tumors and 50 percent for large tumors. Remarkably, there has...
been no demonstrable improvement in survival since the 1970s, despite substantial progress in diagnosis and treatment of the primary tumor. Scientists now attribute this to a propensity for early micrometastasis prior to treatment. As such, most specialists have adopted a systemic approach to management that involves some form of prognostic testing. Certain clinical and pathologic factors, such as tumor diameter, thickness and ciliary body involvement are associated with increased metastatic risk. However, these variables are susceptible to inter- and intra-observer variability and exhibit poor positive and negative predictive value for individual patients. For example, the AJCC TNM staging system, which is valuable for comparing cohorts of patients between different centers, is ill-suited for routine clinical prognostic testing. Alternatively, most leading centers now use molecular biomarkers for prognostic testing. The earliest molecular biomarkers to be used were chromosomal gains and losses, with monosomy 3 being strongly associated with metastasis. However, the frequent intratumoral heterogeneity and potential for sampling error for monosomy 3, along with the need for large biopsy samples to perform chromosomal analysis, led to exploration of other molecular biomarkers.

Gene expression profiling (GEP) revealed two basic molecular subtypes of uveal melanoma that correspond to their metastatic risk. About two-thirds of tumors have a class 1 profile (low metastatic risk), and about one-third have the class 2 profile (high metastatic risk). Several groups have shown that GEP is a more accurate predictor of metastasis than chromosomal gains and losses. As a result, our group developed a clinical-grade test for routine clinical use, utilizing a 12-gene expression signature performed using real-time PCR on a microfluidics platform. This GEP prognostic assay requires much smaller biopsy samples and is less prone to sampling error than chromosomal testing. Validated in a prospective multicenter study, the GEP assay is now commercially available under the trade name DecisionDx-UM, and most ocular oncology centers in North America have used it. Recently, we discovered a new biomarker that enhances the prognostic accuracy of the GEP assay. A small percentage of tumors with the low-risk class 1 profile give rise to metastasis, and we recently showed that mRNA expression of the cancer-testis antigen PRAME identifies this subset of class 1 tumors. PRAME is now being added to the DecisionDx-UM test and allows class 1 patients to be divided into those with minimal versus intermediate metastatic risk (Table 1).

### Therapeutic Challenges for Advanced Disease

The lack of broadly effective treatments for metastatic uveal melanoma has been a major barrier to progress. Unlike cutaneous melanoma, where immune checkpoint inhibitors and targeted molecular therapies have ushered in a new era of improved treatments, no comparable breakthroughs have occurred for uveal melanoma.

### Immunotherapy

To date, immune-based therapy with single agent checkpoint inhibitors has had disappointing efficacy in uveal melanoma. Response rates to ipilimumab (Yervoy®) and PD-1 blockades have been estimated in the single digits. This may be due to the lower mutational burden of uveal melanoma, which could reasonably be inferred to correlate with lower rates at baseline of CD8+ T cell infiltration, which in cutaneous melanoma has been associated with responses to PD-1 blockade monotherapy. A role remains for immune-based therapy in uveal melanoma, but future efforts should focus on improving immune infiltration and modulating the microenvironment. One reasonable approach may be combining ipilimumab with nivolumab (a successful FDA-approved combination for metastatic cutaneous melanoma). Another approach is a CD3 antibody fused to an engineered MHC Class 1 molecule that recognizes the surface protein gp100 (IMCgp100). The ongoing phase 1 trial of this agent reported that two of five patients with metastatic uveal melanoma achieved objective responses.

Another possible experimental approach to treatment is utilizing regional hepatic-directed therapy. Hepatic artery embolization could be investigated as an adjunct to other immune-based or targeted therapies. Hepatic artery embolization with granulocyte-macrophage colony stimulating factor led to objective responses in 10 of 31 patients in a phase 1 trial. Another approach is hepatic perfusion, where the portal venous system is

<table>
<thead>
<tr>
<th>Gene Expression Profile-Based Prognostic Classification</th>
<th>Approximate Percentage of Patients</th>
<th>Associated Mutations</th>
<th>Estimated 5-Year Metastatic Risk</th>
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</thead>
<tbody>
<tr>
<td>Class 1/PRAME-negative</td>
<td>53 percent</td>
<td>EIF1AX</td>
<td>0-5 percent</td>
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<tr>
<td>Class 1/PRAME-positive</td>
<td>14 percent</td>
<td>SF3B1</td>
<td>30-35 percent</td>
</tr>
<tr>
<td>Class 2</td>
<td>33 percent</td>
<td>BAP1</td>
<td>70-75 percent</td>
</tr>
</tbody>
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Table 1.
isolated to perfuse the liver with higher doses of cytotoxic agents than would be possible systemically.

**Molecular Pathogenesis and Targeted Therapy**

Targeted molecular therapies have similarly fallen short. We most likely will need a better understanding of the mutational landscape of uveal melanoma to develop more effective targeted therapies. Uveal melanomas rarely harbor mutations in BRAF, KIT, NRAS and other genes that are commonly mutated in cutaneous melanoma. Rather, they demonstrate a distinctive set of driver mutations. The vast majority of uveal melanomas contain single nucleotide mutations in GNAQ or GNA11, which are thought to represent early or initiating events in tumorigenesis. Mutations in BAP1, SF3B1 and EIF1AX, almost mutually exclusive, are thought to occur later in tumor progression and to be associated with high, intermediate and low metastatic risk, respectively. BAP1 mutations are strongly associated with class 1/PRAME- tumors. Mutations in GNAQ or GNA11, which are thought to represent early or initiating events in tumorigenesis. Mutations in BAP1, SF3B1 and EIF1AX, almost mutually exclusive, are thought to occur later in tumor progression and to be associated with high, intermediate and low metastatic risk, respectively.

GNAQ/11 mutations activate the MEK, PI3-kinase/AKT, Hippo-YAP and other pathways that are amenable to pharmacologic modulation. BAP1 mutations may render tumor cells susceptible to inhibitors of epigenetic regulators such as HDAC and EZH2. Also, since PRAME encodes an immunogenic protein that has been successfully targeted for immunotherapy in other cancers, PRAME expression in uveal melanoma may serve as a "companion prognostic" test that identifies patients with increased metastatic risk who may respond to immunotherapy. Currently a phase 1b trial is open to accrual utilizing the protein kinase C inhibitor AEB071 (which in phase 1 trials led to a median PFS of 16 weeks) in combination with the Phosphoinositol-3-Kinase alpha inhibitor BYL710 (NCT02273219). In addition, an ongoing randomized trial of the MEK inhibitor trametinib with or without the Akt inhibitor GSK2141795 (NCT01979523) has matched baseline and in-treatment biopsies that should provide additional pharmacodynamic and epigenetic analyses to fuel further trials. Ongoing preclinical work has identified novel targets, such as YAP/Hippo signaling, EZH2 and BRD4, which should lead to new clinical trials.

Moving forward, these novel treatment targets and an increasing understanding of the role of immune surveillance in this disease offer patients with advanced disease hope for improved therapeutic options.

**Key Considerations**

Uveal melanoma differs in important ways from cutaneous melanoma in its metastatic pattern, prognostication, mutation landscape and responsiveness to targeted molecular therapy and immunotherapy. Recent discoveries in the molecular pathogenesis of uveal melanoma may pave the way to more effective therapies and more personalized management of high-risk patients.

**References**

melanomas, are about 15 percent for small tumors, 30 percent for medium tumors and 50 percent for large tumors. Finally, no effective therapy has yet been found for metastatic disease; the great successes achieved in cutaneous melanoma with checkpoint blockade and targeted therapies have not translated well to uveal melanoma.

The situation could improve in the near future. Recent advances in our understanding of the biology and molecular pathogenesis of uveal melanoma have begun to yield important insights that could improve prognostic accuracy and are laying the groundwork for exciting new therapy approaches for advanced disease.

In this issue of The Melanoma Letter, Drs. Francis, Shoushtari, Barker and Abramson present a wonderful review of our current knowledge of uveal melanoma, from the etiological and genetic underpinnings of the disease to the important refinements being made in metastatic risk assessment and management. They report on the state-of-the-art, eye-saving advances made in treating primary disease and both the existing limitations and rising potential for treating advanced disease.

In our second story, Matthew Field and Drs. Tarlan and Harbour report on the most promising directions in research for diagnosis, prognosis and management of high-risk and advanced metastatic uveal melanoma, exploring recent discoveries in the molecular pathogenesis of the disease that are beginning to impact on treatment. They discuss the use of molecular biomarkers and gene expression profiling to enhance prognostication, the advent of hepatic artery embolization and combination drugs to enhance immunotherapy and the discovery of specific mutations that provide a framework for targeted molecular therapy.

With the increasingly precise methods for narrowing in on prognosis and a burgeoning understanding of the role of driver mutations and immune surveillance, uveal melanoma patients with advanced disease have their first real hope for improved therapeutic options.

Allan C. Halpern, MD • Editor-in-Chief
Ashfaq A. Marghoob, MD • Associate Editor