Published in final edited form as:

Semin Ophthalmol. 2016 ; 31(4): 304–309. doi:10.3109/08820538.2016.1154175.

Tumor Characteristics, Genetics, Management, and the Risk of Metastasis in Uveal Melanoma

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Abstract

Uveal melanoma is the most common intraocular malignancy in adults. Although rates of local control for uveal melanoma exceed 95% with radiotherapy or enucleation, as many as 50% of patients develop hematogenous metastases, which manifest in the decades following initial diagnosis and are uniformly and rapidly fatal. Recent compelling evidence suggests that not all uveal melanomas are themselves equivalent with respect to metastatic potential and patient survival. This review focuses on the mounting evidence of survival disparities based on intrinsic tumor clinical and histopathologic characteristics and based on tumor genetics and gene expression profiles.

Keywords

Disparities; epidemiology; genetics; metastasis; ocular tumors; ophthalmology; prognosis; risk factors; survival; uveal melanoma

INTRODUCTION

Uveal melanoma, the most common intraocular tumor, refers to intraocular melanomas arising from melanocytes of the uveal tract, which is comprised of the choroid, ciliary body, and iris.^{1–3} The annual incidence of uveal melanoma has remained stably estimated at 6–7 cases per million in recent decades.^{1–3} Despite significant strides in eye-preserving treatments for primary uveal melanomas, the five-year survival rate remains 72–84%.^{4–7}

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Though rates of uveal melanoma local control exceed 90% with radiotherapy, as many as 50% of patients develop hematogenous metastases in the decades following initial diagnosis.^{3,8,9} In over 90% of patients, these metastases involve the liver.¹⁰ Despite limited capacity for detection of occult metastasis during this interim period, there is evidence based on mathematical modeling of cell doubling times that such uveal melanoma hepatic micrometastasis are present at the time of initial diagnosis.¹¹ Approximately 50% of uveal melanoma patients develop clinically apparent metastases, which are uniformly fatal, with average survival less than six months.^{3,5,6,9}

This review focuses on the mounting evidence of disparities in tumor characteristics, genetics, and management as these features relate to the risk of fatal uveal melanoma metastatic progression.

DIAGNOSIS AND MANAGEMENT

Though early treatment has not been conclusively shown to positively impact patient survival in uveal melanoma, several studies have shown that diagnostic delays impact disease-related morbidity. Fat et al. evaluated the management of 50 consecutive uveal melanoma patients treated at a single referral center in the United Kingdom. They found that 72% of patients presented symptomatically, most commonly experiencing blurred vision. As many as 42% of patients experienced diagnostic delays secondary to initial misdiagnosis. Such diagnostic delays resulted in significant treatment delays, with an average time between initial presentation and initiation of treatment of 6.6 months (for those who had a delay in diagnosis) vs. 4.2 weeks (for those without a delay in diagnosis). Such delays further corresponded to increased morbidity with a higher likelihood of treatment by enucleation rather than eye-sparing treatment, with a 52% enucleation rate in those with delayed diagnosis vs. 17% in those without diagnostic delays.¹²

Damato et al. conducted a prospective cohort study of 2,384 patients diagnosed with uveal melanoma in the United Kingdom. Similar to Ah Fat, they found that 69.8% of uveal melanoma patients presented symptomatically. A total of 23% of surveyed patients reported initial misdiagnosis, and in 19.8% of patients the time to treatment was greater than six months, compared to a median time to treatment of 49 days in those patients who did not experience delays. As with Ah Fat's study, such delays were associated with a significant increase in the rate of enucleation (44.8% vs. 29.8%). Damato et al. found that failure to detect tumors during examination was related to tumor location, such as ciliary body and anterior choroid, due to both technical difficulty of examination as well as the tendency for tumors in these locations to remain asymptomatic until they have grown relatively large. They further hypothesize that tumors missed by ophthalmologists could be the result either of examination without dilation or without careful examination of the peripheral fundus. Alternatively, this may be due to the co-existence of other ocular pathology that could itself explain the patient's symptoms (e.g., posterior vitreous detachment explaining photopsias) or impede thorough examination (e.g., cataract).¹³

Bove and colleagues conducted a retrospective cohort study of 433 uveal melanoma patients at a single US referral center. According to the results of questionnaires completed by

surviving patients, as many as 37% of surveyed patients had been examined by an ophthalmologist or optometrist within one year of diagnosis. Of those whose records were available, 71% of patients who had had an eye examination in the preceding year had undergone a dilated funduscopy exam. Given the slow rate of uveal melanoma growth, the authors suggested that there is a high likelihood that tumors diagnosed within a year of funduscopy examination were, in fact, present at the time of initial evaluation, but were either not detected or misdiagnosed. They suggest that the rarity of this disease is such that a general ophthalmologist practicing in the US may expect to see as few as one new case of uveal melanoma for each decade of practice. They hypothesize that the rarity of this disease contributes to uveal melanoma's misdiagnosis, even when a dilated funduscopy examination is performed. They further extrapolate that eye care professionals' limited exposure to the disease reduces the hypothetical utility of routine uveal melanoma screening.¹⁴

Important advances have been made in the approach to local control of primary intraocular uveal melanoma. The Collaborative Ocular Melanoma Study (COMS) Group conducted a multi-center randomized controlled trial of enucleation versus iodine-125 plaque brachytherapy for medium-sized (2.5–10 mm apical height, maximum basal diameter of 16 mm or less) choroidal melanomas. The group demonstrated that all-cause patient mortality at the 5-, 10-, and 12-year time points was equivalent between the two treatment groups.¹⁵ Additionally, this randomized control trial evaluated the impact of pre-enucleation radiotherapy on the survival of patients with large choroidal melanomas (apical height >10 mm or maximum basal diameter > 16 mm). Investigators found no difference in survival between the two treatment arms.¹⁶

Despite >90% primary tumor control with enucleation or eye-conserving brachytherapy, approximately 50% of patients develop metastases, usually involving the liver, often developing many years later.^{17,18} Uveal melanoma metastases spread hematogenously, unlike cutaneous melanomas, and 90% of all uveal melanoma metastases involve the liver.¹⁷ Though most metastases develop within five years, metastatic disease remains the most common cause of death in patients with uveal melanoma, even 20 years after the initial diagnosis, despite the advanced age of most patients with this disease.¹⁹ Once metastases develop, progression is rapid, despite the fact that no evidence of metastatic disease could be detected using current imaging technologies in the many years between initial diagnosis of the primary tumor and the subsequent development of overt metastases.¹⁰ Despite limited capacity for metastasis detection during this interim period, there is evidence based on mathematical modeling of cell doubling times that such UM hepatic micrometastases must have been present at the time of initial diagnosis.¹¹ In addition, the presence of these hepatic micrometastases has been directly visualized histopathologically.¹⁷

CLINICAL AND HISTOPATHOLOGIC TUMOR CHARACTERISTICS

Just as with patients, it is widely understood that not all uveal melanomas themselves are created equal with respect to behavior, and characteristics of the primary tumor itself have a clear bearing on prognosis. More specifically, tumor location, size, histology, and tumor genetics have been clearly demonstrated to impact metastasis and patient survival.

With respect to tumor location, ciliary body involvement is associated with a worse prognosis and more specifically with accelerated progression and increased risk of metastasis.^{20,21} Schmittel and colleagues retrospectively reviewed a patient cohort of 271 patients at a single center and determined that ciliary body involvement alone significantly increased the risk of metastasis within the first three years following diagnosis (hazard ratio = 6.9; $p < 0.001$). Notably, ciliary body involvement was not found to significantly impact the risk of metastasis *after* three years.²⁰ Similarly, Seddon and colleagues conducted a retrospective analysis of 267 patients, but unlike Schmittel focused on patients treated with enucleation. They found that, independent of tumor size, tumors anterior to the equator, often involving the ciliary body, had a worse prognosis. They suggest metastatic progression of uveal melanomas involving the ciliary body may be aided by contractions of the ciliary body and proximity of the ciliary vessels.²² It should be noted, however, that anterior tumors or tumors involving the ciliary body are often incidentally discovered on exam, or do not present until they have grown large and finally become symptomatic. Thus, anterior location may be a surrogate for late presentation, and therefore may be a confounding variable. However, since Seddon et al. limited their study to eyes treated with enucleation, all tumors were already large enough that radiotherapy was not the primary treatment option, and therefore all tumors presumably were large, including those that were located posteriorly. In contrast, iris melanomas have a much lower rate of metastasis compared to uveal melanomas that arise in the choroid or ciliary body.²¹ The authors suggest that the better prognosis of iris melanomas may reflect the early detection of iris melanomas due to their visible location, and the better prognosis may, therefore, be in part due to treatment at a relatively early stage in the natural history of the tumor.²¹

Larger tumor size, and more specifically tumor thickness and largest basal diameter, is associated with increased likelihood of metastasis and reduced survival.^{16,23} Diener-West et al. conducted a meta-analysis in which they grouped uveal melanomas according to size into three categories based on tumor height and diameter: small (height < 3 mm and diameter < 10 mm), medium (height 3–8 mm and diameter < 15 mm) and large (height > 8 mm and diameter > 15 mm). They found that small, medium, and large uveal melanomas had mortality rates after enucleation of 16%, 32%, and 53%, respectively.²⁴ Similarly, Shields et al. focused solely on uveal melanoma thickness, grouping tumors into categories of small, medium, and large, utilizing the same thickness parameters as Diener-West et al. They found that, as tumor thickness increased, so too did the 3-, 5-, and 10-year mortality rates. Additionally, they were able to calculate a 10-year metastasis-per-millimeter increment, which demonstrates the increasing impact on mortality of increasing tumor thickness.²⁵ Size-related prognostic criteria are encompassed in the American Joint Committee on Cancer (AJCC) classification. This system, based on clinical data only, utilizes measurements of tumor basal diameter, thickness, involvement of the ciliary body, and degree of extraocular tumor extension to classify uveal melanomas as T1–T4.^{23,26} Shields et al. conducted a retrospective analysis of 7,731 patients with posterior uveal melanoma, which revealed a two-fold increase in risk of both metastasis and death for each increase in AJCC category (e.g., T1, T2, T3, T4).²⁶

Uveal melanoma cell type was acknowledged as prognostically relevant as early as 1931 when Callendar put forth his classification system based on cell type. Cell type ranges from

spindle cell to mixed spindle and epithelioid to epithelioid. An increasing proportion of epithelioid cells corresponds with a progressively worse prognosis.²¹ Histopathologic cell type is often measured using the number of epithelioid cells per high-powered field. Seddon and colleagues found that amongst the 267 patients studied, the 10-year mortality was five-times higher in patients with >0.5 epithelioid cells per high-powered field.²² Additionally, mitotic activity, measured as the number of mitoses per high-powered field, has been shown to relate to uveal melanoma prognosis. McLean et al. showed that, in a study of 217 patients, increased mitotic activity was a significant prognostic factor, independent of tumor size, with a 3.6-fold higher six-year mortality rate in patients with high mitotic activity (9–48 mitotic events per high-powered field) vs. low mitotic activity (0 mitotic events per high-powered field).²⁷ Additionally, nine distinct microvascular patterns readily identified in uveal melanoma specimens further aid in histopathologic prognostication. One such pattern, known as a vascular network, has been demonstrated to reduce the survival rate from 90% to 50% in a study of 234 uveal melanoma patients.²⁸

TUMOR GENETICS

It has long been appreciated that uveal melanoma chromosomal abnormalities contribute prognostically significant information. Monosomy 3 is widely accepted as the most significant chromosomal abnormality with respect to patient prognosis. This abnormality, present in approximately half of all uveal melanomas, is strongly associated with metastatic progression and death.²⁹ This observation led to the suspicion, and later the discovery, of a tumor suppressor gene on chromosome 3 associated with metastatic risk in uveal melanoma, namely *BAP1*.³⁰

BAP1 (*BRCA1*-associated protein 1) encodes a nuclear deubiquitinase whose roles in cellular processes are numerous, ranging from cell differentiation to DNA repair, but whose exact role in carcinogenesis remains unclear.³¹ Though most cases of uveal melanomas are sporadic, there is evidence of familial susceptibility to uveal melanoma, which likely reflects the *BAP1* hereditary cancer predisposition syndrome. This syndrome is the result of germline mutations in the *BAP1* gene. This syndrome has not only been linked to a predisposition to uveal melanoma, but also to the development of cutaneous melanoma, malignant mesothelioma, renal cell carcinoma, and other malignancies.³¹ *BAP1* mutations can be either germline mutations, resulting in the familial cancer predisposition syndrome, or sporadic in the uveal melanoma tumor cells. Either type of recessive *BAP1* mutation is unmasked by a loss of chromosome 3. *BAP1* mutations have been shown to relate to uveal melanoma metastatic potential and the classification of tumors as higher-risk, class 2 tumors (see section on gene expression profile that follows).³² Importantly, advanced techniques, such as use of single nucleotide polymorphisms, have enabled detection of loss of heterozygosity rather than simply alterations in chromosome 3 copy number. Such advances highlight the impact of isodisomy 3, which is associated with higher-risk, class 2 tumors and metastatic progression, and extend the story of alterations in chromosome 3 beyond simple haploinsufficiency.³³

In addition to monosomy 3, alterations in chromosomes 6 and 8 influence uveal melanoma prognosis. Chromosome 6 aberrations can have both positive and negative prognostic

impacts, depending on which arm of the chromosome is involved.^{29,30} Gain of chromosome 6p is present in ~25% of uveal melanomas and is associated with improved prognosis. It is unclear whether 6p gain is truly protective or just more commonly present in the absence of monosomy, which itself would negatively impact prognosis.^{29,30} Alternatively, chromosome 6q loss (also present in ~25% of uveal melanomas) is associated with increased risk of metastasis.^{29,34} Gain of chromosome 8q, present in approximately 40% of uveal melanomas, is associated with metastasis and has been shown to have a dose-dependent negative impact on survival.^{30,35} Notably, chromosome 8q boasts several potential oncogenes including MYC, DDEF1/ASAP1, and NSB1/NBN.³⁰ Just as alterations of 8q affect prognosis, loss of the short p-arm of chromosome 8 also impacts prognosis. This cytogenetic alteration is present in approximately 25% of uveal melanomas and has been shown to be associated with more rapid metastasis. Onken and colleagues identified LZT1 as a likely 8q “metastasis suppressor” and demonstrated that modulation of LZT1 mRNA expression in metastatic uveal melanoma cell lines effectively impacted *in vitro* measures of tumor cell motility and invasion.³⁶

Recently, *GNAQ* or *GNA11* mutations have been identified in over 80–90% of uveal melanomas in a mutually exclusive fashion.^{37,38} Both genes encode q-class G-protein alpha subunits. Activating mutations in either *GNAQ* or *GNA11* interfere with the G-protein subunit’s intrinsic GTPase activity, leading to activation of the MAPK/MEK/ERK pathway.³⁰ These mutations are found in both malignant and benign melanocytic lesions, suggesting a role in early mutational events leading to nevogenesis.^{30,38,39} The most common mutation in both *GNAQ* and *GNA11* is at the Q209 residue.³⁸ Mutations in *GNAQ* and *GNA11* are independent of prognostically relevant cytogenetic alterations or tumor gene expression profile (GEP) class.³⁰

GEP is now used clinically to distinguish between two prognostic tumor classes: lower-risk, class 1 tumors and higher-risk, class 2 tumors.⁴⁰ Class 2 tumors have a higher risk of metastasis (five-year risk of metastasis is 72%) and death and are associated with *BAP1* mutations. Alternatively, class 1 tumors are associated with *SF3B1* and *EIF1AX* mutations and are sub-divided into class 1A and class 1B, which have a five-year risk of metastasis of 2% and 21%, respectively.⁴⁰ GEP has been recently incorporated into a 15-gene prognostic assay, which utilizes PCR to quantify mRNA of key genes from samples obtained from fine-needle aspiration (FNA) biopsies or uveal melanoma tumor tissue sections.⁴⁰ In 2012, a prospective, multicenter study compared GEP classification to chromosome 3 status and TNM classification and showed GEP to be a more accurate determinant of prognosis. Recent evidence suggests that tumor basal diameter also plays a role in interpreting GEP. Patients with small tumors with class 2 profiles have a better prognosis than do patients with large class 2 tumors. In addition to advancing prognostication and patient care, GEP has enabled advances in understanding uveal melanoma pathobiology. For instance, it has been shown that class 2 profile relates to an overall de-differentiation of uveal melanoma cells, such that the tumor cells begin to more closely resemble stem cells and epithelial cells.^{41,42} Continued identification of specific pathway alterations in more aggressive class 2 tumors may lead to targeted therapies with the potential to reduce metastatic progression.⁴²

Multiplex ligation-dependent probe amplification (MLPA) offers an alternative modality for predicting uveal melanoma prognosis based on genetic features. This technique utilizes a set of probes, which hybridize to specific genomic sequences, enabling interrogation of DNA isolated from uveal melanomas, followed by PCR and gel electrophoresis. Damato and colleagues utilized 73 patient specimens to assess the ability of MLPA to predict death from uveal melanoma metastasis. They concluded that MLPA in conjunction with analysis of chromosomes 3 and 8, clinical staging, and histologic tumor grade are, in fact, able to estimate risk of death from metastasis.⁴³ Both Damato et al. and Vaarwater et al. have investigated the use of MLPA in the detection of prognostically relevant chromosomal abnormalities, ultimately supporting the use of MLPA in the assessment of risk of metastatic death.^{44,45}

IMPLICATIONS FOR PATIENT MANAGEMENT

In our practice at the Vanderbilt Eye Institute and Vanderbilt-Ingram Cancer Center, patients with class 1B or class 2 tumors are monitored with imaging of the liver every six months. This practice usually involves a multiphasic contrasted CT scan of the abdomen. Also, these patients are referred to one of the medical oncologists at the Vanderbilt-Ingram Cancer Center, who specialize in metastatic melanoma specifically. Patients with class 1A tumors are either monitored less frequently or without radiation-based imaging modalities, in light of the cost-benefit analysis of the additional radiation exposure over time.

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