Uveal Melanoma: An Update

By Hassan A. Aziz, MD, and Arun D. Singh, MD

In this edition of Road to Recertification, Hassan A. Aziz, MD, and Arun D. Singh, MD, provide an update of recent developments in uveal melanoma treatment. Their overview does not substitute for a comprehensive review course. Rather, it highlights key areas within this particular subspecialty and encourages a thorough review prior to taking the Demonstration of Ophthalmic Cognitive Knowledge examination.

—Diana V. Do, MD

Uveal melanoma is the most common primary intraocular tumor in adults, with an estimated incidence of 6 cases per million each year. Uveal melanoma is most commonly diagnosed in the sixth decade of life. Unlike cutaneous melanoma, the incidence of uveal melanoma has remained unchanged in the United States over the past 25 years at about 5 cases per million individuals. Uveal melanoma can occur anywhere in the uveal tract, including the iris (4%), ciliary body (6%), and choroid (90%).

The content of this article is limited to a discussion of ciliary and choroidal melanomas.

CHARACTERISTICS

In most cases the diagnosis of ciliary and choroidal melanoma is made exclusively based on clinical findings. Therefore, a careful examination supplemented with appropriate imaging is essential to make the correct diagnosis. The Table lists hallmark clinical, imaging, and histologic characteristics.

Clinical and histologic features associated with poor prognosis include large tumor size, diffuse melanoma, location within the ciliary body, extraocular extension, advanced age, predominance of epithelioid cell type, closed pseudovascular loops and networks on histology, and high mitotic rate.

TUMOR GENOTYPING

Study of tumor genetics is currently the most accurate prognostication technique for ciliary and choroidal melanomas. The major chromosomal abnormalities present in ciliary and choroidal melanomas that portend a poor prognosis include monosomy of chromosome 3 and 8q gain. Recently, genetic expression profiling and multiplex ligation-dependent probe amplification-based tests have become commercially available. These tests analyze a tumor sample obtained by fine needle aspiration biopsy, which is performed during plaque brachytherapy. Based upon tumor genotyping, ciliary and choroidal melanomas...
can be classified into 2 groups: class 1 (low propensity to metastasize) and class 2 (high propensity to metastasize).  

**COMS STUDY**

The Collaborative Ocular Melanoma Study (COMS) was a landmark multicenter randomized prospective study in which investigators categorized choroidal melanoma into 3 groups depending on the size of the primary tumor. Small size melanoma was defined as having a height between 1.5 and 2.4 mm and basal dimension less than 16.0 mm; medium size melanoma had a height between 2.5 and 10.0 mm and basal dimension less than or equal to 16.0 mm; large size melanoma was characterized as having a height greater than 10.0 mm and basal dimension greater than 16.0 mm. The size of the tumor determined the treatment decision. Small tumors were observed, eyes with medium tumors were randomized to enucleation or brachytherapy, and eyes with large tumors were randomized to enucleation or enucleation with external radiation therapy.

Researchers in the study found that a majority of small size melanomas (66%) did not grow under observation, indicating that lesions included in this group, although labeled as melanoma, were likely nevi rather than melanoma. For medium size choroidal melanoma, brachytherapy proved to be equivalent to enucleation in terms of tumor-specific mortality. No survival advantage was associated with enucleation for medium size melanoma. For large size melanoma, preoperative external beam radiation prior to enucleation did not improve survival rates.

**CURRENT TREATMENT OPTIONS**

A number of treatment options exist for choroidal melanoma. These include laser therapy, radiation, local resection, and enucleation.

**Laser Therapy**

Transpupillary thermotherapy alone was initially used for small choroidal melanomas, but this treatment fell out of favor when tumor control rates were found to be inferior to radiation therapy. 

**Radiation**

In radiation brachytherapy, multiple isotopes have been used in the treatment of ciliary and choroidal melanomas, including iodine-125, ruthenium-106, palladium-103, and cobalt-60. In the United States, iodine-125 is the most commonly used isotope.

Only a few centers around the world have access to proton beam radiation technology. The theoretical benefit is that it provides a homogeneous dose to the target tissue while sparing the surrounding normal ocular tissue. Potential considerations in treatment of juxtapapillary tumors include the location of the tumor (although it
is sometimes challenging to place the radiotherapeutic plaque close to the optic nerve). Those using proton beam radiation need to ensure that they have adequate radiation coverage of the whole tumor.

Local Resection
Exeresis and enucleation of the tumor with preservation of the vitreous and retina are no longer commonly performed due to the technical difficulty and high risk of short-term complications, including vitreous hemorrhage, retinal detachment, and cataract formation, as well as long-term concerns for local tumor recurrence.

Enucleation
Enucleation is indicated in large melanoma not amenable to radiation therapy or in cases of optic nerve invasion. Enucleation is also the treatment of choice for all melanomas if there is no useful vision or potential for useful vision. The patient’s preference after detailed counseling is paramount in making a treatment decision.

COMPLICATIONS OF RADIATION
The earliest sign of radiation chorioretinopathy (RCR) is macular edema. Additional features include hard exudates, telangiectasia, microaneurysms, and capillary dropout. Neovascularization of the retina, iris, and/or iridocorneal angle may develop in advanced cases with proliferative RCR. Such patients can progress to develop vitreous hemorrhage, tractional retinal detachment, neovascular glaucoma, and eventual phthisis bulbi.

Manifestations of RCR peak at 1 to 2 years after treatment. Treatment with anti-VEGF agents have shown transitory improvement in visual acuity but has failed to demonstrate consistent results after long-term follow up. Laser photocoagulation of peripheral ischemic retina is indicated in cases of proliferative RCR.

Radiation optic neuropathy is an irreversible cause of visual loss following radiation therapy. Systemic steroids, anticoagulation, intravitreal anti-VEGF injections, and hyperbaric oxygen therapy have shown no significant or sustainable benefit in the treatment of radiation optic neuropathy.

FUTURE DIRECTIONS
Despite advances in local tumor control rates, survival rates have remained unchanged during the past 40 years. It is believed that occult micrometastasis is already present at the time of diagnosis of most primary uveal melanomas. Overt metastasis is often detected months or years later. After metastasis occurs, the prognosis is dismal; thus, treatment of the primary tumor may be considered palliative rather than curative.

Tumor genotype-based prognostication not only provides the specific risk of metastasis to the patient for appropriate counseling but also influences the intensity and frequency of systemic surveillance for metastases. Patients with class 2 tumors may be considered for experimental adjuvant therapy (prior to onset of detectable metastases). The aim of adjuvant therapy is to decrease the rate of progression or even potentially stop micrometastasis from transforming to overt metastasis, thereby increasing progression-free and overall survival rates. Multiple phase 2 and 3 studies are being planned and conducted to access efficacy of adjuvant therapy in the management of uveal melanoma.

Improved understanding of the molecular genetic pathways implicated in causing ciliary and choroidal melanomas is also providing new targets for intervention and agents to be used in adjuvant treatment trials.

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