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Management of Choroidal Melanoma

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After completing this activity, the participant should be better able to:

- Identify the types of patients at risk for developing choroidal melanoma and describe the necessary workup and staging for choroidal melanoma.
- Understand the basis for conservative (eye-preserving) management of choroidal melanoma.
- Describe the treatment options available for choroidal melanoma, including external photon beam, brachytherapy, and charged particle options.

Introduction

It is estimated that there will be 2,810 new cases of malignancy of the eye and orbit in 2016 and 210 deaths from eye diseases;[1] of these, the most common primary intraocular malignancy is uveal melanoma, a malignancy arising from melanocytes of the uveal tract, accounting for approximately 60-80 percent of new presentations each year. Choroidal melanoma is the largest subsite of uveal melanoma, which also includes melanoma malignancies arising from the iris or the ciliary body. The choroid is a pigmented layer of the eye. Melanoma arising from the choroid is a relatively rare disease that previously was treated with enucleation, or removal of the eye.[2]

The mean age of diagnosis for ocular melanoma is 60, and men and women are equally affected. There is a predilection for occurrence in fair-skinned and light-eyed (blue irides more often than brown irides) patients, and the disease is almost always unilateral. Dysplastic nevi syndrome may predispose to melanoma.

The majority of choroidal melanomas present with painless loss or distortion of vision, but lesions that cause detachment of the retina may be associated with visual symptoms such as flashing lights, and eye pain can rarely be a presenting symptom.[3] The diagnosis of choroidal is primarily clinical, made by an experienced ophthalmologist.

With direct or indirect ophthalmoscopy, subretinal fluid or orange pigment may be noted, and serial exams may document growth; these all suggest a malignant lesion. Ocular ultrasound is a key diagnostic study: A-scans are one-dimensional scans that identify material/acoustic properties, and low internal reflectivity is associated with malignant melanoma; B-scans are two-dimensional scans that document shape and size factors, such as the oft-described "collar button" or mushroom appearance that indicates disruption of Bruch's membrane and is associated with malignant melanoma. Additionally, B-scans can identify retinal detachment and the presence of subretinal fluid and detect orbital extension. Any lesion >3 mm in height is most likely a melanoma.

The official staging systems by the Collaborative Ocular Melanoma Study (COMS) and American Joint Committee on Cancer (AJCC) are presented in Table 1.[4] Choroidal melanoma is usually localized to the globe on presentation. All patients with choroidal melanoma must undergo cross-sectional imaging of the abdomen, not just liver function tests, as the primary site of spread for the disease is to the liver (>90 percent of all metastases).[5] Liver function tests (LFTs) and abdominal ultrasound do not have sufficient sensitivity to detect small lesions in the liver. FDG-PET imaging is reasonable due to the avidity of melanoma but may miss small lesions; either triphasic contrast-enhanced CT or MR imaging is optimal for metastasis screening.[6]

Treatment by stage

The COMS Group conducted a series of studies from 1986-2003 to find the optimal treatment for ocular melanomas at various points in the disease process. The COMS Medium trial was a pivotal study that proved conservative eye-preserving therapy is a viable treatment option for patients presenting with relatively early-stage choroidal melanomas.[7]

In that trial, 1,317 patients with unilateral choroidal melanoma 2.5-10 mm in height and up to 16 mm in diameter were randomized to enucleation or iodine-125 (125I) plaque brachytherapy. Outcomes at 12 years showed no significant difference; mortality was 41 percent in the enucleation group and 43 percent in the 125I plaque group, and 17 percent had developed distant metastases in the enucleation group vs. 21 percent in the 125I plaque group. In the companion quality-of-life study, 125I plaque brachytherapy was associated with better visual function for driving and peripheral vision, although increased anxiety was present.[8] The final report did not

provide details on local control, but an earlier report provided an enucleation rate of 12 percent at five years, due to recurrence and/or symptoms.[9] Outcomes for multiple institutional studies using episcleral plaque brachytherapy were summarized in the American Brachytherapy Society (ABS) report on brachytherapy for uveal melanoma;[10] five-year local control for 125I-based plaque brachytherapy ranged from 81-92 percent.

For patients with larger lesions, the role of radiation therapy is less clear. In the COMS Large Choroidal Melanoma trial,[11] 1,003 patients with larger lesions (either ≥16 mm in basal diameter or ≥10 mm in height, or ≥8 mm in height and within 2 mm of the optic disc) were randomized to enucleation or enucleation plus external beam radiation therapy (a prescribed dose of 20 Gy in 5 daily fractions of 4 Gy per fraction). Outcomes were not improved with additional radiation therapy; 10-year mortality was 61 percent for both arms, and rates of metastases were unchanged. It should be noted that the radiation doses used in this study were very low, and doses above 4 Gy per fraction are generally recommended as melanoma is considered to be relatively radiation-insensitive.[12] Adjuvant dosing schedules for melanoma are generally much higher (on the order of 48 Gy in 20 fractions, or 30-36 Gy in 5-7 fractions).[13-15] While an increased dose theoretically may have yielded superior outcomes, such high doses would likely result in unacceptable toxicity when administered to the orbit.

Small lesions (1-3 mm in height and at least 5 mm in basal diameter) are generally observed. In the COMS Small Choroidal Melanoma Observational Study, 204 patients were followed and were noted to have only a 1 percent melanoma-specific mortality at five years.[16] These patients can be followed with periodic photos of the fundus and ultrasound imaging. Patients with orange pigment, absence of drusen (yellow lipid-rich deposits between Bruch's membrane and the retinal pigment epithelium [RPE] of the eye) or absence of changes in RPE near the lesion, and larger size are associated with increased likelihood of growth.[17] Several risk factors for progression have been identified, including tumor thickness >2 mm, the posterior margin touching the optic disc, visual symptoms, orange pigment, or subretinal fluid.[18] The presence of even one of these symptoms predicts growth in 36 percent of patients, increasing to 50 percent for patients with three factors.

Eye plaque brachytherapy procedure

While the COMS study used 125I-based brachytherapy plaques, a variety of radioactive isotopes may be used. "High energy" plaques include 60Co (which emits 1.17 and 1.33 MeV gamma rays) and 106Ru (which emits 36 keV beta-particles). "Low energy" plaques include the standard 125I source (which emits 35 keV photons) and the 103Pd source (which emits 21 keV photons). Plaques are fabricated to deliver a dose of 75-85 Gy to the apex of the intraocular tumor, with a 2 mm margin all around the tumor (such that a 10 mm diameter tumor would be treated with a 14 mm diameter plaque). (Figure 1) Per American Brachytherapy Society (ABS) recommendations, the minimum dose to the apex of the tumor should be 85 Gy, with a dose rate of 0.6-1.05 Gy/hour when using an 125I-based plaque.[10] Patients with gross extrascleral extension, ring melanoma, involvement of the irides, and significant involvement of the ciliary body (>⅓) are not suitable for plaque brachytherapy.

Plaque placement is generally performed under general anesthesia. After the conjunctiva is reflected, the choroidal lesion is localized by intraoperative ultrasound, transillumination (most effective for pigmented lesions), and/or indirect ophthalmology. Many practitioners first place a nonradioactive "dummy" plaque of identical size and shape to the brachytherapy plaque over the site to confirm coverage and then place sutures that can be used to quickly secure the actual plaque in position (reducing radiation exposure to the ophthalmic surgeon). (Figure 2) It may be necessary to sever the lateral rectus muscles or other extraocular muscles to ensure adequate placement.

The plaque remains in position for three to seven days (generally three). Shorter placement times are associated with increased toxicity while longer placement times are inconvenient to the patient, increase the risk of infection, and potentially compromise successful reimplantation of extraocular muscles if severed for placement. Adequate treatment is defined as no tumor growth or reduction in size. Surveillance following treatment includes regular ophthalmic follow-up, imaging of the liver (CT or MRI), and LFTs at scheduled intervals.

The complications of plaque brachytherapy are well-characterized. Early complications include bleeding, infec-

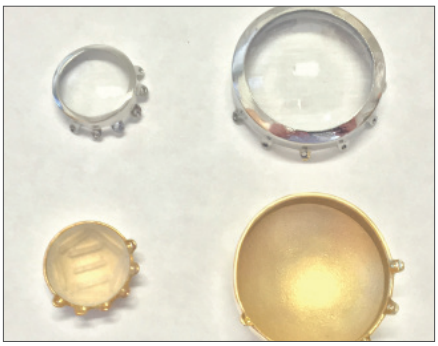

Figure 1. Example of "dummy plaques" (top row) and treatment plaques (bottom row) used for choroidal melanoma. Plaque on bottom left shows the silastic insert used to hold the 125I seeds.

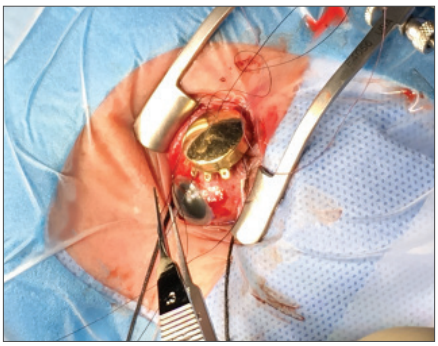

Figure 2. Treatment plaque secured in place.

tion, and diplopia (especially if an extraocular muscle such as the lateral rectus is temporarily severed). Late complications include radiation retinopathy (42 percent at five years), cataracts, optic neuropathy, and keratitis. For all patients treated with COMS-style 125I-based plaque brachytherapy, regardless of baseline visual acuity, five-year visual acuity was <20/200 in 63 percent of treated patients, and <5/200 in 45 percent of treated patients. Five years after 125I-based plaque brachytherapy, the rate of enucleation is 12 percent due to recurrence and/or ocular toxicity.[9]

Alternative eye-preserving therapy options for choroidal melanoma

While plaque brachytherapy is considered the standard of care, other therapies have been employed to good effect, including charged-particle therapy, photon-based stereotactic radiosurgery (Gamma Knife or CyberKnife), and ophthalmic interventional techniques for eye preservation.

Proton beam radiation therapy for ocular melanoma also has a long history. In one of the largest series reported, Lane et al. presented long-term outcomes data for 3,088 patients with uveal melanoma treated with proton beams from 1975 to 2005.[19] At 15 years, all-cause mortality was 49 percent with melanoma-specific mortality of 24.6 percent. A recent review by Verma and Mehta examined 14 original investigations at 10 institutions utilizing proton beam therapy (dose ranges 50-70 CGE) for uveal melanoma and noted consistent local control rates of >90 percent at five years, five-year enucleation rates between 7-10 percent, and good visual outcomes, with most patients retaining purposeful vision.[20] Proton beam radiation therapy has also been shown to be useful for salvage reirradiation.[21]

Photon-based stereotactic radiosurgery is a treatment option available at many centers that have specialized technology such as the Gamma Knife or CyberKnife for treating other diseases of the central nervous system. These techniques are helpful for treatment of lesions near the optic nerve or anterior eye, as plaque brachytherapy may have less utility in these anatomic subsites. Single fraction treatments with marginal doses of <25 Gy can be delivered with Gamma Knife radiosurgery (GK-SRS), with local control rates above 90 percent.[22]

While no direct comparison exists between GK-SRS and plaque brachytherapy, in a single-institution experience in the UK, 170 patients treated with GK-SRS (doses ranging from 35-70 Gy in a single fraction) were compared to 620 patients treated with enucleation.[23] No difference was found in survival, and in the least toxic treatment group receiving 35 Gy in a single fraction, only 6.5 percent proceeded to post-radiation enucleation. High-dose single fraction radiation therapy can be associated with acute swelling, which may require steroid management post-treatment.

Other nonradiation-based methods include transpupillary thermotherapy (TTT) using an infrared diode laser, photodynamic therapy (PDT), and laser photocoagulation.[24]

Adjuvant therapy options

The predominant mode of disease progression for choroidal melanoma is distant metastasis; therefore, adjuvant therapy following definitive treatment of the primary disease is an area of active research. Poor prognostic factors that have been used to guide additional therapy include larger tumor diameter and thickness, ciliary body invasion, lesions arising near the fovea/macula, tumor invasion through the sclera, optic nerve invasion, and older age. Tissue is rarely available at initial diagnosis, but mixed or epithelioid histology and/or pleomorphic nucleoli, high mitotic rate, Ki-67 positivity, lymphocytic infiltration, monosomy of chromosome 3, additional copies of chromosome 8q, and codeletions in chromosome 1 and 3 are also poor prognostic factors.[27-29]

Thus far, no adjuvant treatment has had any success. Interferon-α, bacillus Calmette-Guerin (BCG), and infusional fotemustine (an alkylating agent) have all been explored without benefit in terms of overall or progression-free survival. A range of trials incorporating tyrosine kinase inhibitors (sunitinib), HDAC inhibitors (valproic acid), and ALK inhibitors (crizotinib) for patients with high-risk disease are concluding or underway. Immune checkpoint inhibitors in particular have increasing application in the treatment of melanoma, and their utility in the management of choroidal melanoma is under investigation.[6]

CONCLUSION

For medium-sized choroidal melanomas, or small choroidal melanomas with adverse features, conservative treatment with eye preservation should be the standard of care. For most patients, plaque brachytherapy is the simplest treatment, requiring only two operative visits (one for placement and one for removal), with flexible treatment times ranging from three to seven days. For patients with lesions near the optic nerve or anterior eye, stereotactic radiosurgical techniques may provide superior dosimetry. Charged-particle techniques (proton, helium ion, and others) are well-established and provide an alternative treatment option, and they have additional application to larger and/or recurrent tumors.

Management of distant metastases is an area that still needs a great deal of work because a significant portion of patients will develop distant metastases, even in the setting of adequately treated local disease. Therapies that perhaps augment the systemic immune response to the malignant lesion may help to prevent early micrometastases from taking hold.

COMS Stage	Apical height	Basal Diameter
Small	<3 mm	5 - 16 mm
Medium	3 - 10 mm	5 - 16 mm
Large	>10 mm	>16 mm
Diffuse	Flat growth, thickness <20% basal dimension	
Metastic	Any N1 or M1	

T1: Tumor size category 1	T3: Tumor size category 3
T1a: size category 1 without both ciliary body involvement and extraocular extension	**T3a:** size category 3 without both ciliary body involvement and extraocular extension
T1b: size category 1 with ciliary body involvement	**T3b:** size category 3 with ciliary body involvement
T1c: size category 1 without ciliary body involvement with extraocular extension ≤5 mm	**T3c:** size category 3 without ciliary body involvement with extraocular extension ≤5 mm
T1d: size category 1 with ciliary body involvement and extraocular extension ≤5 mm	**T3d:** size category 3 with ciliary body involvement and extraocular extension ≤5 mm
T2: Tumor size category 2	**T4: Tumor size category 4**
T2a: size category 2 without both ciliary body involvement and extraocular extension	**T4a:** size category 4 without both ciliary body involvement and extraocular extension
T2b: size category 2 with ciliary body involvement	**T4b:** size category 4 with ciliary body involvement
T2c: size category 2 without ciliary body involvement with extraocular extension ≤5 mm	**T4c:** size category 4 without ciliary body involvement with extraocular extension ≤5 mm
T2d: size category 2 with ciliary body involvement and extraocular extension ≤5 mm	**T4d:** size category 4 with ciliary body involvement and extraocular extension ≤5 mm
	T4e: Any tumor size category with extraocular extension >5 mm in diameter

Table 1. COMS and AJCC 2010 staging for melanoma of the choroid and ciliary body

Construction update

The new state-of-the-art radiation oncology building under construction across from the Harold C. Simmons Comprehensive Cancer Center is going up quickly! All structural steel has been installed in the building, and in March a topping-out ceremony was held, with remarks given by UT Southwestern Medical Center President Daniel K. Podolsky, M.D.

Visit our webcam to watch real-time progress on the facility: oxblue.com/open/whitingturner/UTSRO.

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