PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

OCULAR ONCOLOGY

UVEAL MELANOMA

Site Group: Ocular – Uveal Melanoma

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1. INTRODUCTION

Uveal melanoma affects four to seven persons per million each year in the United States and causes significant vision loss and mortality. This is the most common primary intraocular malignancy in adults and metastasizes to distant sites in half of all patients. Once this occurs, the cancer can be fatal because there are currently no effective treatments for systemic metastasis. The iris, ciliary body, or choroid may be involved. Tumors usually present unilaterally and are slightly more common in men. Mortality from metastatic melanoma increases with age (especially after age 60).

2. PREVENTION

There are no known modifiable risk factors for uveal melanoma.

3. SCREENING AND EARLY DETECTION

Early detection during routine eye examinations may lead to timely local control of the tumor before visual compromise or metastasis occurs. No specific screening policies are yet in place.

4. DIAGNOSIS

Patients are typically referred from across Canada by vision care specialists who have detected a uveal mass suspicious for malignancy. During the initial assessment following referral, patients undergo a complete ophthalmological examination and ancillary testing as described below. All new patients are presented to the Ocular Oncology consultants group on a weekly basis as part of a multi-disciplinary review to formulate a management plan.

Clinical features

Ophthalmic examination

Although iris melanomas may be diagnosed earlier because they are more readily visible, posterior (ciliary body, choroidal) uveal melanomas are diagnosed only after patients are evaluated specifically for a visual change or a suspicious lesion detected incidentally during ophthalmoscopy. Iris melanomas are better differentiated and less aggressive compared with posterior uveal melanomas. For the latter, indirect ophthalmoscopic fundus drawing and fundus imaging are performed at every visit. Lesions can be pigmented or amelanotic, in a flat, dome or mushroom configuration, and can be associated with overlying orange pigment (lipofuscin) and or subretinal fluid. Simulating lesions are considered in the differential diagnosis (see Table 1).

Table 1. Lesions simulating (posterior) uveal melanoma

Lesion	Clinical Features
melanocytic nevus	small, pigmented
indeterminate melanocytic	as above with variable risk factors for progression to

lesion (IML)	malignancy
melanocytoma	darkly pigmented, exhibits growth, often juxtapapillary
metastatic tumors	light color, uni- or bilateral, multifocal, RPE mottling, known primary (i.e. lung cancer)
hemangioma	orange-red, solitary, high IR consider Sturge-Weber syndrome
osteoma	yellow-white, juxtapapillary, very high IR more common in females
ARMD	subretinal or sub-RPE hemorrhage, disciform scar
inflammatory	uveitis, vitritis, scleritis
RPE proliferation	post-(trauma, infection, retinal detachment)

ON - optic nerve, RPE - retinal pigment epithelium, IR - internal reflectivity, ARMD - age-related macular degeneration

Ancillary testing

Uveal melanoma demonstrates characteristic features on echography that are highly reliable to make an accurate diagnosis. In the recent Collaborative Ocular Melanoma Study (COMS) report, 88% of tumors had low to medium reflectivity with ultrasound, a mushroom configuration, or both. Extrascleral extension can be detected using echography if at least 1.5 mm in size. See Table 2 for a summary of clinical and echographic features of uveal melanoma. Ultrasound biomicroscopy (UBM) can be employed for anterior uveal lesions. Neuroimaging (MRI, CT) is helpful when a lesion is suspicious for posterior extrascleral extension. Angiographic studies including intravenous fluorescein angiography (IVFA) and indocyanine green angiography (ICGA) can show intrinsic tumor vasculature (double circulation). Abnormal leakage (i.e. hot spots) or blockage (i.e. lipofuscin) may be seen on IVFA. Static perimetry is useful to monitor visual field changes. Certain patients will also undergo optical coherence tomography (OCT) when vision loss occurs secondary to sub-retinal or intra-retinal swelling. Patients with an indeterminate lesion may be a candidate for fine-needle aspiration biopsy (FNAB). This decision is made on a case-by-case basis in discussion with the patient.

Table 2. Clinical and echographic features of uveal melanoma

Location	Ophthalmoscopy	Echography
Choroid	mushroom configuration dome configuration	acoustic hollowness* choroidal excavation *

	presence of subretinal fluid transillumination blockage variable pigmentation presence of lipofuscin absence of drusen	orbital shadowing* low to medium internal reflectivity◆
Ciliary body	sentinel (feeder) vessels sectoral cataract	UBM to establish morphology and extent
Iris	discrete or diffuse pigmentation	UBM to establish morphology and extent

* immersion B-scan echography
◆ A-scan echography
UBM—ultrasound biomicroscopy

Systemic metastatic disease

Uveal melanoma should be managed as a systemic disease. In addition to local spread, patients must be evaluated for metastatic lesions. In the COMS trial, only 45% of uveal melanoma patients were alive and cancer-free 12 years after treatment. The 12-year mortality rate with histologic confirmation of melanoma metastasis was 21%. Patients with small or medium-sized tumors almost never have evidence of systemic involvement on initial presentation and less than 1% of large lesions may do so. The most common site of involvement is the liver (up to 90%). Other sites include skin (subcutaneous nodules), lungs, bone, and the central nervous system. Patients typically undergo routine blood work for hepatic enzymes (AST, ALT, bilirubin) and chest/abdominal imaging using ultrasonography or CT. There is, however, a lack of consensus regarding the desired frequency and choice of testing for metastatic screening. In fact, it may be futile to discriminate between various metastatic screening protocols because none have proven useful in improving disease-related survival. A recent review of the literature found no evidence that routine surveillance for metastasis confers any survival benefit to patients with primary uveal melanoma. The main advantage of surveillance may be limited to patient and practitioner reassurance.

Predictors of disease-related metastasis and mortality

Patient age and tumor size are the main predictors of time to death from all causes and metastatic melanoma-related mortality. Involvement of the ciliary body tends to increase risk and local recurrence after treatment failure is weakly associated with a higher metastatic rate. Other high-risk clinical features include extraocular extension, diffuse growth pattern, ring configuration, and optic nerve involvement.

5. PATHOLOGY

The two predominant histopathological cell types of uveal melanoma are spindle cells (elongated nuclei, scant cytoplasm, cohesive) and epithelioid cells (round or oval nuclei, abundant cytoplasm, discrete, large, and pleomorphic). A spectrum exists

between these two cell types and many lesions exhibit a mixed cellular population. The epithelioid cell type is strongly associated with higher rates of metastasis and mortality while the spindle cell type is associated with a better prognosis. Serum immunoassays for biomarkers including PC-10 monoclonal antibody, osteopontin, S-100 beta, melanoma-inhibitory activity, and human leukocyte antigens, can detect malignant uveal melanoma cells in the serum and may predict metastasis but direct inference to metastatic potential is not always significant.

Immunohistochemistry (IHC) has improved traditional histologic methods. For example, IHC staining with anti-Phospho-Histone H3 Ser10 (PHH3) produces higher mitotic counts than traditional hematoxylin-eosin (H&E) staining techniques. Immunopositivity for the proliferation marker Ki-67 can distinguish uveal melanomas that are low- versus high-risk for metastasis. Most melanomas are diagnosed by H&E alone but indeterminate specimens can be confirmed using IHC with Human Melanoma Black (HMB)-45, melan-A, tyrosinase, and NK1 C3 stains.

The high-risk histologic features for uveal melanoma metastasis and disease-related mortality are epithelioid cell type, high mitotic rate, closed periodic acid-Schiff (PAS)-positive loops, mean diameter of 10 largest nucleoli, degree of pigmentation, inflammation, vascular invasion, and tumor necrosis.

Genetic testing. Chromosomal and molecular testing have elucidated several key genetic alterations that occur during the transition of a normal melanocyte to a malignant melanoma cell. The genetic profile for a given uveal melanoma lesion will impact its clinical behavior. Early disruption of cell cycling seems to occur from a GNAQ gene mutation, which leads to activation of downstream signaling pathways (i.e. MAPK, receptor tyrosinase kinase) and subsequent inhibition of tumor suppression mechanisms (i.e. Bcl-2). Ultimately, malignant proliferation ensues and a clinically evident lesion develops. At this stage, cytogenetic gene hybridization studies will show minimum aneuploidy and gene expression profiling (GEP) will show a class 1 signature (class 1A melanoma). The lesion may then undergo one of two pathways. Firstly, it may become more differentiated, less aggressive and unlikely to undergo metastasis (class 1B melanoma, associated with 6p gain). However, a mutation of BAP1 or similar genes will make the lesion less differentiated, more aggressive and likely to metastasize (class 2A genetic signature, associated with monosomy 3). About 25% of these latter tumors will become even more aggressive and genetically unstable (class 2B genetic signature, associated with 8p gain).

Gene expression profiling separates uveal melanoma patients into one of two groups; those who are likely (class 2) versus those who are unlikely (class 1) to undergo metastasis (see Table 3). The predictive value of molecular class supersedes clinical, histologic, and cytologic prognosticators. However, important limitations include lack of accuracy due to tumor heterogeneity (i.e. sampling error), lack of availability of the various molecular genetic tests, and the fact that progression from class 1 to class 2 cannot be anticipated. Currently, genetic analysis is accomplished off-site when considered advisable.

Table 3. Gene-expression profiling (GEP) reveals two distinct molecular classes of uveal melanoma

	Class 1	Class 2
Cellular differentiation	well-differentiated	stem-cell like ectodermal cells
Cytogenetics	chr 6p gain (disomy 3)	loss of heterozygosity for chr 3 (monosomy 3)
Chromosomal aneuploidy	low	high
Ki-67 antibody positivity	low	high
Predominant cell type	spindle	epithelioid
Metastatic rate	low	high

chr - chromosome

***Tumor-Node-Metastasis (TNM) classification to stage disease*.** The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUCC) TNM staging systems for uveal melanomas were revised in 2009. The clinical (c) and pathologic (p) TNM classifications are distinguished. The former is determined by the clinician prior to treatment while the latter by the pathologist after specimen analysis. Iris melanomas are classified separately from posterior (ciliary body, choroidal) melanomas. Tumor size, ciliary body involvement, and extrascleral extension are used to grade lesions (T). This grade, along with metastasis to regional lymph nodes (N) and distant lymph nodes (M), is used to stage the tumor. The multi-gene clinical prognostic assay is included in this recent TNM classification.

TNM Classification of Uveal Melanoma

Primary Tumor (T) mm size
a – no ciliary body (CB) involvement
b – with CB involvement
c – no CB involvement + extraocular extension (EOE) less than 5mm
d – with CB involvement + extraocular extension (EOE) less than 5mm
e – any size with EOE greater than 5mm

Thickness (mm)							
>15	4	4	4	4	4	4	4
12.1-15.0	3	3	3	3	3	4	4
9.1-12.0	3	3	3	3	3	3	4
6.1-9.0	2	2	2	2	3	3	4
3.1-6.0	1	1	1	2	2	3	4
Less than or equal to 3.0	1	1	1	1	2	2	4
	Less than or equal to 3.0	**3.1-6.0**	**6.1-9.0**	**9.1-12.0**	**12.1-15.0**	**15.1-18.0**	**>18**
	Largest basal diameter (mm)						

Regional Lymph Nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant Metastasis (M)
MX: Distant metastasis cannot be assessed
N0: No distant metastasis
M1: Distant metastasis
M1a: Largest diameter of the largest metastasis less than or equal to 3cm
M1b: Largest diameter of the largest metastasis 3.1-8.0cm
M1c: Largest diameter of the largest metastasis greater than or equal to 8.0cm

STAGING

Stage				**10-year survival**
Stage I	**T1**	**N0**	**M0**	**88%**
	T1a	**N0**	**M0**	
Stage IIA	**T1b-d**	**N0**	**M0**	**80%**
	T2a	**N0**	**M0**	
Stage IIB	**T2b**	**N0**	**M0**	**68%**
	T3a	**N0**	**M0**	
Stage IIIA	**T2c-d**	**N0**	**M0**	**45%**
	T3b-c	**N0**	**M0**	
	T4a	**N0**	**M0**	
Stage IIIB	**T3d**	**N0**	**M0**	**26%**
	T4b-c	**N0**	**M0**	
Stage IIIC	**T4d-e**	**N0**	**M0**	**21%**
Stage IV	**Any T**	**N1**	**M0**	**0%**
	Any T	**Any N**	**M1a-c**	

6. MANAGEMENT

6.1 Management algorithms

Decision to treat
If the systemic work-up is negative, the management options involve serial observation or local therapy (radiation, surgery, or laser—see Table 4). Treatment goals are to prevent metastasis and maintain vision for lesions that are growing or exhibit high-risk features for growth. Patients with a lesion demonstrating clinical and echographic features consistent with uveal melanoma (Stage IIIC or less) are offered radiation therapy or surgery. A histopathological diagnosis is only available from an enucleation specimen or by FNAB. Overall, surgery and I-125 brachytherapy were found to result in similar survival rates for patients with medium-sized lesions in the COMS study.

Although most agree that medium and large tumors should be treated promptly, the decision regarding management of smaller indeterminate tumors can be more

difficult. Shields *et al.* looked at more than 1,300 small melanocytic lesions and found the following features were predictive of subsequent growth—lipofuscin, visual symptoms, juxtapapillary location, increased thickness, and subretinal fluid. Patients may be offered serial observation, FNAB (for select cases), or occasionally surgery. Most agree that a small tumor can be observed unless it demonstrates growth or has high-risk features for growth. This approach may change, however, in light of new evidence based on molecular genetic testing. There are currently many clinical trials underway for various systemic therapies to treat metastatic disease, but none have been effective to date. Except for rare cases that may improve after local hepatic resection, by and large there are no effective treatments for melanoma metastasis and patients succumb to the cancer within one year.

Table 4. Treatment options for uveal melanoma

Laser	Radiation	Surgery
TTT diode+	plaque brachytherapy (Iodine-125)* (Ruthenium-106) (Palladium-103) (Cobalt-60) external beam therapy (protons)* (helium ions) gamma knife radiosurgery	local resection sclerouvectomy◆ partial choroidectomy transretinal endoresection enucleation

TTT-transpupillary thermotherapy
+ mainly adjunctive therapy
* most commonly used
◆ lamellar resection or en bloc (eyewall) resection reconstructed with scleral graft

6.2 Surgery

Uveal melanoma can be treated by enucleation surgery when the clinical diagnosis is clear. However, when globe-preserving therapy is a viable option, every effort is made to present the risks versus benefits of all options to the patient. Enucleation is a definitive procedure whereby the entire eyeball is removed with the sclera intact, with disinsertion of the extraocular muscle attachments and the optic nerve. Tumors that have progressed despite prior radiation therapy are often treated by enucleation. A permanent orbital implant is inserted during surgery, which replaces orbital volume and is covered by the Tenon's fascial and conjunctival layers after the extraocular muscles are attached to it. A temporary plastic conformer is left in place for six weeks after which time the ocularist fashions a customized prosthetic shell to rest on the mucous membrane tissue. Some iris or ciliary body melanomas can be excised by local resection. Exenteration for recurrence is of limited value.

6.3 Chemotherapy

There is no role for systemic chemotherapy in treating the primary intraocular tumor. Systemic therapies including chemotherapeutics, hepatic artery infusion of melphalan and other agents have not been shown to improve patient survival once metastasis occurs.

6.4 Radiation therapy

See Table 4 for a summary of possible radiation delivery methods for uveal melanoma. At PMH/UHN, I-125 plaque brachytherapy is employed for medium-sized tumors with minimal optic nerve involvement and no to limited extraocular extension, and stereotactic arcs are utilized for peripapillary tumours not suitable for I-125 plaques.

Iodine-125 Plaques

Tumours with a height of 2-10 mm and basal diameter $\leq$ 16 mm are eligible for brachytherapy.
Plaque diameter is 4 mm wider than the widest basal dimension of the melanoma, in order to provide 2 mm clearance circumferentially (plaque range 10-22 mm in 2 mm increments)

Prescription point:	85 Gy to tumour apex
Dose rate:	50 cGy/hour, delivered over 7 days

External Beam RT:

Posterior peripapillary medium size tumours (height 2-10 mm, basal diameter < 16 mm, anterior edge of tumour does not cross equator of eye)

Immobilization:	relocatable stereotactic GTC frame with eye fixation device
Simulation:	CT, MRI
Technique:	VMAT, 2 partial arcs

Daily image guidance with cone beam CT
Dose: 50 Gy/5 fractions, delivered on alternate days over 10 days

6.5 Other therapy

There are currently several clinical trials underway for systemic treatment of advanced uveal melanoma based on targeted molecular pathways. Agents include Sorafenib (NCT01377025), CP-675, 206 (NCT01034787), and Imatinib (NCT00421317). Transpupillary thermotherapy (TTT) is a non-invasive laser treatment that was used initially at PMH but was found to be of limited benefit as primary therapy for choroidal melanoma and is used only as adjunctive therapy for select cases. Patients with vision loss secondary to macular edema may be treated with intravitreal injection of anti-VEGF agents (bevacizumab or ranibizumab).

6.6 Oncology nursing practice

Patients seen at the Ocular Oncology clinic are invariably outpatients. The initial history and assessment of visual acuity and pupil reactivity is performed by the clinic RN. She proceeds to instill dilating eye drops in one or both eyes prior to photography, echography, and examination by the consultant. The RN is often used as an initial point of contact by patients when new symptoms develop or other questions arise.

6.7 Clinic Coordination/Management

The identification of a specific disease complex and the direction to appropriate subspecialty care is usually accomplished by a trained ocular oncology clinic coordinator/manager (Lee Penney). This individual is frequently an experienced ophthalmic assistant. Knowledge of the vision care referral base and collection of investigational materials for new patients is of paramount importance as first steps to providing optimal patient care. The coordinator also serves an invaluable function in supporting both patient and family during investigation, therapy, and convalescence.

7 SUPPORTIVE CARE

7.1 Patient education

Patients and family members are educated on a one-on-one basis by a consultant during the initial assessment and at every follow-up visit.

7.2 Psychosocial care

When patients express or display emotional, psychological, or social concerns an effort is made to address these during the clinical encounter. In rare instances when this is insufficient to deal with all issues, the patient may be referred to the Department of Psychosocial Oncology.

7.3 Symptom management

Patients with uveal melanoma may or may not present with visual symptoms including visual field loss, blurriness, or flashes of light. Those treated by radiation

are educated about the short-term symptoms including eye redness, double vision, and discomfort while recovering, and about the long-term possibility of dry eyes, cataract formation, or vision loss related to the radiation therapy. Patients undergoing enucleation surgery are educated about the possibility of pain, discharge, and swelling that can last several weeks after surgery. Each patient is encouraged to discuss ocular symptoms during every clinical encounter and is managed accordingly.

7.4 Clinical nutrition

The role of nutritional advice and support in the ocular oncology patient population is very limited. Patients with dry eye syndrome may be educated about the value of omega-3-fatty acid and flax seed intake while those with age-related macular degeneration may be encouraged to eat green leafy vegetables.

7.5 Palliative care

When systemic metastasis is detected, the primary uveal melanoma may be untreated. However, in cases of intractable ocular pain, palliative enucleation surgery may be considered. Patients with systemic metastases typically succumb to the disease because there are currently no effective therapies. The radiation and medical oncology groups facilitate end-of-life palliative care.

7.6 Other

Many patients travel from across Canada to the Ocular Oncology service of PMH. The clinic makes every effort to accommodate patients based on travel dates and facilitate lodging when required.

8 FOLLOW-UP CARE AND SURVEILLANCE

<u>Monitoring for growth</u>
The natural history of uveal melanoma is to progress locally and systemically. Growth of the tumor can be horizontal, vertical, focal or diffuse. Over time, tumors may extend anteriorly through Bruch's membrane, posteriorly through sclera, or undergo extraocular extension via neurovascular or aqueous channels. Horizontal growth is best observed by comparing serial fundus images of the lesion while vertical growth by comparing serial measurements of thickness using echography. However, the rate of growth is variable amongst patients. Those patients demonstrating a faster doubling time and growth rate have a greater likelihood of developing metastatic disease and tend to be less responsive to radiation treatment. Overall, I-125 plaque brachytherapy achieves good local tumor control. Patients are followed every 3 to 6 months for the first 5 years after treatment and annually thereafter. Patients are encouraged to come in sooner if new visual symptoms develop during the interval between follow-up visits. Those patients who undergo enucleation surgery are monitored yearly after the post-operative recovery period.

Refining the classification and staging of cancer requires continual validation of the existing system in order to modify future schema. A web-based survey, produced at PMH/UHN, to validate the current TNM classification for uveal melanoma is being

utilized to evaluate and, if appropriate, modify the existing 7th edition of the AJCC Cancer Staging Manual for this important malignancy. Such a survey is intended to provide a collaborative international mechanism to collect and analyze extensive information about a rare eye cancer over a short time interval. In this manner, the continued evaluation of the metrics, biomarkers, and genomics for uveal melanoma will assist the development of improved strategies for surveillance and management.

9 References

In preparation of this document, some data and tables were incorporated from the following publication.

Gill HS, Char DH. Uveal melanoma prognostication: from lesion size and cell type to molecular class. Can J Ophthalmol. 2012;47(3):246-53.